Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-026-01651-3

ORIGINAL RESEARCH ARTICLE

Vutrisiran-Mediated Knockdown of Transthyretin in Patients with ATTR Amyloidosis

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Received: 22 September 2025 / Accepted: 22 April 2026

Abstract

Background and Objective We assessed the consistency of serum transthyretin (TTR) knockdown with the RNA interference therapeutic vutrisiran across subpopulations of patients with hereditary TTR amyloidosis (ATTR) with polyneuropathy (ATTRv-PN) in HELIOS-A (NCT03759379) and ATTR with cardiomyopathy (ATTR-CM) in HELIOS-B (NCT04153149).

Methods Patients received vutrisiran 25 mg subcutaneously every 3 months (Q3M). Serum TTR was measured during randomized treatment through Month 18 in HELIOS-A (post-dose/peak and pre-dose/trough sampling) and Month 30 in HELIOS-B (trough only, except Week 6). The effects of intrinsic/extrinsic factors on serum TTR knockdown from baseline were assessed. Pharmacokinetic/pharmacodynamic modeling was used to support consistency in TTR knockdown between studies.

Results Observed median (95% confidence interval [CI]) serum TTR knockdown with vutrisiran was 64.2% (61.6–67.8) at Week 3 ($n = 114$), with steady-state trough knockdown 86.2% (84.1–92.6) ($n = 118$) in HELIOS-A, and 69.0% (66.0–72.0) at Week 6 ($n = 294$), with steady-state trough knockdown 82.5% (80.5–84.9) ($n = 307$) in HELIOS-B. There were no meaningful differences in serum TTR percent knockdown across subgroups defined by baseline characteristics, including age, sex, ethnicity/race, weight, *TTR* genotype, *N*-terminal pro-B-type natriuretic peptide, and serum TTR concentration (both studies), and ATTRwt/ATTRv, disease stage/severity, troponin I, and tafamidis use (HELIOS-B), or anti-drug antibodies. Model-predicted peak serum TTR knockdown in HELIOS-B was sustained and consistent with observed knockdown in HELIOS-A; predicted median (95% CI) reduction at Month 30 was 87.1% (84.8–89.4).

Conclusions Vutrisiran led to rapid, sustained, and consistent TTR knockdown in HELIOS-A and HELIOS-B, supporting fixed-dose vutrisiran 25 mg Q3M across patients with ATTRv-PN and ATTR-CM.

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Published online: 27 May 2026

Graphical abstract

Vutrisiran-mediated knockdown of transthyretin in patients with ATTR amyloidosis

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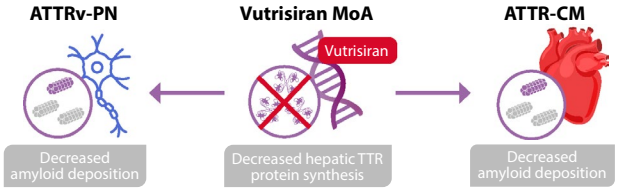
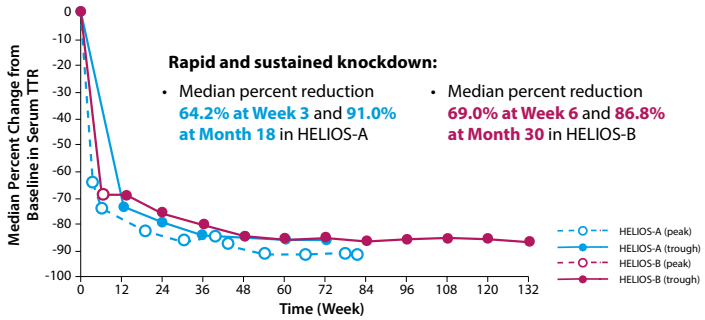
The RNAi therapeutic vutrisiran inhibits hepatic synthesis of both wild-type and variant TTR, resulting in rapid knockdown of amyloidogenic TTR protein



Vutrisiran 25 mg Q3M treatment in HELIOS-A and HELIOS-B was **associated with beneficial effects** on mortality and CV outcomes in ATTR-CM and a broad range of clinically meaningful disease manifestations in both ATTR-CM and ATTRv-PN

Observed data show consistent serum TTR knockdown over time with vutrisiran in HELIOS-A (ATTRv-PN) and HELIOS-B (ATTR-CM)



Rapid and sustained knockdown:

- Median percent reduction **64.2% at Week 3** and **91.0% at Month 18** in HELIOS-A
- Median percent reduction **69.0% at Week 6** and **86.8% at Month 30** in HELIOS-B

Model-predicted median serum TTR knockdown was comparable between HELIOS-A and HELIOS-B, supporting consistency in TTR suppression across ATTRv-PN and ATTR-CM populations

Consistent TTR knockdown observed across patient subgroups with ATTR according to baseline:

General patient characteristics
- Age
- Ethnicity
- Sex
- Body weight

ATTRv-PN disease characteristics
- TTR genotype
- Baseline serum TTR level
- Cardiac biomarker level

ATTR-CM disease characteristics
- Amyloidosis type: ATTRv/ATTRwt
- Functional capacity
- TTR genotype
- QoL/health status
- Baseline tafamidis use
- NYHA heart failure class
- Amyloidosis disease stage
- Cardiac biomarker
- Baseline serum TTR level

Conclusions

Vutrisiran led to rapid, sustained, and consistent observed and model-predicted TTR knockdown over time in HELIOS-A and HELIOS-B, with consistent knockdown observed across patient subgroups. These findings support fixed-dose vutrisiran 25 mg Q3M across patients with ATTRv-PN and ATTR-CM

ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv-PN, variant (hereditary) ATTR with polyneuropathy; ATTRwt, wild-type ATTR; CV, cardiovascular; MoA, mechanism of action; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics; Q3M, every 3 months; QoL, quality of life; RNAi, RNA interference; TTR, transthyretin.

Key Points

The aim of treatment for transthyretin amyloidosis (ATTR) is to stop the formation of the transthyretin (TTR) protein that is causing amyloid deposition.

This analysis showed a consistent reduction in serum TTR levels with vutrisiran, an RNA interference therapeutic, in patients with ATTR in the phase III studies, with a TTR knockdown of 82–92% at steady state.

The effect was consistent across all subgroups of patients, including patients whose predominant ATTR manifestation was polyneuropathy or cardiomyopathy.

1 Introduction

Transthyretin amyloidosis (ATTR) is a progressive, debilitating, and fatal disease caused by misfolded transthyretin (TTR) protein accumulating as amyloid fibrils in multiple organs and tissues, including the peripheral and autonomic nerves and heart [1, 2]. ATTR can result from inherited *TTR* gene variants (hereditary or variant TTR [ATTRv]), or occurs with aging in those with wild-type TTR (wild-type ATTR [ATTRwt]) [1, 2]. The clinical presentation of ATTR is heterogeneous; patients with ATTRwt have predominantly cardiac manifestations, while ATTRv can present with cardiac, neurologic, or other manifestations, or, as increasingly recognized, a mixed phenotype [3].

Circulating serum TTR is the disease-causing protein in ATTR of either type (i.e., ATTRv or ATTRwt) [1, 2]. In patients with systemic amyloidosis (including ATTR, light-chain amyloidosis, and serum amyloid A amyloidosis secondary to inflammatory conditions), the equilibrium between the rate of amyloid formation and clearance, both of which may vary between patients, determines the overall rate of amyloid accumulation. Therefore, reduction in the levels of the amyloidogenic protein is expected to translate to favorable clinical outcomes [4–10]. Available treatments for ATTR aim to reduce further deposition of amyloid fibrils [11, 12]. While therapies such as tafamidis and acoramidis stabilize tetrameric TTR protein, decreasing its tendency to misfold and accumulate in tissues as amyloid fibrils, RNA interference (RNAi) therapeutics and antisense oligonucleotides reduce synthesis of TTR protein [11, 12].

Vutrisiran is an N-acetylgalactosamine (GalNAc)-conjugated RNAi therapeutic, administered subcutaneously (SC) once every 3 months, that inhibits hepatic synthesis of both wild-type and variant TTR, resulting in rapid knockdown of amyloidogenic TTR protein [13]. Vutrisiran is approved for the treatment of ATTRv with polyneuropathy (ATTRv-PN), based on the HELIOS-A study [14–16], and for ATTR with cardiomyopathy (ATTR-CM; ATTRv or ATTRwt), based on the HELIOS-B study [17].

Although vutrisiran's mechanism of action results in consistent and reliable pharmacodynamic (PD) knockdown of circulating serum TTR in patients with ATTRv-PN and ATTR-CM [16, 17], its impact across patient subgroups defined by demographic and disease characteristics has not been described in detail for HELIOS-A or HELIOS-B. Furthermore, differences in sample collection timepoints, such as Week 3 and peak (post-dose) knockdown timepoints in HELIOS-A but not HELIOS-B, have limited direct comparison of PD effects of vutrisiran in these two studies to trough knockdown timepoints.

Here, we sought to further investigate serum TTR knockdown across subgroups of patients with ATTRv-PN and ATTR-CM in the respective pivotal vutrisiran phase III trials, HELIOS-A and HELIOS-B. Secondly, we used a population pharmacokinetic (PK)/PD modeling approach to generate a full set of predicted peak and trough TTR knockdown values across both studies, and to provide supportive evidence for the consistency in the serum TTR knockdown profile between patients with ATTRv-PN and ATTR-CM.

2 Methods

2.1 Study Designs

PD analyses of observed serum TTR measurements were conducted using data from the global, randomized, open-label, multicenter, phase III HELIOS-A study (ClinicalTrials.gov identifier: NCT03759379) in patients with ATTRv-PN, and the global, randomized, double-blind, multicenter, placebo-controlled phase III HELIOS-B study (NCT04153149) in patients with ATTR-CM. In brief, patients with ATTRv-PN ($n = 164$) in HELIOS-A received vutrisiran 25 mg subcutaneously (SC) every 3 months (Q3M) ($n = 122$) or patisiran 0.3 mg/kg by intravenous infusion ($n = 42$) every 3 weeks (vutrisiran was also compared with an external placebo); and patients with ATTR-CM ($n = 654$) in HELIOS B received vutrisiran 25 mg SC Q3M ($n = 326$) or placebo ($n = 328$) [16, 17].

A population PK/PD model of serum TTR was developed using pooled data from HELIOS-A, HELIOS-B, and a phase I, randomized, single-blind, placebo-controlled, single-ascending dose study in healthy volunteers (Study 001; NCT02797847). Subjects in Study 001 ($n = 80$) received a single SC injection of vutrisiran 5, 25, 50, 100, 200, or 300 mg, or placebo [13]. Comprehensive details of the population PK/PD modeling and simulations will be provided in a separate publication.

The studies were conducted in accordance with all applicable regulatory requirements, the International Council for Harmonisation 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 study protocol and amendments. All patients provided written informed consent.

Full details of the study designs and inclusion/exclusion criteria, and the primary results for these three studies have been reported [13, 16, 17].

2.2 Pharmacodynamics (PD) and Immunogenicity Assessments

Details of sampling for serum TTR measurement and anti-drug antibodies (ADA) are provided in the electronic supplementary materials (ESM). To minimize patient burden in HELIOS-B, serum sampling for TTR measurement was timed to coincide with vutrisiran administration, resulting in sampling only at trough (pre-dose) knockdown timepoints, with exception of Week 6, versus HELIOS-A where both peak (post-dose) and trough knockdown samples were collected (see Fig. 1). Serum concentrations of circulating TTR were measured using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification of 1.13 ng/mL. Serum samples were tested for ADA using a validated ELISA.

2.3 PD Analyses of Observed Data

The PD analysis populations included all vutrisiran-treated participants who had baseline and one or more evaluable post-baseline serum TTR measurement.

The effects of intrinsic/extrinsic factors on the PD of vutrisiran were assessed based on the percent serum TTR knockdown relative to baseline at Month 18 in HELIOS-A and at Month 30 in HELIOS-B. The following assessments of PD based on baseline characteristics were conducted: sex (male vs female); ethnicity/race (White vs Other); age and body weight tertiles established from baseline demographics; *TTR* genotype (V30M vs non-V30M [HELIOS-A] or V122I vs non-V122I [HELIOS-B]); and *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) and serum TTR baseline concentration tertiles. In addition, disease type (ATTRv vs ATTRwt); National Amyloidosis Centre (NAC) ATTR disease stage (1 vs 2/3); New York Heart Association (NYHA) class (I/II vs III); 6-minute walk test (6MWT), Kansas City Cardiomyopathy Questionnaire—Overall Summary (KCCQ-OS), and troponin I baseline score tertiles; and tafamidis use (yes vs no) were assessed for HELIOS-B.

For both studies, assessments of serum TTR were also conducted according to ADA status during treatment (positive vs negative).

2.4 Population PK/PD Modeling of Serum Transthyretin (TTR) Knockdown

The population PK/PD model was developed using pooled data from Study 001, HELIOS-A (up to Month 18), and HELIOS-B (up to Month 30). In brief, the effect of allometrically scaled vutrisiran hepatic concentrations on serum TTR was modeled as an inhibitory function through an intermediary RNA-induced silencing complex effect compartment [18]. Simulations of serum TTR knockdown in HELIOS-A and HELIOS-B were performed using the final PK/PD model.

2.5 Statistical Analyses

Median observed serum TTR percent changes from baseline with 95% confidence intervals (CIs) at Month 18 (HELIOS-A) and Month 30 (HELIOS-B) were determined for the overall vutrisiran-treated population and for patient subgroups. In addition, the area under the curve of the percent TTR remaining at trough versus time profile was calculated using observed data up to Month 30 (Week 132) in HELIOS-B (ESM).

Graphical analyses were performed using R® version 4.0.4 or higher, and modeling and simulation were performed using NONMEM version 7.5.

3 Results

3.1 Serum TTR Knockdown with Vutrisiran in Patients with ATTRv-PN and ATTR-CM

Median (95% CI) serum TTR concentration at baseline was 203.2 (192.9–220.6) µg/mL in vutrisiran-treated patients with ATTRv-PN in HELIOS-A ($n = 122$). In HELIOS-B, median (95% CI) serum TTR concentration at baseline was 270.0 (256.3–285.2) µg/mL in the overall vutrisiran-treated population ($n = 317$). The observed profiles of median percent serum TTR knockdown with vutrisiran 25 mg Q3M in HELIOS-A and HELIOS-B are shown in Fig. 1.

In HELIOS-A (Fig. 1a; Table 1), median (95% CI) serum TTR percent knockdown in the overall vutrisiran-treated population (PD analysis population, $n = 122$) at the earliest TTR sampling time (Week 3) was 64.2% (61.6–67.8). Median (95% CI) steady-state peak, trough, and average percent TTR knockdown were 91.6% (86.4–96.9), 86.2% (84.1–92.6), and 86.9% (82.5–91.6), respectively, with median (95% CI) peak to trough fluctuation of 5.4% (2.3–4.3). The median (95% CI) knockdown at Month 18 was 91.0% (87.6–93.3).

In HELIOS-B (Fig. 1b; Table 1), median (95% CI) serum TTR percent knockdown in the overall vutrisiran-treated population (PD analysis population, $n = 317$) at the earliest TTR sampling time (Week 6) was 69.0% (66.0–72.0).

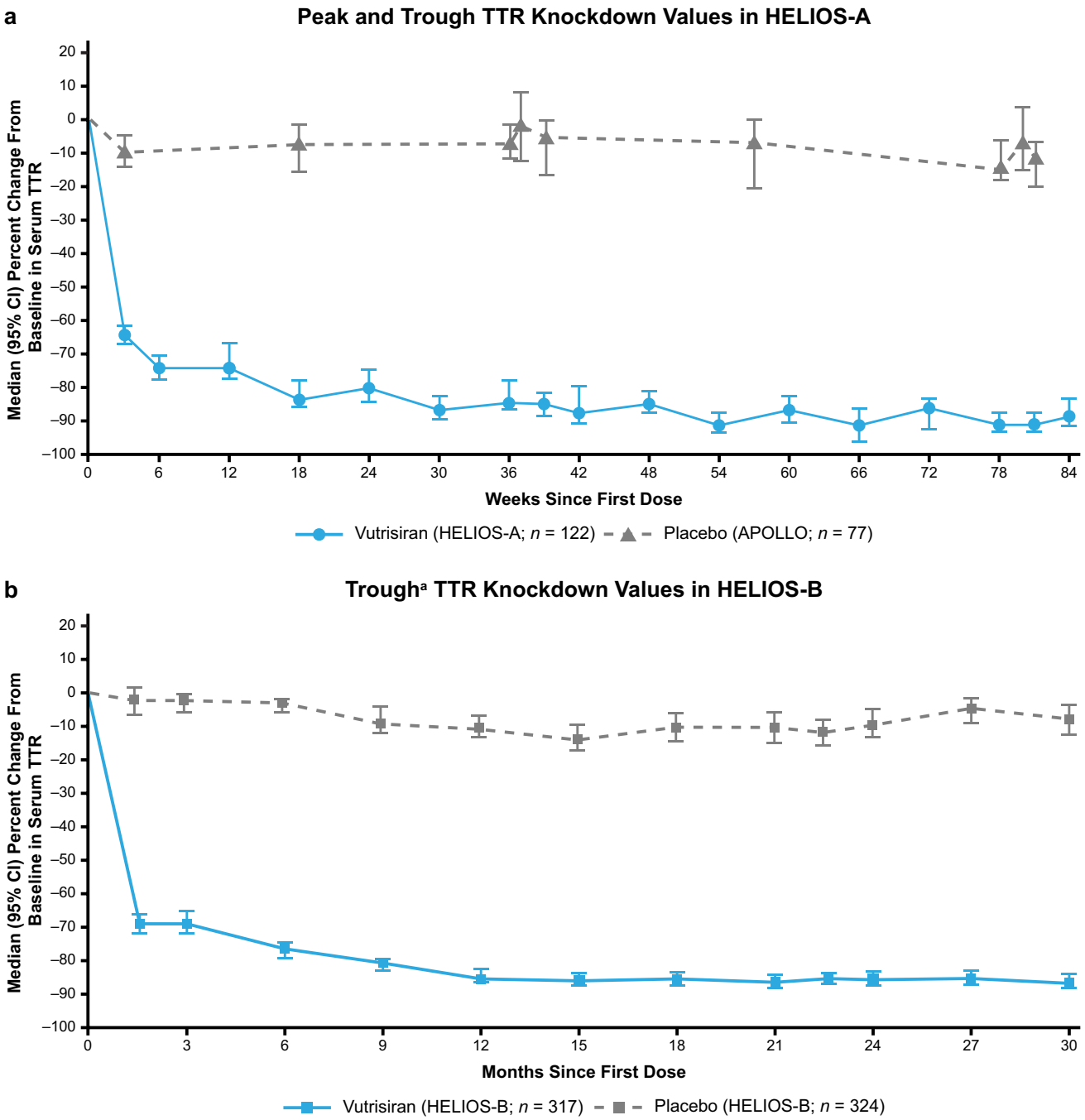


Fig. 1 Observed median serum TTR percent knockdown in the overall PD analysis population in **a** HELIOS-A and **b** HELIOS-B. HELIOS-A did not include a within-study placebo arm due to ethical considerations, thus the placebo arm from APOLLO was included as an external control (as per the HELIOS-A protocol) [16]. [a]Peak value at week 6 only. *CI* confidence interval, *PD* pharmacodynamic, *TTR* transthyretin.

Median (95% CI) steady-state trough TTR percent knockdown was 82.5% (80.5–84.9) (peak knockdown was not determined due to sampling timepoints), and median (95% CI) TTR percent knockdown from baseline at Month 30 was 86.8% (83.7–88.2).

3.2 Impact of Baseline Covariates on Serum TTR Knockdown in Patients with ATTRv-PN in HELIOS-A

The majority of patients with ATTRv-PN in the vutrisiran group were male (64.8%) and White (70.5%); 44.3% had the

Table 1 Serum TTR knockdown with vutrisiran 25 mg Q3M in HELIOS-A and HELIOS-B

	Timepoint	*n*	TTR percent reduction from baseline			
			Mean (SD)	Median	IQR	95% CI of the median
HELIOS-A						
Overall population	Week 3	114	63.8 (16.4)	64.2	53.3–77.3	61.6–67.8
	$Peak_{ss}$ [a]	15	87.6 (15.8)	91.6	87.1–96.4	86.4–96.9
	$Trough_{ss}$ [a]	118	81.0 (21.0)	86.2	75.7–94.6	84.1–92.6
	$Average_{ss}$ [a]	119	81.4 (18.8)	86.9	73.1–94.8	82.5–91.6
	Month 18	114	85.4 (14.2)	91.0	79.0–95.4	87.6–93.3
HELIOS-B [b]						
Overall population	Week 6	294	67.3 (19.7)	69.0	57.7–81.5	66.0–72.0
	$Trough_{ss}$ [c]	307	78.8 (15.8)	82.5	70.0–90.1	80.5–84.9
	Month 30	246	81.0 (16.1)	86.8	73.3–92.4	83.7–88.2

CI confidence interval, *IQR* interquartile range, *n* number of patients with baseline and post-baseline TTR measurement, *Q3M* every 3 months, *SD* standard deviation, *ss* steady state, *TTR* transthyretin

[a]Measured at Month 6 through Month 18

[b]TTR sampling was conducted at Week 6 and at trough knockdown timepoints (i.e., pre-dose) only thereafter

[c]Measured at Month 6 through Month 30

V30M *TTR* variant; and 63.9% had Neuropathy Impairment Score <50, 77.1% had polyneuropathy disability score I/II, and 43.3% had prior tafamidis use at baseline (Supplemental Table 1, ESM). Details have been published previously [16].

Data for the percent serum TTR knockdown with vutrisiran at Month 18 of HELIOS-A were available for 114 patients. The median percent change from baseline in serum TTR at Month 18 was generally consistent across vutrisiran-treated patient subpopulations categorized according to baseline characteristics (Fig. 2).

The median (95% CI) percent serum TTR knockdown relative to baseline at Month 18 was 86.5% (82.4–91.5) for males; 94.0% (91.7–95.8) for females; 89.3% (82.3–94.2) and 91.1% (85.5–95.1), respectively, for the lowest and highest body weight tertiles; and 89.8% (77.3–95.1) and 92.7% (89.4–95.2), respectively, for the lowest and highest NT-proBNP concentration tertiles. The median (95% CI) absolute serum TTR concentration at Month 18 was 12.1 (6.8–19.5) µg/mL and 31.2 (17.6–50.1) µg/mL, respectively, and median (95% CI) percent serum TTR knockdown was 91.7% (86.1–95.1) and 87.5% (81.6–93.6), respectively, for the lowest and highest baseline serum TTR concentration tertiles (Fig. 2).

3.3 Impact of Baseline Covariates on Serum TTR Knockdown in Patients with ATTR-CM in HELIOS-B

The majority of patients with ATTR-CM (ATTRwt and ATTRv) in the vutrisiran group were male (91.7%) and White (85.0%) with ATTRwt (88.7%); 24 of 37 patients with ATTRv had the *TTR* V122I variant; and 76.7% had NYHA class II heart failure, 63.8% had NAC Stage 1 disease, and 39.9% were receiving concomitant tafamidis at baseline (Supplemental Table 1, ESM). Details have been published previously [17].

Data for the percent serum TTR knockdown with vutrisiran at Month 30 of HELIOS-B were available for 246 patients. The median percent change from baseline in serum TTR at Month 30 was generally consistent across vutrisiran-treated patient subpopulations categorized according to baseline characteristics (Fig. 3a) and markers of disease severity (Fig. 3b).

The median (95% CI) percent serum TTR knockdown relative to baseline at Month 30 was 85.6% (83.0–88.2) for males; 88.4% (82.3–93.8) for females; 88.4% (83.7–90.3) and 84.2% (79.1–88.0), respectively, for the lowest and highest body weight tertiles; and 87.0% (78.7–89.8) and 87.9% (83.9–89.8), respectively, for the lowest and highest NT-proBNP concentration tertiles. The median (95% CI) absolute serum TTR concentration was 30.5 (21.0–42.6) µg/mL and 53.4 (38.8–66.0) µg/mL, respectively, and median (95% CI) percent serum TTR knockdown was 84.0% (77.6–89.0) and 87.4% (81.9–90.0), respectively, for the lowest and highest baseline serum TTR concentration tertiles (Fig. 3).

3.4 Serum TTR Knockdown in Patients Receiving Baseline Tafamidis

Patients in HELIOS-B were permitted to receive concomitant tafamidis during the study, with 130 patients in the vutrisiran group receiving tafamidis at baseline (total daily dose: 20 mg, $n = 13$; 61 mg, $n = 73$; 80 mg, $n = 44$) and an additional 44 patients initiating tafamidis during the double-blind period (total daily dose: 20 mg, $n = 1$; 61 mg, $n = 38$;

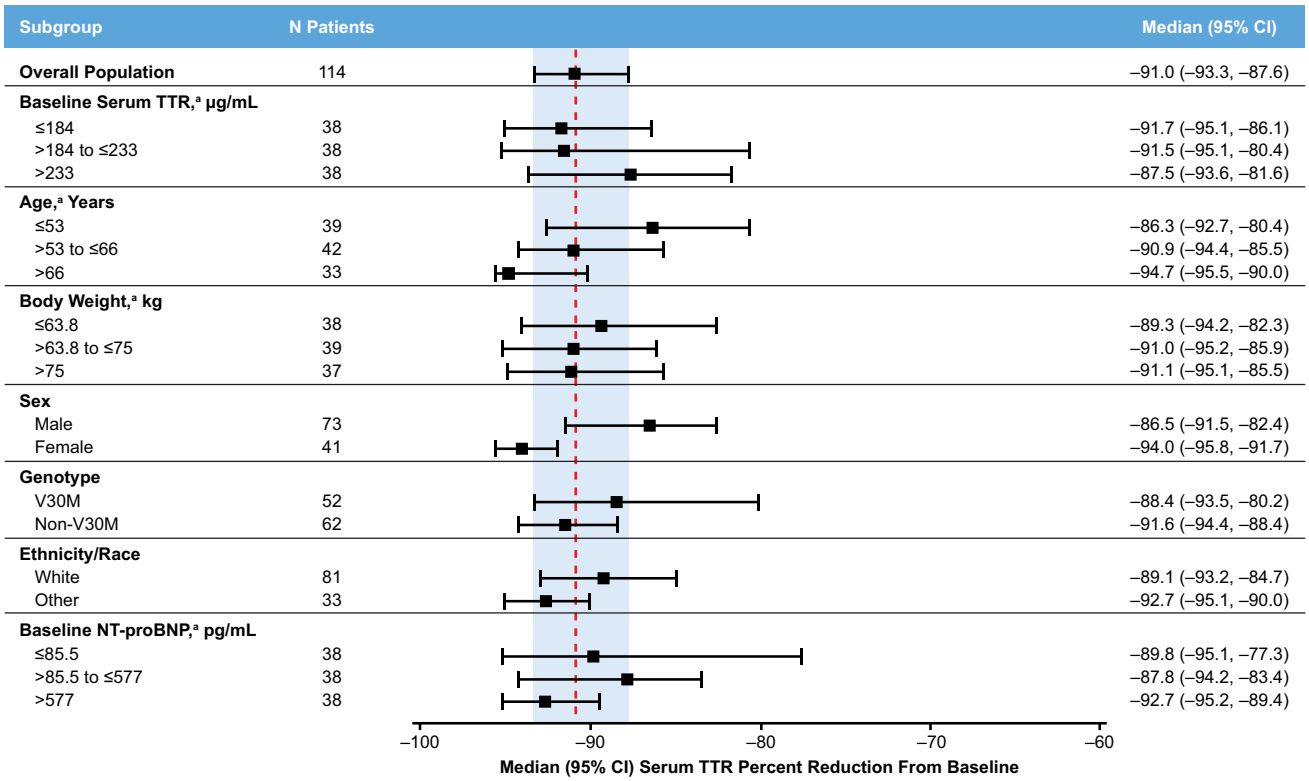


Fig. 2 Forest plot of observed TTR knockdown in HELIOS-A. Median percent serum TTR knockdown at Month 18 in vutrisiran-treated patient subgroups with ATTRv-PN relative to the overall vutrisiran-treated population categorized by baseline characteristics (mITT population). The *red dashed line* and *gray shaded area* represent the median and 95% CI, respectively, for percent change from baseline for the overall vutrisiran-treated population. [a]Analysis based on tertiles established from baseline data. *ATTRv-PN* variant (hereditary) transthyretin amyloidosis with polyneuropathy, *CI* confidence interval, *mITT* modified intent-to-treat, *NT-proBNP* *N*-terminal pro-B-type natriuretic peptide, *TTR* transthyretin

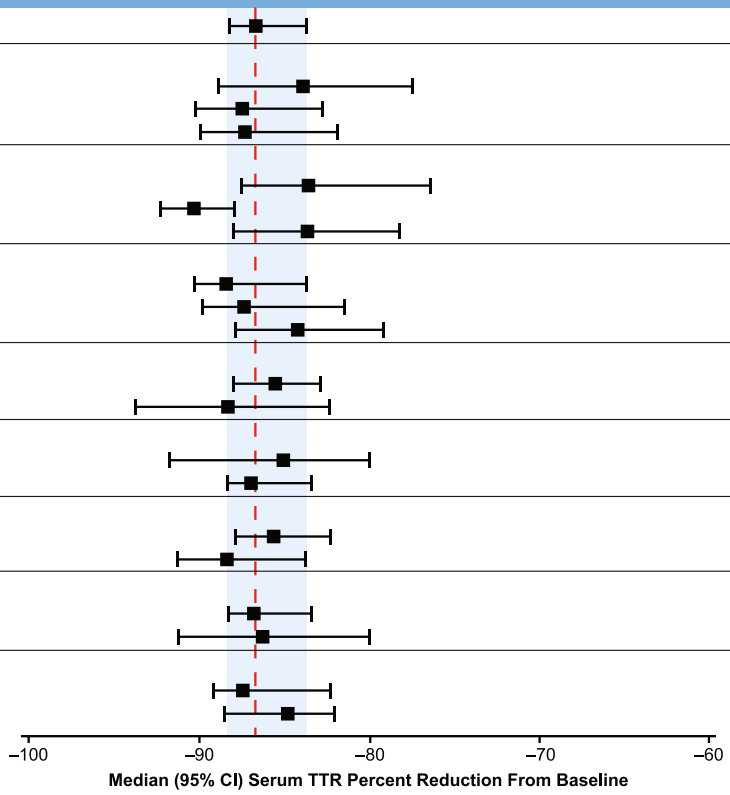
80 mg, $n = 5$; median [range] time to initiation of tafamidis during the study, 17.7 months [6.4–39.1]). Consistent with the mechanism of action of tafamidis, in patients receiving vutrisiran, baseline serum TTR levels were higher in patients who were on tafamidis at baseline ($n = 127$; median [95% CI] 326.2 µg/mL [305.1–345.8]) compared with patients who received vutrisiran monotherapy ($n = 190$; median [95% CI] 237.4 µg/mL [225.1–248.8]). At Month 30, the absolute median (95% CI) serum TTR concentration was only slightly higher at 46.6 µg/mL (36.6–55.8) in patients with baseline tafamidis use compared with 35.5 µg/mL (23.6–44.2) in the monotherapy subgroup, although baseline tafamidis use had little impact on the percent change from baseline at Month 30 (Fig. 3a). Median (95% CI) percent reduction from baseline was 87.5% (82.3–89.3) for patients with baseline tafamidis use and 84.8% (82.0–88.6) for those in the monotherapy subgroup (Fig. 3a). Results were consistent for the subgroup of patients who initiated tafamidis during the double-blind period (data not shown).

3.5 Impact of Immunogenicity on Serum TTR Knockdown in Patients with ATTRv-PN and ATTR-CM

The incidence of ADA to vutrisiran post-baseline was low in HELIOS-A (4.1%; 5/121) and HELIOS-B (1.2%; 4/321). In all cases, ADA titers were low (50–100) and transient and did not impact TTR knockdown. In HELIOS-A, maximum median serum TTR knockdown through Month 18 was 93.4% for the five patients who tested positive for ADA (four patients with treatment-emergent ADA and one with positive ADA at baseline and ≥ 1 post-baseline assessment), which was similar to the maximum median serum TTR knockdown of 91.6% in patients who tested negative for ADA ($n = 116$). In HELIOS-B, maximum median serum TTR knockdown through Month 30 was 81.3% for the four patients who tested positive for ADA (one patient with treatment-emergent ADA and three who tested positive at baseline and ≥ 1 post-baseline assessment). In vutrisiran-treated patients who tested

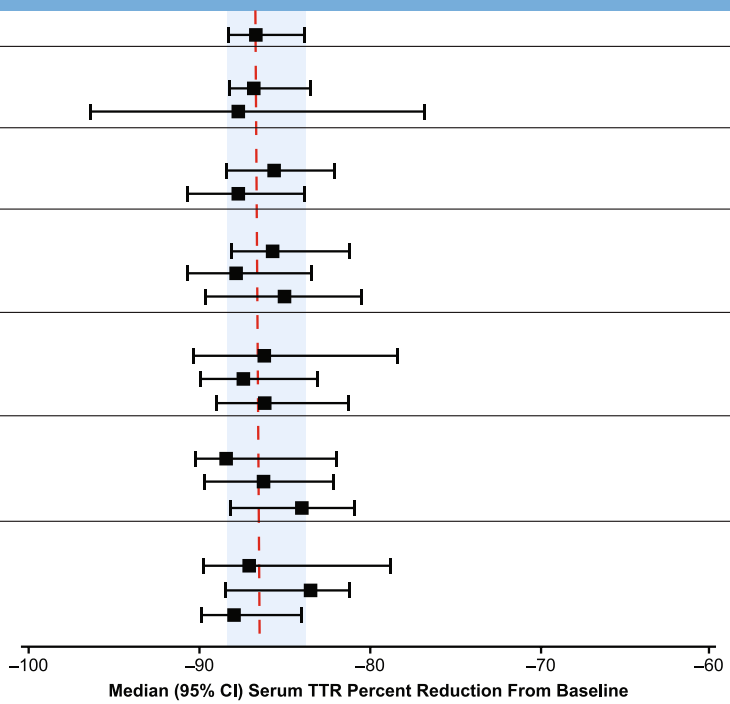
a

Subgroup	N Patients	Median (95% CI)
Overall Population	246	
Baseline Serum TTR,[a] µg/mL		
≤246.6	82	–84.0 (–89.0, –77.6)
>246.6 to ≤313.3	82	–87.5 (–90.3, –82.8)
>313.3	82	–87.4 (–90.0, –81.9)
Age,[a] Years		
≤73	90	–83.7 (–87.6, –76.4)
>73 to ≤79	87	–90.4 (–92.5, –88.0)
>79	69	–83.7 (–88.1, –78.2)
Body Weight,[a] kg		
≤75	83	–88.4 (–90.3, –83.7)
>75 to ≤83.5	81	–87.4 (–90.0, –81.5)
>83.5	82	–84.2 (–88.0, –79.1)
Sex		
Male	224	–85.6 (–88.2, –83.0)
Female	22	–88.4 (–93.8, –82.3)
Genotype		
V122I	14	–85.1 (–91.8, –80.1)
Non-V122I	232	–87.0 (–88.4, –83.4)
Ethnicity/Race		
White	207	–85.7 (–88.0, –82.3)
Other	39	–88.4 (–91.4, –83.7)
Type of Amyloidosis		
ATTRwt	222	–86.8 (–88.4, –83.4)
ATTRv	24	–86.4 (–91.4, –80.1)
Tafamidis Use at Baseline		
Yes	110	–87.5 (–89.3, –82.3)
No	136	–84.8 (–88.6, –82.1)



b

Subgroup	N Patients	Median (95% CI)
Overall Population	246	–86.8 (–88.3, –83.7)
NYHA Class at Baseline		
I/II	226	–86.8 (–88.3, –83.4)
III	20	–87.6 (–96.4, –76.7)
ATTR Amyloidosis Disease Stage[b]		
1	173	–85.6 (–88.4, –81.9)
2/3	73	–87.7 (–90.7 –83.7)
Baseline KCCQ-OS[a]		
≤69.8	83	–85.7 (–88.2, –81.1)
>69.8 to ≤84.8	80	–87.9 (–90.9, –83.4)
>84.8	82	–85.0 (–89.7, –80.5)
Baseline 6MWT Distance,[a] Meters		
≤344	82	–86.1 (–89.0, –81.1)
>344 to ≤431	81	–87.4 (–90.0, –83.0)
>431	82	–86.2 (–90.4, –78.2)
Baseline Troponin-I,[a] pg/mL		
≤49.4	82	–88.3 (–90.3, –81.9)
>49.4 to ≤82.7	82	–86.1 (–89.7, –82.1)
>82.7	82	–83.9 (–88.3, –80.7)
Baseline NT-proBNP,[a] pg/mL		
≤1260	82	–87.0 (–89.8, –78.7)
>1260 to ≤2460	82	–83.3 (–88.4, –81.1)
>2460	82	–87.9 (–89.8, –83.9)



◂**Fig. 3** Forest plot of observed TTR knockdown in HELIOS-B. Median percent serum TTR knockdown at Month 30 in vutrisiran-treated patient subgroups with ATTR-CM versus the overall vutrisiran-treated population, categorized by **a** baseline demographics and disease characteristics and **b** disease severity (PD Analysis Set). The *red dashed line* and *gray shaded area* represent the median and 95% CI, respectively, for percent change from baseline for the overall vutrisiran-treated population. [a]Analysis based on tertiles established from baseline data. [b]NAC disease stage based on published criteria [19]. *6MWT* 6-minute walk test, *ATTR* transthyretin amyloidosis, *ATTR-CM* transthyretin amyloidosis with cardiomyopathy, *ATTRv* variant (hereditary) transthyretin amyloidosis, *ATTRwt* wild-type transthyretin amyloidosis, *CI* confidence interval, *KCCQ-OS* Kansas City Cardiomyopathy Questionnaire—Overall Summary, *mITT* modified intent-to-treat, *NAC* National Amyloidosis Centre, *NT-proBNP* *N*-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *PD* pharmacodynamic, *TTR* transthyretin

negative for ADA ($n = 313$), maximum median serum TTR knockdown was 90.4% through Month 30.

3.6 Model-Predicted Serum TTR Knockdown with Vutrisiran in Patients with ATTRv-PN and ATTR-CM

Data from 843 participants who contributed 10,376 serum TTR samples were used in the PK/PD modeling. Details are provided in the ESM. The observed data on which modeling analyses were conducted (peak [post-dose] and trough [pre-dose] TTR knockdown sampling timepoints in HELIOS-A and trough knockdown sampling timepoints [except Week 6] in HELIOS-B) are shown in Fig. 4a. Model-predicted median percent serum TTR knockdown at both peak and trough serum TTR knockdown sampling timepoints for HELIOS-A and HELIOS-B showed a consistent profile over time between the studies (Fig. 4b). Predicted median (95% CI) TTR knockdown at Week 3 was 50.4% (46.6–54.2) for HELIOS-B and 54.7% (49.9–60.1) for HELIOS-A. The model-predicted steady-state median (95% CI) peak, trough, and average TTR knockdown based on HELIOS-A at Month 18 were 87.2% (83.9–90.1), 86.4% (82.7–89.5), and 86.7% (83.3–89.8), respectively. The respective values based on the HELIOS-B study at Month 30 were 87.1% (84.8–89.4), 86.4% (83.7–88.9), and 86.7% (84.2–89.2). This supports consistency in trough and peak serum TTR knockdown between the ATTRv-PN and ATTR-CM populations.

4 Discussion

Observed PD data from the HELIOS-A and HELIOS-B phase III clinical trials of the RNAi therapeutic vutrisiran demonstrated rapid and sustained serum TTR knockdown that was consistent between patients with ATTRv-PN and ATTR-CM. Observed median percent TTR knockdown was approximately 64% in patients with ATTRv-PN and approximately 70% in patients with ATTR-CM within 3 and 6 weeks (the earliest timepoints evaluated), respectively, following the first administered dose of vutrisiran. Upon subsequent administrations, additional TTR knockdown was achieved which was sustained with steady-state median (95% CI) peak and trough knockdown of 91.6% (86.4–96.9) and 86.2% (84.1–92.6), respectively, after 18 months in HELIOS-A, and steady-state median (95% CI) trough knockdown of 82.5% (80.5–84.9) after 30 months in HELIOS-B. The impact of the unique enhanced stabilization chemistry design of GalNAc-conjugated RNAi therapeutics such as vutrisiran on cellular uptake and metabolic stability [20] may explain the rapid and sustained TTR knockdown observed and the consistency of the knockdown profile in patients with ATTRv-PN and ATTR-CM.

Importantly, comparisons of the PD effect of vutrisiran on TTR in patient subgroups in both studies indicated no meaningful differences in serum TTR reduction with vutrisiran 25 mg Q3M across patient subgroups characterized by baseline covariates—including demographics, *TTR* genotype, and markers of disease severity—and baseline tafamidis use (HELIOS-B). Of note, TTR knockdown with vutrisiran in both studies was consistent regardless of baseline serum TTR concentration. In addition, we found no evidence of an impact of immunogenicity on serum TTR reduction in the very small numbers of vutrisiran-treated patients with ADA (9 out of 443 [2.0%]), inclusive of patients with pre-baseline ADA. This low immunogenicity observed with vutrisiran in HELIOS-A and HELIOS-B is consistent with the low incidence of immunogenicity reported with other GalNAc-conjugated RNAi therapeutics (e.g., lumasiran, givosiran, nedosiran, and inclisiran). The 2′-O-methyl (2′-OME) and 2′-fluoro (2′-F) chemical modifications to the structure of the small-interfering RNA have been shown to reduce their immunostimulatory potential [21]. Only four of 121 patients in HELIOS-A and one of 321 patients in HELIOS-B showed treatment-emergent ADA, and even in these cases, the ADA titers were very low and transient, indicating very low concentrations of circulating ADA. Taken together, these findings reflect reliable and consistent TTR knockdown across patient subgroups, supporting vutrisiran 25 mg Q3M for patients with ATTRv-PN and ATTR-CM without the need for dose adjustment, and are consistent with subgroup analyses of clinical and biomarker outcomes in these studies [16, 17, 22–24].

The PK/PD model-simulated serum TTR time course based on HELIOS-B demonstrated rapid and consistent serum TTR knockdown with minimal variability across the 3-month dosing interval, consistent with the observed and simulated profiles for HELIOS-A. This suggests that variation in the observed serum TTR time course between the individual studies may be accounted for by the difference

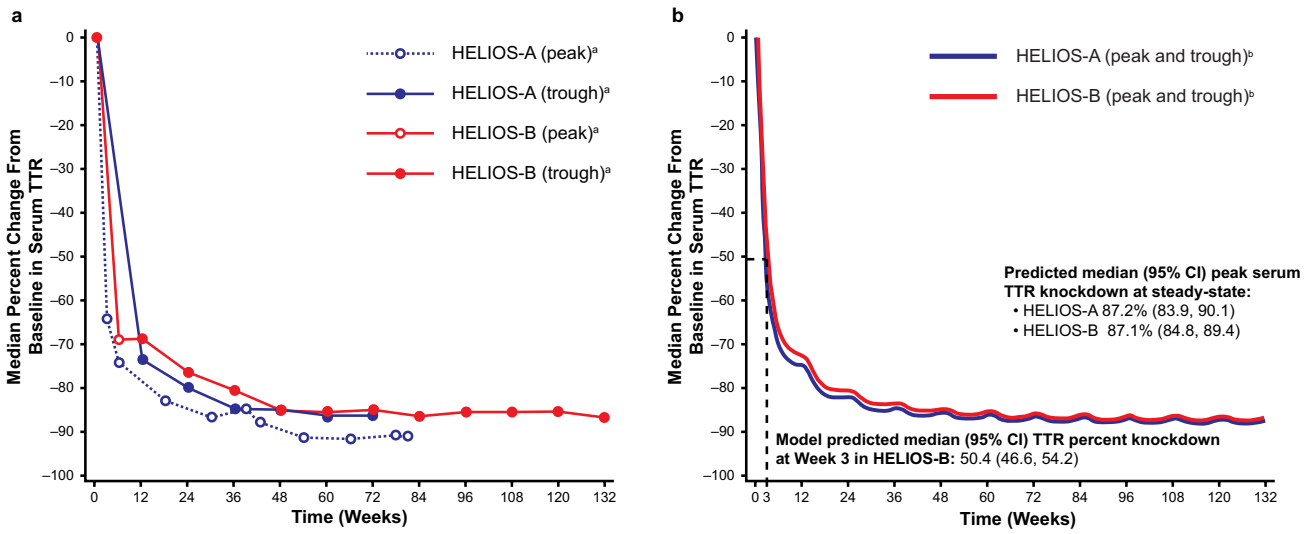


Fig. 4. Observed (**a**) and model-predicted (**b**) median percent serum TTR knockdown across studies. [a]Observed peak data values (*open circles*) are based on TTR measurements from serum samples collected between consecutive doses of vutrisiran, and observed trough values (*closed circles*) refer to pre-dosing TTR measurements. Note that only trough sampling was conducted in HELIOS-B except for Week 6. [b]Model-predicted data for both peak and trough sampling timepoints. *CI* confidence interval, *PD* pharmacodynamic, *Q3M* once every 3 months, *TTR* transthyretin

in serum TTR sampling times. Specifically, in HELIOS-B, in order to minimize patient burden, serum sampling was timed to coincide with vutrisiran administration, resulting in measurements representing pre-dose timepoints at the end of the dosing interval (i.e., trough knockdown), which may reflect lower knockdown versus measurement at both peak and trough knockdown timepoints in HELIOS-A. By the earliest timepoint at which serum TTR was measured in HELIOS-A (i.e., 3 weeks after the first vutrisiran dose), the model-predicted median serum TTR knockdown was approximately 50% for HELIOS-A and HELIOS-B. The consistency of the observed and model-predicted TTR knockdown profiles over time between the studies indicates a similar rapid and sustained knockdown of TTR by RNAi with vutrisiran in patients with ATTR-CM and ATTRv-PN.

TTR is the disease-causing protein in ATTR [1, 2], and ongoing accumulation of amyloid in patients with ATTR is associated with disease progression [2]. Greater lowering of pathogenic TTR protein is expected to potentially translate to better clinical outcomes, analogous to observations from other forms of systemic amyloidosis [6–9]. It is unknown if there is an absolute threshold of TTR knockdown above which all patients will benefit, or below which they will not benefit from the treatment. The low variability in TTR knockdown observed across patients treated with vutrisiran limits the ability to determine a relationship between serum TTR levels and clinical response. It is likely that the extent of the knockdown required for clinical benefit varies between individual patients and tissues due to factors such as differences in rates of amyloid formation and clearance. The rapid and sustained TTR knockdown observed with RNAi has the potential to delay or even halt deposition of amyloid fibrils, providing a sound mechanistic hypothesis for the biomarker, imaging, functional, quality of life, and clinical efficacy results from HELIOS-A and HELIOS-B.

In patients with ATTR, pre-treatment TTR level has been associated with general health status, with higher levels of TTR associated with milder disease and lower levels indicative of more severe disease [25, 26]. Lower circulating levels of TTR pre-treatment are likely to be a consequence of a higher rate of amyloid formation and deposition in tissues. From a treatment perspective, there is a need to reduce the level of pathogenic protein, and the clinical benefits of lowering circulating TTR levels have been demonstrated in multiple well-controlled studies [16, 17, 27, 28]. The normal function of TTR appears dispensable, likely because of redundant mechanisms, as indicated by safety data for RNAi-mediated TTR knockdown across the combined vutrisiran and patisiran clinical and post-marketing experience—which includes approximately 15,000 treated patients with ATTR, some of whom have received patisiran continuously for > 7 years, and represents > 30,000 patient-years of treatment exposure in ATTR amyloidosis. This data shows no safety concerns with long-term TTR knockdown [29–34]. The observed serum TTR knockdown in HELIOS-B was consistent regardless of baseline serum TTR. A higher serum level of TTR was observed at baseline in patients receiving tafamidis. This is consistent with results from a PK/PD analysis of patients with and without prior use of TTR stabilizers in the APOLLO study of patisiran in patients with ATTRv-PN [35],

which is as expected based on the mechanism of action of tafamidis, which stabilizes the circulating tetrameric form of TTR. Relative to the monotherapy population, tafamidis use at baseline resulted in a modestly higher (~ 10 µg/mL) absolute median TTR concentration at Month 30, and a ~ 3% greater percent TTR reduction. Collectively, these findings suggest that vutrisiran's impact on serum TTR is consistent, regardless of concomitant tafamidis use or baseline TTR concentrations.

4.1 Limitations

Limitations of our analysis include the small numbers of patients in some subgroups categorized by baseline covariates. In addition, the two studies were conducted sequentially. As well as inherent differences between patient populations with ATTRv-PN and ATTR-CM, the rapidly evolving clinical landscape and advances in diagnosis and management of ATTR amyloidosis during the time between the studies [36–38] may have led to further differences between the characteristics of the patients enrolled in HELIOS-A and HELIOS-B.

5 Conclusions

Treatment with the RNAi therapeutic vutrisiran was associated with rapid and sustained knockdown of TTR that was consistent between the HELIOS-A and HELIOS-B clinical trials, as well as across patient subgroups within the two trials. The rapid and sustained TTR knockdown in patients with ATTRv-PN and ATTR-CM was followed by beneficial impact on outcomes of death and CV events as well as a broad range of important disease manifestations. These data support the use of a fixed dose of vutrisiran 25 mg Q3M across patients with ATTRv-PN and ATTR-CM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-026-01651-3.

Acknowledgements The authors would like to thank the patients, their families, investigators, study staff, and collaborators for their participation in HELIOS-A and HELIOS-B, and Dr Anh Duong (former employee of Alnylam Pharmaceuticals Inc) for her contribution to the analysis and manuscript development. Medical writing support, under the guidance of the authors, was provided by Kirsteen Munn, PhD, on behalf of, and Kristen Brown, PhD, an employee from the Publications and Medical Affairs Division of Omnicom Health Medical Communications, and was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice, GPP 2022 (*Ann Intern Med* 2022;175:1298–1304).

Declarations

Funding This study was funded by Alnylam Pharmaceuticals Inc. The funder collaborated with the authors during the study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and took final responsibility for the decision to submit the manuscript for publication.

Conflicts of Interest M.F. reports research support from AstraZeneca; consultancy and/or advisory board membership for Alexion, Alnylam Pharmaceuticals, Attralus, Caelum Biosciences, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Novo Nordisk, Pfizer, and Prothena; support for attending meetings from Alnylam Pharmaceuticals, AstraZeneca, and Attralus; and ownership of equity in Lexeo Therapeutics and Mycardium. V.A. reports consulting fees and research funding from Alnylam Pharmaceuticals, AstraZeneca, Bayer, Biotronik, and Pfizer. P.G.-P. reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, Neuroimmune, Novo Nordisk, and Pfizer; and research/educational support to their institution from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia Therapeutics, Novo Nordisk, and Pfizer. M.S.M. reports receiving research support from Alnylam Pharmaceuticals, Attralus, BridgeBio, Intellia Therapeutics, and Ionis Pharmaceuticals; and consulting fees from Akcea Therapeutics, Alnylam Pharmaceuticals, AstraZeneca, Intellia Therapeutics, Novo Nordisk, and Roche. J.D.G. reports research support from Alnylam Pharmaceuticals; consulting fees from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, and Lycia Therapeutics; and payment for lectures or speaker fees from Alnylam Pharmaceuticals and AstraZeneca. F.C. reports consulting fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, and Pfizer. K.K., X.G., S.J., G.R., and P.B. are employees of and own shares in Alnylam Pharmaceuticals. N.M. was a previous employee of Alnylam Pharmaceuticals and own shares in Alnylam Pharmaceuticals.

Ethics Approval The studies were conducted in accordance with all applicable regulatory requirements, the International Council for Harmonisation 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 study protocol and amendments.

Availability of Data and Material Access to anonymized individual participant data that support these results is made available 12 months after trial completion and not less than 12 months after the product and indication have been approved in the USA and/or the EU. Data will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website: http://www.vivli.org.

Author Contributions MF, VA, PG-P, MSM, JDG and FC were responsible for the acquisition of the data. XG was responsible for data analysis. All authors contributed to the interpretation of the data and the development and final approval of the manuscript. All authors take accountability for the work.

Consent for Publication Consent was obtained from participants in all trials.

Consent to Participate Written informed consent was obtained for all participants before conducting any study procedures.

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