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 was evaluated over the double-blind period of up to 36 months.[2]
  - All AEs classified under the GI disorders SOC were compared between the vutrisiran and placebo groups in the overall population, monotherapy population, and baseline tafamidis subgroup.[2]
  - Overall GI event rates were lower in the vutrisiran group compared with the placebo group. In the overall population, 271 out of 654 patients experienced 529 GI events; 195 in the vutrisiran group (23.4 events/100 PY) and 334 in the placebo group (40.6 events/100 PY; RR, 0.58; p<0.0001).[2]

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STUDY DESIGN

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]

Post-Hoc Analysis of GI AEs

In a post hoc analysis of the HELIOS-B study, GI AE data were analyzed in the overall population, monotherapy population (patients not receiving tafamidis at baseline), and in the baseline tafamidis subgroup (patients receiving tafamidis at baseline).[2]

Treatment-emergent AEs classified according to PTs under the GI disorders SOC were assessed during the double-blind period of the study. PTs consisted of distinct descriptors of a sign or symptom to standardize clinical data.[2]

Adjusted ERs and RRs for GI events were calculated using Poisson regression with treatment arm, age group (<75 years vs. ≥75 years of age), ATTR type (hATTR vs. wtATTR), baseline NYHA Functional Classification (I/II vs. III) and log-transformed baseline NT-proBNP as covariates, and the logarithm of the follow-up time as an offset variable. In the overall population, baseline tafamidis use term and vutrisiran-by-baseline tafamidis use interaction term were included as covariates.[2]

The mean cumulative number of GI events per patient by treatment arm over time was estimated through the nonparametric Nelson–Aalen estimator for the overall population, monotherapy population, and baseline tafamidis subgroup, and for patients with hATTR and wtATTR.[2]

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A total of 655 patients were enrolled and randomly assigned to receive vutrisiran (n=326) or placebo (n=329). One patient randomized to placebo withdrew and did not receive study drug. 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.[1,3]

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]

A summary of reported GI disorders in medical histories are presented in **Table 1**.[4]

Table 1. History of GI Disorders Reported in Patients Enrolled in HELIOS-B.[4]

	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=129)	Vutrisiran (n=130)
History of GI disorders, n (%)[a]	143 (44)	133 (41)	76 (38)	67 (34)	67 (52)	66 (51)
GERD	55 (17)	50 (15)	22 (11)	20 (10)	33 (26)	30 (23)
Constipation	35 (11)	23 (7)	14 (7)	9 (5)	21 (16)	14 (11)
Inguinal hernia	24 (7)	21 (6)	11 (6)	13 (7)	13 (10)	8 (6)
Hiatus hernia	14 (4)	15 (5)	9 (5)	8 (4)	5 (4)	7 (5)
Large intestine polyp	15 (5)	9 (3)	4 (2)	2 (1)	11 (9)	7 (5)

	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=129)	Vutrisiran (n=130)
Hemorrhoids	11 (3)	11 (3)	7 (4)	5 (3)	4 (3)	6 (5)
Diverticulum	13 (4)	6 (2)	11 (6)	3 (2)	2 (2)	3 (2)
Diarrhea	9 (3)	8 (2)	2 (1)	1 (1)	7 (5)	7 (5)
Umbilical hernia	6 (2)	6 (2)	2 (1)	3 (2)	4 (3)	3 (2)
Dysphagia	4 (1)	7 (2)	1 (1)	1 (1)	3 (2)	6 (5)
Gastritis	7 (2)	4 (1)	4 (2)	2 (1)	3 (2)	2 (2)
Barrett's esophagus	3 (1)	4 (1)	1 (1)	1 (1)	2 (2)	3 (2)
Nausea	6 (2)	0	2 (1)	0	4 (3)	0

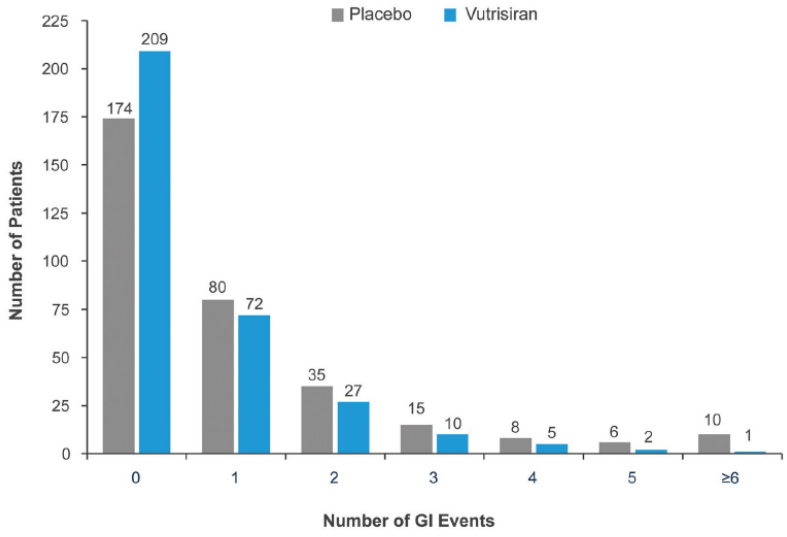
Abbreviations: GERD = gastroesophageal reflux disease; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities.
[a]Collection of information on previous medications, hospitalizations, and procedures was restricted to 1 year prior to randomization. There was no time limit on general medical history. Medical history was coded using MedDRA version 23.0 and disorders reported in ≥2% of patients in any treatment arm are listed.

SAFETY RESULTS

GI Event Rates

In the overall population, 64% of patients in the vutrisiran group and 53% of patients in the placebo group experienced no GI events, with similar results in the monotherapy population (62% vs. 52%) and baseline tafamidis subgroup (67% vs. 55%). The number of GI events experienced in the overall population are shown in **Figure 1**.[2]

Figure 1. Number of GI Events Experienced in Patients in the Overall Population.[2]

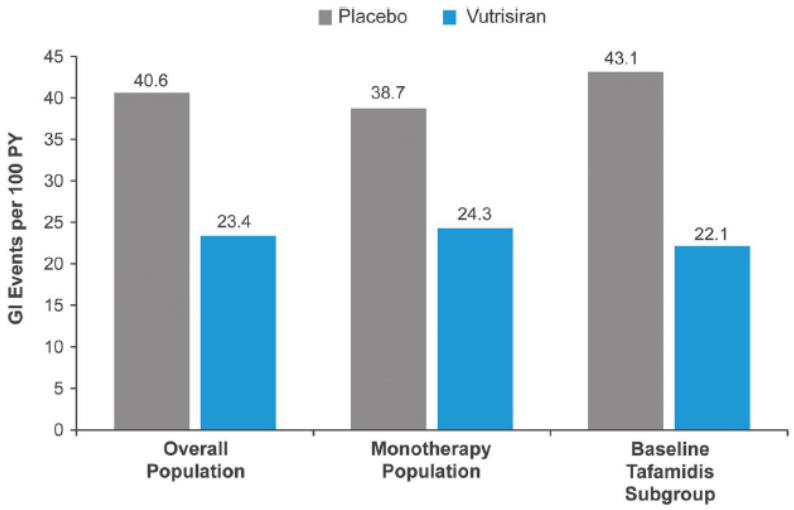


Abbreviations: GI = gastrointestinal.
From Urey et al.[2]

Overall GI event rates were lower in the vutrisiran group compared with the placebo group. A total of 529 GI events were reported during the double-blind period of the study, with 195 events in 117 patients (36%) treated with vutrisiran (23.4 events/100 PY) and 334 events in 154 patients (47%) treated with placebo (40.6 events/100 PY; unadjusted RR 0.58). A total of 10 GI events (8 in the placebo group and

2 in the vutrisiran group) were considered to be related to treatment by the investigator. The unadjusted RRs and estimates for adjusted RRs of GI events are shown in **Figure 2**.[2]

Figure 2. GI Event Rates and Rate Ratios.[2]

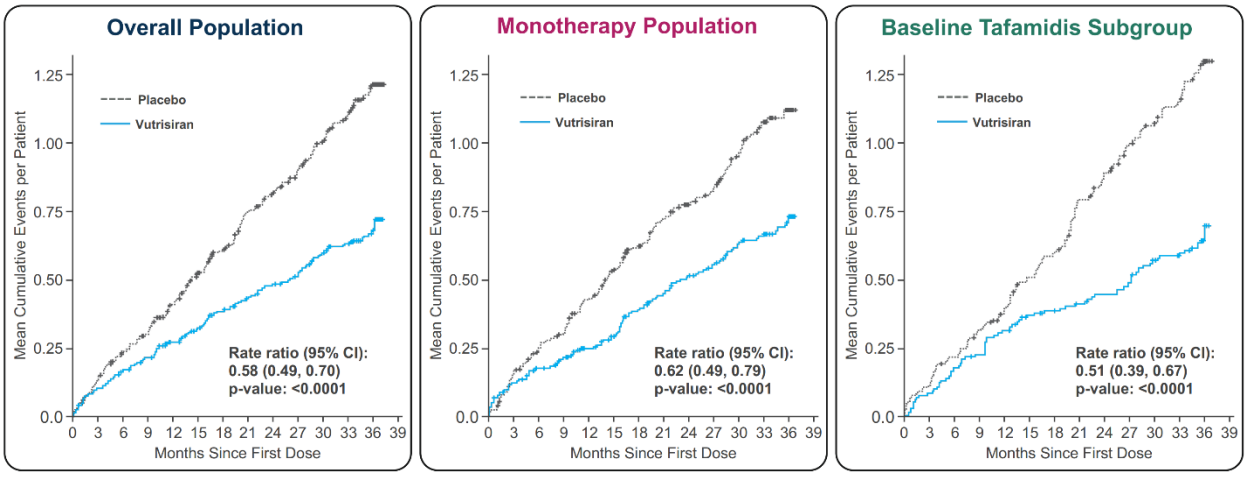


	Overall Population	Monotherapy Population	Baseline Tafamidis Subgroup
Unadjusted rate ratio Vutrisiran/Placebo	0.58	0.63	0.51
Adjusted rate ratio[a] Vutrisiran/Placebo	0.58 ($p < 0.0001$)	0.62 ($p < 0.0001$)	0.51 ($p < 0.0001$)

Abbreviations: ATTR = GI = gastrointestinal; PY = patient-years; RR = rate ratio.
[a]Adjusted RR and p-value estimated with Poisson regression.

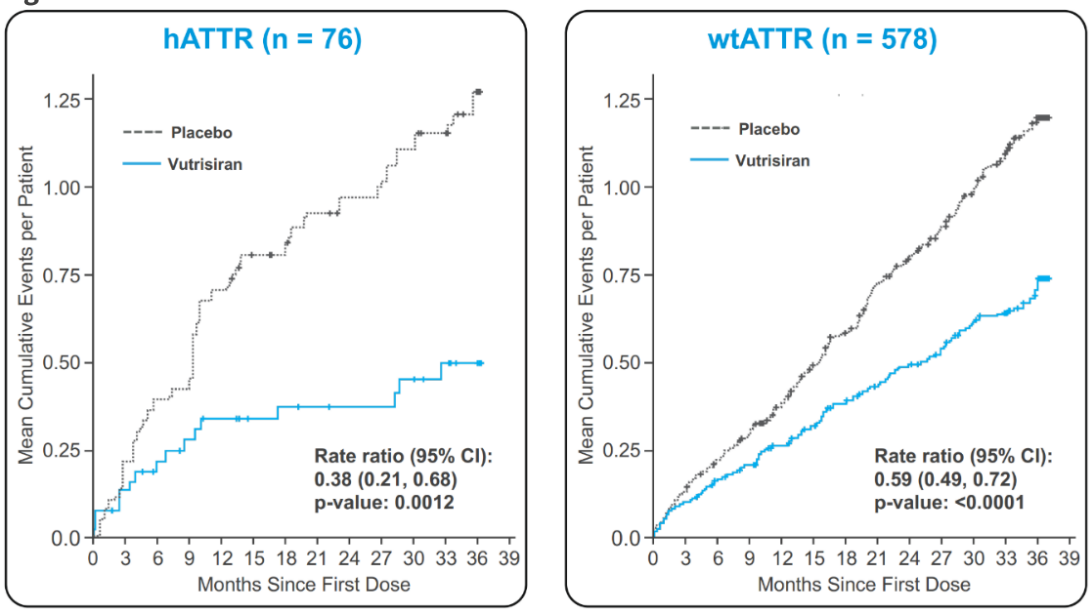
Mean cumulative GI events per patient were lower in patients treated with vutrisiran compared with placebo across the 3 populations analyzed (**Figure 3**). GI event rates were generally consistent across predefined subgroups assessed. GI event rates by patients with hATTR and wtATTR are shown in **Figure 4**.[2,5]

Figure 3. Mean Cumulative GI Events Per Patient.[5,a]



Abbreviations: CI = confidence interval; GI = gastrointestinal; RR = rate ratio.
[a]RR, 95% CI, and p-values are from a Poisson regression model. Lines are truncated after reaching less than 5 patients at risk.
From Urey et al.[5]

Figure 4. Mean Cumulative GI Events Per Patient.[5,a]



Abbreviations: CI = confidence interval; GI = gastrointestinal; hATTR = hereditary transthyretin amyloidosis; RR = rate ratio; wtATTR = wild-type transthyretin amyloidosis.

[a]RR, 95% CI, and p-values are from a Poisson regression model. Lines are truncated after reaching less than 5 patients at risk.

From Urey et al.[5]

PTs for Individual GI Events

Within the GI disorder SOC, 103 PTs were reported in the overall population. Treatment with vutrisiran compared with placebo resulted in a RR for all GI events of 0.58, 0.63, and 0.51 in the overall population, monotherapy population, and baseline tafamidis subgroup, respectively. Treatment with vutrisiran compared with placebo was associated with lower rates of GI events more commonly associated with a negative impact on quality of life in patients with ATTR-CM (**Tables 2 and 3**).[2]

Table 2. Overview of GI AEs in the Overall Population and Monotherapy Population.[2]

GI Event[a]	Overall Population					Monotherapy Population				
	Placebo (n=328, PY=823.2)		Vutrisiran (n=326, PY=834.9)		RR	Placebo (n=199, PY=475.6)		Vutrisiran (n=196, PY=473.5)		RR
	n (%)	Events[b]	n (%)	Events[b]		n (%)	Events[b]	n (%)	Events[b]	
All GI events	154 (47.0)	334/40.6	117 (35.9)	195/23.4	0.58	96 (48.2)	184/38.7	74 (37.8)	115/24.3	0.63
All serious GI events	21 (6.4)	26/3.2	13 (4.0)	16/1.9	0.59	11 (5.5)	14/2.9	8 (4.1)	10/2.1	0.72
All severe GI events	20 (6.1)	25/3.0	7 (2.1)	10/1.2	0.39	14 (7.0)	16/3.4	6 (3.1)	8/1.7	0.50
Selected GI AEs with a negative impact on quality of life										
Constipation	43 (13.1)	57/6.9	33 (10.1)	35/4.2	0.61	24 (12.1)	30/6.3	23 (11.7)	24/5.1	0.81
Diarrhea	30 (9.1)	34/4.1	15 (4.6)	16/1.9	0.46	20 (10.1)	23/4.8	10 (5.1)	11/2.3	0.48
Abdominal pain grouping[c]	23 (7.0)	30/3.6	13 (4.0)	13/1.6	0.44	11 (5.5)	15/3.2	7 (3.6)	7/1.5	0.47
Nausea	26 (7.9)	28/3.4	9 (2.8)	10/1.2	0.35	12 (6.0)	12/2.5	2 (1.0)	2/0.4	0.16
Vomiting	11 (3.4)	12/1.5	2 (0.6)	2/0.2	0.13	7 (3.5)	8/1.7	2(1.0)	2/0.4	0.24

Abbreviations: AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; ER = event rate; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; RR = rate ratio; SOC = system organ class.

[a]Treatment-emergent AEs classified according to PTs under the GI SOC of the MedDRA v23.0.

[b]Events are reported as n/ER per 100 PY.

[c]Includes PTs of abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

Table 3. Overview of GI AEs in the Baseline Tafamidis Subgroup.[2]

GI Event[a]	Baseline Tafamidis Subgroup				
	Placebo (n=129, PY=347.7)		Vutrisiran (n=130, PY=361.4)		RR
	n (%)	Events[b]	n (%)	Events[b]	
All GI events	58 (45.0)	150/43.1	43 (33.1)	80/22.1	0.51
All serious GI events	10 (7.8)	12/3.5	5 (3.8)	6/1.7	0.49
All severe GI events	6 (4.7)	9/2.6	1 (0.8)	2/0.6	0.21
Selected GI AEs with a negative impact on quality of life					
Constipation	19 (14.7)	27/7.8	10 (7.7)	11/3.0	0.38
Diarrhea	10 (7.8)	11/3.2	5 (3.8)	5/1.4	0.44
Abdominal pain grouping[c]	12 (9.3)	15/4.3	6 (4.6)	6/1.7	0.40
Nausea	14 (10.9)	16/4.6	7 (5.4)	8/2.2	0.48
Vomiting	4 (3.1)	4/1.2	0	0	0

Abbreviations: AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; ER = event rate; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; RR = rate ratio; SOC = system organ class.

[a]Treatment-emergent AEs classified according to PTs under the GI SOC of the MedDRA v23.0.

[b]Events are reported as n/ER per 100 PY.

[c]Includes PTs of abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; DB = double-blind; ER = event rate; GERD = gastroesophageal reflux disease; 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; PT = preferred term; PY = patient-years; RR = rate ratio; SGLT2 = sodium-glucose cotransporter 2; SOC = system organ class; wtATTR = wild-type transthyretin amyloidosis; wtATTR-CM = wild-type transthyretin amyloidosis with cardiomyopathy.

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