Exploratory Biomarker Analyses from HELIOS-B, a Phase 3 Study of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

Mathew S. Maurer[1], John L. Berk[2], Thibaud Damy[3], Farooq H. Sheikh[4], José González-Costello[5], Caroline Morbach[6], Diego Delgado[7], Antoine Bondue[8], Olga Azevedo[9], Steen Poulsen[10], Ewa A. Jankowska[11], Lili Yang[12], Shaun Bender[12], Satish Eraly[12], Patrick Jay[12], John Vest[12], Marianna Fontana[13]

[1]Columbia University Irving Medical Center, New York, NY, US; [2]Boston University School of Medicine, Boston, MA, US; [3]Referral Center for Cardiac Amyloidosis, Hôpital Henri Mondor, Créteil, France; [4]MedStar Heart and Vascular Institute, MedStar Health/Georgetown University School of Medicine, Washington, DC, US; [5]Department of Cardiology, Hospital Universitari de Bellvitge, Barcelona, Spain; [6]Department of Clinical Research and Epidemiology, Comprehensive Heart Failure Center & Department of Internal Medicine I, Cardiology, University Hospital Würzburg, Würzburg, Germany; [7]Peter Munk Cardiac Center, University Health Network, Toronto, ON, Canada; [8]Department of Cardiology, Hôpital Universitaire de Bruxelles, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; [9]Cardiology Department, Hospital da Senhora da Oliveira, Guimarães, Portugal; [10]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [11]Department of Translational Cardiology and Clinical Registries, Institute of Heart Diseases, Wrocław Medical University, Wroclaw, Poland; Institute of Heart Diseases, University Hospital in Wrocław, Wroclaw, Poland; [12]Alnylam Pharmaceuticals, Cambridge, MA, US; [13]National Amyloidosis Centre, University College London, Division of Medicine, Royal Free Hospital, London, UK

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Declaration of Interests for Mathew Maurer, MD

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Introduction

Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM)

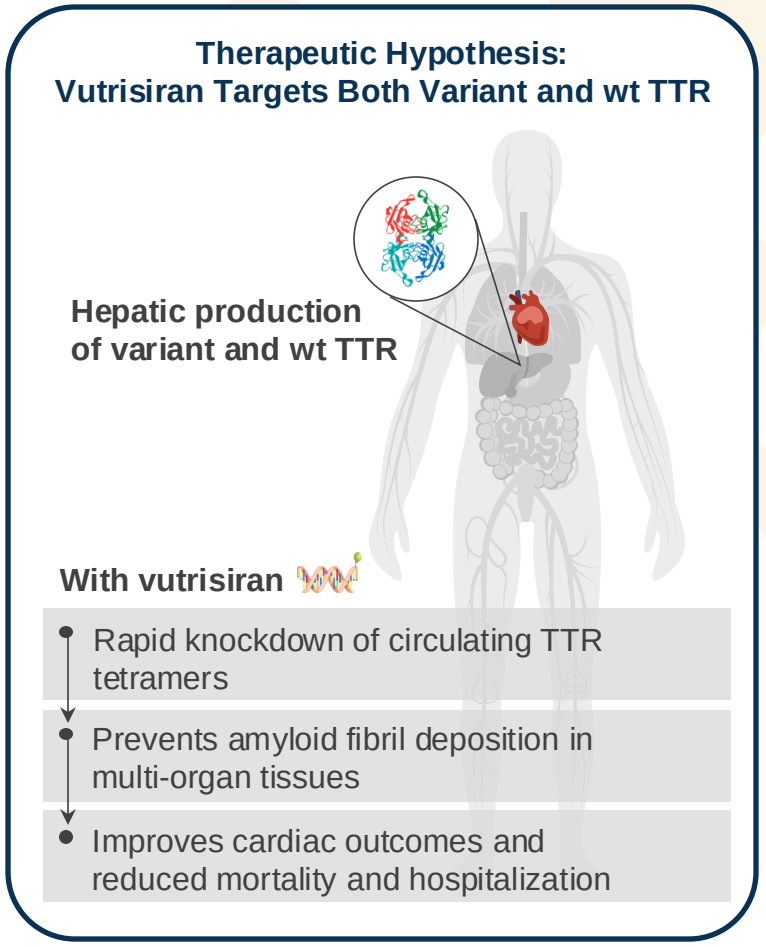
- Results from accumulation of wild-type or variant TTR amyloid fibrils in the heart[1–5]
- Ongoing TTR amyloid deposition causes worsening heart failure, arrhythmias, loss of functional capacity and QOL, hospitalizations, and reduced survival[6–10]
- Rising levels of NT-proBNP or troponin I have been associated with an increased risk of cardiovascular events and mortality in patients with ATTR-CM[11,12]
- Contemporary patients have less advanced disease because of earlier diagnosis and improved heart failure management. Many receive tafamidis, SGLT2 inhibitors, and diuretics[12]

HELIOS-B Study

- Evaluated vutrisiran, a SC-administered RNAi therapeutic (quarterly dosing), in patients with ATTR-CM in a Phase 3, randomized, placebo-controlled trial[13]

Objectives

- Evaluate the association of increased cardiac biomarker NT-proBNP and troponin I on later risk of cardiac outcomes and mortality
- Determine the effect of vutrisiran on cardiac biomarkers over time



Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; QOL, quality of life; RNAi, RNA interference; SC, subcutaneous; SGLT2, sodium-glucose cotransporter 2; TTR, transthyretin; wt, wild-type. **References:** 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 4. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Castano et al. *Heart Fail Rev* 2015;20:163–78; 7. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 8. Lane et al. *Circulation* 2019;140:16–26; 9. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875–84; 10. Gillmore et al. *Eur Heart* J 2018;39:2799–806; 11. Ioannou et al. *J Am Coll Cardiol* 2024;83:1276–91; 12. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:895–905; 13. Fontana et al. *N Engl J Med* 2024. DOI:10.1056/NEJMoa2409134. Epub ahead of print.

HELIOS-B Study Design

A phase 3 study to evaluate vutrisiran in patients with ATTR-CM

Patient Population (n=655)

- ATTR: Wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III; 6-MWT ≥150 m; NT-proBNP limits[b] at baseline
- Approximately 40% of patients on tafamidis at baseline

Select Exclusion Criteria:

- NYHA Class IV HF
- PND score ≥III at the screening visit
- Received prior TTR-lowering treatment

➢ *All endpoints were prespecified for analysis separately in the **Overall** and **Monotherapy** populations*

Primary Endpoints

- Composite outcome of ACM and recurrent CV events during double blind (DB) period (Months 33–36)

Secondary Endpoints

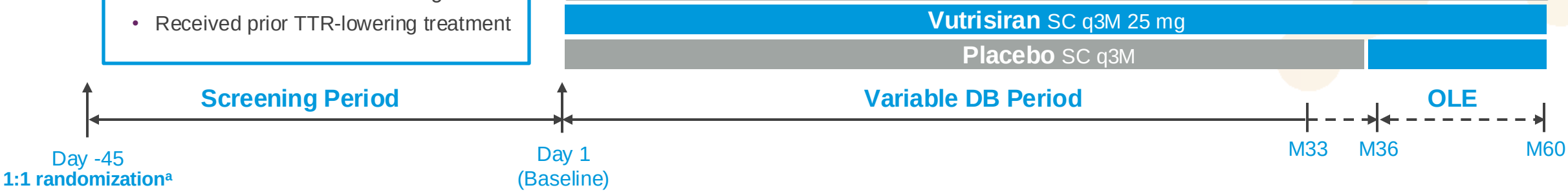
- Change from baseline in 6-MWT, KCCQ-OS, ACM through 42 months, NYHA Class

Select Exploratory Endpoints

- NT-proBNP to Month 30
- Troponin I to Month 30[c]

Additional Analyses

- Risk of primary composite outcome and ACM, based on baseline levels of and increases from baseline at Month 6 in NT-proBNP or troponin



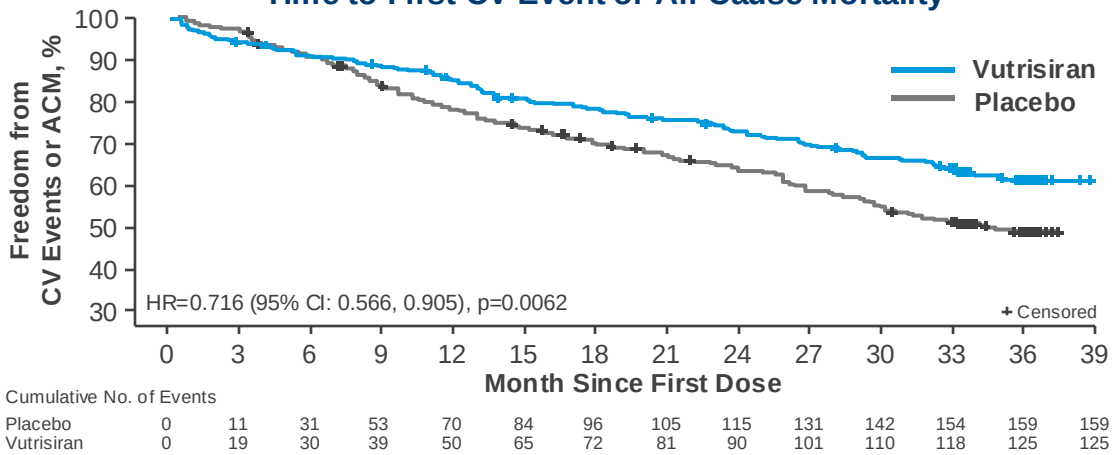
- **Tafamidis:** Baseline ~40% in both treatment arms; drop-in during DB ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors:** Baseline ~3% in both treatment arms; drop-in during DB ~35% and ~31% for placebo and vutrisiran, respectively
- **Substantial use of diuretics:** Baseline ~80% in both treatment arms; Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

[a]Randomization was stratified according to the use of tafamidis at baseline (yes vs no), ATTR disease type (hATTR vs wtATTR),and NYHA Class and age at baseline (NYHA Class I or II and age <75 years vs all others). [b]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation). [c]Troponin I levels were measured as hs-troponin I. **Abbreviations:** 6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; DB, double-blind; hATTR, hereditary ATTR; HF, heart failure; hs, high-sensitivity; M, Month; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; SGLT2, sodium-glucose cotransporter 2; TTR, transthyretin; wtATTR, wild-type ATTR. **Reference:** Clinicaltrials.gov identifier: NCT04153149.

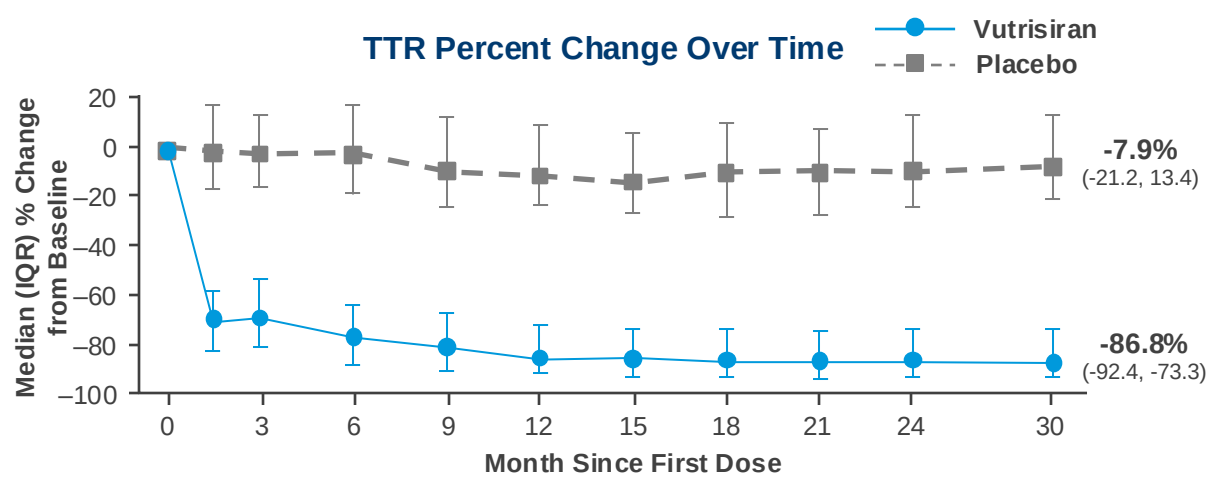
HELIOS-B Met All 10 Primary and Secondary Endpoints in the Overall and Monotherapy Populations

HELIOS·B

Time to First CV Event or All-Cause Mortality[a,b]



TTR Percent Change Over Time



TTR % change at Month 30: Mean (SD): placebo -1.98 (35.4); vutrisiran -80.98 (16.1)

Endpoint	Treatment Effect Estimation	Overall Population (N=654) Treatment Effect	Overall Population (N=654) p-value	Monotherapy Population (N=395) Treatment Effect	Monotherapy Population (N=395) p-value
Primary endpoint Composite outcome of all-cause mortality and recurrent CV events[c,d]	Hazard ratio	**0.718**	**0.0118**	**0.672**	**0.0162**
Secondary endpoints					
6-MWT change at Month 30[e]	LS Mean difference	**26.46**	**0.00008**	**32.09**	**0.0005**
KCCQ-OS change at Month 30[e]	LS Mean difference	**5.80**	**0.0008**	**8.69**	**0.0003**
All-cause mortality through Month 42[b]	Hazard ratio	**0.645**	**0.0098**	**0.655**	**0.0454**
NYHA class: % stable or improved at Month 30[f]	Adjusted % difference	**8.7%**	**0.0217**	**12.5%**	**0.0121**

- **Vutrisiran met all 10 primary and secondary endpoints**
- **Rapid and durable TTR knockdown through Month 30**
- **Knockdown comparable to prior studies with vutrisiran**

[a]Based on IPTW-adjusted Kaplan-Meier curves. [b]HR derived from Cox PH model, p-value derived from log-rank test. [c]Primary analysis based on the modified Andersen-Gill model, also known as LWYY. [d]Assessed at 33–36 months. [e]Based on a MMRM model. [f]Based on CMH method. From *N Engl J Med*, Fontana et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. DOI: 10.1056/NEJMoa2409134. Epub ahead of print. Copyright © (2024). Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. **Abbreviations:** CV, cardiovascular; 6-MWT, 6-minute walk test; IQR, interquartile range; KCCQ-OS, Kansas City cardiomyopathy questionnaire – Overall Summary; LS, least squares; NYHA, New York Heart Association. **Reference:** Fontana et al. *N Eng J Med* 2024. DOI: 10.1056/NEJMoa2409134. Epub ahead of print.

NT-proBNP and Troponin I Are Well-Established Prognostic Biomarkers of Increased Mortality in ATTR-CM[1–3]

In HELIOS-B, baseline levels and changes from baseline as early as Month 6 were likewise associated with risk of adverse outcomes

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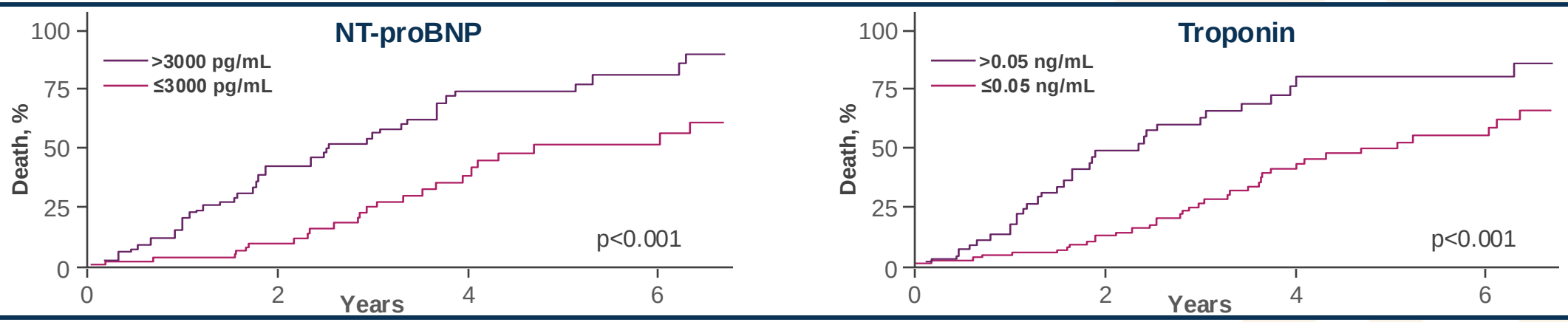
Mayo Clinic[1]



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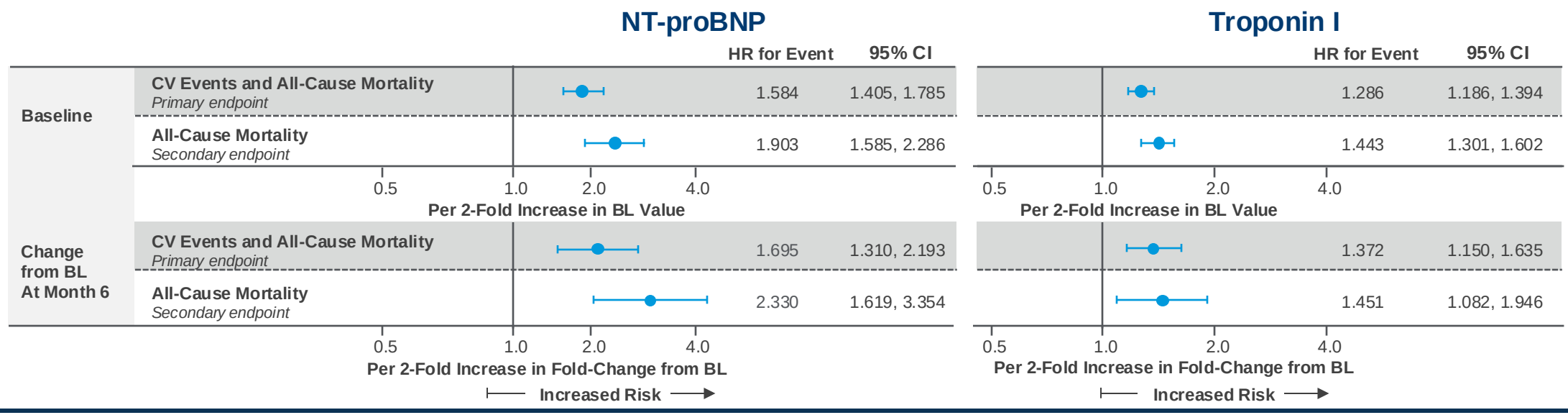


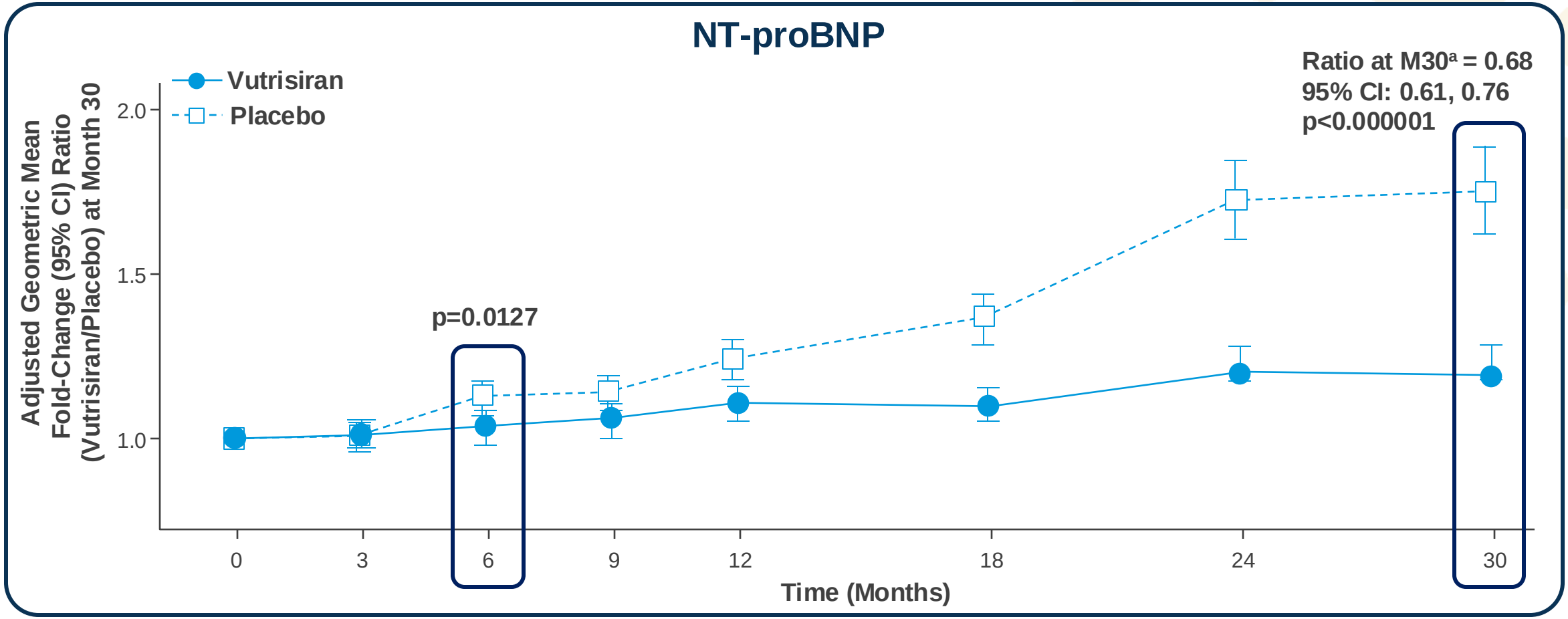
Survival curves (top panel) reprinted from Grogan et al. *J Am Coll Cardiol* 2016; 68:1014–20 with permission from Elsevier. All-cause mortality includes heart transplantation and left ventricular assist device placement. HRs for the primary endpoint are based on the modified Andersen-Gill model with a robust variance estimator. HRs for the secondary endpoint are based on the Cox model. For baseline analysis, the log-transformed baseline biomarker is the only covariate. For Month 6 analysis, the covariates includes base 2 log-transformed baseline biomarker and change from baseline in base 2 log-transformed biomarker. Each model is stratified by treatment group and baseline tafamidis use. Patients are censored at the end of the double-blind period. **Abbreviations:** CI, confidence interval; CV, cardiovascular; HR, hazard ratio; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide. **References:** 1. Grogan et al. *J Am Coll Cardiol* 2016; 68:1014–20; 2. Damy et al. *Amyloid* 2016;23:194–202; 3. Kristen et al. *PLoS One* 2017;12:e0173086.

Vutrisiran Maintained Stability of NT-proBNP Compared with Placebo

Favorable treatment effect on NT-proBNP compared with placebo observed as early as 6 months, and growing over time; 32% relative reduction at Month 30

HELIOS-B

Overall Population



[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.

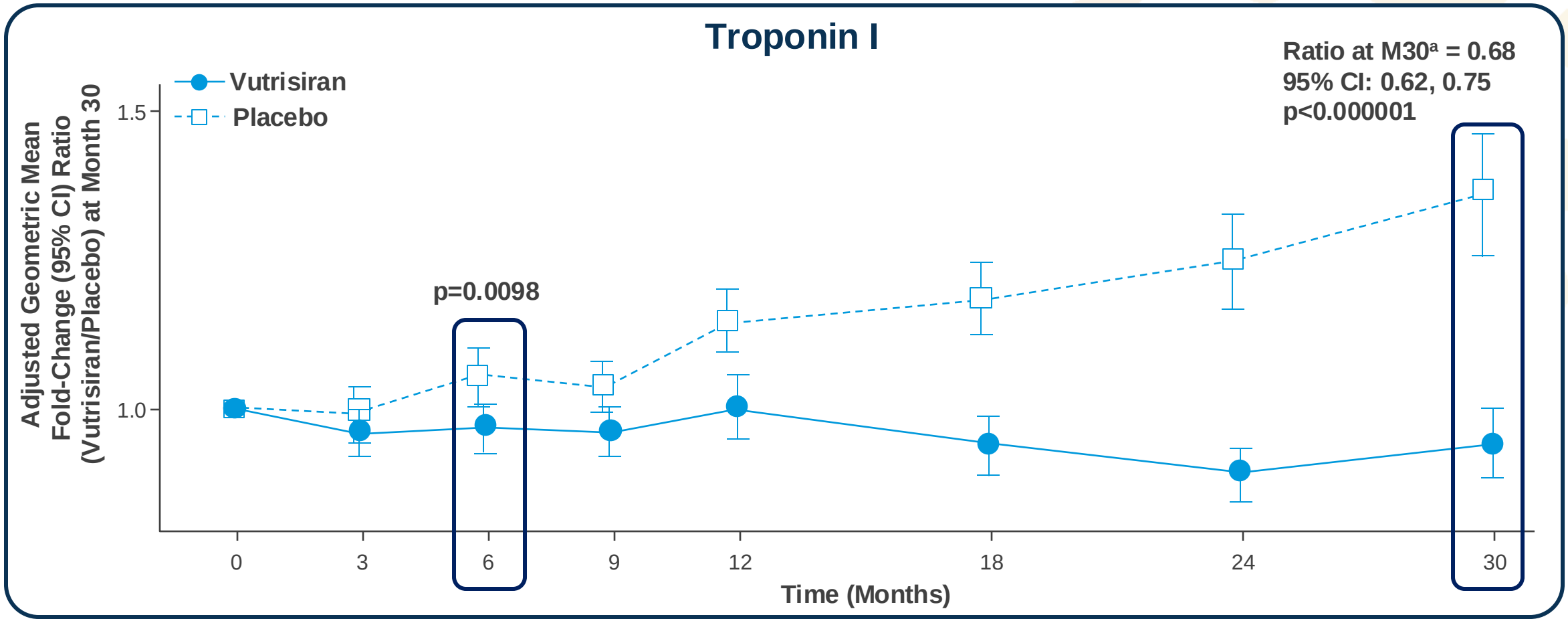
Abbreviations: BL, baseline; CI, confidence interval; LS, least squares; M, Month; MMRM, mixed models for repeated measures.

Vutrisiran Maintained Stability of Troponin I Compared with Placebo

Favorable treatment effect on troponin I compared with placebo observed as early as 6 months, and growing over time; 32% relative reduction at Month 30

HELIOS-B

Overall Population

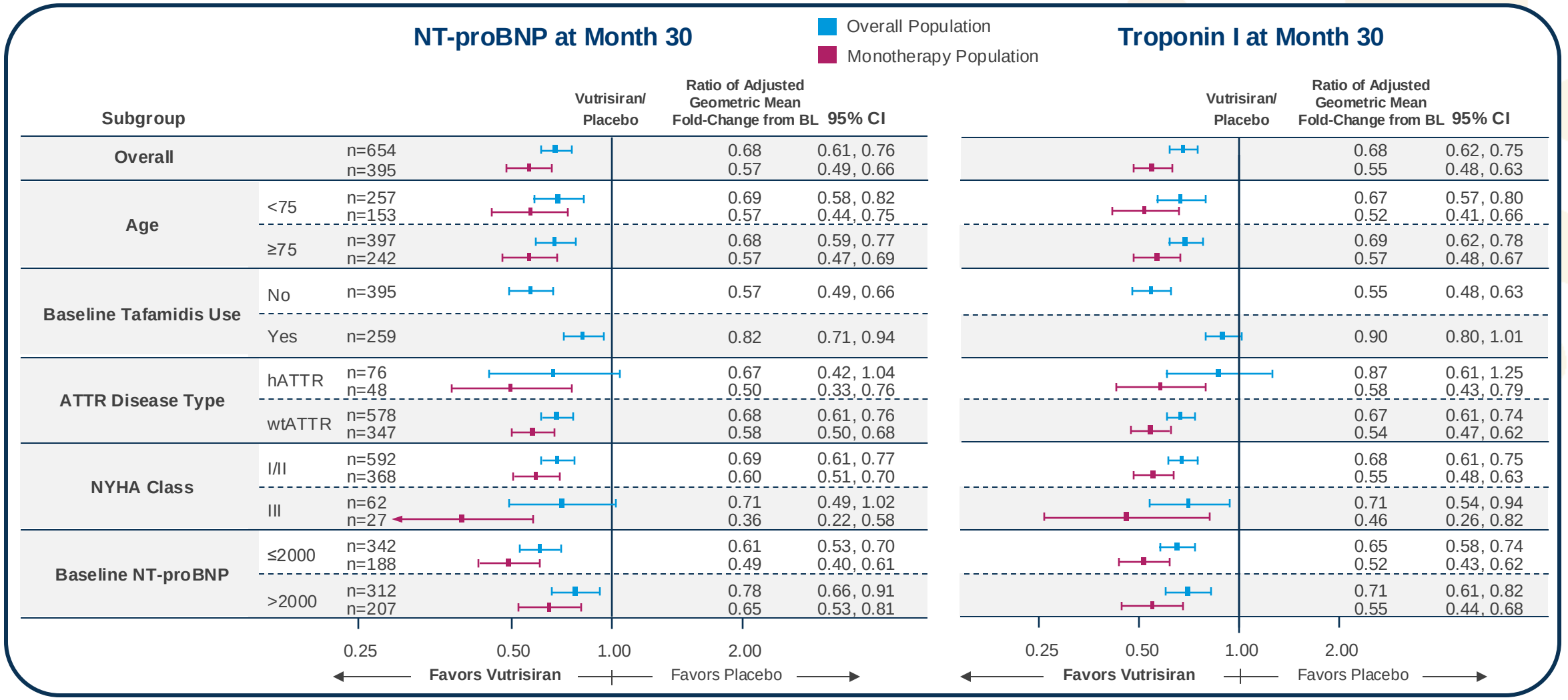


[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.

Abbreviations: BL, baseline; CI, confidence interval; LS, least squares; M, Month; MMRM, mixed models for repeated measures.

Beneficial Effect of Vutrisiran on NT-proBNP and Troponin I was Consistent in All Prespecified Subgroups

HELIOS-B



For all subgroups, results are based on subgroup data only from MMRM with change from baseline in log-transformed biomarker as the outcome, log-transformed baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. For baseline tafamidis subgroup, the model also includes type of ATTR and age group but excludes baseline tafamidis use term. For patients in the vutrisiran monotherapy group with tafamidis drop-in during the study, data collected after tafamidis drop-in are excluded from analysis.

Abbreviations: ATTR, transthyretin amyloidosis; BL, baseline; CI, confidence interval; hATTR, hereditary transthyretin amyloidosis; MMRM, mixed models for repeated measures; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; wtATTR, wild-type transthyretin amyloidosis.

Improvement in NT-proBNP and Troponin I Compared with Placebo with Vutrisiran Monotherapy

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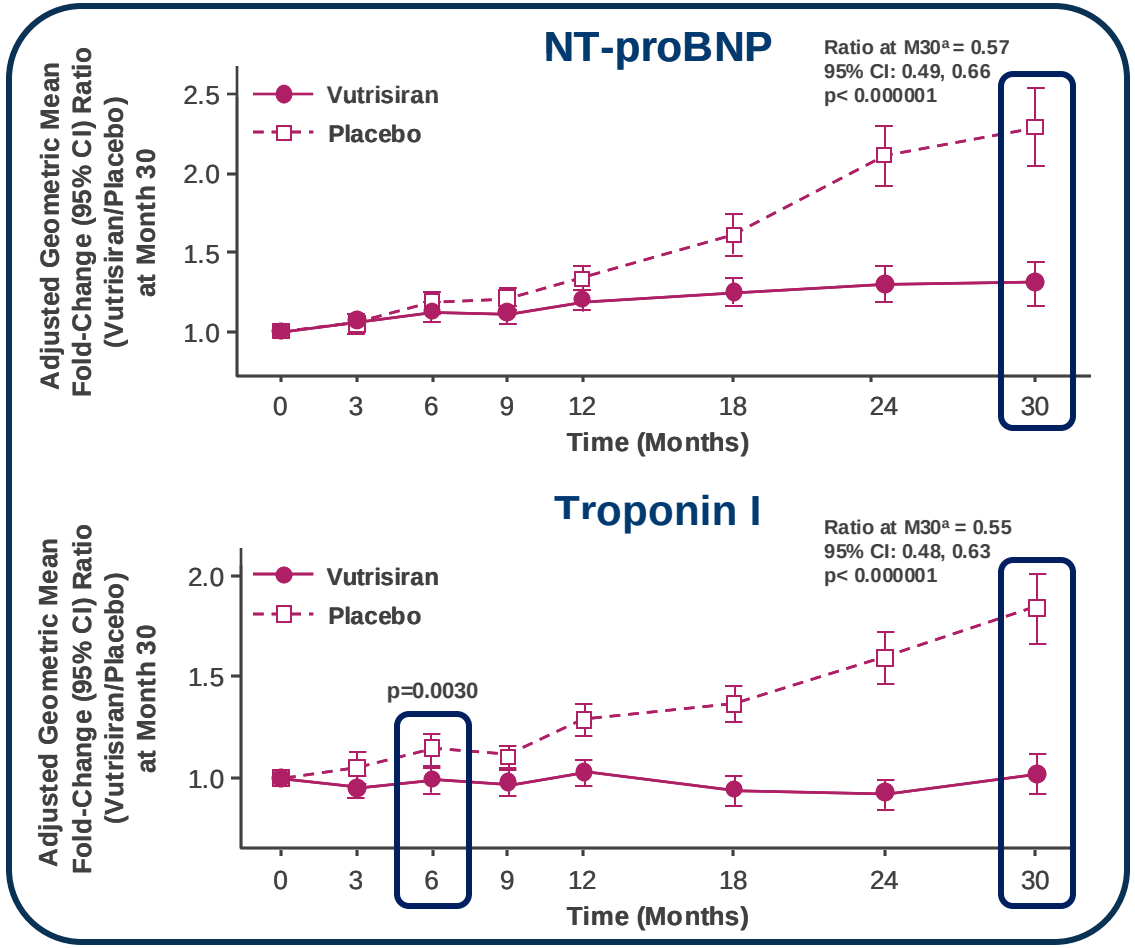
MONOTHERAPY POPULATION



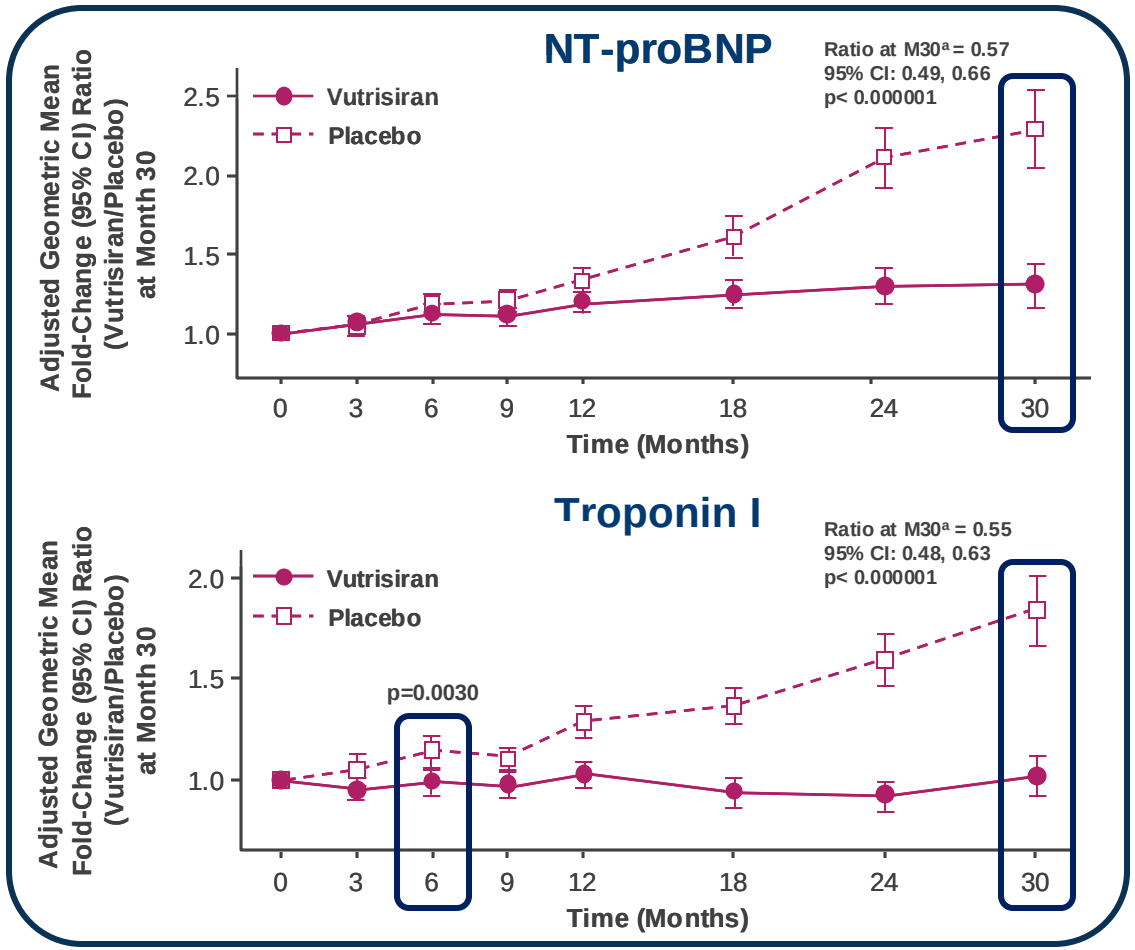
Relative reduction with vutrisiran of 43% and 45% at M30 for NT-proBNP and troponin I vs placebo, respectively

[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP or troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP or troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. In the vutrisiran monotherapy subgroup, terms related to baseline tafamidis use are removed from the model.

Abbreviations: BL, baseline; CI, confidence interval; LS, least squares; M, Month; MMRM, mixed models for repeated measures; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

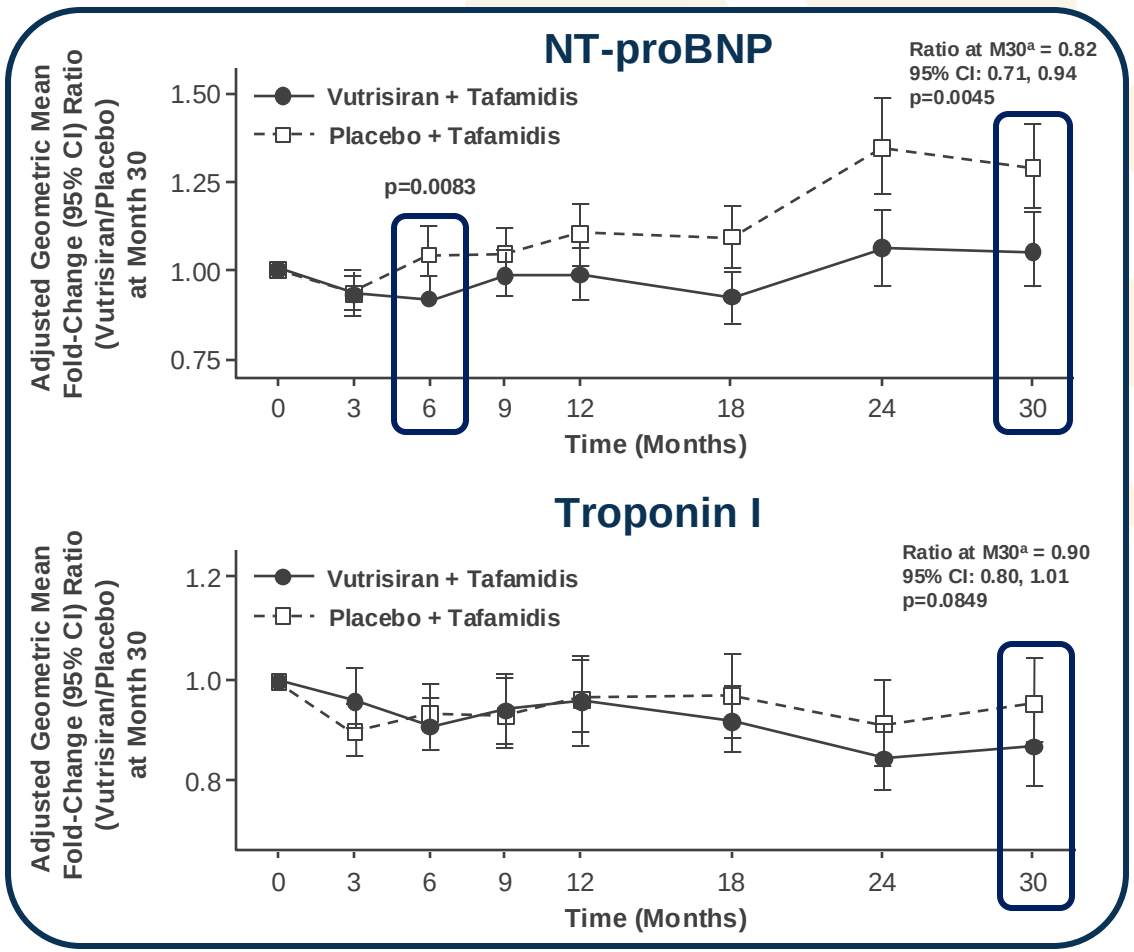
Improvement in NT-proBNP and Troponin I Compared with Placebo with Vutrisiran Monotherapy, and on Top of Tafamidis

Monotherapy Population



Relative reduction with vutrisiran vs placebo of 43% and 45% at M30 for NT-proBNP and troponin I, respectively

Baseline Tafamidis Subgroup



On top of tafamidis, relative reduction with vutrisiran vs placebo of 18% and 10% at M30 for NT-proBNP and troponin I, respectively

[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP or troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP or troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. In the vutrisiran monotherapy subgroup, terms related to baseline tafamidis use are removed from the model.

Abbreviations: BL, baseline; CI, confidence interval; LS, least squares; M, Month; MMRM, mixed models for repeated measures; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide..

Vutrisiran Maintained Long-Term Stability of NT-proBNP and Troponin I

Effects of vutrisiran on cardiac biomarkers are consistent with benefits on CV events and all-cause mortality

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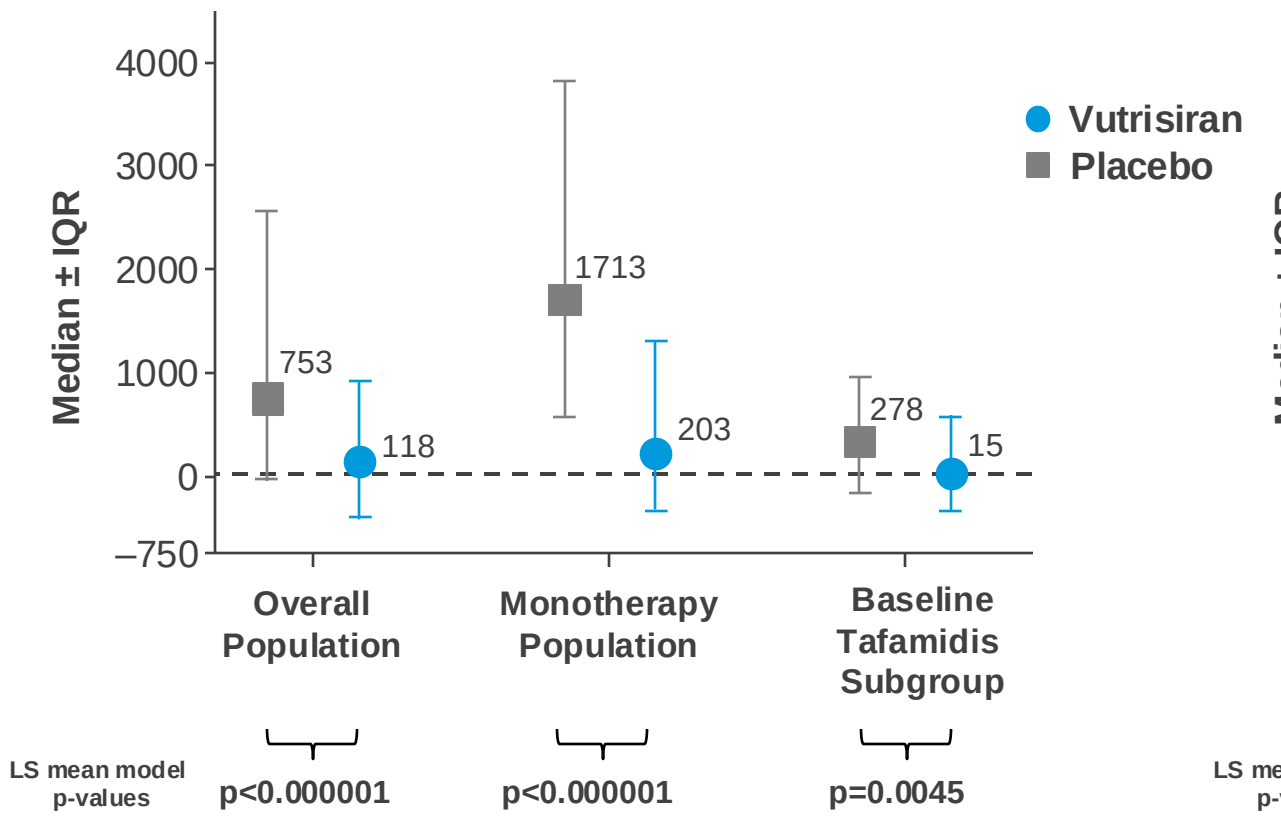

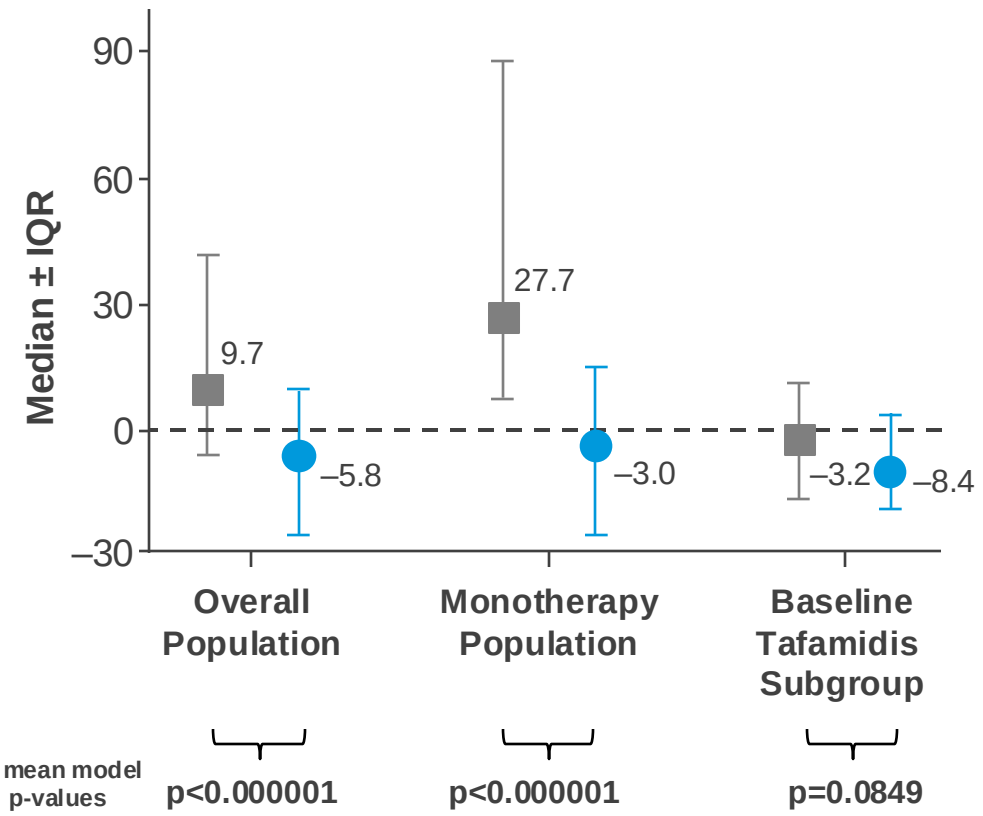

Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP or troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP or troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. In the vutrisiran monotherapy subgroup, terms related to baseline tafamidis use are removed from the model. **Abbreviations**: CV, cardiovascular; IQR, interquartile range; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Summary

For US HCPs Only

- Vutrisiran rapidly knocked down TTR, lowered risk of all-cause mortality and CV events compared with placebo, and preserved functional capacity and quality of life in a contemporary population with ATTR-CM, including substantial use of background therapy
- Vutrisiran maintained stability of NT-proBNP and troponin I, both well-established prognostic biomarkers of increased mortality in ATTR-CM
- The treatment effect of vutrisiran on NT-proBNP and troponin I was observed as early as 6 months and increased over time
- Results were consistent across all prespecified subgroups
  - Larger treatment effect observed in vutrisiran monotherapy
  - Evidence of added benefit on top of tafamidis
- Acceptable safety and tolerability profile, as previously established

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

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Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; hs, high-sensitivity; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; TTR, transthyretin.