Primary Results from HELIOS-B, a Phase 3 Study of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

Funded by Alnylam Pharmaceuticals

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Declaration of Interest

Dr. Fontana reports consultancy/advisory boards for Alnylam, Alexion/Caelum Biosciences, Astrazeneca, Bridgbio/Eidos, Prothena, Attralus, Intellia Therapeutics, Ionis Pharmaceuticals, Cardior, Lexeo Therapeutics, Janssen Pharmaceuticals, Prothena, Pfizer, Novonordisk.

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HELIOS-B: Take Home Points

- Vutrisiran achieved statistical significance on primary and all secondary endpoints in both overall and monotherapy populations
- Vutrisiran demonstrated profound and unequivocal benefits on CV outcomes (including mortality) and disease progression in a contemporary patient population who were also receiving multiple effective therapies, including tafamidis, SGLT2 inhibitors, and diuretics
- Vutrisiran maintained functional capacity, health status, quality of life, and NT-proBNP, all measures of disease progression
- Consistent efficacy seen across all patient subgroups, including patients on baseline tafamidis
- Particularly large effects seen in patients with early disease, highlighting the need to begin most effective treatment as early as possible
- If approved by regulators, data support vutrisiran as the new standard of care for patients with ATTR-CM: as first-line for newly diagnosed patients, and as a switch or add-on therapy in patients progressing on a stabilizer

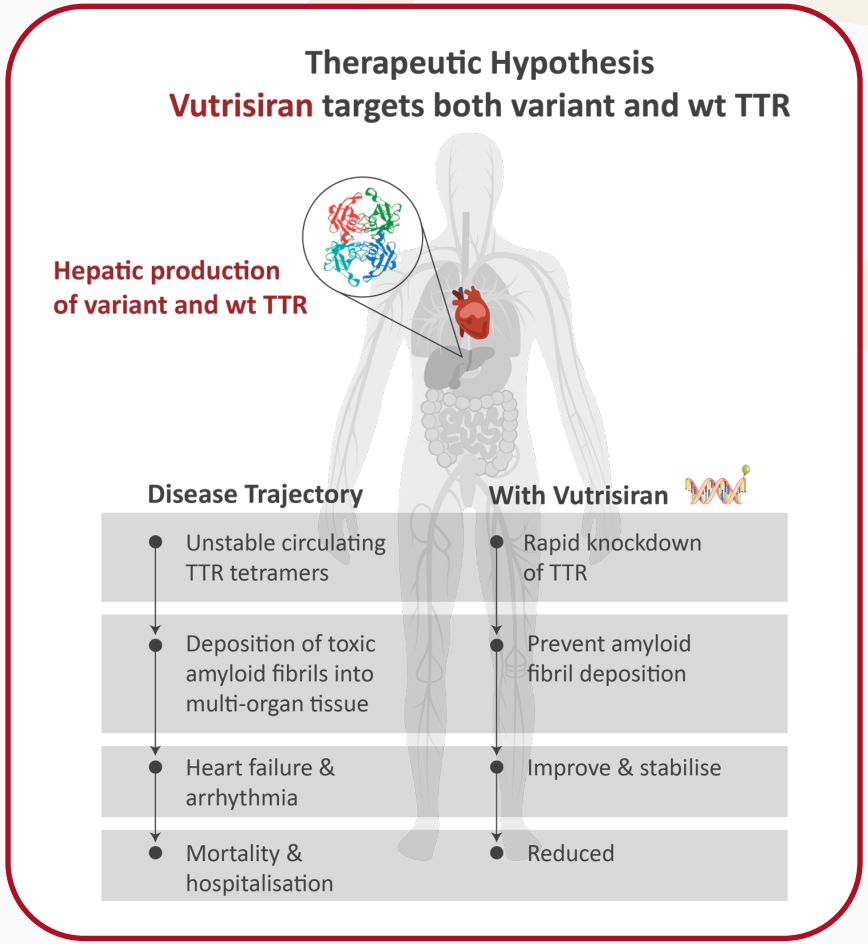
Introduction

ATTR Cardiomyopathy

- Results from accumulation of wild type or variant TTR amyloid fibrils in the heart[1-5]
- Leads to progressive heart failure, arrhythmias, declines in functional status and QOL, increased hospitalisations and reduced survival[6–10]
- Evolution toward earlier diagnosis and improved HF management; contemporary patients have less advanced disease, and are managed with tafamidis, SGLT2 inhibitors, and diuretics

HELIOS-B study

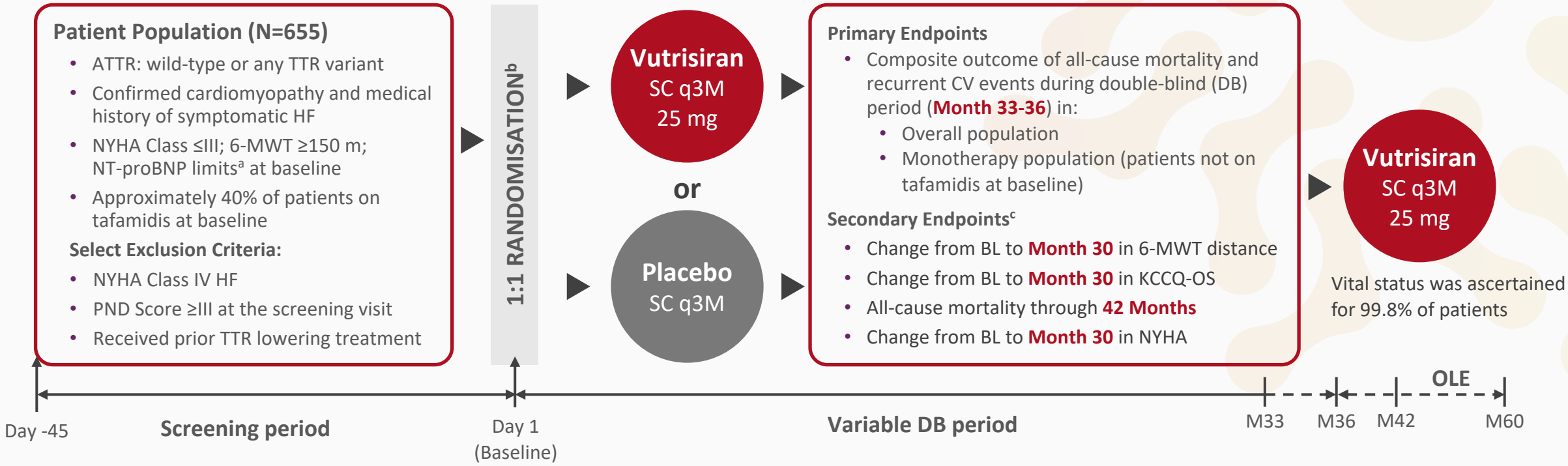
- Evaluated vutrisiran, a SC administered RNAi therapeutic (quarterly dosing)
- Objective: Establish efficacy and safety in a contemporary ATTR-CM patient population



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. Swiecicki et al. *Amyloid* 2015;22:123–31; 8. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 9. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 10. Gertz et al. *Mayo Clin Proc* 1992;67:428–40.
Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HF, heart failure; QOL, quality of life; RNAi, RNA interference; SC, subcutaneous; SGLT2, sodium/glutamate cotransporter 2; TTR, transthyretin; wt TTR, wild-type transthyretin.

HELIOS-B Study Design

A randomised, double-blind outcomes study in ATTR amyloidosis patients with cardiomyopathy



[a]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation).
[b]Randomisation was stratified according to the use of tafamidis at baseline (yes versus no), ATTR disease type (ATTRv or ATTRwt), and NYHA class and age at baseline (NYHA class I or II and age <75 years versus all others).
[c]Assessed in the overall population and monotherapy population as separate endpoints.

- Baseline characteristics were generally balanced between arms and consistent across populations
- This was a contemporary population with substantial use of background medications (drop-in allowed)
- Vital status was ascertained for 99.8% of patients

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; BL, baseline; CV, cardiovascular; DB, double-blind; HF, heart failure; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; OLE, open label extension; PND, polyneuropathy disability; SC, subcutaneous; q3M, every 3 months; TTR, transthyretin.
References: Clinicaltrials.gov identifier: NCT04153149

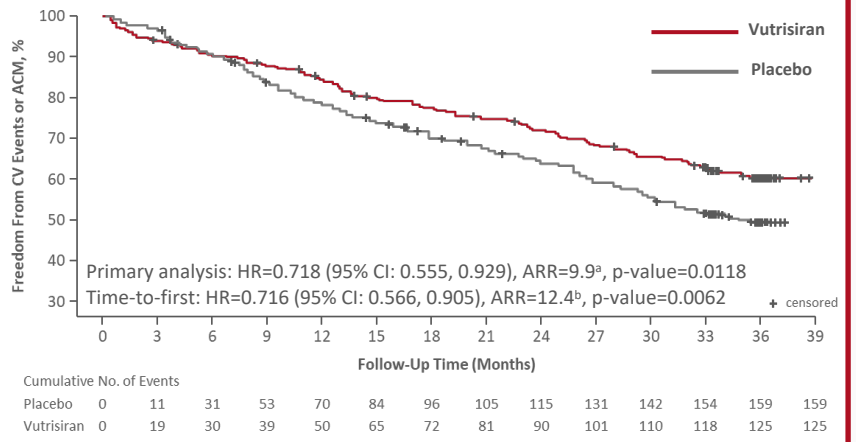
HELIOS-B Results

Vutrisiran met all 10 primary and secondary endpoints, in both overall and monotherapy populations

OVERALL POPULATION

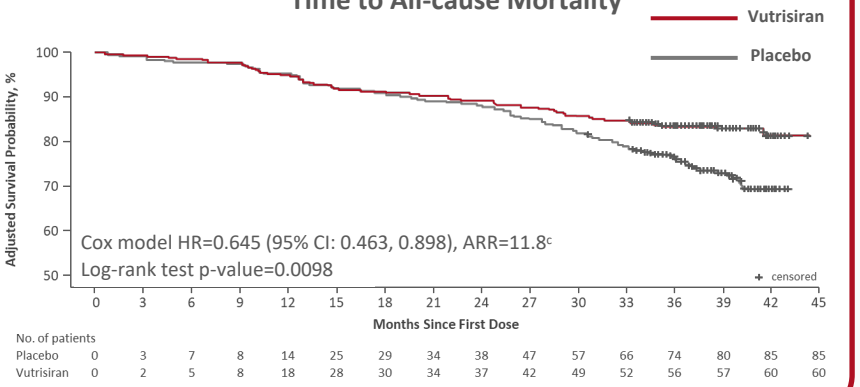
Primary Composite Endpoint

Time to First CV Event or All-cause Mortality

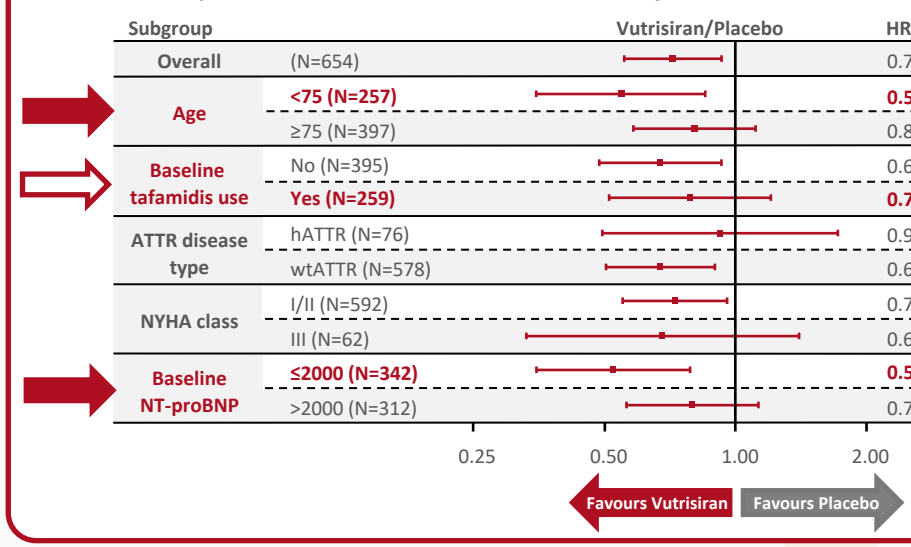


Secondary Endpoint

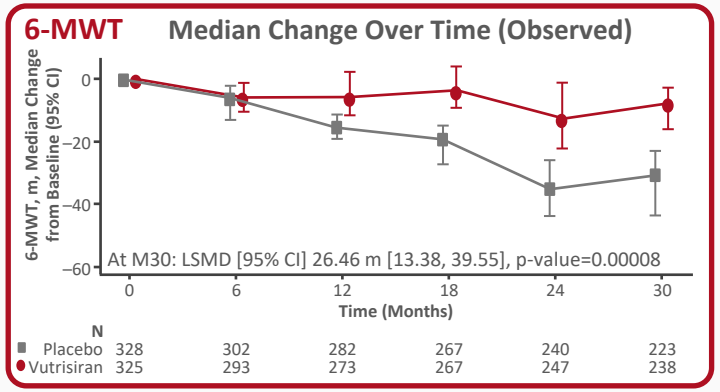
Time to All-cause Mortality



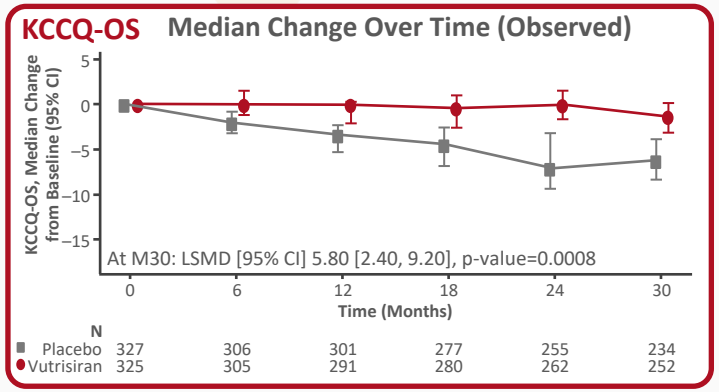
Composite Outcome of All-Cause Mortality and Recurrent CV Events



6-MWT Median Change Over Time (Observed)



KCCQ-OS Median Change Over Time (Observed)



Vutrisiran showed acceptable safety and tolerability profiles, as previously established

[a]ARR for primary analysis (difference in composite event rate per 100 patient-years); [b]ARR for time-to-first event (difference at Month 36); [c]ARR for all-cause mortality (difference in mortality rate at Month 42).

Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; ARR, absolute risk reduction; ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; DB, double-blind; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary score; LS, least squares; LSMD, least squares mean difference; NYHA, New York Heart Association; M, month; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide.

Conclusions

Vutrisiran achieved statistical significance on primary and all secondary endpoints

- Reduced all-cause mortality and recurrent CV events in a contemporary population with ATTR-CM, including substantial use of background therapy
- Demonstrated significant benefit on multiple clinical measures of disease progression, as well as NT-proBNP
- Results consistent across all prespecified subgroups, including patients on vutrisiran monotherapy and those on background tafamidis
- Safety and tolerability profile consistent with the established profile for vutrisiran. Rates of AEs, serious AEs, severe AEs, and AEs leading to study drug discontinuation were similar between the vutrisiran and placebo arms
- If approved by regulators, vutrisiran has the potential to become the standard of care for newly diagnosed patients and those progressing on stabilising therapies

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Abbreviations: AE, adverse event; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide.