Vutrisiran: Gastrointestinal Events in HELIOS-B

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SUMMARY

- HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR.[1]
  - Treatment with vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events, in both the overall population (HR 0.72; 95% CI 0.56, 0.93; P=0.01) and monotherapy population (HR 0.67, 95% CI 0.49, 0.93; P=0.02).[1]
- In a post hoc analysis of the HELIOS-B study, the rate of GI AEs in patients with ATTR-CM was evaluated over the double-blind period of up to 36 months.[2]
  - All AEs classified under the GI disorders SOC during the double-blind period were compared between the vutrisiran and placebo groups in the overall population, monotherapy population, and baseline tafamidis subgroup.[2]
  - Treatment with vutrisiran resulted in 42%, 37%, and 49% rate reduction of overall GI events per 100 PY in the overall population, monotherapy population, and baseline tafamidis subgroup, respectively, when compared with patients in the placebo group.[2]

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CLINICAL DATA

HELIOS-B Study

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the

monotherapy population (patients not receiving tafamidis at baseline). After the double-blind period, all remaining eligible patients were allowed to receive vutrisiran in an OLE.[1]

Patient Demographics and Baseline Characteristics

A total of 655 patients were enrolled and randomly assigned to receive vutrisiran (n=326) or placebo (n=329). The median age of study participants was 77 years, 93% were male, 88% had wtATTR, and 78% had NYHA Class II heart failure. The patient demographic and clinical characteristics at baseline were similar between the vutrisiran and placebo groups, except that NT-proBNP and troponin I levels were higher in the vutrisiran group than the placebo group in the monotherapy population; and they were not substantially different between the overall and monotherapy populations.[1]

At baseline, concomitant tafamidis use was 40% and 39% in the vutrisiran and placebo groups, respectively. Baseline use of SGLT2 inhibitors was 3% in both treatment groups, and baseline use of diuretics was 80% and 79% in the vutrisiran and placebo groups, respectively.[3]

Primary Endpoint

Treatment with vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events, in both the overall population (HR 0.72; 95% CI 0.56, 0.93; P=0.01) and monotherapy population (HR 0.67, 95% CI 0.49, 0.93; P=0.02).[1]

Post-Hoc Analysis of HELIOS-B

In a post hoc analysis of the HELIOS-B study, the rate of GI AEs in patients with ATTR-CM was evaluated. All AEs classified under the GI disorders SOC during the double-blind period were compared between the vutrisiran and placebo groups in the overall population, monotherapy population, and baseline tafamidis subgroup.[2]

GI Events

GI events commonly associated with a negative impact on QoL were evaluated in patients with ATTR-CM (**Table 1**). Treatment with vutrisiran resulted in 42%, 37%, and 49% rate reduction of overall GI events per 100 PY in the overall population, monotherapy population, and baseline tafamidis subgroup, respectively, when compared with patients in the placebo group (**Figure 1**).[2]

Table 1. GI Events per 100 PY.[2]

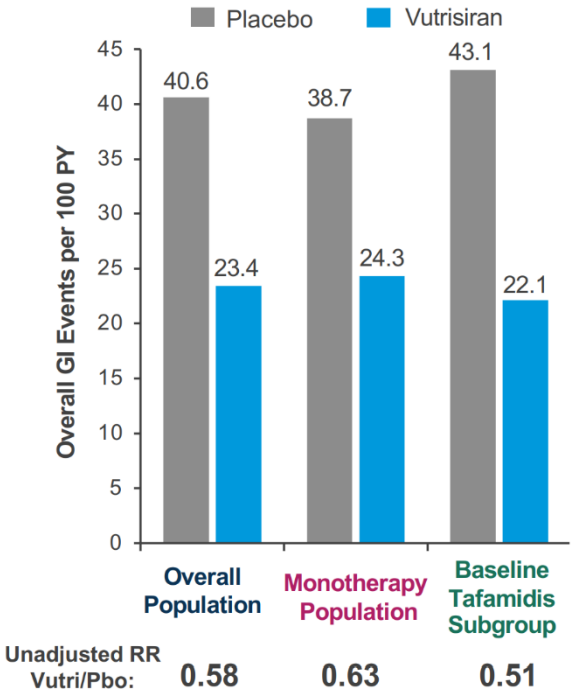
GI Event[a]	Overall Population[b,c]			Monotherapy Population[d]			Baseline Tafamidis Subgroup[e]		
	ER per 100 PY		RR	ER per 100 PY		RR	ER per 100 PY		RR
	Placebo	Vutrisiran		Placebo	Vutrisiran		Placebo	Vutrisiran	
Constipation	6.9	4.2	0.61	6.3	5.1	0.80	7.8	3.0	0.39
Diarrhea	4.1	1.9	0.46	4.8	2.3	0.48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

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	
Vomiting	1.5	0.2	0.16	1.7	0.4	0.25	1.2	0	0.00

Abbreviations: AE = adverse event; ER = event rate; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; PI = principal investigator; PT = preferred term; PY = patient-years; RR = rate ratio; SOC = system organ class.

[a]GI events are coded using MedDRA v23.0 PTs. 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.

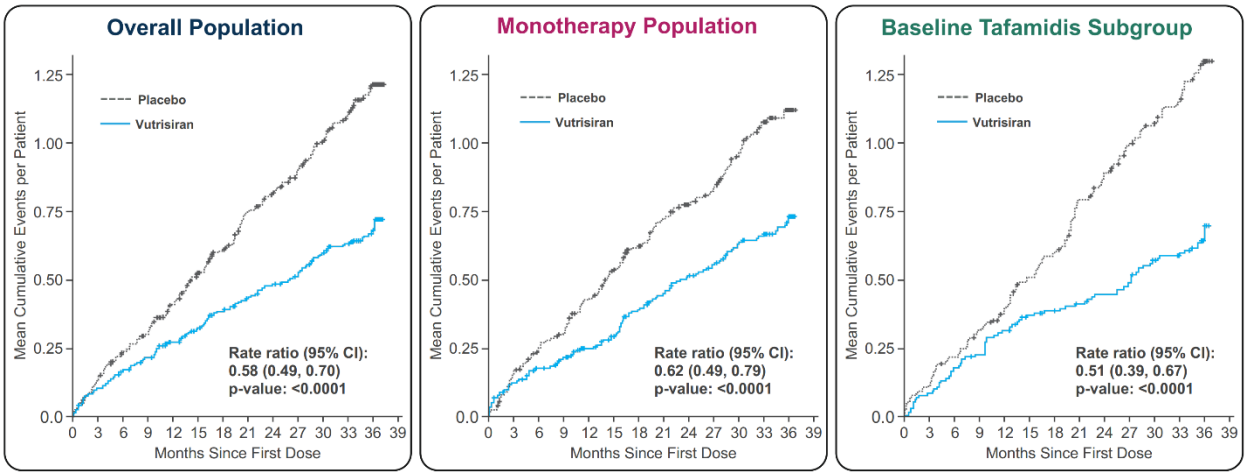
Figure 1. Rates of Overall GI Events per 100 PY.[2]



Abbreviations: GI = gastrointestinal; Pbo = placebo; PY = patient-years; RR = rate ratio; vutri = vutrisiran.
From Urey et al.[2]

There were reductions in rates of GI events with vutrisiran compared with placebo observed by month 3 of the double-blind period in the overall population, monotherapy population, and baseline tafamidis subgroup (**Figure 2**).[2]

Figure 2. Mean Cumulative GI Events Per Patient.[2]



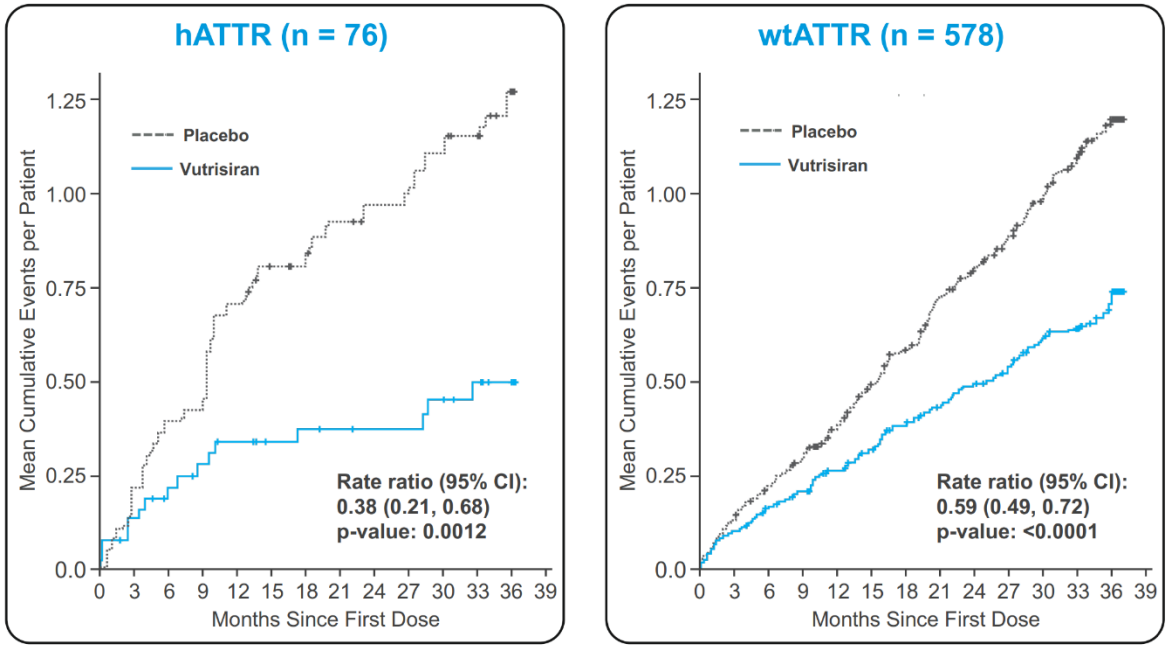
Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; GI = gastrointestinal; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association.

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.

From Urey et al.[2]

Reductions in rates of GI events were seen in patients with either hATTR-CM or wtATTR-CM (**Figure 3**).[2]

Figure 3. Mean Cumulative GI Events Per Patient.[2]



Abbreviations: CI, confidence interval; GI, gastrointestinal; hATTR, hereditary transthyretin amyloidosis; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; wtATTR, wild-type transthyretin amyloidosis.

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.

From Urey et al.[2]

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; DB = double-blind; ER = event rate; GI = gastrointestinal; hATTR = hereditary transthyretin amyloidosis; hATTR-CM = hereditary transthyretin amyloidosis with cardiomyopathy; HR = hazard ratio; MedDRA = Medical Dictionary for Regulatory Activities; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; Pbo = placebo; PI = principal investigator; PT = preferred term; PY = patient-years; QoL = quality of life; RR = rate ratio; SGLT2 = sodium-glucose cotransporter 2; SOC = system organ class; vutri = vutrisiran; wtATTR = wild-type transthyretin amyloidosis; wtATTR-CM = wild-type transthyretin amyloidosis with cardiomyopathy.

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REFERENCES

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2. Urey MA, Bui QM, Obici L, et al. Evidence of fewer gastrointestinal events in ATTR-CM patients treated with vutrisiran compared with placebo: Analysis from HELIOS-B. Presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting; September 26-29, 2025; Minneapolis, MN, USA.
3. Supplement to: Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134