

# Vutrisiran-Mediated Knockdown of Transthyretin in Patients with Transthyretin Amyloidosis

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# Introduction

## Vutrisiran in Patients with Transthyretin Amyloidosis (ATTR)

- ATTR is a progressive, debilitating and fatal disease caused by misfolded TTR protein accumulating as amyloid fibrils in multiple organs; manifestations include polyneuropathy and cardiomyopathy<sup>1,2</sup>
- The RNAi therapeutic vutrisiran inhibits hepatic synthesis of wild-type and variant TTR, resulting in rapid knockdown of amyloidogenic TTR protein,<sup>3</sup> and is approved for the treatment of ATTRv-PN and ATTR-CM based on HELIOS-A (NCT03759379) and HELIOS-B (NCT04153149), respectively<sup>4-7</sup>
- Direct comparison of serum TTR knockdown in these studies has been limited due to study design differences<sup>6,7</sup>

**Objectives: To assess the consistency of serum TTR knockdown with vutrisiran across patients with ATTRv-PN in HELIOS-A and ATTR-CM in HELIOS-B, and to compare TTR knockdown with vutrisiran in these studies using a population PK/PD model**



### HELIOS-A<sup>6</sup>

- Randomized, open-label, phase 3 study in **ATTRv-PN**
- **18-month** treatment period:
  - Vutrisiran 25 mg SC Q3M (n=122)
  - Patisiran 0.3 mg/kg IV Q3W (n=42)
  - External placebo from APOLLO (n=77)
- Serum TTR measured at **Week 3** and **both peak (post-dose) and trough (pre-dose) timepoints** through **M18**



### HELIOS-B<sup>7</sup>

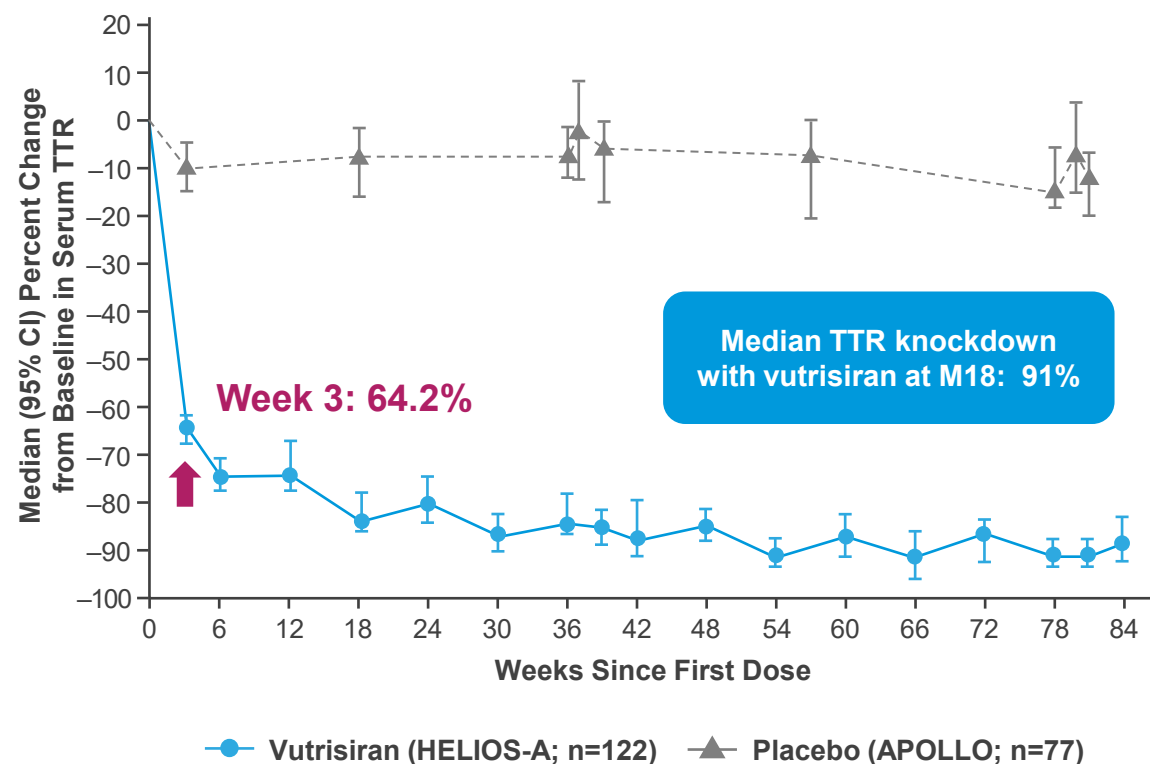
- Randomized, placebo-controlled, DB, phase 3 study in **ATTR-CM**
- **33–36 month** DB treatment period:
  - Vutrisiran 25 mg SC Q3M (n=326)
  - Placebo (n=329)
- Serum TTR measured at **Week 6** and **trough (pre-dose) timepoints only** through **M30**

**Population PK/PD model of serum TTR knockdown:** Pooled data from phase 1 study in healthy volunteers,<sup>3</sup> HELIOS-A and HELIOS-B; predicted peak and trough TTR knockdown values at all timepoints across HELIOS-A and HELIOS-B generated

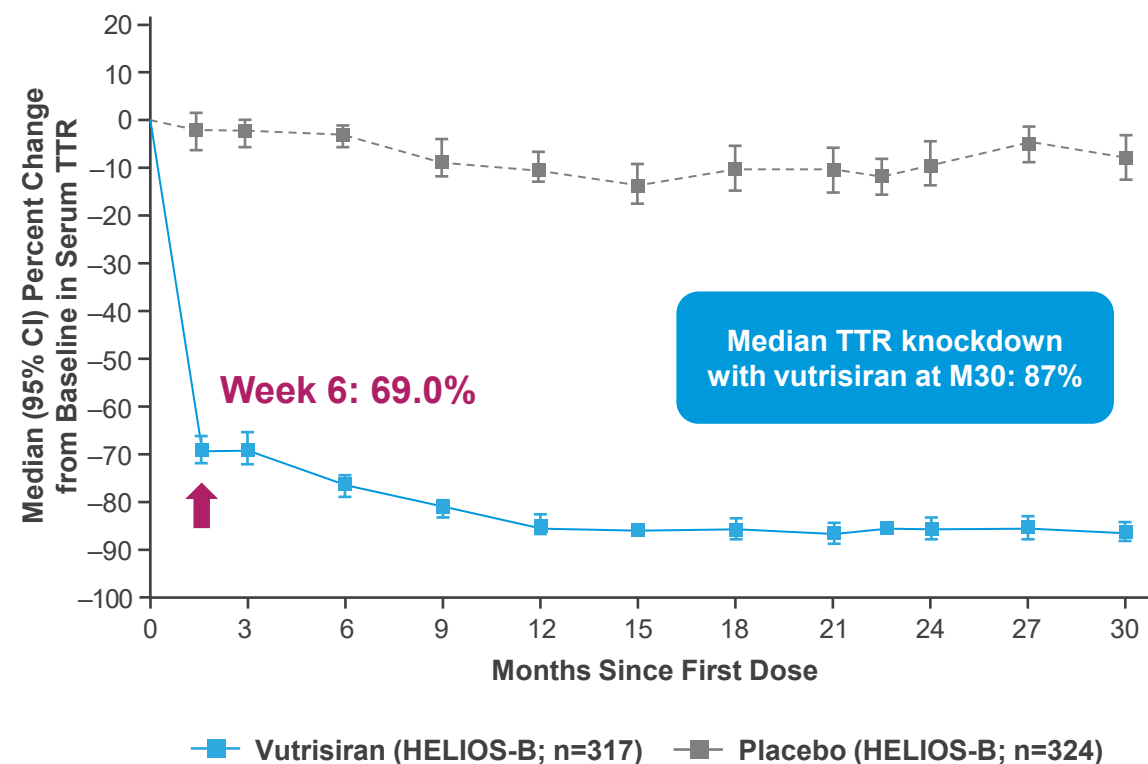
# Observed Data Showed Rapid and Sustained Serum TTR Knockdown with Vutrisiran in HELIOS-A and HELIOS-B

TTR knockdown profile was consistent between patients with ATTRv-PN and ATTR-CM

## HELIOS-A: Peak and Trough Percent TTR Knockdown



## HELIOS-B: Trough Percent TTR Knockdown<sup>a</sup>



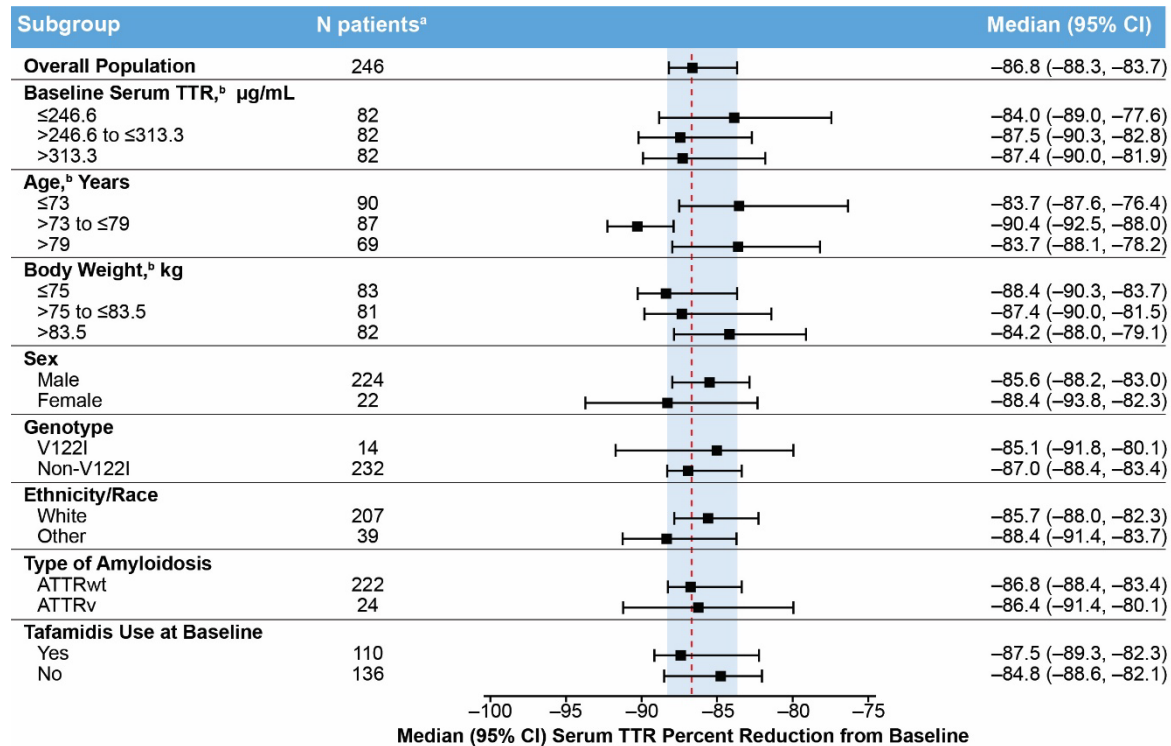
<sup>a</sup>Peak value at Week 6 only. All other timepoints show trough values.

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, variant (hereditary) transthyretin amyloidosis with polyneuropathy; CI, confidence interval; M, month; TTR, transthyretin.

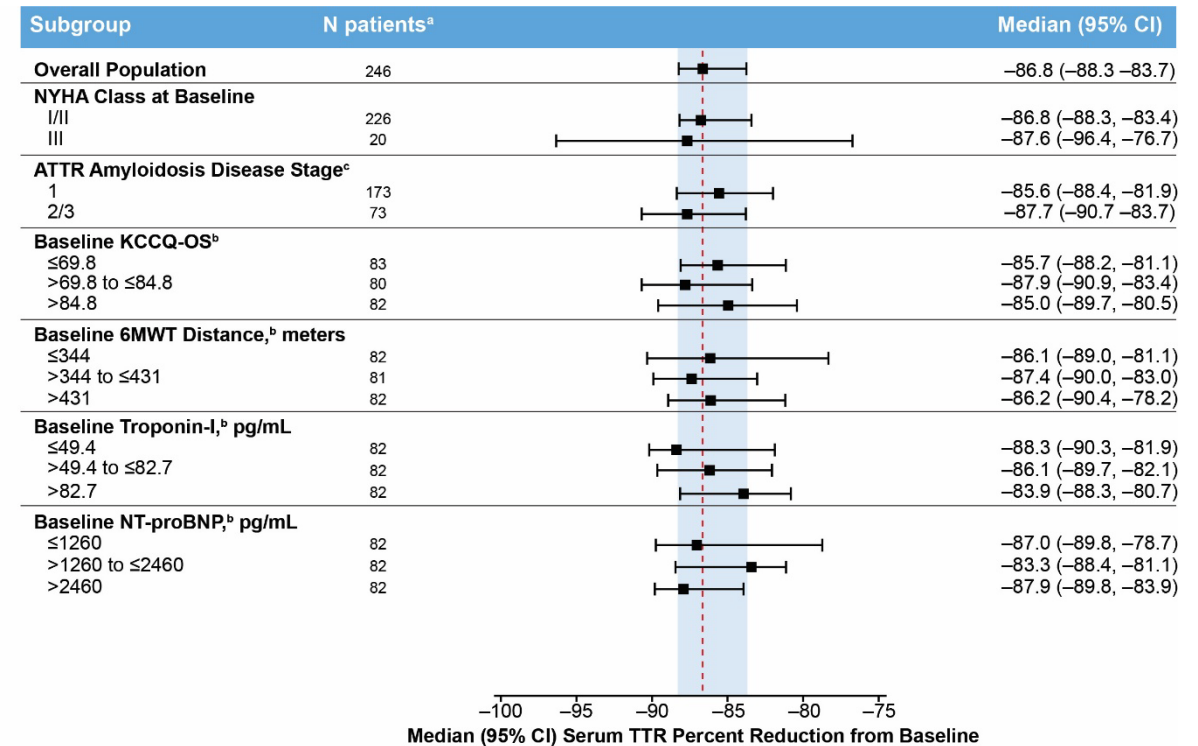
# Serum TTR Knockdown in HELIOS-B Was Generally Consistent Across Subpopulations of Patients with ATTR-CM

TTR knockdown at Month 30 in HELIOS-B was generally consistent regardless of baseline characteristics or disease severity

HELIOS-B: Baseline Characteristics and Tafamidis Use



HELIOS-B: Measures of Baseline Disease Severity



Serum TTR knockdown at Month 18 in HELIOS-A was also generally consistent across patients with ATTRv-PN, regardless of baseline characteristics including demographics, TTR variant and baseline levels of NT-proBNP and serum TTR

The red dashed line and grey shaded area represent the median and 95% CI, respectively, for percent change from baseline for the overall vutrisiran-treated population.

<sup>a</sup>PD analysis populations included all vutrisiran-treated participants who had baseline and ≥1 evaluable post-baseline serum TTR measurement; <sup>b</sup>Analysis based on tertiles established from baseline data; <sup>c</sup>NAC disease stage 1.

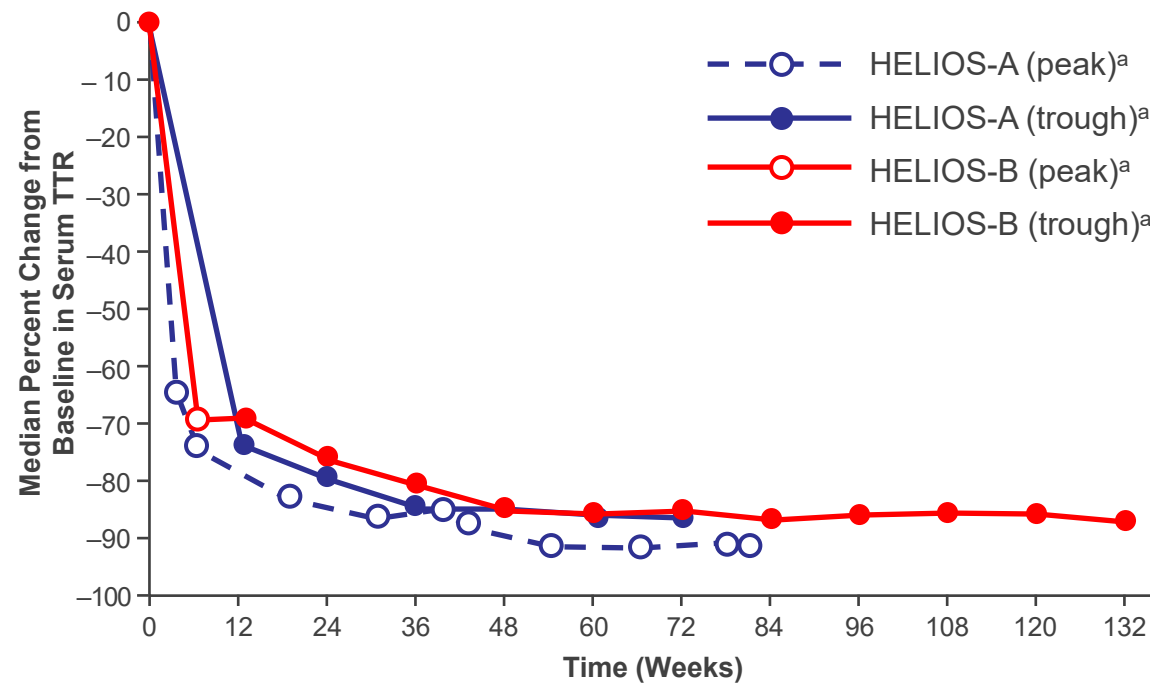
**Abbreviations:** 6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, variant (hereditary) transthyretin amyloidosis with polyneuropathy; ATTRwt, wild-type transthyretin amyloidosis; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamic; TTR, transthyretin.

**Reference:** Gillmore et al. *Eur Heart J* 2018;39:2799–806.

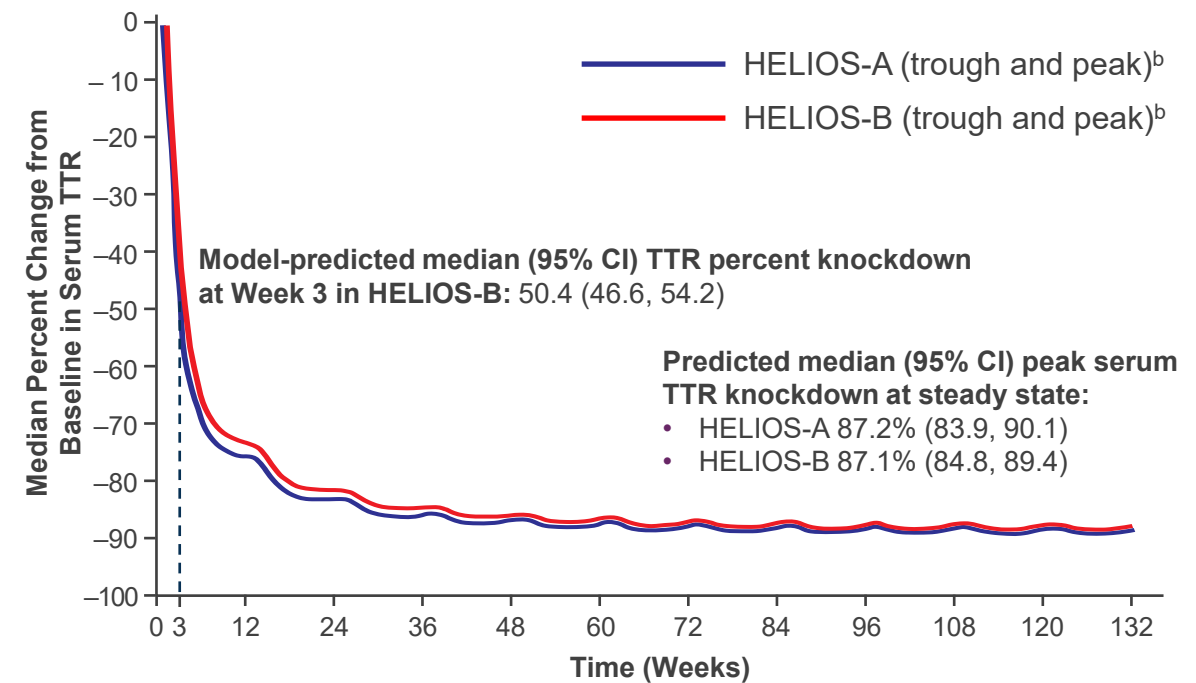
# Comparison of Observed and Model-Predicted TTR Knockdown across Vutrisiran Studies

Model-predicted peak and trough median percent serum TTR knockdown showed a consistent profile between the ATTRv-PN and ATTR-CM populations

Observed TTR Knockdown in HELIOS-A and HELIOS-B



Model-Predicted TTR Knockdown in HELIOS-A and HELIOS-B



Population PK/PD model was developed using pooled data from a phase 1 study in healthy volunteers,<sup>1</sup> HELIOS-A (up to 18 months) and HELIOS-B (up to 30 months).

<sup>a</sup>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. <sup>b</sup>Model-predicted data for both trough and peak sampling timepoints.

**Abbreviations:** ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, variant (hereditary) transthyretin amyloidosis with polyneuropathy; CI, confidence interval; PD, pharmacodynamic; PK, pharmacokinetic; TTR, transthyretin.

**Reference:** 1. Habtemariam et al. *Clin Pharmacol Ther* 2021;109:372–82.

# Conclusions

- Vutrisiran produced rapid, sustained TTR knockdown across HELIOS-A and HELIOS-B in patients with ATTRv-PN and ATTR-CM
  - In ATTRv-PN, median knockdown of 64% was achieved as early as Week 3 and median knockdown of 69% as early as Week 6 in ATTR-CM after the first dose
  - Vutrisiran 25 mg Q3M achieved consistent serum TTR reduction across patient subgroups, with no meaningful differences by demographics, TTR genotype, disease severity or baseline tafamidis use
  - Median percent TTR knockdown was 91% and 87% in HELIOS-A at M18 and in HELIOS-B at M30, respectively
  - Model-predicted median serum TTR knockdown at peak and trough timepoints was comparable between HELIOS-A and HELIOS-B, supporting consistency in TTR suppression across ATTRv-PN and ATTR-CM populations
- Vutrisiran treatment was also associated with beneficial effects on mortality, cardiovascular outcomes and a broad range of clinically meaningful disease manifestations

**We thank the patients, their families, investigators, staff and collaborators for their participation in HELIOS-A and HELIOS B**

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