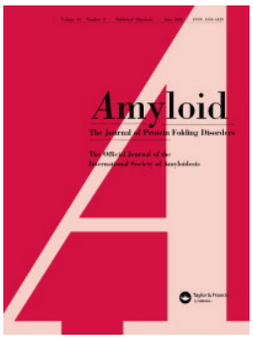

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Fewer gastrointestinal events with vutrisiran versus placebo in patients with transthyretin amyloidosis with cardiomyopathy: analysis from the phase 3 HELIOS-B study

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ABSTRACT

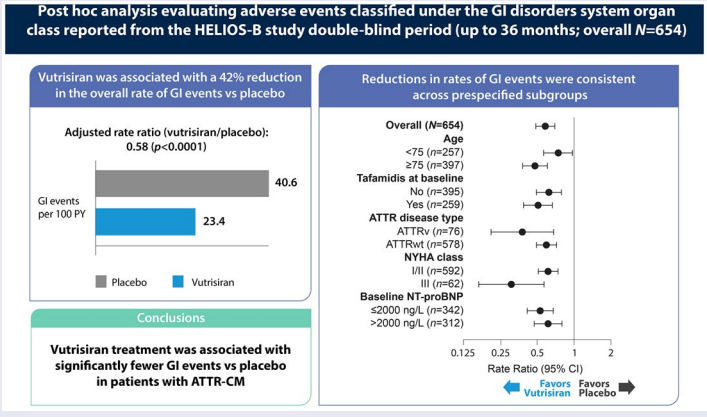
Background: Patients with transthyretin amyloidosis (ATTR) with cardiomyopathy (CM) can experience extracardiac manifestations, including gastrointestinal (GI) manifestations that negatively impact their quality of life.

Methods: In the double-blind HELIOS-B study, patients received vutrisiran 25 mg or placebo every 12 weeks for up to 36 months. Reported adverse events classified using preferred terms of the MedDRA GI disorders system organ class were compared between treatment arms in the overall population, the monotherapy population (not receiving tafamidis at baseline) and the baseline tafamidis subgroup.

Results: Overall, 271/654 patients experienced 529 GI events, 195 in the vutrisiran arm (23.4 events per 100 patient-years) and 334 in the placebo arm (40.6 events/100 patient-years; rate ratio, 0.58; $p < 0.0001$). With vutrisiran, lower rates were observed for almost all GI events including constipation, diarrhea, nausea, abdominal pain and vomiting, versus placebo, with rates of overall GI events reduced by 38–49% across populations (all $p < 0.0001$). Reductions in mean cumulative GI events with vutrisiran versus placebo were observed from Month 3.

Conclusions: Treatment with vutrisiran was associated with substantially fewer GI events versus placebo in patients with ATTR-CM, with the difference beginning early in treatment. Future trials should consider assessment of extracardiac manifestations.

GRAPHICAL ABSTRACT



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Abbreviations: ACM: all-cause mortality; ATTR: transthyretin amyloidosis; ATTR-CM: ATTR with cardiomyopathy; ATTRv: variant ATTR; ATTRwt: wild-type ATTR; ATTRv-PN: ATTR with polyneuropathy; CM: cardiomyopathy; E: events; GI: gastrointestinal; RNAi: RNA interference; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PY: patient-years; TTR: transthyretin

Introduction

Transthyretin (TTR) amyloidosis (ATTR) is a progressive, systemic disease caused by misfolded TTR (variant [hereditary] or wild type) that aggregates into amyloid fibrils, which then deposit into organs and tissues as amyloid [1–3]. Accumulation of TTR amyloid in the myocardium causes cardiomyopathy (ATTR-CM), one of the most frequent and severe ATTR phenotypes [1,2]. ATTR-CM leads to progressive heart failure [1,4,5] and median survival after diagnosis is less than 5 years if patients remain untreated [2,3].

ATTR is a systemic disease, so patients with ATTR-CM often experience extracardiac involvement, leading to somatic and autonomic polyneuropathy (PN), as well as musculoskeletal, ocular, renal and gastrointestinal (GI) manifestations [4,6–8]. Frequent GI manifestations include nausea, vomiting, diarrhea, constipation and abdominal pain [4,6–8]. GI manifestations in ATTR can be caused by various mechanisms, such as direct involvement of the GI system, autonomic neuropathy as a part of ATTR-PN, or bowel edema caused by heart failure of ATTR-CM; they may also be side effects associated with medications used by the patients [9–11]. While GI manifestations tend to be more prevalent in variant ATTR (ATTRv), they have also been reported in wild-type ATTR (ATTRwt) [7,12]. A global analysis of 1579 patients with ATTRv and 160 patients with ATTRwt from the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry reported the prevalence of GI manifestations as 63% and 15%, respectively [7]. Importantly, GI manifestations can have a substantial impact on quality of life [7,8], as demonstrated by an analysis of patients with ATTRv in the aforementioned study, where a statistically significant relationship between both upper and lower GI manifestations and impaired quality of life was observed [7]. Moreover, a study in patients with ATTRv-PN showed that rapid onset of GI manifestations after the first emergence of neurologic symptoms was associated with reduced survival [13]. Management of GI manifestations can be challenging, and studies in patients with ATTR and GI manifestations are lacking [8].

Current treatment options for ATTR-CM include TTR stabilizers and RNA interference (RNAi) therapeutics. Vutrisiran is a subcutaneously administered RNAi therapeutic that reduces hepatic TTR synthesis by inhibiting the translation of both wild-type and variant TTR [2,14]. Vutrisiran is approved for the treatment of ATTR-CM and ATTRv-PN [15–17]. In the phase 3 HELIOS-B study, vutrisiran reduced the risk of the primary composite endpoint of all-cause mortality (ACM) and recurrent cardiovascular events vs. placebo during the double-blind period, in both the overall population (hazard ratio [HR]: 0.72, $p = 0.0118$) and monotherapy population (HR: 0.67, $p = 0.0162$) [18]. Vutrisiran also demonstrated benefit in the secondary endpoint of ACM through 42 months in both the overall population (HR: 0.65, $p = 0.0098$) and the monotherapy population (HR: 0.66, $p = 0.0454$), and met all other secondary endpoints vs. placebo.

The impact of vutrisiran on GI manifestations of ATTR-CM has not been studied. Here, we present an analysis of HELIOS-B evaluating the effects of vutrisiran on GI manifestations up to 36 months during the double-blind period.

Materials and methods

Trial design

Full details of the HELIOS-B trial design (ClinicalTrials.gov: NCT04153149) have been published previously [18]. In brief, HELIOS-B was a phase 3 multicenter, randomized, placebo-controlled trial in patients aged 18–85 years with a diagnosis of ATTR-CM (either ATTRwt or ATTRv). Patients receiving tafamidis at baseline were eligible for inclusion, and patients who were not receiving tafamidis could begin receiving tafamidis during the study if the investigator deemed it necessary. Patients were randomized 1:1 to receive vutrisiran 25 mg or placebo subcutaneously every 3 months for up to 36 months in the double-blind period. On completion of the double-blind period, patients could enter an ongoing open-label extension (up to 24 months), in which all patients receive vutrisiran 25 mg every 3 months.

GI adverse event (AE) data were analyzed in the overall population, in patients who were receiving monotherapy at baseline (no concomitant tafamidis; monotherapy population) and in the subgroup of patients who were receiving tafamidis at baseline (baseline tafamidis subgroup).

The trial has been conducted in accordance with all applicable regulatory requirements, Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. The institutional review board or independent ethics committee at each center approved the trial protocol and amendments, and all participants provided written informed consent.

Endpoints and analysis

Treatment-emergent AEs, classified according to preferred terms under the GI disorders system organ class of the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 [19], were assessed from the double-blind period of HELIOS-B. Preferred terms consisted of distinct descriptors of a sign or symptom (i.e. a single medical concept) in order to standardize clinical data, such as 'nausea' or 'vomiting'. Preferred terms relating to abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness and GI pain) were combined into a single 'abdominal pain' grouping. The counts, percentages, number of events, event rates and unadjusted rate ratios (RRs) of GI events for vutrisiran vs. placebo were reported in all populations assessed. In addition, event rates and RRs were reported separately for events more commonly associated with a negative impact on quality of life in patients with ATTR-CM (i.e. constipation, diarrhea, abdominal pain grouping, nausea and vomiting) and for any other event reported in ≥2% of patients in either treatment arm across all populations assessed.

Adjusted event rates and RRs for GI events were calculated using Poisson regression with treatment arm, age group (<75 years vs. ≥75 years of age), ATTR type (ATTRv vs. ATTRwt), baseline New York Heart Association (NYHA) Functional Classification (I/II vs. III) and log-transformed baseline N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as covariates, and the logarithm of the follow-up time as an offset variable. The overall population also included a baseline tafamidis use term and vutrisiran-by-baseline tafamidis use interaction term as covariates.

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 and monotherapy populations and baseline tafamidis subgroup, and for patients with ATTRv and ATTRwt. Adjusted RRs were also calculated by subgroups, including age, ATTR type, baseline NYHA class and baseline NT-proBNP (descriptions as listed above). Adjusted RRs for subgroups were calculated using Poisson regression with treatment arm and log-transformed baseline NT-proBNP as covariates, and the logarithm of the follow-up time as an offset variable. Subgroup analysis within the overall population also included baseline tafamidis use as a covariate. Within-subgroup treatment effects are based on a model that included data only from that subgroup.

Results

Patients

Overall, 654 patients were randomized and received treatment in HELIOS-B (vutrisiran $n=326$; placebo $n=328$) [18]. The monotherapy population included 395 patients who were not receiving tafamidis at baseline (vutrisiran, $n=196$; placebo, $n=199$) and the baseline tafamidis subgroup included 259 patients (vutrisiran + tafamidis, $n=130$; placebo + tafamidis, $n=129$).

Baseline demographics and disease characteristics in the overall and monotherapy populations [18] and the baseline tafamidis subgroup were generally similar between the vutrisiran and placebo arms (Supplementary Table 1). In the monotherapy population, biomarker levels (NT-proBNP, high-sensitivity troponin I) were higher in patients in the vutrisiran arm compared with the placebo arm (as previously reported [18]). Baseline characteristics were also generally similar across the three populations and generally representative of the global population of patients with ATTR-CM, although the median time since ATTR diagnosis was longer in the baseline tafamidis subgroup than the monotherapy population (Supplementary Table 1). A similar proportion of patients in the placebo and vutrisiran arms had a previous medical history of one or more GI disorders (44% and 41%, respectively). The most frequently reported GI disorders in the medical histories were gastroesophageal reflux disease, constipation, inguinal hernia, hiatus hernia, large intestine polyp and hemorrhoids (Supplementary Table 1).

Unadjusted GI event rates in the double-blind period

In the overall population, a higher proportion of patients experienced no GI events with vutrisiran (64%) vs. placebo (53%; Figure 1), with similar results

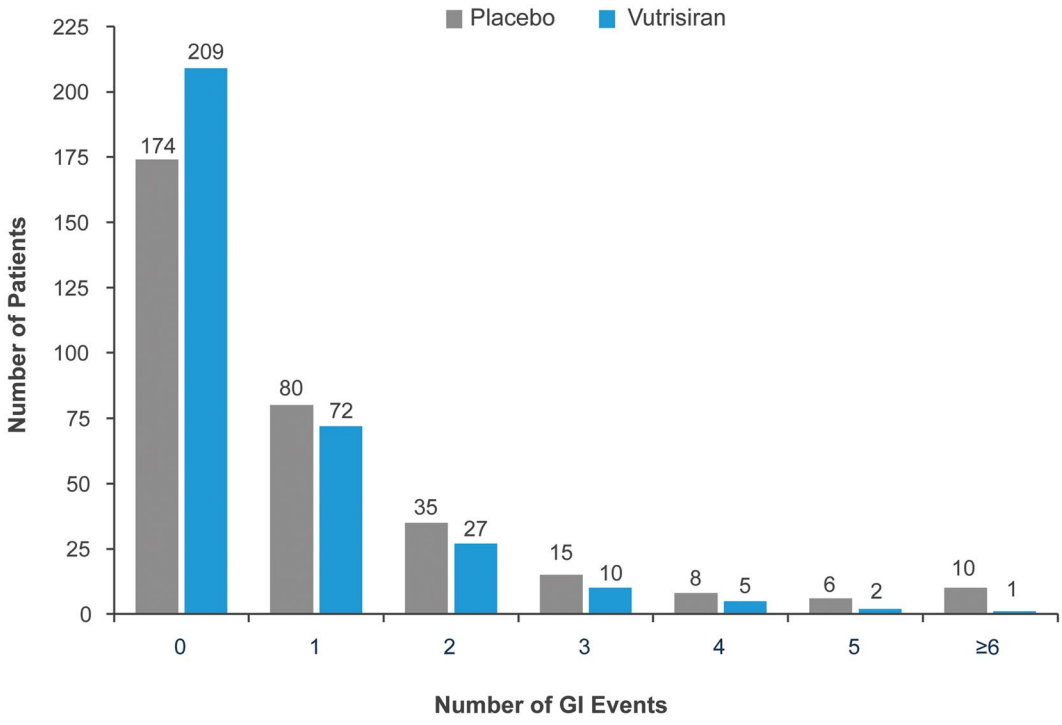

Figure 1. Number of GI events experienced in patients with ATTR-CM in the overall population. ATTR-CM, transthyretin amyloidosis with cardiomyopathy; GI, gastrointestinal.

in the monotherapy population (62% vs. 52%) and baseline tafamidis subgroup (67% vs. 55%). A lower proportion of patients had one or more GI events with vutrisiran vs. placebo, and the difference in proportion showed a trend toward increasing in favor of vutrisiran as the number of GI events increased.

In total, 529 GI events were reported during the study, 195 events in 117 patients (36%) treated with vutrisiran (23.4 events per 100 patient-years [E/100 PY]) and 334 events in 154 patients (47%) treated with placebo (40.6 E/100 PY; unadjusted RR 0.58; Figure 2). Similar event rates and RRs were observed in the monotherapy population (vutrisiran: 24.3 E/100 PY; placebo: 38.7 E/100 PY; unadjusted RR: 0.63) and in the baseline tafamidis subgroup (vutrisiran: 22.1 E/100 PY; placebo: 43.1 E/100 PY; unadjusted RR: 0.51). Of patients with ATTRv and ATTRwt, respectively, 44% and 47% of those receiving placebo, and 24% and 37% of those receiving vutrisiran, experienced at least one GI event.

Of the 529 GI events reported in the double-blind phase, 10 (8 in the placebo arm, 2 in the vutrisiran arm) were considered by the investigator to be related to treatment. In the vutrisiran arm, 13 patients (4%) reported 16 serious GI events (1.9 E/100 PY) and 7 patients (2%) reported 10 severe GI events (1.2 E/100 PY), while 21 placebo-treated patients (6%) reported 26 serious GI events (3.2 E/100 PY) and 20 patients (6%) reported 25 severe GI events (3.0 E/100 PY) (Table 1).

Adjusted GI event rates in the double-blind period

Estimates for adjusted RRs of GI events were consistent with unadjusted RRs, with reductions of 38–49% compared with placebo over the three populations analyzed ($p < 0.0001$ for each population, Figure 2). Point estimates of mean cumulative GI events per patient favored vutrisiran vs. placebo around Month 3 across all populations assessed (Figure 3), and the difference continued to increase over the course of the double-blind period.

GI event rates in predefined subgroups

Rates of GI events were consistent across subgroups during the double-blind period, with RRs favoring vutrisiran vs. placebo for all subgroups except one in the baseline tafamidis subgroup (Figure 4). A consistent trend favoring vutrisiran emerged in patients with either ATTRv ($p = 0.0012$; $n = 76$) or ATTRwt ($p < 0.0001$; $n = 578$), with separation in mean cumulative GI events per patient between vutrisiran and placebo around Month 3 that continued to increase (Figure 5). The difference between vutrisiran and placebo was more pronounced for patients with ATTRv.

Preferred terms for individual GI events

Within the GI disorder system organ class, 103 preferred terms were reported in the overall population

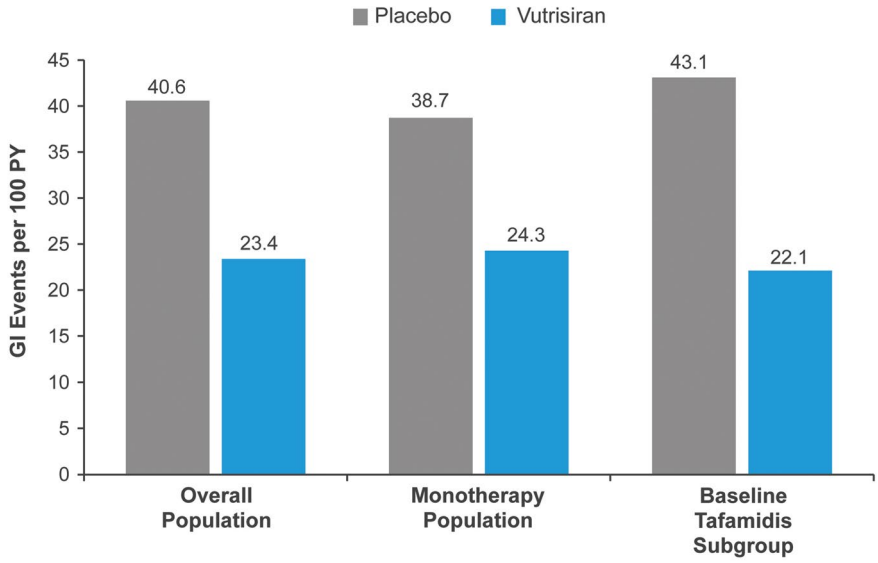

Figure 2. GI event rates and rate ratios in the overall and monotherapy populations, and the baseline tafamidis subgroup. [a]Adjusted rate ratio and *p*-value estimated with Poisson regression. GI, gastrointestinal; PY, patient-years.

in HELIOS-B; all had either event RRs that favored vutrisiran vs. placebo (76/103 preferred terms) or had differences in frequencies of <1% between the vutrisiran and placebo arms (27/103 preferred terms; Table 1 and Supplementary Table 2). Treatment with vutrisiran was associated with lower rates vs. placebo of GI events that are more commonly associated with a negative impact on quality of life in patients with ATTR-CM, with reductions in the overall population of 39% in constipation, 54% in diarrhea, 56% in abdominal pain grouping, 65% in nausea and 87% in vomiting (Table 1). Results were generally similar in the monotherapy population and baseline tafamidis subgroup.

Discussion

Although PN and CM are the two most common phenotypes of ATTR, it is well known that extracardiac manifestations involving GI, musculoskeletal, renal and other systems are also reported, and contribute to the morbidity and mortality of the disease. To our knowledge, this analysis of the HELIOS-B study is the first to quantify potential GI manifestations in patients receiving amyloid-specific therapies.

Overall, a similar percentage of patients with ATTR-CM in the placebo (44%) and vutrisiran (41%) arms had a history of GI disorders before entering HELIOS-B. There was a statistically significant difference in GI events, with patients receiving vutrisiran reporting fewer events vs. those who received placebo, and reductions were observed in the rates of events that are known to be more commonly associated with a negative impact on quality of life. The observed difference in event rates was large, ranging from 39% to 87%. The reduction in mean cumulative GI events per patient began no later than 3 months for all populations assessed, with consistent results in subgroups based on baseline characteristics (age, tafamidis use, ATTR type [ATTRv, ATTRwt], NYHA class and NT-proBNP). These results, demonstrating a substantial and statistically significant difference in GI events reported in favor of vutrisiran treatment, suggest that vutrisiran may provide a benefit on GI manifestations in patients with ATTR-CM.

In general, GI manifestations are considered primarily to be associated with ATTRv and have been extensively investigated in this population [20]. However, high rates have been consistently reported – though not extensively analyzed – in phase 3 studies of disease-modifying treatments for ATTR-CM, wherein the majority of patients had ATTRwt [21,22]. In the present analysis, a substantial proportion of patients with ATTRwt experienced at least one GI

Table 1. Descriptive statistics for GI AEs, serious GI AEs, and selected GI events more commonly associated with a negative impact on quality of life in patients with ATTR-CM.

	Overall population					Monotherapy population					Baseline tafamidis subgroup				
	Placebo (*n* = 328, PY = 823.2)		Vutrisiran (*n* = 326, PY = 834.9)			Placebo (*n* = 199, PY = 475.6)		Vutrisiran (*n* = 196, PY = 473.5)			Placebo (*n* = 129, PY = 347.7)		Vutrisiran (*n* = 130, PY = 361.4)		
GI event[a]	*n* (%)	Events, *n*/ER per 100 PY	*n* (%)	Events, *n*/ER per 100 PY	RR	*n* (%)	Events, *n*/ER per 100 PY	*n* (%)	Events, *n*/ER per 100 PY	RR	*n* (%)	Events, *n*/ER per 100 PY	*n* (%)	Events, *n*/ER per 100 PY	RR
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	58 (45.0)	150/43.1	43 (33.1)	80/22.1	0.51
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	10 (7.8)	12/3.5	5 (3.8)	6/1.7	0.49
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	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	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	19 (14.7)	27/7.8	10 (7.7)	11/3.0	0.38
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	10 (7.8)	11/3.2	5 (3.8)	5/1.4	0.44
Abdominal pain grouping[b]	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	12 (9.3)	15/4.3	6 (4.6)	6/1.7	0.40
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	14 (10.9)	16/4.6	7 (5.4)	8/2.2	0.48
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	4 (3.1)	4/1.2	0	0	0

[a]Treatment-emergent AEs classified according to PTs under the GI SOC of the MedDRA v 23.0.
[b]Includes PTs of abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
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.

event during the double-blind period of HELIOS-B (88% of patients had ATTRwt overall), with events reported by 48% of placebo-treated patients in the monotherapy population. Similarly, 56% and 46% of ATTR-CM patients in the placebo arms of the ATTR-ACT trial of tafamidis and ATTRibute-CM trial of acoramidis reported GI events (76% and 90% of patients, respectively, had ATTRwt in these studies) [21,22]. This challenges the concept that ATTRwt is a single-organ disease, although this remains to be further confirmed. Despite the reduction in GI event rates being observed with vutrisiran for both ATTRv and ATTRwt populations in the present analysis, pathophysiologic mechanisms underlying GI symptoms may differ between ATTRv and ATTRwt. This is implied by previously reported differences in symptom prevalence within these patient populations, with weight loss and early satiety more commonly observed in ATTRv and alternating bowel habits more commonly observed in ATTRwt [7].

Previous phase 3 studies of disease-modifying treatments for ATTR-CM have demonstrated slight differences in rates of GI events with active treatment vs. placebo. In the ATTRibute-CM trial, at least one GI AE was observed in 52% and 46% of patients receiving acoramidis and placebo, respectively [21]. GI AEs in patients receiving acoramidis included constipation (12%), diarrhea (12%) and nausea (6%). Furthermore, the US prescribing information for acoramidis highlights the increased incidence of GI AEs vs. placebo, including diarrhea and abdominal pain [18]. The phase 3 ATTR-ACT trial reported GI AEs in 51% and 56% of tafamidis- and placebo-treated patients, respectively, including constipation, diarrhea and nausea in 15%, 12% and 11% of tafamidis-treated patients, respectively [22]. This is in contrast to our results, which demonstrated a lower rate of GI AEs with vutrisiran vs. placebo, suggesting that fewer GI AEs may be considered an advantage of vutrisiran compared with TTR stabilizers.

GI event rates are either very low or not published in many recent major heart failure trials (for instance, the dapagliflozin trial of heart failure with reduced ejection fraction reported serious GI events in 2.7% of placebo-treated patients), limiting the ability to contextualize results from the current analysis within a wider patient population [23–26]. This reporting gap underscores the importance of clinical vigilance; notably, a review published in 2020 recommended gastroenterologists be aware that the presence of chronic diarrhea, chronic constipation, or upper GI symptoms combined with CM (or PN) may warrant genetic testing or tissue biopsy to exclude ATTR [20],

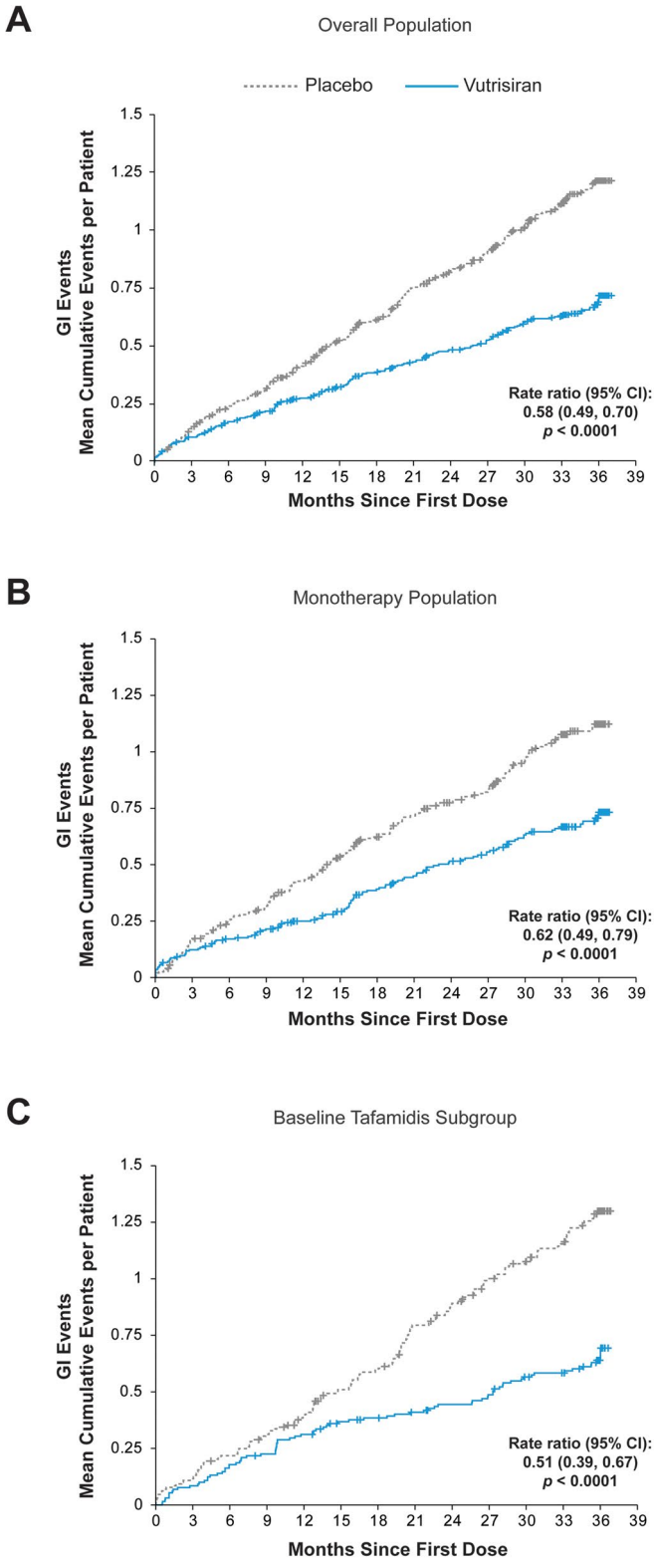

Figure 3. Mean cumulative number of GI events per patient in the overall population (A), monotherapy population (B), and baseline tafamidis subgroup (C). Estimates are truncated after reaching fewer than five patients at risk. Rate ratio, 95% CI, and *p*-value are estimated with Poisson regression. CI, confidence interval; GI, gastrointestinal.

though similar guidance may also be useful for cardiologists. Indeed, results from the present analysis suggest that the presence of GI manifestations should be considered in all patients with ATTR to ensure timely investigation as the presence of GI manifestations may influence treatment [27]. Supporting this, a study

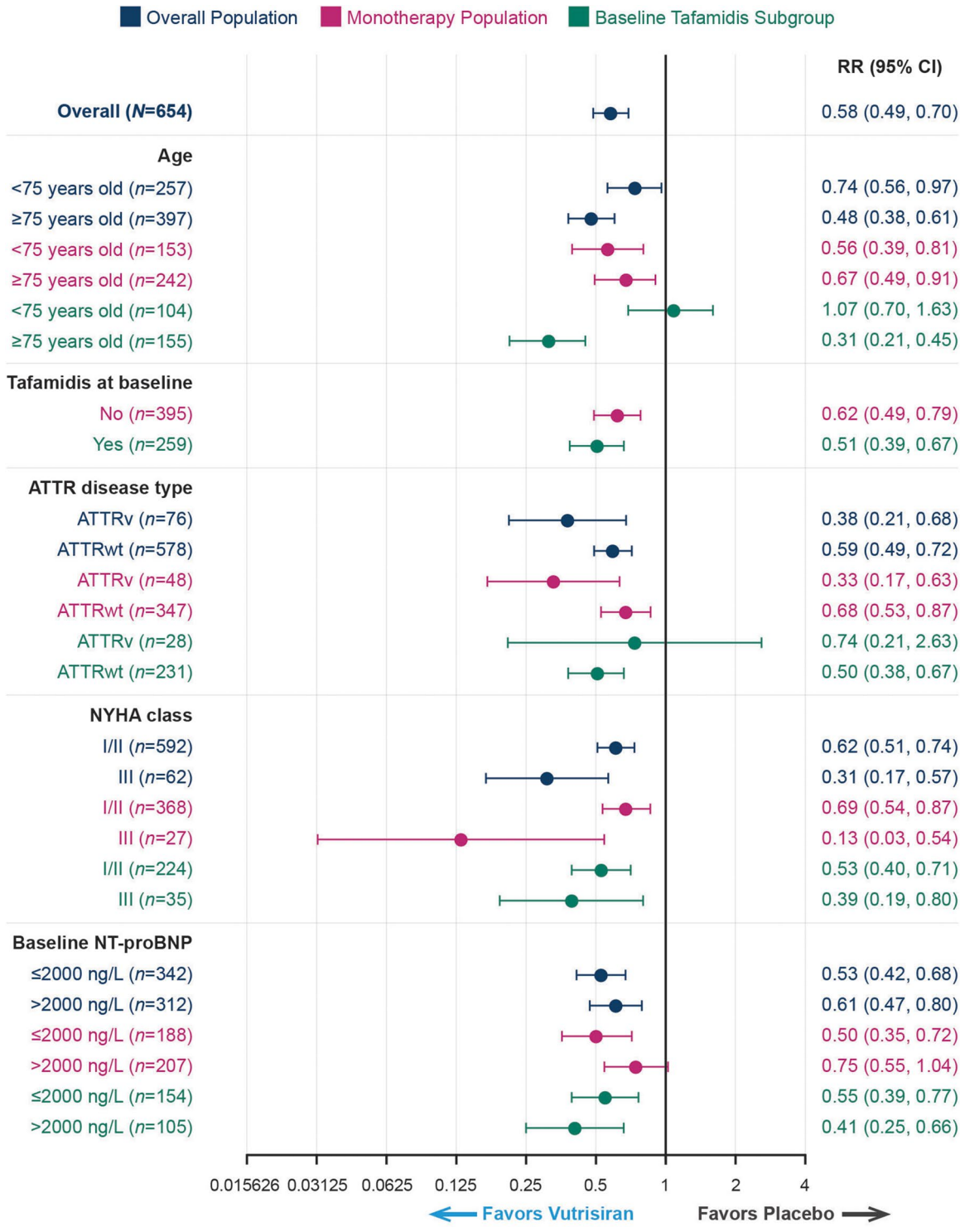

Figure 4. Subgroup analyses of GI events in the overall population, monotherapy population, and baseline tafamidis subgroup. RR and 95% CIs are estimated through Poisson regression. ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CI, confidence interval; GI, gastrointestinal; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; RR, rate ratio.

of 240 patients with ATTR-CM showed that autonomic dysfunction, assessed using COMPASS-31, was associated with more advanced disease and was an independent predictor of cardiovascular hospitalization [28]. There may be a further need for routine and more systematic collection of data on these manifestations to better understand their impact and the potential benefits of available treatments.

This analysis has certain limitations that are important to note. Firstly, the HELIOS-B study did

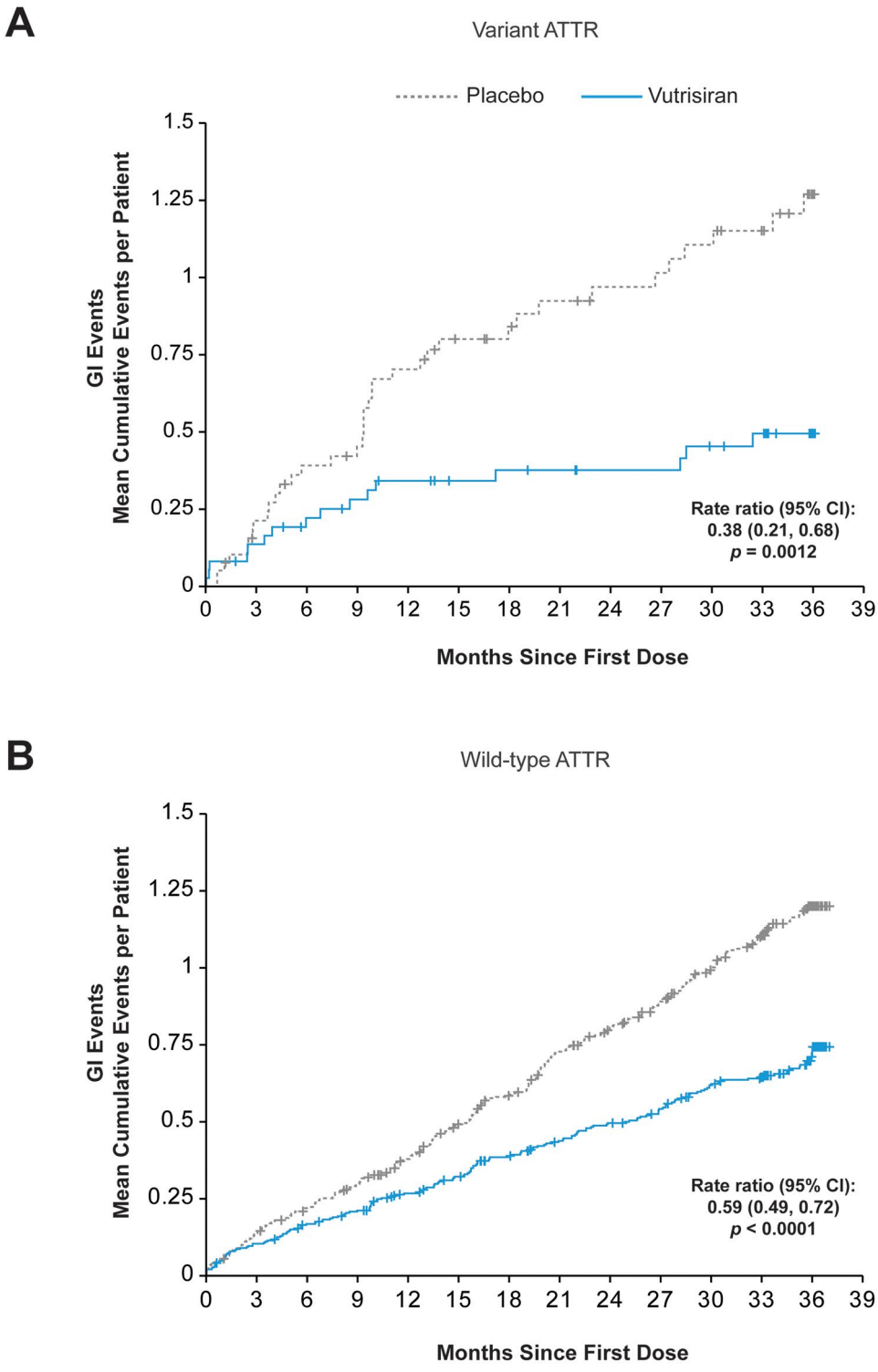

Figure 5. Mean cumulative GI events per patient with variant ATTR ($n = 76$) (A) and wild-type ATTR ($n = 578$) (B). Estimates are truncated after reaching fewer than five patients at risk. RR, 95% CI, and *p*-value are estimated from Poisson regression. ATTR, transthyretin amyloidosis; CI, confidence interval; GI, gastrointestinal.

not include an efficacy assessment specifically focused on GI manifestations. The source of GI event data was from AE reporting, and events were not adjudicated nor confirmed to be caused by ATTR. GI events were based on investigator AE reporting using the MedDRA coding system rather than a formal definition (e.g. a specified number of bowel movements for diarrhea), and so there may have been variability in what constituted each AE. Additionally, as a specific measure of autonomic function, such as COMPASS-31,

was not used in the HELIOS-B study, investigating potential correlations between GI events and autonomic dysfunction was not possible in this analysis. Lastly, the total number of GI events was not high in certain subgroups. Despite these limitations, the high level of consistency of the results, and the similar percentage of patients with a previous medical history of one or more GI disorders between the vutrisiran and placebo arms, suggest a possible benefit of vutrisiran on GI manifestations in this patient population. The finding that there were fewer GI events with vutrisiran is aligned with the benefit of vutrisiran on quality of life-related parameters (such as the Kansas City Cardiomyopathy Questionnaire – Overall Summary and the EuroQol 5-Dimension 5-Level questionnaire) in the HELIOS-B study, compared with placebo [18,29].

In summary, this *post hoc* analysis of the phase 3 HELIOS-B study provides additional evidence for substantial GI involvement in patients with ATTR-CM. Vutrisiran treatment was associated with fewer GI events compared with placebo, and rate reductions were observed for events more commonly considered to have a negative impact on quality of life. Therefore, vutrisiran may provide a treatment benefit on GI manifestations associated with ATTR. Given the multisystem nature of ATTR-CM, future trials should consider systematic assessment of extracardiac manifestations to better understand the impact of TTR-targeted treatments beyond cardiac impairment.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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