EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2025
EMA/CHMP/177587/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Amvuttra

International non-proprietary name: Vutrisiran

Procedure No. EMEA/H/C/005852/II/0015

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
6-MWT	6-minute walk test
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
APOLLO	ALN-TTR02-004 pivotal Phase 3 study of patisiran in patients with hATTR amyloidosis with polyneuropathy
APOLLO-B	ALN-TTR02-011 Phase 3 study of patisiran in patients with ATTR amyloidosis with cardiomyopathy
AST	Aspartate aminotransferase
ATTR amyloidosis	Transthyretin-mediated amyloidosis
ATTR-ACT	Phase 3 study of tafamidis in patients with ATTR amyloidosis with cardiomyopathy
ATTRibute-CM	Phase 3 study of acoramidis in patients with ATTR amyloidosis with cardiomyopathy
C_{4h}	Plasma concentrations 4 hour postdose
CEC	Clinical Events Committee
CI	Confidence interval
CM	Cardiomyopathy
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
DB	Double-blind
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End of Phase 2
EU	European Union
FDA	Food and Drug Administration
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
hATTR amyloidosis	Hereditary ATTR amyloidosis
HELIOS-A	ALN-TTRSC02-002 Phase 3 study of vutrisiran in patients with hATTR amyloidosis with polyneuropathy
HELIOS-B	ALN-TTRSC02-003 Phase 3 study of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy
HF	Heart failure
HR	Hazard ratio
IPTW	Inverse Probability of Treatment Weighting

Abbreviation	Definition
ISR	Injection site reaction
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	KCCQ Overall Summary
LFT	Liver function test
LS	Least square
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model repeated measures
mRNA	Messenger RNA
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OLE	Open-Label Extension
PASS	Post-authorization safety study
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
q3M	Once every 3 months
QTcF	QT corrected using Fridericia's formula
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT2	Sodium-glucose cotransporter 2
siRNA	Small interfering RNA
SMQ	Standardized MedDRA Query
SOC	System organ class
TTR	Transthyretin
ULN	Upper limit of normal
US	United States
wt	Wild-type
wtATTR amyloidosis	Wild-type ATTR amyloidosis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alnylam Netherlands B.V. submitted to the European Medicines Agency on 15 October 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of wild-type or hereditary transthyretin-mediated amyloidosis in adult patients with cardiomyopathy (ATTR-CM), based on primary analysis results from study HELIOS-B (ALN-TTRSC02-003); a Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. An updated version 1.3 of the RMP has also been submitted. As part of the application the MAH applied for +1 year of additional market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Amvuttra, was designated as an orphan medicinal product (EMA/OD/019/18) on 25 May 2018 in the following indication:

Treatment of transthyretin-mediated amyloidosis

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Amvuttra as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/amvuttra

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s)

(EMEA-002425-PIP01-18 – P/0015/2019) on the granting of a product-specific waiver covering all subsets of the paediatric population (0 to 18 years).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

The Marketing Authorisation Holder (MAH) decided to withdraw the request for an additional year of market protection in accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004. Accordingly, a withdrawal letter in this regard was sent to the EMA Product Lead for this procedure of AMVUTTRA on 14 February 2025.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 20 May 2021 (EMA/SA/0000055285), 27 June 2019 (EMEA/H/SA/3876/2/2019/PA/II) and 24 March 2022 (EMA/SA/0000071629). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Fátima Ventura

Timetable	Actual dates
Submission date	15 October 2024
Start of procedure:	2 November 2024
CHMP Rapporteur's preliminary assessment report circulated on	2 January 2025
PRAC Rapporteur's assessment report circulated on	6 January 2025
PRAC members comments	8 January 2025
CHMP Co-Rapporteur's comments circulated on	13 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur(s) (Joint) assessment report circulated on	23 January 2025
Request for supplementary information (RSI) adopted by the CHMP on:	30 January 2025
Withdrawal of request for one-year extra market protection	14 February 2025
MAH's responses submitted to the CHMP on:	24 February 2025
CHMP and PRAC Rapporteur's joint assessment report assessment report on the MAH's responses circulated on:	31 March 2025

Timetable	Actual dates
PRAC members comments	2 April 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur Assessment Report	17 April 2025
CHMP Opinion	25 April 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Transthyretin-mediated amyloidosis is a rapidly progressive, multisystem, debilitating, and ultimately fatal disease encompassing wtATTR and hATTR amyloidosis. Wild-type ATTR amyloidosis is associated with aging, and hATTR amyloidosis results from genetic variants in the TTR gene. Progressive, chronically debilitating morbidity and mortality are caused by the deposition of TTR as amyloid in various organs and tissues, including the heart, peripheral nerves, and the gastrointestinal (GI) tract. The most common manifestations of ATTR amyloidosis are cardiomyopathy and polyneuropathy.

Vutrisiran (AMVUTTRA®) is a ribonucleic acid interference (RNAi) therapeutic designed to suppress production of both variant and wild-type TTR in the liver and was approved by the European Commission on 15 September 2022 for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

State the claimed the therapeutic indication

Current approved therapeutic indication:
"Amvuttra is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy."

Proposed new additional ATTR-CM indication:
Within this procedure the MAH applies for an extension of the indication as follows:

Amvuttra is indicated for the treatment of hereditary transthyretin ~~-mediated~~ amyloidosis ~~(hATTR amyloidosis)~~ in adult patients with stage 1 or stage 2 polyneuropathy (hATTR-PN).

Amvuttra is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

Epidemiology and risk factors, screening tools/prevention

Variant transthyretin amyloid cardiomyopathy (ATTRv-CM) is thought to be present in over 40,000 persons worldwide. The prevalence of wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) has been more difficult to estimate accurately but is increasing, due to an evolving diagnostic landscape (including enhanced disease awareness and the broadening availability of a non-invasive diagnostic methods like scintigraphy with technetium 99m). Recent estimates found ATTR-CM to be the etiology in up to 13% of an otherwise unselected population of patients presenting with heart failure and preserved ejection fraction.

Biologic features, aetiology and pathogenesis

The mechanisms underlying the pathophysiology of ATTRwt and its association with aging are currently poorly understood. In contrast, for ATTRv, more than 120 intrinsically destabilizing TTR gene variants have been identified that are transmitted in an autosomal dominant fashion. V122I is the most common pathogenic variant found in the United Kingdom (UK) and in the United States (US), affecting 3% to 4% of people of Afro-Caribbean descent, with a variable documented penetrance and clinical expressivity. The V30M pathogenic variant was the first to be described and is most commonly found in three geographic locations demonstrating a founder effect. The clinical syndrome associated with the early onset V30M variant was initially described in Portugal in 1952 as Familial Amyloid Polyneuropathy, and subsequently in unrelated populations in Northeastern Sweden and Southwestern Japan, where the V30M variant displays an older age of disease onset than in Portugal. Also first described in Portugal was a highly stabilizing (~37-fold more stable than wild-type) variant (T119M) that protects V30M carriers (compound heterozygotes) from either developing or progressing the otherwise rapidly progressive polyneuropathy associated with V30M carriage.

Clinical presentation, diagnosis and stage/prognosis

Patients diagnosed with ATTR-CM tend to be male, on average 60 years old or older, and present with heart failure with preserved ejection fraction, often with cardiac conduction abnormalities (varying degrees of heart block) on an electrocardiogram (ECG), along with thickened ventricular walls, and evidence of diastolic dysfunction on echocardiogram. In addition, a carefully taken medical history might reveal prior bilateral carpal tunnel syndrome (without predisposing risk factors for that condition) or lumbar spinal stenosis in the prior 5 to 10 years.

Until recently, ATTR-CM was underdiagnosed due to non-specific signs and symptoms often mistakenly attributed to more common conditions and the need to perform an endomyocardial biopsy for specific diagnostic confirmation in the absence of any available treatment. However, the past 10 years have borne witness to a profound transformation of the disease landscape due to several critical advances: (1) diagnostic confirmation is now possible by non-invasive means including scintigraphy (with bone radiotracers) coupled with the exclusion of a monoclonal gammopathy consistent with amyloid light chain (AL) amyloidosis by serum and urine protein biochemistry; (2) a widespread, global engagement by professional societies, and advocacy organizations to raise awareness among cardiologists and the broader medical community has driven increasingly earlier recognition and diagnosis. Disease awareness has been driven in part by the recognition of so-called red flags, like a history of bilateral carpal tunnel syndrome, leading to an earlier diagnosis and subsequent treatment than was previously achieved. The availability of an approved treatment, tafamidis, that was shown to reduce mortality and CV-related hospitalizations by 30% and 32%, respectively, has contributed to this trend in earlier recognition of ATTR-CM as well. However, despite increased disease awareness, earlier specific diagnosis, and therapeutic advances, ATTR-CM remains an important, under-recognized cause of heart failure leading to excess mortality, CV morbidity, impaired physical function, and QoL.

Anticipating novel therapies in development that could alter the course of ATTR-CM, in 2021 an expert panel recommended a set of criteria to monitor disease progression. The assessments fall into three domains:

- Clinical and Functional domains: heart failure-related hospitalizations, New York Heart Association (NYHA) Classification, 6-Minute Walk Distance (6MWD), and Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Laboratory Biomarkers domain: N-terminal prohormone of brain natriuretic peptide (NT-proBNP), troponin I (TnI), and National Amyloidosis Centre (NAC) ATTR-CM disease staging
- Imaging (with imaging-based assessments of left ventricular [LV] structure or function) and ECG domains (conduction disturbances).

Management

Historically, the treatment of ATTR amyloidosis with cardiomyopathy has focused on palliative therapies directed at symptoms, such as diuretics for congestive symptoms and antiarrhythmic drugs, pacemakers, and automatic implantable cardioverter defibrillators for arrhythmias and conduction defects.
Center-based studies suggest that heart transplantation in ATTR amyloidosis with cardiomyopathy can be an effective option with outcomes similar to those transplanted for other causes of HF.[Barrett 2020; Razvi 2022] However, cardiac transplantation continues to be a less pursued option due to the need for lifelong immunosuppression and long waiting times associated with transplantation.

In regions such as the United States (US), European Union (EU), and Japan, the only approved treatment for cardiomyopathy in adult patients with wtATTR or hATTR amyloidosis is tafamidis, which acts by stabilising the tetrameric TTR protein and reducing its rate of dissociation into amyloidogenic monomers. Acoramidis has been approved in the US and has received a positive opinion by the CHMP in December 2024. All together there is still an unmet medical need for patients with ATTR amyloidosis with cardiomyopathy.

2.1.2. About the product

AMVUTTRA (vutrisiran) is a chemically stabilized double-stranded small interfering RNA (siRNA) that specifically targets variant and wild-type (wt) transthyretin (TTR) messenger RNA and is covalently linked to a ligand containing 3 N-acetylgalactosamine residues to enable delivery of the siRNA to hepatocytes. Based on the mechanism of RNA interference, vutrisiran is specifically designed to reduce the hepatic synthesis of variant and wt TTR protein. By reducing expression of TTR, vutrisiran ameliorates the signs and symptoms of transthyretin mediated amyloidosis (ATTR). Vutrisiran is categorized to the Anatomical Therapeutic Chemical Classification System group N07XX18 Other nervous system drugs.

The active moiety is vutrisiran, and the active ingredient is vutrisiran sodium. AMVUTTRA is supplied as a 0.5-mL solution containing 25 mg of vutrisiran in a single-use 1-mL prefilled syringe with a needle shield. The recommended dose of AMVUTTRA (vutrisiran) is 25 mg administered once every 3 months (q3M) by subcutaneous (SC) injection.

The drug product is approved for hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (hATTR -PN) and for the proposed new additional wild-type or hereditary ATTR-CM indication has the same formulation and presentation as commercial vutrisiran (AMVUTTRA®).

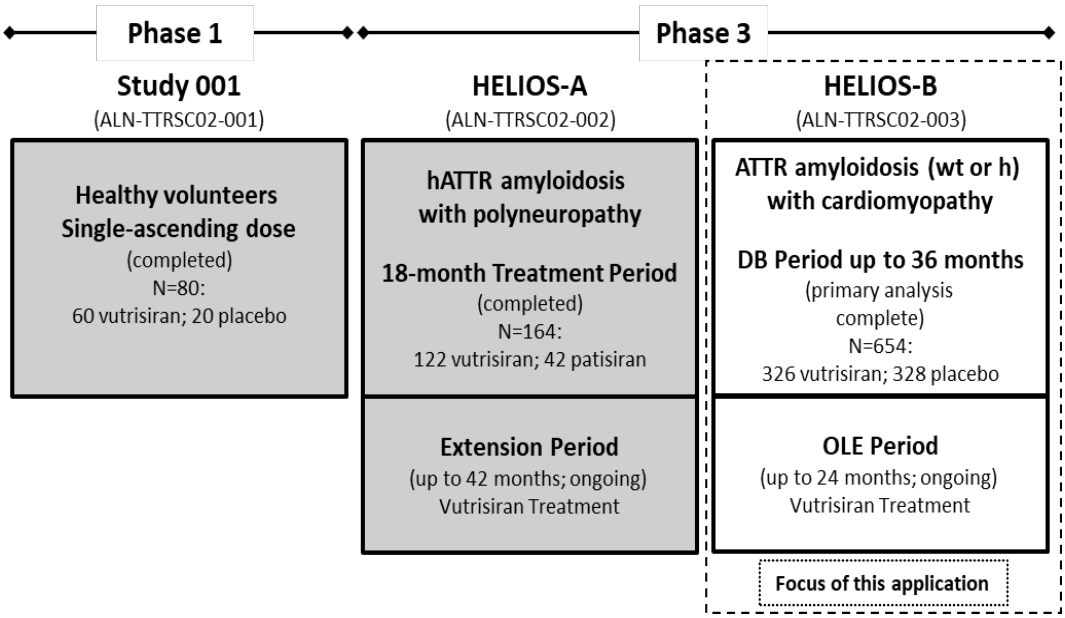
2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Vutrisiran (AMVUTTRA®) was approved by the European Commission on 15 September 2022 for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Vutrisiran has also been approved for this indication in a number of other countries/regions, including the US (for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults) and Japan (for the treatment of transthyretin familial amyloid polyneuropathy).

Vutrisiran is currently in clinical development for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). The primary efficacy data to support this proposed new additional ATTR-CM indication come from HELIOS-B, an ongoing, Phase 3, global, randomized, double-blind, placebo-controlled study of vutrisiran in patients with ATTR amyloidosis (hATTR or wtATTR) with cardiomyopathy, who were either not on tafamidis at baseline (vutrisiran monotherapy subgroup) or were receiving concomitant tafamidis at baseline per the inclusion criteria (background tafamidis subgroup). The results from the completed double-blind period and the ongoing open-label extension (OLE) period of HELIOS-B comprise the primary focus of this type II variation. The safety of vutrisiran has been established in HELIOS-B and across the vutrisiran clinical development program.

An overview of the vutrisiran clinical development program is presented below. The clinical program consists of a clinical pharmacology study in healthy volunteers (Study ALN-TTRSC02-001 [Study 001]), a Phase 3 study of patients with hATTR amyloidosis with polyneuropathy (HELIOS-A), and a Phase 3 study of patients with ATTR amyloidosis with cardiomyopathy (HELIOS-B).

Vutrisiran Clinical Development Program



2.1.4. General comments on compliance with GCP

All clinical studies included in this submission were claimed to be conducted and reported in accordance with the ethical principles originating from the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols. The study protocol of the pivotal study (HELIOS-B) was reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB) prior to commencement of the study.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment (ERA) in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

Vutrisiran is not a PBT substance as log Kow does not exceed 4.5.

The PECsurfacewater has been refined with prevalence data from the Orphan Designation EU/3/18/2026.

The PECsurfacewater value is below the action limit of 0.01 µg/L.

A Phase II environmental fate and effects analysis is not required.

Summary of main study results

Substance (INN/Invented Name): Vutrisiran			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	OECD107	< -2.9 at pH 7	Potential PBT N
PBT-assessmen			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log Kow	< -2.9 at pH 7	not B
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, refined with prevalence	0.0000027	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

Considering the above data, vutrisiran is not expected to pose a risk to the environment.

2.2.2. Discussion on non-clinical aspects

Additional non-clinical data have not been generated for this proposed type II variation.

Vutrisiran PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, vutrisiran is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of vutrisiran

- Considering the above data, vutrisiran is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies
- Tabular overview of clinical studies

A tabular overview over the clinical studies supporting the clinical development of Vutrisiran in patients with amyloidosis is provided in Table 1 below. Study 001 and study 002 (HELIOS A) have been assessed previously, study 003 (HELIOS B) is the pivotal study to support the proposed extension of indication to include treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

Table 1. Vutrisiran clinical development program

Study, Status, Data Cutoff	Study Design/Objectives, Location	Vutrisiran Presentation(s)[a]	Dose(s)	N, Study Population	Data Collected
ALN-TTRSC02-001 (Study 001) *Completed Data lock: 13 February 2018*	Phase 1, randomized, single-blind SAD to evaluate safety, tolerability, PK, PD, and ADA of vutrisiran 1 clinical study center in the United Kingdom	Solution for injection, 0.5 mL in 2 mL glass vial administered with syringe Formulated in water for injection	Single SC injection of 5, 25, 50, 100, 200, and 300 mg	N=80, healthy volunteers N=60 on vutrisiran N=20 on placebo	Plasma and urine concentrations of vutrisiran Serum concentrations of TTR and vitamin A ADA Safety
ALN-TTRSC02-002 (HELIOS-A) *Ongoing 18-month Treatment Period completed Data cutoff:* 26 August 2021	Phase 3, randomized (3:1 vutrisiran:patisiran), open-label study to evaluate the efficacy, safety, PK, and PD of vutrisiran 57 centers across 22 countries	Solution for injection, 0.5 mL in 2 mL glass vial administered with syringe Solution for injection, 0.5 mL in 1 mL prefilled syringes with passive needle safety system Formulated in 10 mM sodium phosphate and 110 mM sodium chloride, pH 7	<u>18-Month Treatment Period</u> Vutrisiran: 25 mg SC injection administered q3M Patisiran (reference comparator): 0.3 mg/kg IV infusion administered q3w	N=164, patients with hATTR amyloidosis N=122 on vutrisiran N=42 on patisiran	Vutrisiran and patisiran plasma concentrations Serum concentrations of TTR and vitamin A Efficacy data (mNIS+7, Norfolk QoL-DN, 10-meter walk test) ADA Safety

Study, Status, Data Cutoff	Study Design/Objectives, Location	Vutrisiran Presentation(s)[a]	Dose(s)	N, Study Population	Data Collected
ALN-TTRSC02-003 (HELIOS-B) *Ongoing* *Primary analysis completed* *Data cutoff: 08 May 2024*	Phase 3, randomized (1:1 vutrisiran:placebo), DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of vutrisiran. 87 centers across 26 countries	Solution for injection, 0.5 mL in 1 mL PFS-S Formulated in 10 mM sodium phosphate and 110 mM sodium chloride, pH 7	Vutrisiran: 25 mg SC injection administered q3M or placebo (sodium chloride 0.9% w/v)	N=654, patients with ATTR amyloidosis with cardiomyopathy N=326 on vutrisiran N=328 on placebo[b]	Vutrisiran plasma concentrations Serum concentrations of TTR and vitamin A All-cause mortality and CV events (CV hospitalizations and urgent HF visits) Functional secondary efficacy endpoints (6-MWT, KCCQ-OS, NYHA Class) ADA Safety

2.3.2. Pharmacokinetics

The pharmacokinetic profile of vutrisiran has already been characterized after single ascending doses from 5 to 300 mg in healthy volunteers and after 25 mg q3m dosing in patients. The analytical methods and this results from Study 001 still have been assessed at the time of the initial marketing authorisation application.

In brief:

Study 001 utilized intensive sampling to characterize the plasma PK, PD, and urine excretion profiles of vutrisiran after a single dose. This study characterized the clinical pharmacology aspects (absorption, distribution, metabolism, and elimination) of vutrisiran in humans.

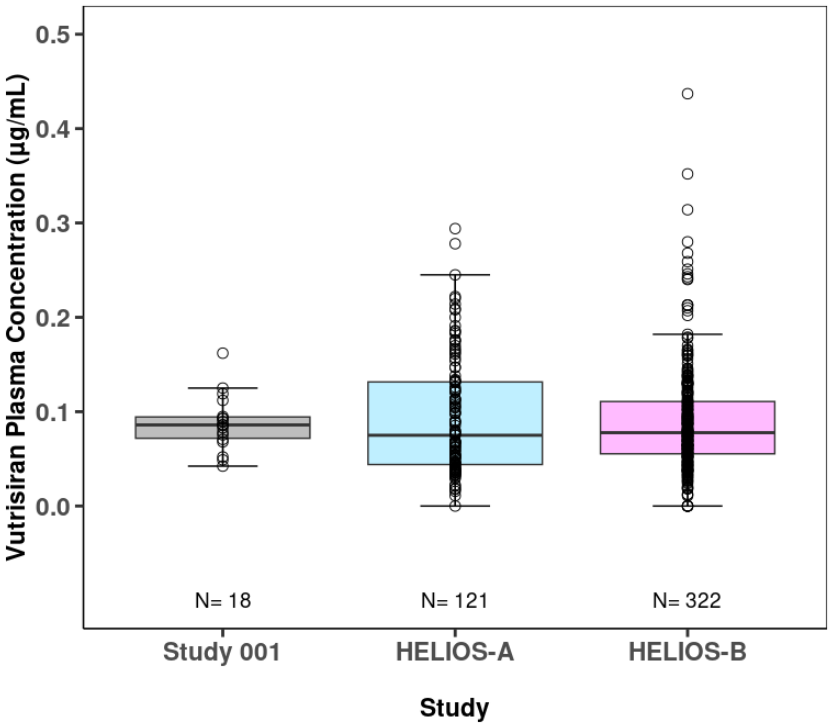
After vutrisiran is administered SC, the GalNAc conjugate ensures targeted delivery of the siRNA to hepatocytes in the liver. Once delivered to the cytoplasm of hepatocytes, vutrisiran is primarily metabolized by endo- and exonucleases to fragments of varying sizes.[An 2023; McDougall 2022] Plasma protein binding of vutrisiran was concentration-dependent, since the percent bound decreased with increasing concentrations of vutrisiran, indicating saturation of the binding sites, and is expected to be around 80%.[Jing 2023] The ADME properties are similar and consistent across intrinsic and extrinsic factors and indications (hATTR amyloidosis with polyneuropathy and ATTR amyloidosis with cardiomyopathy). Vutrisiran has not been studied in patients with severe hepatic impairment, severe renal impairment, or end-stage renal disease.

Vutrisiran PK analysis

Vutrisiran plasma concentrations 4 hour postdose (C4h) at different visits during the DB Period were similar, and C4h values at steady state (Month 30) were similar to their respective first dose values, indicating lack of accumulation of vutrisiran in plasma after q3M dosing of 25 mg. These results are consistent with the observed PK of vutrisiran in patients with hATTR amyloidosis with polyneuropathy in HELIOS-A. Median

plasma concentrations of vutrisiran 4 hours postdose at Month 30 were similar for patients with wtATTR and hATTR amyloidosis (Figure 1).

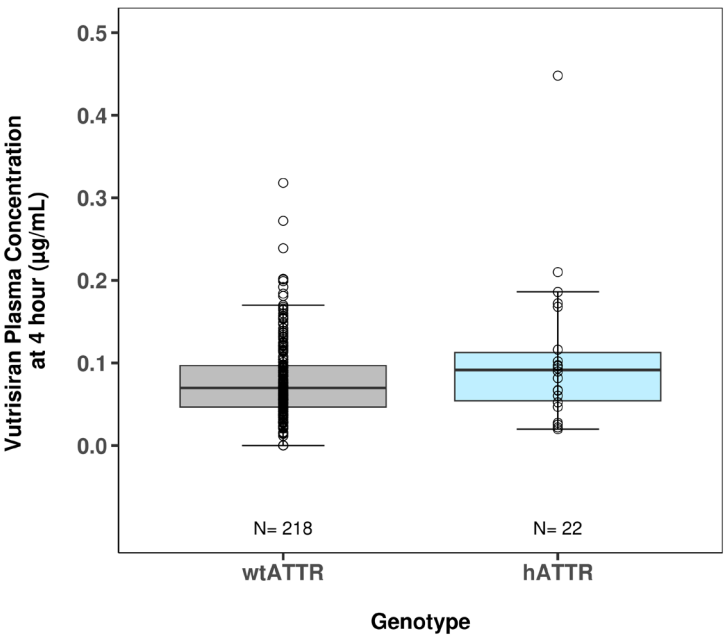
Figure 1. Vutrisiran plasma concentrations 3 to 4 hours after the first dose



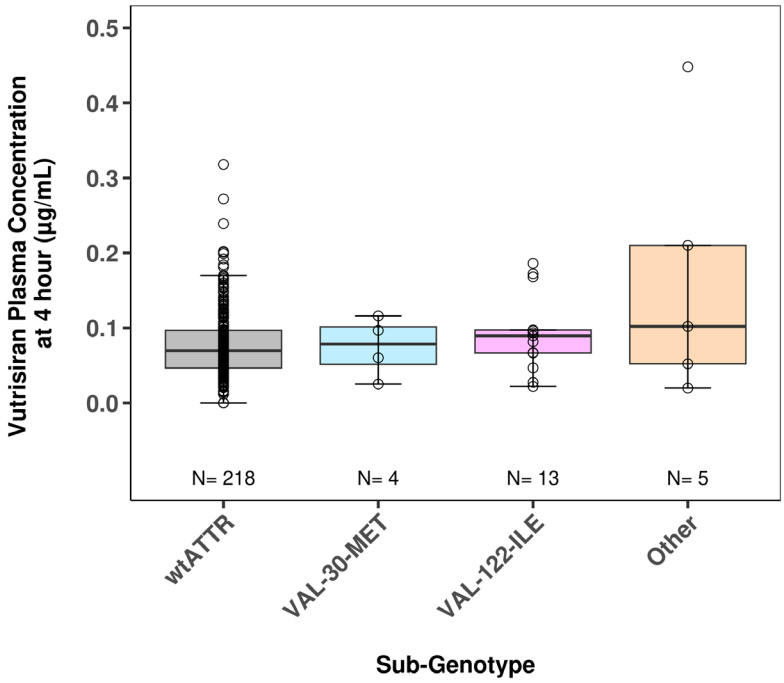
Median plasma vutrisiran C_{4h} at Month 30 were similar across *TTR* genotypes, and there was considerable overlap in the range of observed values (Figure 2 A and B).

Figure 2. Vutrisiran plasma concentrations at 4 hours by TTR genotype

A)



B)



Intrinsic factors

Intrinsic factors such as sex, race, age, body weight, genotype, NYHA class, and mild to moderate renal impairment and hepatic impairment, and the extrinsic factor of tafamidis use did not meaningfully influence the PK of vutrisiran. Data for renal and hepatic impairment as analysed in HELIOS B are summarized below.

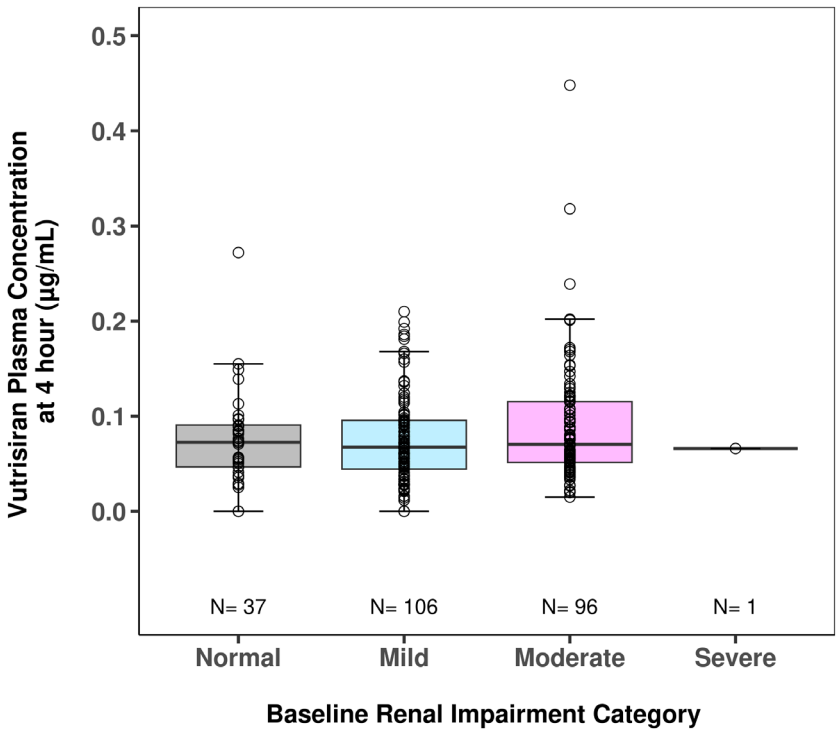
Renal impairment

The impact of mild or moderate renal impairment on the PK and PD of vutrisiran was assessed in HELIOS B (Figure 3). Overall, the plasma PK of vutrisiran was comparable in patients with mild or moderate renal impairment and those with normal renal function:

- Median plasma C_{4h} of vutrisiran at Month 30 was similar for patients with normal renal function and those with mild or moderate renal impairment (Figure 3).
- There was one patient with severe renal impairment at baseline; the vutrisiran C_{4h} for this patient was in the range of the other 3 groups (Figure 3.

These results were expected, as CL_R is a minor pathway in the overall elimination of vutrisiran, representing approximately 15.4% to 25.4% of the total plasma clearance, hence a decrease in renal function is not expected to have a meaningful effect on plasma exposure.

Figure 3. HELIOSB: Vutrisiran plasma concentrations 4 hours postdose at month 30 by renal impairment category (PK population)



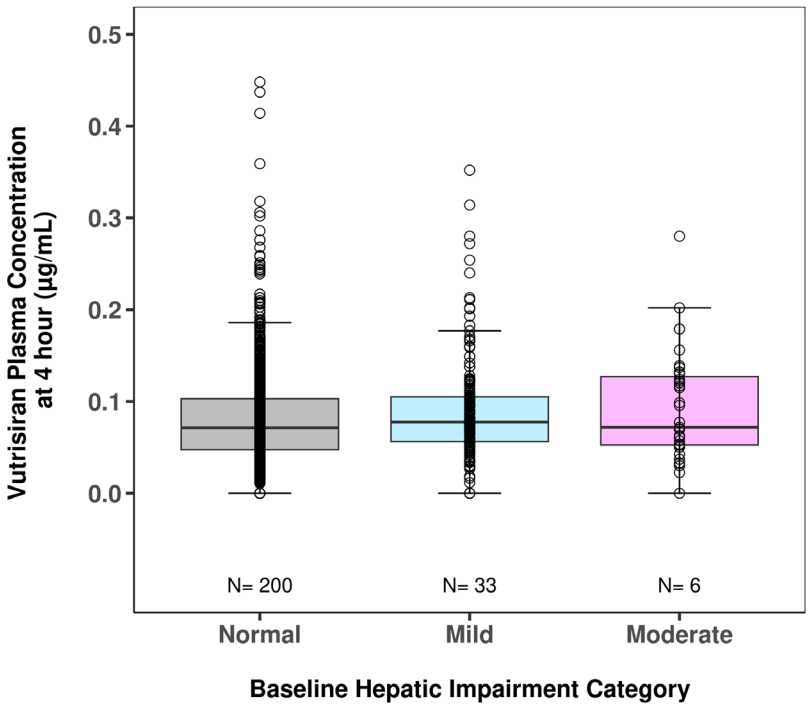
Abbreviation: PK=pharmacokinetics.
Note: Renal Function categories: normal renal function: eGFR ≥90 mL/min/1.73 m^2; mild renal impairment: eGFR ≥60 to <90 mL/min/1.73 m^2; moderate renal impairment: eGFR ≥30 to <60 mL/min/1.73 m^2; severe renal impairment: eGFR ≥15 and <30 mL/min/1.73 m^2.

Hepatic impairment

The impact of impaired hepatic function was evaluated in HELIOS B by comparing the PK and PD of vutrisiran in HELIOS-B patients with mild hepatic impairment (bilirubin ⩽ upper limit of normal (ULN) and aspartate transaminase (AST) > ULN; or ULN < bilirubin ⩽1.5 × ULN, National Cancer Institute Organ Dysfunction Working Group [NCI-ODWG] classification [Patel 2004]) or moderate (bilirubin >1.5 to 3×ULN, NCI ODWG classification) relative to patients with normal hepatic function (bilirubin ⩽ ULN and AST ⩽ ULN). None of the patients had severe hepatic impairment at baseline. (Figure 4) Overall, the plasma PK of vutrisiran was comparable in patients with mild or moderate hepatic impairment and those with normal hepatic function:

- Plasma C4h of vutrisiran at Month 30 was comparable for patients with normal hepatic function and those with mild or moderate hepatic impairment (Figure 4).

Figure 4. HELIOSB: Vutrisiran plasma concentrations 4 hours postdose at month 30 by hepatic impairment category (PK population)



Abbreviation: PK=pharmacokinetics.

Vutrisiran has not been studied in patients with severe hepatic impairment, patients with severe renal impairment, or patients with end-stage renal disease.

Extrinsic factors

Drug-Food Interactions

No studies were conducted to evaluate drug-food interactions because vutrisiran is administered SC.

Drug-Drug Interactions

Dedicated drug-drug interaction studies in humans have not been performed with vutrisiran as it is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP) enzymes or transporters and is not expected to cause clinical drug-drug interactions or to be affected by inhibitors or inducers of CYP enzymes or transporters.

Baseline Tafamidis Use

Tafamidis use at baseline had no effect on the PK of vutrisiran.

2.3.3. Pharmacodynamics

Mechanism of action

Vutrisiran is an RNAi therapeutic comprised of a synthetic, chemically modified, double-stranded small interfering RNA (siRNA) that specifically targets variant and wtTTR and silences TTR messenger RNA (mRNA).

This is accomplished by incorporation of vutrisiran siRNA into the cellular multiprotein enzyme cleavage complex known as the RNA induced silencing complex (RISC). Based on the mechanism of RNA interference, vutrisiran is specifically designed to reduce the hepatic synthesis of variant and wt TTR protein

Primary and secondary pharmacology

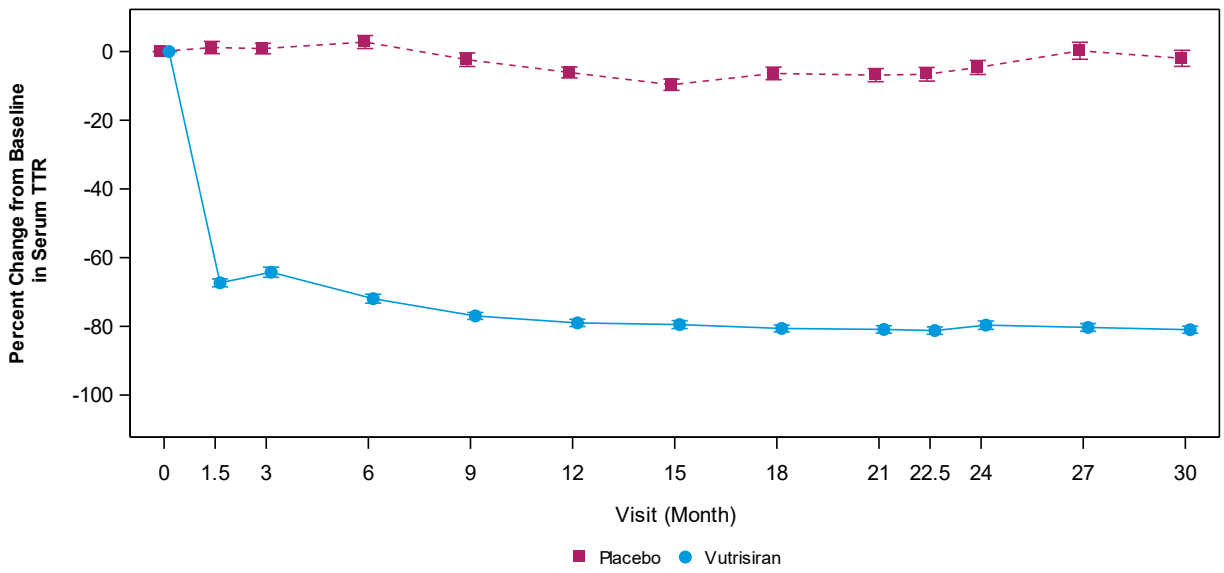
Primary and secondary pharmacodynamic effects of vutrisiran have been investigated in three clinical trials. A dose dependent reduction of TTR with a prolonged effect even after single doses was found.

Serum TTR

Vutrisiran administration resulted in rapid and sustained reduction of TTR in patients with ATTR amyloidosis with cardiomyopathy (Figure 5).

Median TTR percent reduction from baseline was 69.0% at Week 6 and 68.6% at Month 3. Additional TTR lowering was observed with repeat q3M dosing leading to median steady-state trough TTR percent reductions of 82.5% during the period between Month 6 to Month 30. At Month 30, the median TTR percent reduction from baseline was 86.8% in the vutrisiran group and 7.9% in the placebo group.

Figure 5. HELIOS-B: mean (±SEM) percent change from baseline in serum TTR (ELISA) by visit during the DB period (PD analysis set)



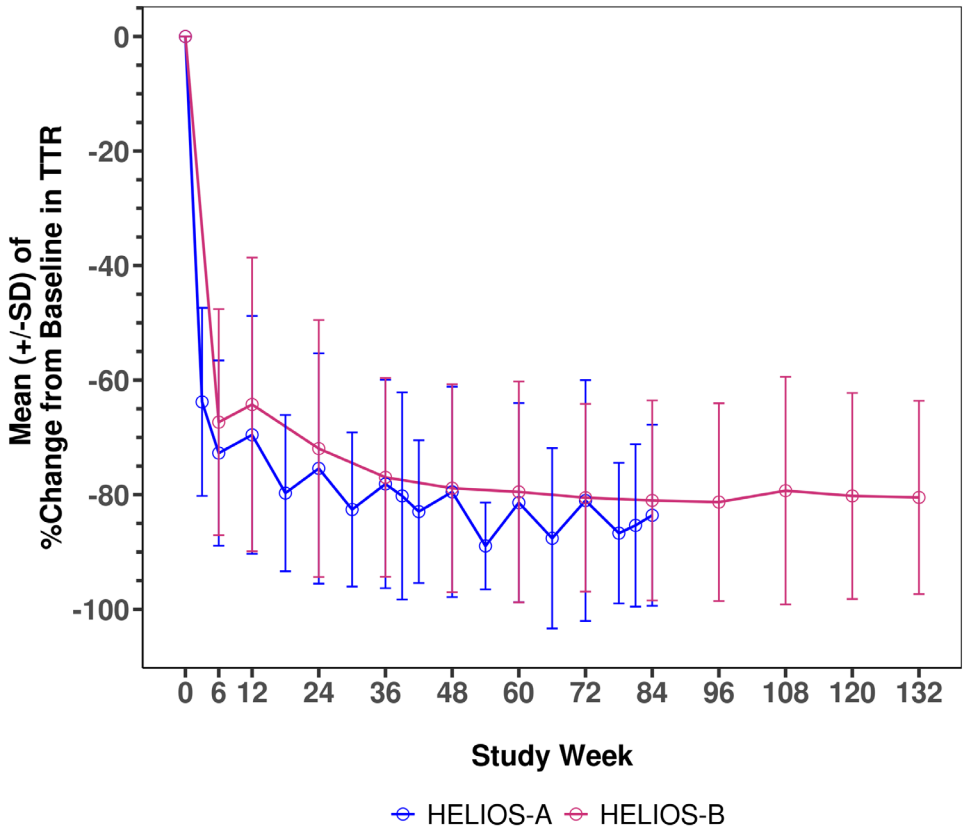
N evaluable													
Placebo	324	304	314	306	302	296	286	274	268	263	257	239	230
Vutrisiran	317	294	304	299	295	285	278	272	263	258	254	250	246

Abbreviations: DB=double-blind; ELISA=enzyme-linked immunosorbent assay; PD=pharmacodynamic; SEM=standard error of the mean; TTR=transthyretin.

The PD effect of vutrisiran over time was similar between HELIOS A and HELIOS B. Overall (Figure 6), a durable and stable reduction of TTR has been established with corresponding secondary reductions of vitamin A, with 99% of predicted steady-state values reached by Month 18.

These results already established for hATTR patients with polyneuropathy have been confirmed in study Helios B for ATTR amyloidosis patients with cardiomyopathy.

Figure 6. Mean (±SD) percent change in TTR from baseline



Intrinsic factors

Intrinsic factors such as sex, race, age, body weight, genotype, NYHA class, and mild to moderate renal impairment and hepatic impairment, and the extrinsic factor of tafamidis use did not meaningfully influence the PD of vutrisiran.

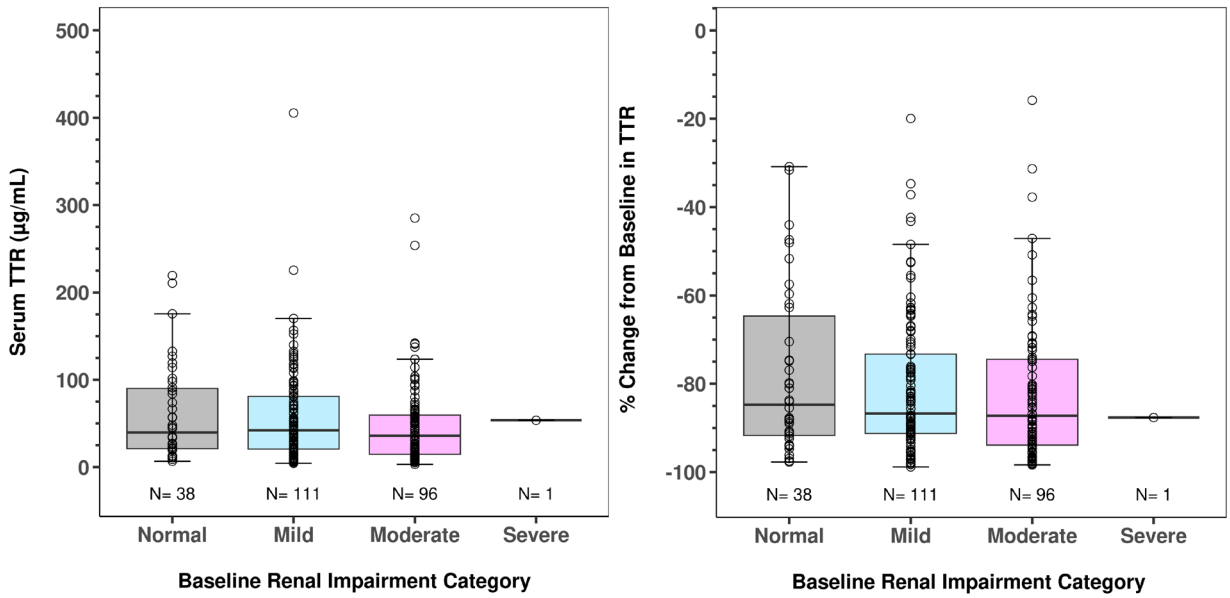
Renal impairment

Impact on PD (in HELIOS B)

Overall, the PD of vutrisiran were comparable in patients with mild or moderate renal impairment and those with normal renal function:

- Median baseline TTR levels were comparable across renal function categories (refer to 2.7.2 PKPD Figure 12.22).
- At Month 30, median absolute TTR and percent change from baseline in TTR were similar for patients with normal renal function and those with mild and moderate renal impairment (Figure 7).
- There was one patient with baseline severe renal impairment; the absolute and percent change in TTR from baseline for this patient was in the range of the other 3 groups (Figure 7).

Figure 7. HELIOS-B: Vutrisiran month 30 absolute TTR concentrations and percent change from baseline in TTR by renal impairment category (PD population)



Abbreviations: PD=pharmacodynamic; TTR=transthyretin.
Source: 2.7.2 PKPD Figure 12.23 and Figure 12.24

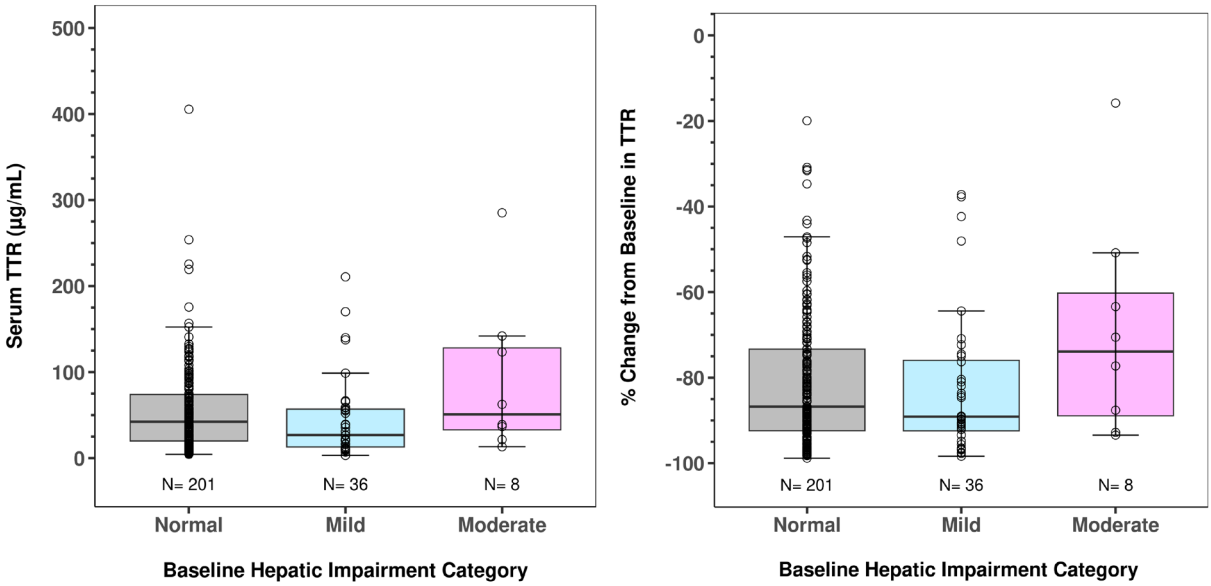
Hepatic impairment

Impact on PD (HELIOS B)

Overall, the PD effect of vutrisiran was comparable in patients with mild or moderate hepatic impairment and those with normal hepatic function:

- Baseline TTR levels were comparable in patients with mild or moderate hepatic impairment and those with normal hepatic function (refer to 2.7.2 PKPD Figure 12.25).
- Absolute serum TTR and TTR percent change from baseline values for patients with mild hepatic impairment was similar to patients with normal hepatic function (Figure 8).
- The TTR percent reduction from baseline at Month 30 for patients with moderate hepatic impairment was lower (73.9%) compared to patients with mild hepatic impairment (89.1%) and normal hepatic function (86.8%) (refer to 2.7.2 PKPD Table 6.9).
  - However, this difference may be attributable to the smaller number of patients with moderate hepatic impairment (n=8), and the observed values overlapped with the values for patients with normal and mild hepatic impairment.

Figure 8. HELIOS-B: Vutrisiran month 30 absolute TTR concentrations and percent change from baseline in TTR by hepatic impairment category (PD population)



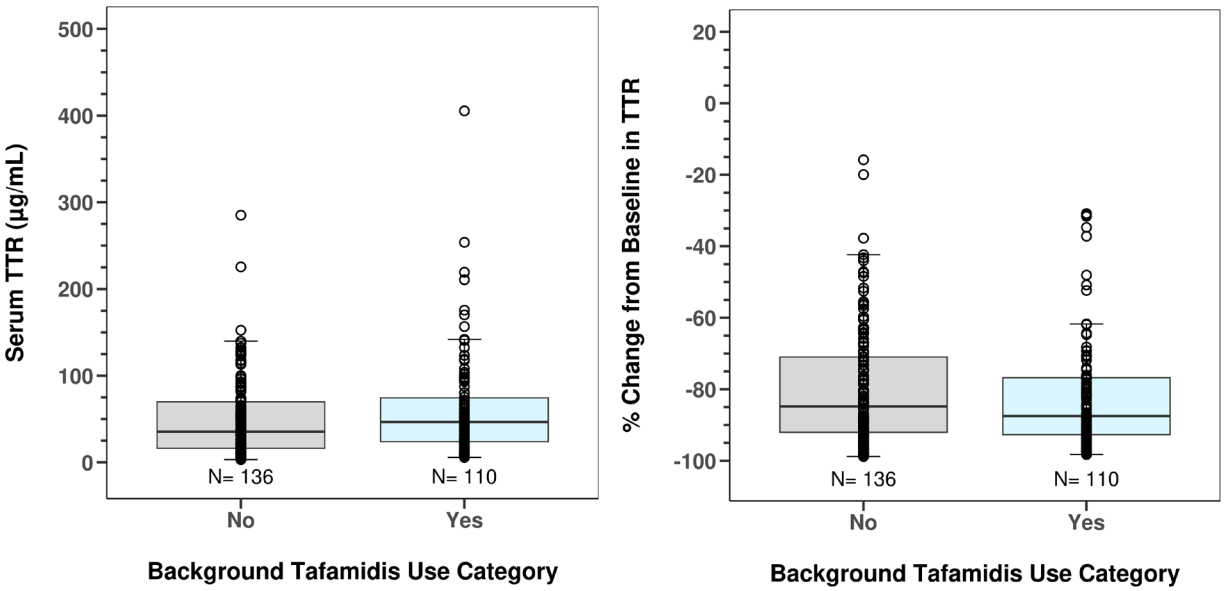
Abbreviations: PD=pharmacodynamic; TTR=transthyretin.
Source: 2.7.2 PKPD Figure 12.26 and Figure 12.27

Extrinsic factors

Baseline Tafamidis Use

At Month 30, absolute TTR concentrations and percent change from baseline in TTR were comparable in patients with and without background tafamidis use (Figure 9).

Figure 9. Serum TTR and percent change in TTR from baseline in HELIOS B by background Tafamidis use category



Vitamin A (Helios B)

Patients were advised to take the recommended daily allowance of vitamin A, as included in the approved vutrisiran product labelling for patients with hATTR amyloidosis with polyneuropathy.

In the overall population, the median percent change from baseline in vitamin A levels at Month 12 was -66.7% in the vutrisiran group and 4.3% in the placebo group. At Month 36, the median percent change from baseline was -70.6 in the vutrisiran group and 0% in the placebo group.

Immunogenicity

The potential for vutrisiran to elicit an immune response was evaluated by measuring ADA titers against vutrisiran drug substance in all clinical studies.

In HELIOS-B, the incidence of treatment-emergent ADA was 0.3% (1/313) in the vutrisiran group and 0.9% (3/322) in the placebo group. Titers were low (50) and transient with patients testing negative at a subsequent visit. One patient with treatment-emergent ADA in the placebo group died before their next ADA assessment.

In addition, a comprehensive immunogenicity assessment was conducted using data across the vutrisiran development program including healthy volunteers (Study 001), patients with hATTR amyloidosis with polyneuropathy (HELIOS-A), and patients with ATTR amyloidosis with cardiomyopathy (HELIOS-B). Across the clinical studies, a total of 1.2% (6/493) vutrisiran participants had low-titer (50), treatment-emergent ADA due to vutrisiran. Antidrug antibody positivity was transient, with most participants testing negative at a subsequent sampling timepoint.

There were no instances of treatment-boosted ADA.

In the rare occasion when ADA were detected, they did not affect the PK or PD profile of vutrisiran in HELIOS-B (Figure 10).

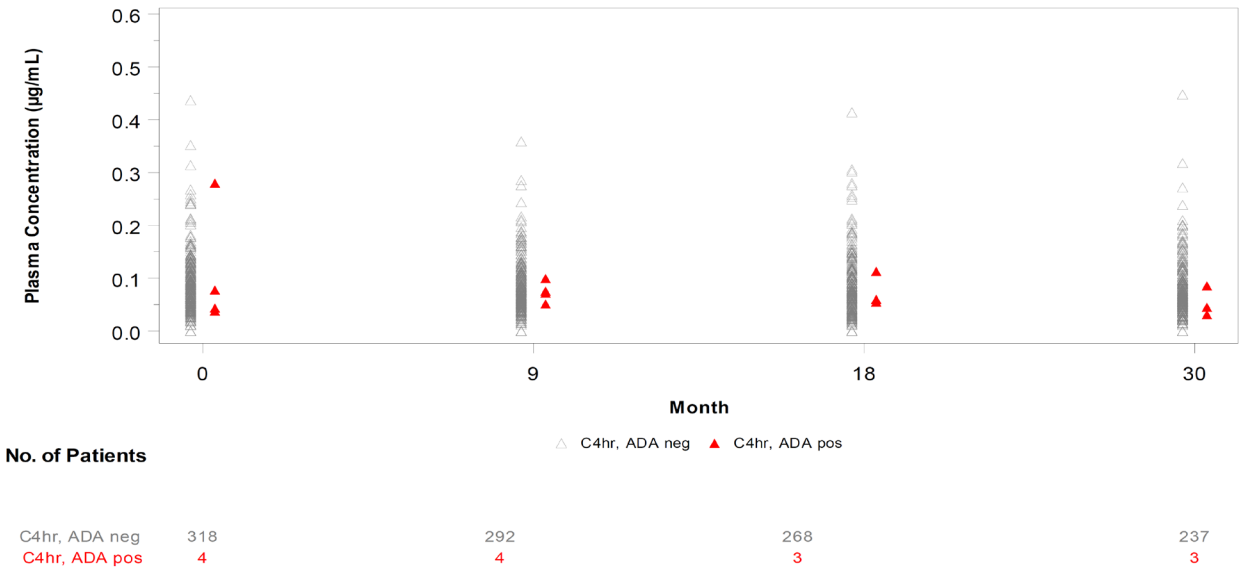
Impact of ADA on Pharmacodynamics

Individual TTR profiles in ADA positive patients were similar to those seen in ADA negative patients indicating no clinically meaningful impact of ADA on pharmacodynamics of vutrisiran.

Impact of ADA on Pharmacokinetics

Individual vutrisiran plasma concentrations over time are provided for ADA positive vutrisiran-treated patients in Figure 10. Plasma concentrations of vutrisiran were comparable in ADA positive and ADA negative patients at all post-baseline time points, indicating no impact of ADA on vutrisiran PK.

Figure 10. Individual Vutrisiran plasma concentrations (µg/mL) over time by ADA status during the DB period (Vutrisiran treated patients, PK population)



Abbreviations: ADA=antidrug antibody; C4h=vutrisiran plasma concentrations 4 hours postdose; DB=double-blind; neg=negative; PK=pharmacokinetic; pos=positive.

2.3.4. Discussion on clinical pharmacology

Vutrisiran drug substance (ALN-65492) is a chemically synthesized double-stranded oligonucleotide conjugated to a triantennary GalNAc moiety through a phosphodiester linkage at the 3'-end of the sense strand. The overall clinical development program of vutrisiran consists of a clinical pharmacology study in healthy volunteers (Study 001), a Phase 3 study of patients with hATTR amyloidosis with polyneuropathy (HELIOS-A), and a Phase 3 study of patients with ATTR amyloidosis with cardiomyopathy (HELIOS-B). The first two studies were assessed in the initial application for hATTR-PN and the third study is the focus of the current application.

HELIOS-B is an ongoing, Phase 3, randomized (1:1), double-blind (DB), placebo-controlled, multicenter study designed to evaluate efficacy, safety, PK, and PD of vutrisiran in adult patients with wtATTR and hATTR amyloidosis with cardiomyopathy that considers a completed, randomized, placebo-controlled DB Period for up to 36 months and an ongoing 24-month open-label extension (OLE) Period. Plasma samples for PK analysis were made at Day 1, Week 36, Week 72 (Month 18), and Week 132 (Month 30) at pre-dose and 4 h after dose during the double-blind period and at 3h and 6h after dosing in the Open-label Treatment Extension (OLE) Period.

The used analytical method - LC/MS-HRAM - is the same that was assessed in the original application being considered acceptable.

The PK of vutrisiran in plasma and urine from individual studies was characterized using non-compartmental analysis (NCA). This is acceptable. Vutrisiran C4h at different visits during the DB Period were similar, and C4h values at steady-state (Month 30) were similar to their respective first dose values, indicating lack of accumulation of vutrisiran in plasma after q3M dosing of 25 mg. Plasma concentrations of vutrisiran were comparable in ADA positive and ADA negative patients at all postbaseline time points indicating no impact of ADA on vutrisiran PK. Plasma PK of vutrisiran was comparable between male and female patients, different races, across age quartiles (<72, ≥72 to <77, ≥77 to <81, and ≥81 years) and between wtATTR and hATTR (including all genotypes) amyloidosis patients. The plasma PK of vutrisiran was lower across higher baseline body weight quartiles (<72 kg, ≥72 to <79.5 kg, ≥79.5 to <87.2 kg, and ≥87.2 kg) but without any PD relevant difference, like also observed in the HELIOS-A study. Overall, the plasma PK of vutrisiran was comparable in patients with mild or moderate renal impairment and those with normal renal function and was also comparable in patients with mild or moderate hepatic impairment and those with normal hepatic function. Since vutrisiran is metabolized by endo- and exo-nucleases and it is not a substrate, inhibitor, or inducer of CYP enzymes or transporters, it is not expected to cause clinical DDI, or to be affected by inhibitors or inducers of CYP enzymes or transporters. As such, no formal clinical DDI studies have been performed. In any case, Plasma C4h values for vutrisiran at Month 30 were similar for patients with and without background tafamidis use at baseline. Overall, this is acceptable.

Regarding the comparison between studies, vutrisiran plasma concentrations 3 to 4 hours after the first dose were comparable across all 3 studies indicating similarity of PK in healthy volunteers, hATTR patients with polyneuropathy, and ATTR amyloidosis patients with cardiomyopathy.

Overall, it is agreed that the PK of vutrisiran is similar in the 3 studies and, thus, between healthy, patients with hATTR amyloidosis with polyneuropathy and patients with ATTR amyloidosis with cardiomyopathy. More detailed comparison of PK/PD data between HELIOS-A and HELIOS-B were provided indicationg no relevant differences between the two populations.

In HELIOS-B, the trough observed median percent TTR reduction from baseline at Month 30 was 86.8%. This sustained TTR reduction was comparable to the reduction previously observed with vutrisiran in patients with hATTR amyloidosis with polyneuropathy (HELIOS-A), as well as comparable to the reduction previously observed with patisiran in patients with hATTR amyloidosis with polyneuropathy (APOLLO).

2.3.5. Conclusions on clinical pharmacology

Intrinsic factors such as sex, race, age, body weight, genotype, NYHA class, and mild to moderate renal impairment and hepatic impairment, and the extrinsic factor of tafamidis use did not meaningfully influence the PK or PD of vutrisiran, indicating that the recommended dose regimen of 25 mg q3M is appropriate for all subgroups of ATTR amyloidosis patients with cardiomyopathy.

Vutrisiran has not been studied in patients with severe hepatic impairment, patients with severe renal impairment, or patients with end-stage renal disease.

Collectively, the results of Studies 001, HELIOS-A, and HELIOS-B support the recommended vutrisiran dosing regimen of 25 mg administered q3M across all subgroups. No dose adjustment is necessary for any of the subpopulations studied.

In the occasion when ADA were detected, they did not affect the PK or PD profile of vutrisiran in HELIOS-B.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The same dose and dosing regimen as administered in HELIOS A supporting the initial marketing authorisation was applied in HELIOS B. The dose and dosing frequency for vutrisiran (25 mg q3M) were selected to achieve TTR reduction with minimal peak-to-trough fluctuation over the dosing interval. Reference is made to the EPAR (EMA/CHMP/689555/2022):

"*Selection of the dosing regimen for vutrisiran was supported by TTR reduction data from the Phase 1 Study 001 in healthy subjects. Additionally, a PK/PD modeling approach was employed by the Applicant to characterize the dose-TTR reduction property of vutrisiran and determine the optimal dosing regimen for the Phase 3 studies in patients. Adequacy of the selected Phase 3 dosing regimen was confirmed in the HELIOS-A study in patients with hATTR amyloidosis with polyneuropathy, where median steady-state trough TTR reduction of 85% was observed together with improvement of neurological disease manifestations at Month 9 (please see relevant Clinical Efficacy sections). […] the 25 mg q3M regimen of vutrisiran was predicted to provide sustained TTR reduction over the 3-month dosing interval similar to the observed TTR reduction profiles with intravenous 0.3 mg/kg q3w patisiran in the APOLLO study and it was well-tolerated. Intrinsic and extrinsic factors did not appear to influence the recommended fixed dose regimen of 25 mg q3M. It is noted, however, that a prefilled syringe equipped with a passive needle safety system (PFS-S) was used in HELIOS-A and it is intended for marketing. The phrase in section 4.2 of the SmPC "Therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis" is acknowledged.*

2.4.2. Main study(ies)

ALN-TTRSC02-003, IND Number: 141923, EudraCT Number: 2019-003153-28

Title of Study

HELIOS-B: A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Methods

Study Initiation Date: 26 November 2019

Primary Analysis Data Cutoff Date: 08 May 2024

Primary Analysis Database Lock Date: 14 June 2024

Sponsor: Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA

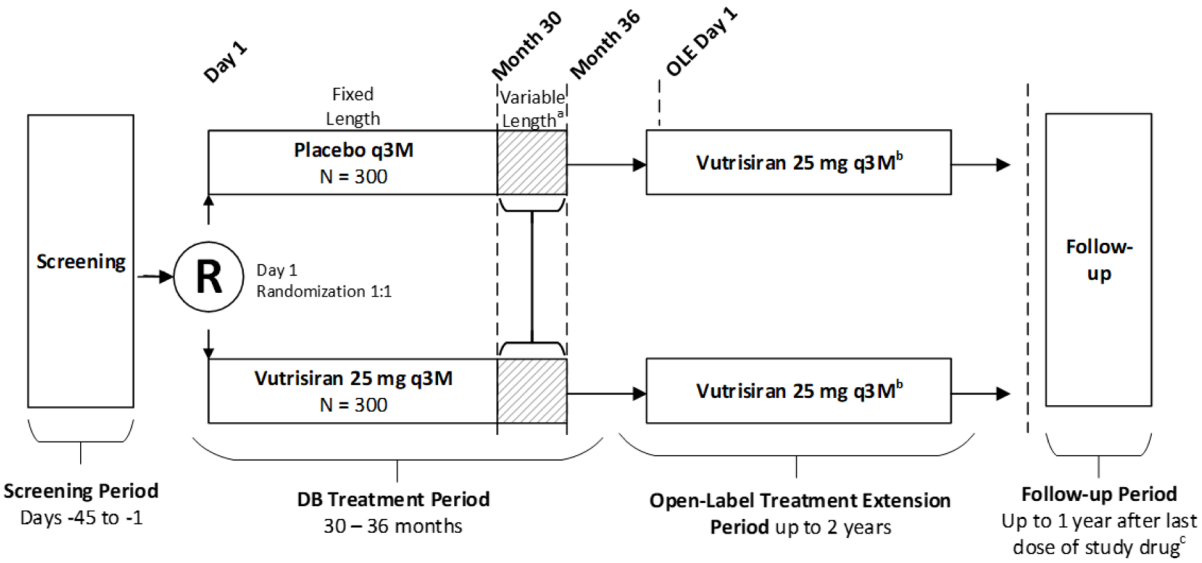
It was a multinational multicenter study conducted in 87 study centers in 26 countries in North America, South America, Europe, Asia, and Australia.

An external independent Data monitoring committee (DMC) was involved in the conduct of this study. The role of the DMC was to provide an independent review and assessment of accumulating safety data in order to further safeguard the interests and safety of the participating patients.

Through the data cutoff date for the primary analysis, an independent Clinical Events Committee (CEC) reviewed deaths, hospitalizations, and urgent heart failure (HF) visits blinded to treatment assignment on an ongoing basis for endpoint adjudication. The CEC made a determination on whether deaths and hospitalizations could be attributed as cardiovascular (CV).

It is an ongoing Phase 3, randomized (1:1), DB, placebo-controlled, multicenter study evaluating the efficacy and safety of vutrisiran in 655 randomized patients with ATTR amyloidosis (hATTR or wtATTR amyloidosis) with cardiomyopathy. The study design is shown in Figure 11. Patients were stratified by baseline tafamidis use

Figure 11. Study design



Abbreviations: DB=double-blind; OLE=open-label extension; q3M=once every 3 months; SC=subcutaneous.

[a] An individual patient's DB Treatment Period visits end after they complete their Month 36 visit, or 30 months after the last patient was randomized, whichever comes first. As such, a patient's last visit during the DB Treatment Period may have varied from 30 to 36 months after enrollment, and the first dose in the OLE Period was Month 33 or 36. The DB exposure period was 33 to 36 months and is referred to as the DB Period.

[b] The dosing schedule is 25 mg vutrisiran every 12 weeks. Upon entry into the OLE Period (OLE Day 1), all eligible patients received open-label doses of 25 mg q3M vutrisiran administered as SC injections.

[c] Following completion of the OLE Period (or completion of the DB Period for patients who did not continue into the OLE Period; or their last dose of vutrisiran for patients who discontinued study drug early), patients will commence Follow-up visits. For women of child-bearing potential, the duration of the Follow-up Period will be up to 18 months from their last dose of study drug.

After screening, eligible patients were randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as an SC injection q3M (every 12 weeks ±7 days) for up to 36 months in the DB Period.

During the OLE Period, all patients receive open-label doses of 25 mg q3M vutrisiran administered as SC injections.

With Protocol Amendment 3 (13 May 2022), an Open-label Randomized Treatment Extension (RTE) Period was added wherein patients were randomized 1:1 to receive treatment with either 25 mg q3M vutrisiran or 50 mg once every 6 months (q6M) vutrisiran. With Protocol Amendment 4 (22 March 2023), the study design was revised to replace the 2-arm RTE Period with a single-arm OLE Period, and all patients in the 50 mg q6M vutrisiran group were transitioned to the 25 mg q3M vutrisiran regimen.

Following completion of the OLE Period (or completion of the DB Period for patients who did not continue into the OLE Period; or their last dose of vutrisiran for patients who discontinued study drug early), patients commenced follow-up visits every 12 weeks for up to 1 year or up to 18 months for women of child-bearing potential.

In addition to study drug, all patients were instructed to take the recommended daily allowance of vitamin A in their country or region during their DB, OLE, and Follow-up Periods.

Study participants

Key Inclusion Criteria

Patients were eligible to be included in the study if all the following criteria applied:

Age

1. Age 18 (or age of legal consent per local regulations, whichever was older) to 85 years, inclusive.

Patient and Disease Characteristics

2. Documented diagnosis of ATTR amyloidosis with cardiomyopathy, classified as either hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis with cardiomyopathy:

a. Hereditary ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

i. Documentation of a TTR pathogenic mutation consistent with hATTR amyloidosis.

ii. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at Screening).

iii. Amyloid deposits in cardiac or noncardiac tissue (e.g., fat pad aspirate, salivary gland, median nerve connective sheath) confirmed by Congo Red (or equivalent) staining OR technetium (99mTc) scintigraphy (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], 99mTc-pyrophosphate [PYP-Tc] or 99Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS had been excluded.

iv. If the patient had evidence of a MGUS based on serum and urine protein electrophoresis and serum free light chains, documentation of TTR protein in tissue with immunohistochemistry or mass spectrometry was required.

b. Wild-type ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

i. Documentation of absence of pathogenic TTR mutation.

ii. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at Screening).

iii. Amyloid deposits in cardiac tissue with TTR protein identification by IHC, mass spectrometry, OR technetium (99mTc) scintigraphy (99mTc-3,3-diphosphono-1,2- propanodicarboxylic acid [DPD-Tc], 99mTc-pyrophosphate [PYP-Tc], or 99Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS had been excluded.

iv. If the patient had evidence of a MGUS based on serum and urine protein electrophoresis and serum free light chains, the following was required: documentation of TTR protein in cardiac tissue with immunohistochemistry or mass spectrometry; OR, documentation of TTR protein in noncardiac tissue (eg, fat pad aspirate, salivary gland, median nerve connective sheath) with immunohistochemistry or mass spectrometry AND Grade 2 or 3 cardiac uptake on 99mTc scintigraphy per item 2biii above.

3. Medical history of HF with at least 1 prior hospitalization for HF (not due to arrhythmia or a conduction system disturbance treated with a permanent pacemaker) OR clinical evidence of HF (with or without hospitalization) manifested by signs and symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on X-ray or auscultation, peripheral edema) that currently required treatment with a diuretic.

4. Patient met one of the following criteria:

a. Tafamidis-naïve and not actively planning to commence treatment with tafamidis during the first 12 months following randomization (per exclusion criterion #7)

(Note: in addition to patients who had never taken tafamidis, those who had previously been on tafamidis and had not received any tafamidis for at least 30 days before the Screening visit were considered tafamidis-naïve for purposes of this study); or

b. On tafamidis (Note: must have been on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use)

5. Patient was clinically stable, with no CV-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.

6. Screening NT-proBNP >300 ng/L and <8500 ng/L; in patients with permanent or persistent atrial fibrillation, Screening NT-proBNP >600 ng/L and <8500 ng/L.

7. Was able to complete ≥150 meters on the 6-MWT at Screening.

8. Had a Karnofsky performance status (KPS) of ≥60%.

among others

Key Exclusion Criteria

Patients were excluded from the study if any of the following criteria applied:

Disease-specific Conditions

1. Had known primary amyloidosis (AL amyloidosis) or leptomeningeal amyloidosis.

2. NYHA class IV HF; or NYHA class III HF AND ATTR amyloidosis disease Stage 3 (defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min).

3. Had a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk due to polyneuropathy, or is wheelchair bound) at the Screening visit.

Laboratory Assessments

4. Had any of the following laboratory parameter assessments at Screening:

a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >2.0× upper limit of normal (ULN),

b. Total bilirubin >2.0×ULN,

c. International normalized ratio (INR) >1.5 (unless patients were on anticoagulant therapy in which case excluded if INR >3.5).

5. Had eGFR <30 mL/min/1.73m^2 (using the modification of diet in renal disease formula) at Screening.

6. Had known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

Prior/Concomitant Therapy

7. Tafamidis-naïve patients (per inclusion criterion #4a) for whom the Investigator actively planned or anticipated commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomization, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.

8. Received prior TTR-lowering treatment (including revusiran, patisiran or inotersen) or participated in a gene therapy trial for hATTR amyloidosis.

among others

Medical Conditions

14. Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease (e.g., prior myocardial infarction with documented history of cardiac enzymes and electrocardiogram [ECG] changes) that the Investigator felt was a significant contributor or the predominant cause of the patient's HF.

15. Unstable CHF (including patients who required adjustment of existing diuretics or addition of new diuretics at time of Screening for purposes of achieving optimal management of CHF).

16. Had acute coronary syndrome or unstable angina within the past 3 months.

17. Had history of sustained ventricular tachycardia or aborted ventricular fibrillation.

18. Had history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.

19. Had persistent elevation of systolic (>170 mmHg) or diastolic (>100 mmHg) blood pressure that was considered uncontrolled by physician.

among others

Instances on when to discontinue study drug or study participation were pre-specified.

Treatments

Study drug (vutrisiran or placebo) was to be administered using single-use prefilled syringes. Each prefilled syringe is filled with either a 25 mg dose of vutrisiran or placebo with a fill volume of 0.5 mL. Each prefilled syringe includes a needle safety device which engaged to cover the exposed needle after injection.

During the DB Period, patients received 25 mg of vutrisiran or placebo administered as an SC injection q3M (every 12 weeks ±7 days) for up to 36 months.

During the OLE Period, patients were originally randomized 1:1 to receive treatment with either 25 mg q3M vutrisiran or 50 mg q6M vutrisiran; however, with Protocol Amendment 4 (22 March 2023), all patients will receive 25 mg of vutrisiran administered as an SC injection q3M (every 12 weeks ±7 days) for up to 2 years.

The Pharmacy Manual provided further details of study drug administration.

As of the data cutoff date (08 May 2024), the following study drug product lot numbers have been used in the study:

Vutrisiran: ADASA01, ADATA01, ADATJ03, ADATL05, ADAUH06, ADAUC02, ADAVI02, ADAWB01

Placebo: ADPSA02, ADPTA02, ADPTJ04, ADPVE01

In addition to other investigations drugs the following prior and concomitant medications were prohibited:

tauroursodeoxycholic acid, and non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) are also prohibited during the study. Doxycycline was permitted if being taken for short-term treatment of infection.

Topical steroids were not to be applied anywhere near the injection site(s) unless medically indicated.

All patients were asked to take the recommended daily allowance of vitamin A for the duration of their participation in the study while being administered study drug.

Concomitant Tafamidis use:

Patients who were on tafamidis at baseline (background tafamidis subgroup) as per inclusion criteria were encouraged, if it was medically appropriate in the opinion of the Investigator, to remain on tafamidis for the duration of the study.

Initiating on-label use of tafamidis in previously naïve patients during the study (tafamidis drop-in) was allowed in countries where tafamidis was approved and commercially available in this patient population.

Compliance with study drug administration was to be verified through oversight by study staff or trained home healthcare professionals.

Doses with a delay of more than 8 weeks were considered "missed" and not administered. Delayed doses within the 8 week frame were considered "delayed".

Objectives and Outcomes/endpoints

Table 2 summarises the objectives and the respective predefined endpoints.

Table 2. Study objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and CV events	• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the overall population • Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)
Secondary	
To evaluate the efficacy of vutrisiran compared with placebo treatment on: • Functional capacity • Patient-reported health status and health-related quality of life • All-cause mortality • Severity of clinical heart failure symptoms	The following secondary endpoints were defined in both the overall population and the vutrisiran monotherapy subgroup: • Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • All-cause mortality • Change from baseline in NYHA class
Exploratory	
To evaluate the efficacy of vutrisiran compared with placebo treatment on: • Additional assessments of death, hospitalizations, and urgent HF visits • Additional biomarkers and biomarker-based risk assessments • Cardiac structure and function • Concomitant use of heart failure medication • Assessments of quality of life	• Composite outcome of all-cause mortality and recurrent all-cause hospitalizations and urgent HF visits • Time to first CV event (including CV hospitalizations and urgent HF visits) or all-cause mortality • Time to second CV event (including CV hospitalizations and urgent HF visits) or all-cause mortality • Time to first CV event (including CV hospitalization, urgent HF visit and any initiation of SGLT2 inhibitor due to cardiac disease progression), or all-cause mortality • Time to first oral diuretic intensification, first CV event (including CV

The secondary endpoints were change from baseline in 6-MWT/KCCQ-OS at Month 30 (Week 132), all-cause mortality in the DB Period and 6 months of the OLE Period, and change from baseline in NYHA class at Month 30 (Week 132).

Unless otherwise noted, all-cause mortality included heart transplantation and LVAD placement; recurrent CV events included CV hospitalizations and urgent HF visits.

For exploratory endpoints see results below.

PK, Pharmacodynamic and Anti Drug Antibody Evaluations

See PK/PD above. The PD parameters measured in HELIOS-B were serum TTR and vitamin A.

Sample size

Based on the following assumptions and the actual enrollment of 655 patients randomized (654 patients dosed), the study had approximately 80% power in both the overall population and the vutrisiran monotherapy subgroup to detect a difference between the treatment groups using a modified Andersen-Gill model with a robust variance estimator, with a 2-sided α = 0.05:

• In the monotherapy subgroup, vutrisiran provided a 25% reduction in mortality rates and a 35% reduction in recurrent CV event rates compared to placebo over 30 months; 0.34 CV events per patient-year and 25% mortality rate at Month 30 were assumed in the placebo group.

• In the background tafamidis subgroup, vutrisiran plus tafamidis provided a 10% reduction in mortality rates and a 15% reduction in recurrent CV event rates compared to placebo plus tafamidis over 30 months; 0.24 CV events per patient-year was assumed in the placebo plus tafamidis group.

• A 9-month and 18-month delay to effect on CV events and death in both subgroups, respectively.

• In the vutrisiran monotherapy subgroup, approximately 20% of patients in both arms initiate tafamidis anytime during the first 24 months on study.

• CV events and mortality data were collected up to 36 months and no more than 15% of patients on both arms are lost to follow-up.

The estimates for death and recurrent CV event rates in the placebo arm (patients randomized to placebo in the tafamidis-naïve strata), and estimates for the reduction in these events for tafamidis (patients randomized to placebo in the baseline tafamidis strata) versus placebo, were based on published results from the tafamidis Phase 3 ATTR-ACT study [Maurer 2018], the patisiran Phase 3 APOLLO-B study [Maurer 2023], and the Phase 3 ATTRibute-CM study with acoramidis [Gillmore 2024]. Power calculations were performed using simulations given that no closed-form sample size estimation solution was available for this study design and primary analysis method.

Randomisation

Using Interactive Response Technology (IRT), patients were randomized 1:1 to the vutrisiran or placebo arm. Randomization was stratified by:

1. Baseline tafamidis use (yes versus no)

2. ATTR amyloidosis disease type (hATTR versus wtATTR amyloidosis with cardiomyopathy)

3. NYHA class I or II and age <75 years versus all other

Blinding (masking)

During the DB Period, all site personnel and patients were blinded to study drug treatment. Vutrisiran and placebo were packaged identically. Because vutrisiran may be visually distinguishable from placebo, the outside of the prefilled syringe barrel was masked in such a way as to hide the identity of the study drug contained within.

All study personnel were blinded to any clinical laboratory results scheduled as part of the study that could potentially unblind them, including TTR levels, vitamin A levels, PK data, and antidrug antibodies (ADA).

As it could affect the blind, patients and their physicians were prohibited from obtaining pre-albumin and vitamin A levels during the DB Period, other than the blinded assessments scheduled in the study, unless clinically indicated and after consultation with the Medical Monitor.

During the DB Period, Investigators, study personnel, and the Sponsor remained blinded to treatment assignment until after the database lock for the primary analysis.

During the OLE Period, vutrisiran is administered in an open-label fashion.

Procedures related to emergency unblinding were prespecified.

Statistical methods

Populations Analyzed:

The following patient populations were evaluated and used for presentation and analysis of the data in this study:

• Full Analysis Set (FAS): All randomized patients who received any amount of study drug. Primary efficacy analyses were based on the FAS. Patients in the FAS were analyzed according to the treatment to which they were randomized.

• Vutrisiran Monotherapy Subgroup FAS (mono-FAS): All patients who were not on tafamidis at the study baseline in the FAS. Patients were analyzed according to the treatment to which they were randomized.

• Safety Analysis Set (SAF): All patients who received any amount of study drug. Safety analyses were based on the SAF. Patients were analyzed according to the treatment received. Patients who were randomized to placebo group but received any amount of vutrisiran during the DB Period were grouped into the vutrisiran arm.

• Vutrisiran Monotherapy Subgroup Safety Analysis Set (mono-SAF): All patients who were not on tafamidis at the study baseline in the SAF. Patients were analysed according to the treatment received.

• PK Analysis Set: All patients who received at least 1 full dose of study drug and had at least 1 postdose blood sample for PK parameters and had evaluable PK data. Patients were analyzed according to the first treatment received.

• PD Analysis Set: All patients who received at least 1 full dose of study drug and had an evaluable baseline and at least 1 evaluable postbaseline sample for TTR assessment. Patients were analyzed according to the first treatment received.

• All Vutrisiran Treated Set: All patients who received any amount of vutrisiran during the study, including patients who took vutrisiran during the DB Period and patients who first took placebo during the DB Period and switched to vutrisiran during the OLE Period.

• Vutrisiran Monotherapy Subgroup All Vutrisiran Treated Set: All patients who were not on tafamidis at the first dose of vutrisiran in All Vutrisiran Treated Set.

Efficacy endpoints were analyzed using the FAS and mono-FAS. As an important subgroup, efficacy endpoints were also analyzed in the background tafamidis subgroup. In general, the same statistical model was used for analyzing the efficacy endpoint for overall population, the vutrisiran monotherapy subgroup, and the background tafamidis subgroup, with the exception that in the analysis of the overall population, baseline tafamidis use was used as an additional covariate or stratification factor.

The primary endpoints of all-cause mortality and recurrent CV events were analyzed using a modified Andersen-Gill model with a robust variance estimator. The model included treatment group, ATTR amyloidosis disease type, NYHA class, age group, and baseline NT-proBNP as covariates. The overall population analysis was also stratified by baseline tafamidis use.

All-cause mortality was analyzed by log-rank test, stratified by baseline NT-proBNP group. Treatment effect between treatment groups were quantified by Cox proportional hazard model, in which treatment, ATTR amyloidosis disease type, NYHA class, age group, and baseline NT-proBNP were included as covariates. The overall population analyses were also stratified by baseline tafamidis use. The analysis included the vital status data collected after study discontinuation.

The component of recurrent CV events was analyzed by Poisson regression model including treatment, ATTR disease type, NYHA class, age group, and baseline NT-proBNP as covariates, adjusting for the event follow-up time (i.e., including this duration as an offset). The overall population analysis also included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates. Recurrent CV events were also analyzed using a Joint Frailty Model (JFM) as a sensitivity analysis.

An overview of the sensitivity analyses for the primary endpoint is outlined in Table 3 below.

Table 3. Overview of the sensitivity analyses for the primary endpoint

Sensitivity Analysis	**Analysis Details**
Win ratio analysis	Calculated from the ranking of each possible vutrisiran-placebo pair based on survival time and the frequency (count) of CV events in a hierarchical order. Stratification factor: baseline NT-proBNP group Overall population analysis: also stratified by baseline tafamidis use
Analyses based on alternative definitions of the composite outcome	The same model from the primary analysis was applied. • All-cause mortality: Heart transplant and left ventricular assist device placement were not included in all-cause mortality. Patients were censored at the date of such procedure or at the censoring date, whichever was earlier. • CV events: In addition to the CV events defined in the primary analysis, SGLT2 inhibitor drop-in with cardiac disease progression as reason was treated as a CV event. • CV events: Using CV events per investigator assessment instead of per CEC adjudication

Sensitivity Analysis	Analysis Details
Analysis based on the DB and the first 6 months of OLE Period	The primary endpoints based on data in the DB Period and up to the first 6 months of OLE Period were also analyzed using the same statistical method used for the primary analysis.
Analysis based on imputing CV events after study discontinuation	A 2-stage multiple imputation process was used to assess the sensitivity of the primary analysis for any missing CV events due to early study discontinuation.
Analysis based on truncating outliers	For patients with >7 events during the DB Period, the first 7 most important events were kept for analysis, with importance ranked in the order of death, CV hospitalization and urgent HF visit. The same model from the primary analysis was applied after the truncation.

Secondary endpoints were analysed for the overall population and the vutrisiran monotherapy subgroup as summarised in Table 4 below.

Table 4. Secondary endpoints: analysis details

	Secondary Endpoints: Analysis Details		
Analysis	**Change from baseline in 6-MWT/KCCQ-OS at Month 30**	**All-cause Mortality through 42 months**	**Change from baseline in NYHA Class at Month 30 (dichotomized into 2 categories: stable/improved vs worsened)**
Primary Analysis	• Performed using a REML based MMRM approach • Model included baseline 6-MWT/KCCQ-OS as a covariate, and treatment, visit, treatment-by-visit interaction, ATTR disease type, and age group as fixed effect terms. • Overall population analysis included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as fixed effect terms	• Survival time was calculated as time from first dose of study drug to last survival follow-up date up to 42 months, regardless of whether the patient entered the OLE Period • Log-rank test, stratified by baseline NT-proBNP group is used to test the difference between vutrisiran and placebo. • Cox PH model with treatment, ATTR disease type, NYHA Class, age group and baseline NT-proBNP as covariates was used to estimate the overall HR and 95% CI. • Adjusted KM curves using inverse probability of	• CMH analysis stratified by baseline NT-proBNP. • Overall population analysis also stratified by baseline tafamidis use.

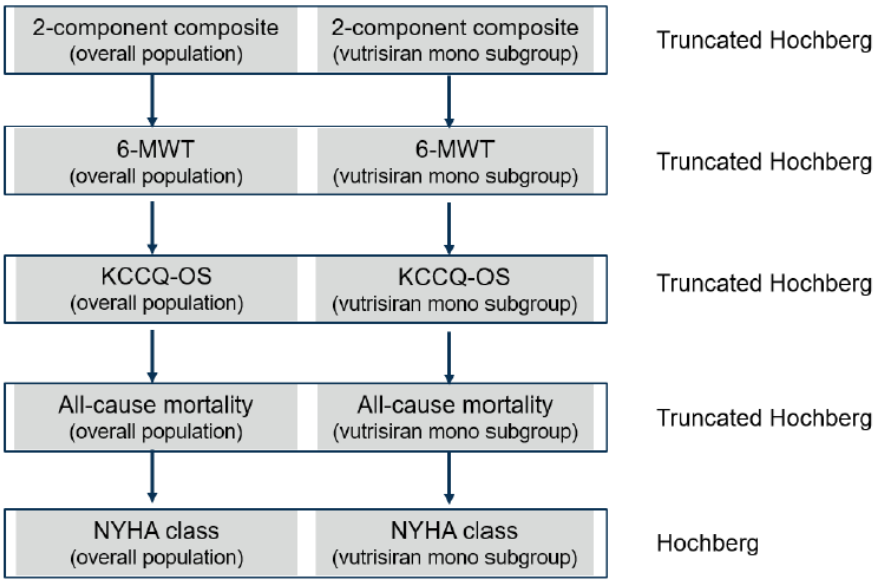
Analysis	Secondary Endpoints: Analysis Details		
	Change from baseline in 6-MWT/KCCQ-OS at Month 30	**All-cause Mortality through 42 months**	**Change from baseline in NYHA Class at Month 30 (dichotomized into 2 categories: stable/improved vs worsened)**
		treatment weighting (IPTW) presented • Overall population analysis stratified by baseline tafamidis use (yes vs. no).	

Two pivotal trials in ATTR amyloidosis with cardiomyopathy, including ATTR-ACT and ATTRibute-CM, indicated that therapeutics with upstream mechanisms of action take approximately 18 months to manifest benefit on mortality. Therefore, the analysis of the secondary endpoint, all-cause mortality, included survival data collected within 6 months after the first dose during the OLE Period (i.e., through 42 months), to improve the precision of estimates and to increase the power to detect a treatment difference.

The missing 6-MWT change from baseline values due to amyloidosis disease progression and death were imputed as the average of 20 random samples with replacement from the worst 10% of observed change from baseline of all patients at the same visit from the same treatment arm and baseline tafamidis use group, capped by 0-baseline distance. After imputation, the change from baseline to Month 30 in 6-MWT was analyzed using a MMRM model. Sensitivity analyses were conducted to assess the impact of missing data and the robustness of the primary analysis using the MMRM model without imputing missing due to death and the pattern mixture model which assumes data is not missing at random.

The overall Type I error rate for the primary endpoints and secondary endpoints was controlled at a 2-sided 0.05 significance level using a prespecified multiplicity testing procedure. The primary endpoint family and the first three secondary endpoint families were tested using a truncated Hochberg test with a truncation fraction of 0.96, and the last secondary endpoint family was tested using a regular Hochberg test. For testing the primary endpoint family, if the larger p-value of the two primary endpoints was ≤0.049, both null hypotheses were rejected and the 6-MWT family continued to test; if the larger p-value was >0.049 and the smaller p-value was ≤0.025, the null hypothesis corresponding to the smaller p-value was rejected and the 6-MWT continued to test defined in the population (at alpha level of 0.001) which was rejected in the primary endpoint testing; if the larger p-value was >0.049 and the smaller p-value was >0.025, both null hypotheses were accepted and the testing procedure was stopped.

Figure 12. Multiplicity testing procedure for testing primary and secondary endpoints



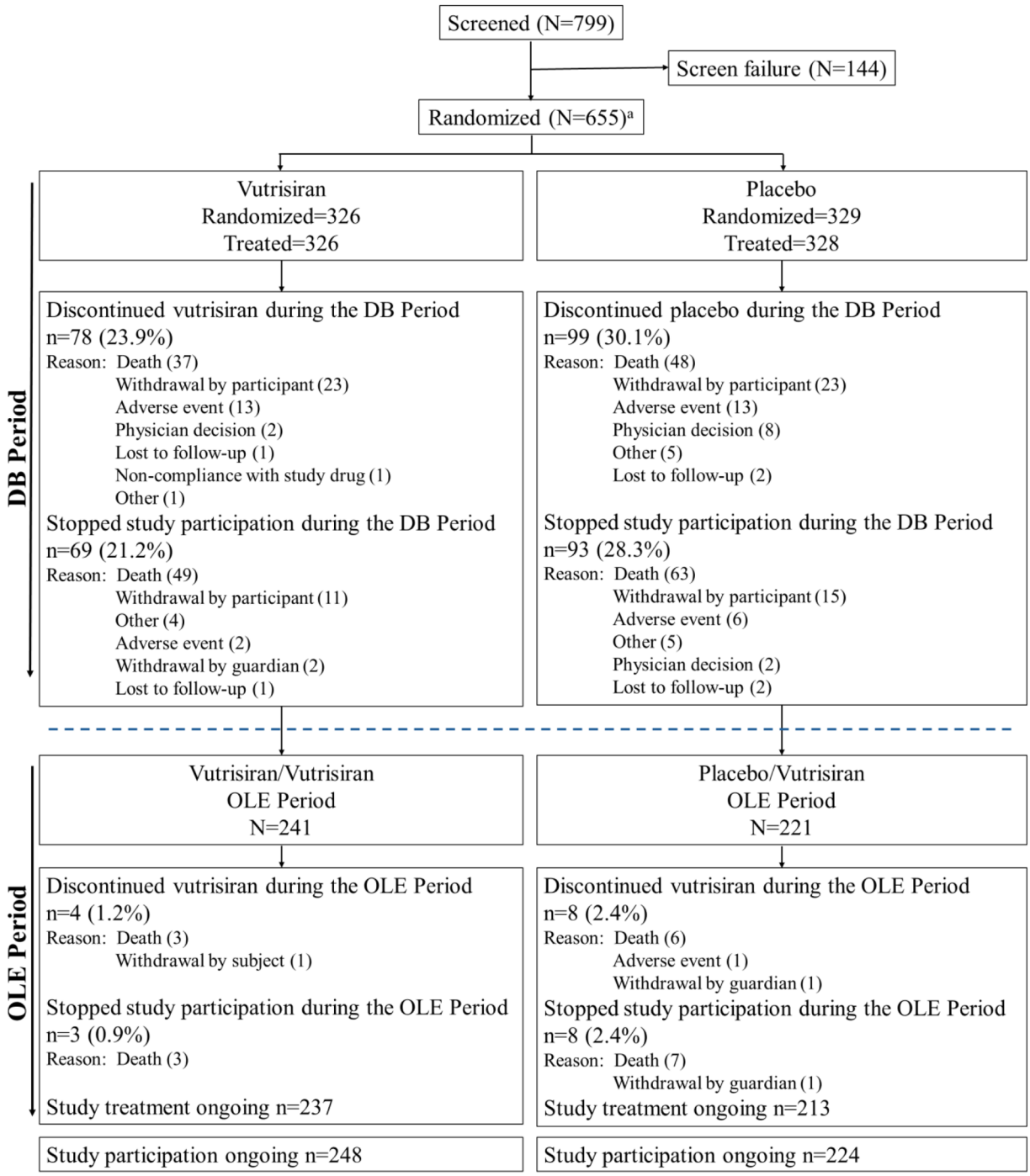
NT-proBNP was prespecified in the SAP as a key factor for adjustment in the outcome endpoint analysis models as it is a well-established risk factor for CV hospitalization and mortality in HF, including ATTR-CM. However, adjustment was not prespecified for Kaplan-Meier curves, as a significant imbalance was not anticipated in a randomized study. After unblinding, due to a significant imbalance in baseline NT-proBNP and troponin I between treatment groups, adjusted Kaplan-Meier curves were generated using the Inverse Probability of Treatment Weighting (IPTW) method for time to event endpoints, including all-cause mortality and time to first CV event or all-cause mortality. The IPTW-adjusted Kaplan-Meier curve provides a more accurate estimate of survival probabilities by accounting for baseline differences between treatment groups.

Results

Patient disposition based on the 08 May 2024 data cutoff date, corresponding to the 14 June 2024 database lock date, is presented in Figure 13. Of the 799 patients screened, 655 patients were randomized to either vutrisiran (326 patients) or placebo (329 patients). Of these 655 patients, 1 patient randomized to placebo was not dosed and not included in the FAS (or analysis populations).

Participant flow

Figure 13. Disposition of patients



Abbreviations: DB=double-blind; OLE=open-label extension.
Note: Patients who discontinued study drug during the DB or OLE Periods could remain in the study to complete safety follow-up.
[a] One subject who was randomized to placebo but did not receive a dose of study drug is not included in the overall treatment disposition.
Sources: Table 14.1.1.1, Table, 14.1.1.1b, Table 14.1.1.4, and Listing 16.2.1.1

Vutrisiran Group

Of the 326 patients in the vutrisiran group, 78 (23.9%) patients discontinued study drug during the DB Period; the most common reasons were death (37 patients), withdrawal by patient (23 patients), and AE (13 patients). Sixty-nine (21.2%) patients stopped study participation during the DB Period; the primary reasons were death (49 patients) and withdrawal by participant (11 patients).

Two hundred and forty-one patients in the vutrisiran group entered the OLE Period. Four (1.2%) patients discontinued study drug during the OLE Period; the primary reasons were death (3 patients) and withdrawal by patient (1 patient). Three (0.9%) patients stopped study participation during the OLE Period; the primary reason for all 3 patients was death.

Placebo Group

Of the 329 patients in the placebo group, 99 (30.1%) patients discontinued study drug during the DB Period; the most common reasons were death (48 patients), withdrawal by participant (23 patients), and AE (13 patients). Ninety-three (28.3%) patients in the placebo group stopped study participation during the DB Period; the primary reasons were death (63 patients) and withdrawal by participant (15 patients)

Two hundred and twenty-one patients in the placebo group entered the OLE Period. Eight (2.4%) patients discontinued study drug during the OLE Period; the primary reasons were death (6 patients), AE (1 patient), and withdrawal by guardian (1 patient). Eight (2.4%) patients in the placebo group stopped study participation during the OLE Period; the primary reasons were death (7 patients) and withdrawal by guardian (1 patient).

Patients who discontinued study drug during the DB or OLE Periods could remain in the study to complete safety follow-up.

As of the data cutoff date, 248 patients in the vutrisiran group and 224 patients in the placebo group were still participating in the study.

Extent of Exposure

DB Period

In the overall population, the median duration of treatment in the vutrisiran group was 35.78 months (range: 0.6 to 38.7 months), with a cumulative treatment exposure of 833.9 person-years. Two hundred and fifty-seven (78.8%) patients had vutrisiran exposure ≥30 months, and 77 (23.6%) patients had vutrisiran exposure ≥36 months. The median duration of treatment in the placebo group was 33.77 months (range: 1.1 to 37.3 months), with a cumulative treatment exposure of 822.4 person-years.

In the vutrisiran monotherapy subgroup, the median duration of treatment in the vutrisiran group was 33.28 months (range: 0.6 to 38.2 months), with a cumulative treatment exposure of 472.6 person-years. One hundred and forty-four (73.5%) patients had vutrisiran exposure ≥30 months, and 35 (17.9%) patients had vutrisiran exposure ≥36 months. The median duration of treatment in the placebo group was 33.15 months (range: 1.1 to 37.0 months), with a cumulative treatment exposure of 474.8 person-years.

All Vutrisiran Treated Set

For the All Vutrisiran Treated Set, the median duration of vutrisiran exposure was 19.25 months (range: 0.0 to 51.6 months), with a cumulative treatment exposure of 979.7 patient-years. The median duration of treatment in the vutrisiran/vutrisiran group was 37.55 months (range: 0.6 to 51.6 months), with a cumulative treatment exposure of 912.3 person-years. The median duration of treatment in the placebo/vutrisiran group was 3.45 months (range: 0.0 to 15.2 months), with a cumulative treatment exposure of 67.4 person-years.

Recruitment

Patients were randomized and treated at 87 study centers in 26 countries. Countries that randomized ≥10 patients were US (165 patients [25.2%]), United Kingdom (151 patients [23.1%]), Spain (64 patients [9.8%]), Germany (37 patients [5.6%]), France (29 patients [4.4%]), Australia (28 patients [4.3%]), Japan (25 patients [3.8%]), Netherlands (22 patients [3.4%]), Portugal (17 patients [2.6%]), Argentina (16 patients [2.4%]), Sweden (15 patients [2.3%]), Norway (14 patients [2.1%]), Denmark (12 patients [1.8%]), Belgium (11 patients [1.7%]), and Austria (10 patients [1.5%]).

Conduct of the study

A Data Quality Assurance system was in place with eCRFs, investigators meetings, clinical monitors in place and risk management processes. 12 sites underwent audits for compliance with GCP requirements.

Protocol Amendments

The protocol was finalized on 22 August 2019. There were 5 global protocol amendments, plus a number of country-specific protocol amendments; the major changes of which are described below:

Amendment 0.1 (France) 20 May 2020

- Changes related to Urgent safety measures (USMs) amid the COVID-19 pandemic.

Amendment 1 (global) 28 May 2020

- Changes related to Urgent safety measures (USMs) amid the COVID-19 pandemic.
- Revised primary and secondary objectives and endpoints. The primary composite endpoint of "all-cause mortality and recurrent CV hospitalizations" was changed to "all-cause mortality and recurrent CV events." Recurrent CV events include CV hospitalizations and urgent HF visits. The composite secondary endpoint of "all-cause mortality and recurrent all-cause hospitalizations" was revised to also include urgent HF visits. The secondary endpoint of "recurrent CV hospitalizations was revised to "recurrent CV events" to include urgent HF visits.
- Modified inclusion and exclusion criteria based in part on feedback from regulators and Investigators that the prior criteria would unnecessarily exclude patients with ATTR amyloidosis with cardiomyopathy for whom the risk benefit profile favors inclusion in the study. The modifications pertained (among others) to documentation of TTR protein in cardiac tissue, allow for lower NT-proBNP levels at entry and modification of several exclusion criteria.
- other changes including exclusion of deaths and hospitalizations due to COVID-19 from all-cause deaths and hospitalizations in the primary analyses of primary and applicable secondary endpoints, and other modifications.

Amendment 1 (France) 28 May 2020

- Integration of global amendment 1 into the country specific amendment.

Amendment 2 (global) 18 February 2021

- Removed limit of 30% on enrollment of patients receiving tafamidis at study entry.
- Adjustments to inclusion criteria 4a and 2biv Amendment 3 (global) 13 May 2022
- and others

Amendment 3 (global) 13 May 2022

- Added an Open-label RTE Period to allow a descriptive comparison of 2 vutrisiran dosing regimens administered during this period, 25 mg q3M (the regimen tested during the DB Period) and 50 mg q6M.
- and others

Amendment 3.1 (United States) 17 May 2022

- Enabled the collection of clinical data on the use of a single prefilled syringe with a fill volume of 1.0 mL (total dose of 50 mg vutrisiran) for the 50 mg q6M dosing regimen after this presentation of the drug product becomes available for use.
- and others

Amendment 4 (global) 22 March 2023 and Amendment 4 (United States) 29 March 2023

- Transitioned all patients in the 50 mg q6M vutrisiran arm of the extension period to receive 25 mg q3M vutrisiran for the remainder of their dosing visits in the study.
- deletion of the planned interim analysis.
- and others

Amendment 5 (global) 12 February 2024

2024

- Expanded the analysis of the existing primary endpoint to include the vutrisiran monotherapy subgroup (defined as the subgroup of patients not on tafamidis at study baseline) in addition to the overall population which was the original analysis.
- Restructuring the existing secondary and exploratory endpoints.
- Additional statistical updates
- and others

Several Urgent Safety Measures due to COVID-19 were implemented as communicated in a Dear Investigator Letter, dated 07 April 2020. These USMs were incorporated into France Amendment 0.1 (dated 20 May 2020) and global Amendment 1 (dated 28 May 2020).

Baseline data

Baseline demographics were similar for patients in the vutrisiran monotherapy subgroup compared with patients in the overall population. In the overall population, the mean age was 75.4 years (range, 45 to 85 years) and the majority of patients were white (84.4%) and male (92.5%) (Table 5).

Baseline demographic characteristics were similar between the vutrisiran and placebo groups in the overall population and in the vutrisiran monotherapy subgroup.

In the background tafamidis subgroup, the majority of patients, 61.0%, were from the US, whereas in the vutrisiran monotherapy subgroup, only 1.5% were from the US. Other baseline demographics were similar for patients who were on tafamidis at baseline (background tafamidis subgroup) compared with patients who were not on tafamidis at baseline (vutrisiran monotherapy subgroup).

Baseline disease characteristics are summarized in Table 6.

Baseline disease characteristic were overall balanced between the groups. In the overall population, 578 (88.4%) patients had wtATTR amyloidosis and 76 (11.6%) patients had hATTR amyloidosis. The mean years since diagnosis of ATTR amyloidosis was 1.43 (range, 0.0 to 11.1) years. The mean age of patients at symptom onset was 73.3 (range, 35 to 85) years. Most (77.7%) patients had NYHA class II HF and were classified as having ATTR amyloidosis disease Stage 1 (66.8%) or Stage 2 (28.6%). In the overall population, baseline disease characteristics were generally similar between the vutrisiran and placebo groups, except for a higher median NT-proBNP level in the vutrisiran group (2020.50 ng/L) compared to the placebo group (1801.00 ng/L), which was primarily driven by an imbalance in the vutrisiran monotherapy subgroup.

In the vutrisiran monotherapy subgroup, there were some imbalances in parameters suggestive of a somewhat greater disease severity in patients randomized to vutrisiran compared to placebo (NT-proBNP and troponin I, percentage of patients with NT-proBNP >2000 ng/L, ATTR amyloidosis disease Stage and NYHA class, Table 6).

Table 5. Demographic characteristics for the DB period (full analysis set)

Demographic	Overall Population			Vutrisiran Monotherapy Subgroup		
	Placebo (N=328)	Vutrisiran (N=326)	Total (N=654)	Placebo (N=199)	Vutrisiran (N=196)	Total (N=395)
Age at randomization (years)						
Mean (SD)	75.2 (6.3)	75.5 (7.2)	75.4 (6.7)	75.5 (6.4)	76.3 (6.8)	75.9 (6.6)
Median (min, max)	76.0 (46, 85)	77.0 (45, 85)	77.0 (45, 85)	76.0 (53, 85)	77.5 (46, 85)	77.0 (46, 85)
Age group (years), n (%)						
<65	20 (6.1)	27 (8.3)	47 (7.2)	11 (5.5)	10 (5.1)	21 (5.3)
65 to <75	114 (34.8)	96 (29.4)	210 (32.1)	69 (34.7)	63 (32.1)	132 (33.4)
≥75	194 (59.1)	203 (62.3)	397 (60.7)	119 (59.8)	123 (62.8)	242 (61.3)
Sex, n (%)						
Male	306 (93.3)	299 (91.7)	605 (92.5)	183 (92.0)	178 (90.8)	361 (91.4)
Female	22 (6.7)	27 (8.3)	49 (7.5)	16 (8.0)	18 (9.2)	34 (8.6)
Race, n (%)						
White	275 (83.8)	277 (85.0)	552 (84.4)	169 (84.9)	169 (86.2)	338 (85.6)
Black or African American	24 (7.3)	23 (7.1)	47 (7.2)	11 (5.5)	10 (5.1)	21 (5.3)
Asian	19 (5.8)	18 (5.5)	37 (5.7)	15 (7.5)	12 (6.1)	27 (6.8)
Not reported	8 (2.4)	6 (1.8)	14 (2.1)	2 (1.0)	3 (1.5)	5 (1.3)
Other	2 (0.6)	2 (0.6)	4 (0.6)	2 (1.0)	2 (1.0)	4 (1.0)
Ethnicity, n (%)						
Not Hispanic or Latino	304 (92.7)	298 (91.4)	602 (92.0)	179 (89.9)	171 (87.2)	350 (88.6)
Hispanic or Latino	16 (4.9)	22 (6.7)	38 (5.8)	16 (8.0)	21 (10.7)	37 (9.4)
Not reported	7 (2.1)	5 (1.5)	12 (1.8)	3 (1.5)	4 (2.0)	7 (1.8)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.5)	0	1 (0.3)
Region[a], n (%)						
Europe	198 (60.4)	206 (63.2)	404 (61.8)	156 (78.4)	160 (81.6)	316 (80.0)
US	83 (25.3)	81 (24.8)	164 (25.1)	1 (0.5)	5 (2.6)	6 (1.5)
Rest of World	47 (14.3)	39 (12.0)	86 (13.1)	42 (21.1)	31 (15.8)	73 (18.5)

Abbreviations: DB=double-blind; max=maximum; min=minimum; SD=standard deviation; US=United States.
Note: Baseline is defined as the last non-missing measurement before the first dose in the DB Period.

[a] Europe includes Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Spain, Sweden, and United Kingdom. Rest of World includes Argentina, Australia, Canada, Israel, Japan, Peru, and South Korea.
Source: Table 14.1.2.1

Table 6. Baseline disease characteristics and ATTR diagnosis during the DB period (full analysis set)

Parameter	Overall Population			Vutrisiran Monotherapy Subgroup		
	Placebo (N=328)	**Vutrisiran (N=326)**	**Total (N=654)**	**Placebo (N=199)**	**Vutrisiran (N=196)**	**Total (N=395)**
ATTR amyloidosis type, n (%)						
wtATTR amyloidosis	289 (88.1)	289 (88.7)	578 (88.4)	174 (87.4)	173 (88.3)	347 (87.8)
hATTR amyloidosis	39 (11.9)	37 (11.3)	76 (11.6)	25 (12.6)	23 (11.7)	48 (12.2)
Time since ATTR amyloidosis diagnosis (years)						
Mean (SD)	1.52 (1.63)	1.35 (1.57)	1.43 (1.60)	1.16 (1.28)	1.03 (1.27)	1.10 (1.28)
Median (min, max)	1.03 (0.0, 10.8)	0.86 (0.0, 11.1)	0.94 (0.0, 11.1)	0.63 (0.0, 6.2)	0.50 (0.0, 8.3)	0.60 (0.0, 8.3)
Age (years) at ATTR amyloidosis symptom onset, n (%)						
Mean (SD)	73.1 (6.7)	73.5 (7.5)	73.3 (7.1)	73.4 (6.7)	74.3 (7.3)	73.9 (7.0)
Median (min, max)	74.0 (44, 85)	75.0 (35, 85)	74.0 (35, 85)	75.0 (52, 85)	75.0 (35, 85)	75.0 (35, 85)
Baseline tafamidis use n (%)						
No	199 (60.7)	196 (60.1)	395 (60.4)	199 (100.0)	196 (100.0)	395 (100.0)
Yes	129 (39.3)	130 (39.9)	259 (39.6)	0	0	0
Time from start of tafamidis therapy to start of study drug (months)						
Median (min, max)	11.30 (1.1, 65.5)	9.18 (1.1, 65.3)	10.84 (1.1, 65.5)	NA	NA	NA
NYHA class, n (%)						
I	35 (10.7)	49 (15.0)	84 (12.8)	12 (6.0)	15 (7.7)	27 (6.8)
II	258 (78.7)	250 (76.7)	508 (77.7)	169 (84.9)	172 (87.8)	341 (86.3)
III	35 (10.7)	27 (8.3)	62 (9.5)	18 (9.0)	9 (4.6)	27 (6.8)
NT-proBNP (ng/L)						
Median (min, max)	1801.00 (317.0, 7988.0)	2020.50 (322.0, 8892.0)	1919.50 (317.0, 8892.0)	1865.00 (335.0, 7988.0)	2402.00 (370.0, 8892.0)	2128.00 (335.0, 8892.0)
NT-proBNP, n (%)						
>2000 ng/L	147 (44.8)	165 (50.6)	312 (47.7)	92 (46.2)	115 (58.7)	207 (52.4)

Parameter	Overall Population			Vutrisiran Monotherapy Subgroup		
	Placebo (N=328)	Vutrisiran (N=326)	Total (N=654)	Placebo (N=199)	Vutrisiran (N=196)	Total (N=395)
>3000 ng/L	86 (26.2)	99 (30.4)	185 (28.3)	54 (27.1)	73 (37.2)	127 (32.2)
Troponin I (ng/L)						
Median (min, max)	65.20 (10.0, 30827.7)	71.90 (10.0, 8712.0)	67.45 (10.0, 30827.7)	62.20 (10.0, 30827.7)	76.25 (10.0, 2304.2)	68.90 (10.0, 30827.7)
eGFR (mL/min/1.73m^2)						
Median (min, max)	65.0 (26, 152)	64.0 (28, 205)	65.0 (26, 205)	65.0 (26, 152)	64.0 (28, 205)	65.0 (26, 205)
ATTR amyloidosis disease stage, n (%)						
Stage 1	229 (69.8)	208 (63.8)	437 (66.8)	138 (69.3)	113 (57.7)	251 (63.5)
Stage 2	87 (26.5)	100 (30.7)	187 (28.6)	55 (27.6)	68 (34.7)	123 (31.1)
Stage 3	12 (3.7)	18 (5.5)	30 (4.6)	6 (3.0)	15 (7.7)	21 (5.3)

Abbreviations: ATTR=transthyretin-mediated amyloidosis; DB=double-blind; eGFR=estimated glomerular filtration rate; hATTR=hereditary ATTR (amyloidosis); max=maximum; min=minimum; NA=not applicable; NT-proBNP=*N*-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; SD=standard deviation; wtATTR=wild-type ATTR (amyloidosis).
Note: Baseline is defined as the last non-missing measurement before the first dose in the DB Period.
Source: Table 14.1.3.1

Baseline disease characteristics were indicative of somewhat greater disease severity among patients not on tafamidis at baseline (vutrisiran monotherapy subgroup) compared with patients who were on tafamidis at baseline (background tafamidis subgroup). Specifically, the proportion of patients in NYHA class I was lower among patients in the vutrisiran monotherapy subgroup compared with those in the background tafamidis subgroup (6.8% and 22.0%, respectively), mean 6-MWT distance was lower (367.808 and 384.918 meters, respectively), mean KCCQ-OS was lower (70.11 and 76.40, respectively), and median NT-proBNP was greater (2128.00 and 1759.00 pg/mL, respectively).

All Vutrisiran Treated Set

The combination of the vutrisiran/vutrisiran group (N=326) and placebo/vutrisiran group (N=221) comprises the All Vutrisiran Treated Set (N=547).

In the All Vutrisiran Treated Set, 493 (90.1%) patients had wtATTR amyloidosis and 54 (9.9%) patients had hATTR amyloidosis. The majority of patients were NYHA class II (72.8%). In addition, there were 76 (13.9%) patients with NYHA class I and 73 (13.3%) patients with NYHA class III; no patients were class IV. Overall, 48.1% of patients were on tafamidis before their first dose of vutrisiran.

The baseline for the All Vutrisiran Treated Set was defined as the latest assessment prior to the first dose of vutrisiran. Thus, although disease severity was similar between patients in the overall placebo and vutrisiran groups at baseline in the DB Period, patients in the placebo/vutrisiran group tended to have more advanced disease at the time they received their first dose of vutrisiran compared to patients in the vutrisiran/vutrisiran group, as demonstrated by an increased proportion of patients with NYHA class III (20.8% and 8.3% [overall population] and 23.9% and 4.6% [vutrisiran monotherapy subgroup]).

Medical History

Overall Population

In the overall population, the most frequently reported (≥50% of patients overall) medical history conditions were in the SOCs of cardiac disorders (99.2%), nervous system disorders (67.7%), metabolism and nutrition disorders and vascular disorders (65.4% each), musculoskeletal and connective tissue disorders (60.6%), and eye disorders (59.3%).

Overall, 35.5% of patients also had a history of neuropathy/polyneuropathy. Of these, 94.8% reported sensory neuropathy, 15.5% reported motor neuropathy, and 8.6% reported autonomic neuropathy.

Vutrisiran Monotherapy Subgroup

In the Vutrisiran Monotherapy Subgroup, the most frequently reported (≥50% of patients overall) medical history conditions were in the SOCs of cardiac disorders (99.5%), nervous system disorders (64.3%), vascular disorders (62.5%), metabolism and nutrition disorders (60.3%), musculoskeletal and connective tissue disorders (54.9%), and eye disorders (53.4%),

Overall, 30.1% of patients also had a history of neuropathy/polyneuropathy. Of these, 93.3% reported sensory neuropathy, 15.1% reported motor neuropathy, and 10.9% reported autonomic neuropathy.

Treatment Compliance

DB Period

In the overall population vutrisiran group, 303 (92.9%) patients had no missed doses of study drug, 16 (4.9%) patients had 1 missed dose, and 7 (2.1%) patients had 2 missed doses. In the overall population placebo group, 311 (94.8%) patients had no missed doses of study drug, 14 (4.3%) patients had 1 missed dose, and 3 (0.9%) patients had 2 missed doses. Treatment compliance was similar for patients in the vutrisiran monotherapy subgroup compared with patients in the overall population.

All Vutrisiran Treated Set

In the All Vutrisiran Treated Set, 515 (94.1%) patients received all planned doses of study drug, 25 (4.6%) patients had 1 missed dose, and 7 (1.3%) patients had 2 missed doses.

Protocol Deviations

In total, major protocol deviations were reported for 157 patients (87 [26.4%] placebo, 70 [21.5%] vutrisiran) during the study:

Major protocol deviations by category reported in ≥20 patients were:

• 60 major protocol deviations (in 52 patients; 34 [10.3%] placebo, 18 [5.5%] vutrisiran) were in the category of Other Protocol Deviation:

– All 60 deviations were related to failure to report SAEs or AEs of clinical interest within 24 hours

• 60 major protocol deviations (in 51 patients; 28 [8.5%] placebo, 23 [7.1%] vutrisiran) were in the category of Informed Consent:

• 25 major protocol deviations (in 24 patients; 12 [3.6%] placebo, 12 [3.7%] vutrisiran) were in the category of Missing Endpoint Assessments.

– All 25 deviations were related to the primary endpoint or secondary endpoint assessments being missed (at baseline or end of DB Period [Month 30]) or that were conducted outside of the analysis window (±3 months).

o 16 deviations were related to secondary endpoint assessments being missed at baseline or Month 30.

o 9 deviations were related to the duration of the DB Period being truncated at 33 months instead of the planned 36 months.

The remaining major protocol deviations were in the categories of study treatment compliance (15 patients), study procedures assessments (10 patients), eligibility criteria (9 patients), study treatment admin/dispense (9 patients), accidental unblinding (6 patients), and concomitant medication (4 patients)

The remaining deviations were minor.

Impact of the COVID Pandemic on Study Participation

The impact of the COVID-19 pandemic on study patients was assessed on the basis of missed, delayed or partially completed visits, missed or delayed study drug doses, and visit location changes, such as home health or phone visits.

In the vutrisiran group, 42 (12.9%) patients were reported to have had their study visits or dosing impacted by the COVID-19 pandemic: 39 (12.0%) patients with a missed, delayed, or partially completed visit; 35 (10.7%) patients with any location change; and 11 (3.4%) patients with a missed or delayed dose.

In the placebo group, 49 (14.9%) patients were reported to have had their study visits or dosing impacted by the COVID-19 pandemic: 42 (12.8%) patients with a missed, delayed, or partially completed visit; 32 (9.8%) patients with any location change; and 10 (3.0%) patients with a missed or delayed dose

Impacted visits consisted primarily of partially completed visits, rather than missed or delayed visits, and location changes were mostly home or telehealth visits.

Numbers analysed

Analysis populations are summarised in Table 7.

Vital status was known for 326 of 326 (100%) vutrisiran patients and for 327 of 328 (99.7%) placebo patients in the overall population at the data cutoff date. The only placebo patient with unknown vital status was censored at approximately Month 30.

Table 7. Analysis populations

Study Population	No. of Patients (%)		
	Placebo (N=329)	Vutrisiran (N=326)	Overall (N=655)
Full Analysis Set (FAS)	328 (99.7)	326 (100)	654 (99.8)
Vutrisiran Monotherapy Subgroup Full Analysis Set (mono-FAS)	199 (60.5)	196 (60.1)	395 (60.3)
Safety Analysis Set	328 (99.7)	326 (100)	654 (99.8)
Vutrisiran Monotherapy Subgroup Safety Analysis Set	199 (60.5)	196 (60.1)	395 (60.3)
PK Analysis Set	328 (99.7)	326 (100)	654 (99.8)
PD Analysis Set	324 (98.5)	317 (97.2)	641 (97.9)
All Vutrisiran Treated Set	221 (67.2)	326 (100)	547 (83.5)
Vutrisiran Monotherapy Subgroup All Vutrisiran Treated Set	88 (26.7)	196 (60.1)	284 (43.4)

Abbreviations: PD=pharmacodynamic; PK=pharmacokinetic.
Source: Table 14.1.1.2

Outcomes and estimation

Analysis of efficacy:

The primary analysis complied comparisons in two different populations:

• Target patient population:

– Overall population: Patients with hATTR or wtATTR amyloidosis with cardiomyopathy regardless of use of tafamidis.

– Vutrisiran monotherapy subgroup: Patients with hATTR or wtATTR amyloidosis with cardiomyopathy who are tafamidis naïve.

The primary analysis cutoff date was prespecified as the date when all patients had completed at least 33 months of follow-up. Patients enrolled earlier were eligible to enter the OLE Period and received their first OLE dose at Month 36, while those enrolled later received their first OLE dose at Month 33. Two main all-cause mortality analyses were conducted using 2 follow-up durations:

Component analysis of all-cause mortality (DB Period; through 36 months):

Survival data were censored at the OLE first dose date for patients who entered the OLE Period, which occurred at approximately 33 or 36 months, depending on the patient's enrollment time. For patients who did not enter the OLE Period, survival data were censored at the earlier of last known alive date or 36 months.

• Secondary endpoint analysis of all-cause mortality (through 42 months): Patients who entered the OLE Period were censored the earlier of last known alive date or 6 months after their first OLE dose, which was approximately 39 or 42 months depending on their first OLE dose date. For patients who did not enter the OLE Period, survival data were censored at the earlier of last known alive date or 42 months.

Primary Endpoint: Composite Outcome of All-cause Mortality and Recurrent CV Events (CV Hospitalizations and Urgent HF Visits)

Events collected during the DB Period were included for the analyses of the primary endpoints, composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits).

In the overall population, vutrisiran patients had a statistically significant 28.2% reduction in the risk of all-cause mortality and recurrent CV events compared to placebo (hazard ratio: 0.718; 95% CI: 0.555, 0.929; P=0.0118) (Table 8 and Figure 14).

In the vutrisiran monotherapy subgroup, vutrisiran patients had a statistically significant 32.8% reduction in the risk of all-cause mortality and recurrent CV events compared to placebo (hazard ratio: 0.672; 95% CI: 0.487, 0.929; P=0.0162) (Table 9 and Figure 15).

Data in the complementary group of patients on background tafamidis therapy are shown in Table 14.2.1.1 (excerpt) below.

Table 8. Composite outcome of all-cause mortality and frequency of recurrent CV hospitalizations and urgent HF visits over the DB period, modified Andersen-Gill model

	Overall Population		Vutrisiran Monotherapy Subgroup	
Statistic	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Total number of events, n	332	251	211	155
All-cause mortality, n	69	51	46	36
CV deaths	53	39	34	28
CV-related	37	23	23	18
Indeterminate	12	13	10	10
Heart transplants	4	3	1	0
LVAD placement	0	0	0	0
Non-CV deaths	16	12	12	8

Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
CV events, n	263	200	165	119
CV hospitalizations	229	178	144	101
CV-related	224	174	139	97
Indeterminate	5	4	5	4
Urgent HF visits	34	22	21	18
Total follow-up time (years)	841.7	864.3	489.4	495.6
Patients with ≥1 event, n (%)	159 (48.5)	125 (38.3)	105 (52.8)	76 (38.8)
All-cause mortality	69 (21.0)	51 (15.6)	46 (23.1)	36 (18.4)
CV events	133 (40.5)	112 (34.4)	87 (43.7)	66 (33.7)
Hazard ratio (vutrisiran versus placebo)[a]	0.718		0.672	
95% CI	(0.555, 0.929)		(0.487, 0.929)	
p-value	0.0118		0.0162	

Abbreviations: ATTR=transthyretin-mediated amyloidosis; CI=confidence interval; CV=cardiovascular; DB=double-blind; HF=heart failure; LVAD=left ventricular assist device; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association.

[a] Based on the modified Andersen-Gill model including treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group as covariates. In the vutrisiran monotherapy subgroup, the analysis was based on the subgroup data only. In the overall population, the model was stratified by baseline tafamidis use.

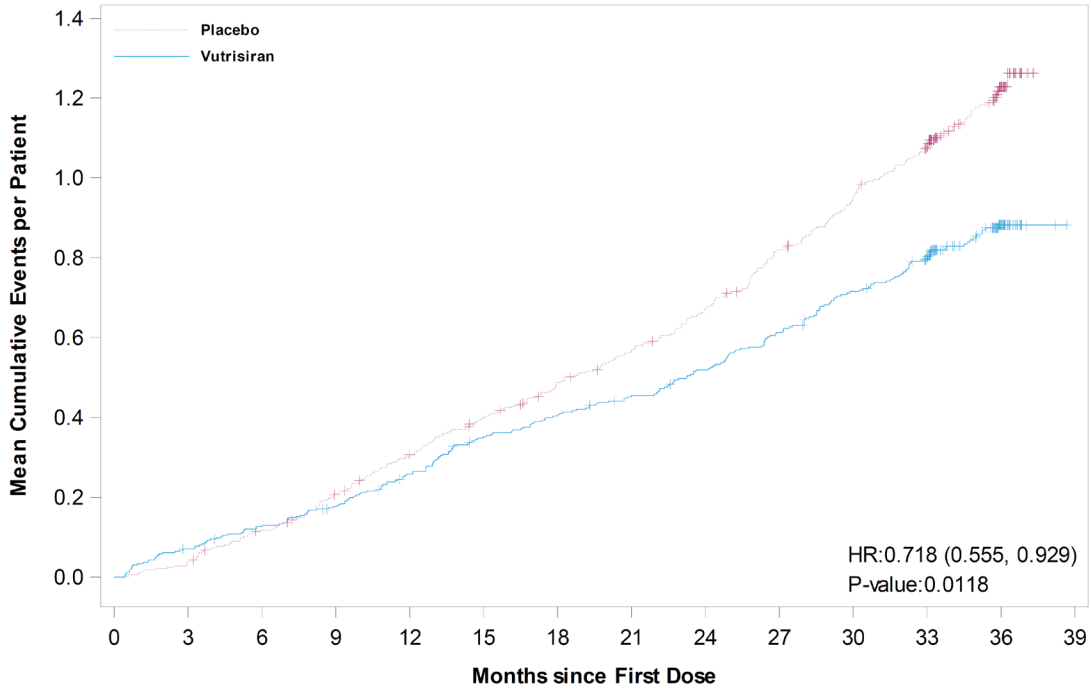
Source: Table 14.2.1.1

Table 14.2.1.1 (excerpt): Primary analysis of composite all-cause mortality and recurrent cardiovascular (CV) events during the double-blind (DB) period, modified Andersen-Gill model full analysis set

Statistic	Background Tafamidis Subgroup	
	Placebo (N=129)	Vutrisiran (N=130)
Total number of events, n	121	96
All-cause mortality, n	23	15
CV deaths	19	11
CV-related	14	5
Indeterminate	2	3
Heart transplants	3	3
LVAD placements	0	0
Non-CV deaths	4	4
CV events, n	98	81
CV hospitalizations	85	77
CV-related	85	77
Indeterminate	0	0
Urgent heart failure visits	13	4
Total follow-up time (years)	352.4	368.6
Observed event rate (total number of events/total follow-up years)	0.343	0.260

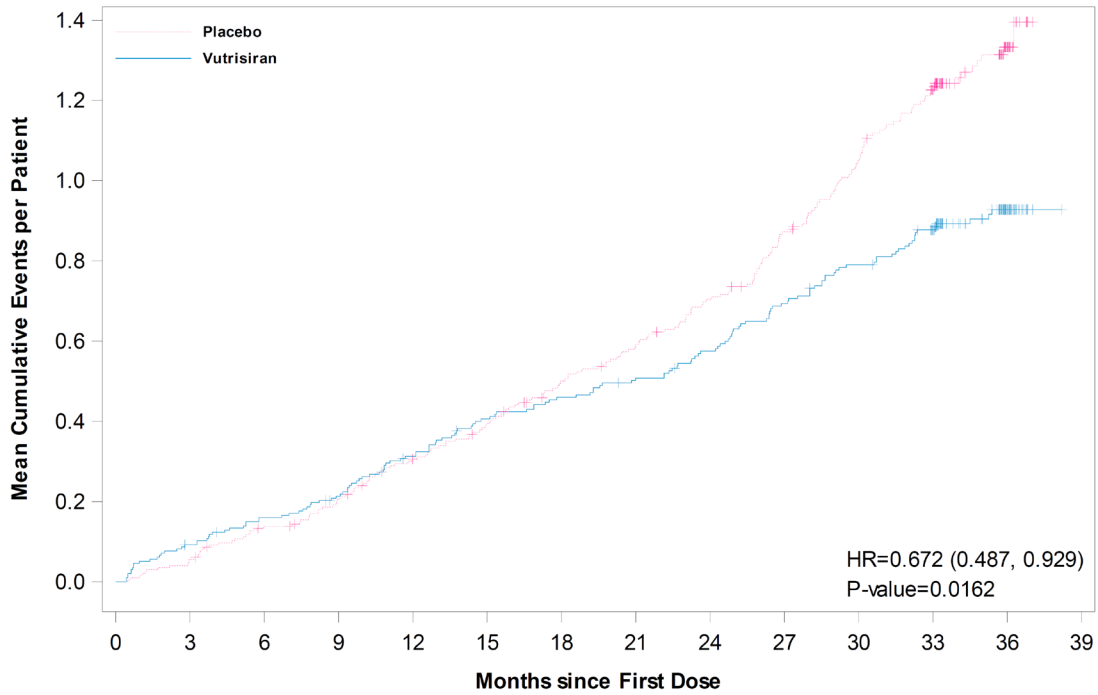
Statistic	Background Tafamidis Subgroup	
	Placebo (N=129)	Vutrisiran (N=130)
Number (%) of patients with at least 1 event, n (%)	54 (41.9)	49 (37.7)
All-cause mortality	23 (17.8)	15 (11.5)
CV events	46 (35.7)	46 (35.4)
Hazard ratio (Vutrisiran vs Placebo) [1]		0.785
95% CI		0.511, 1.207
p-value		0.2701

Figure 14. Mean cumulative function plot of all-cause mortality and recurrent CV events during the DB period (overall population)



Abbreviations: CV=cardiovascular; DB=double-blind; HR=hazard ratio.
Source: Figure 14.2.1.1.1.

Figure 15. Mean cumulative function plot of all-cause mortality and recurrent CV events during the DB period (Vutrisiran monotherapy subgroup)



Abbreviations: CV=cardiovascular; DB=double-blind; HR=hazard ratio.
Source: Figure 14.2.1.1.2.

Individual Components of the Primary Endpoint

Component Analysis: All-Cause Mortality

Events reported after study withdrawal were included for the component analysis of all-cause mortality. In the overall population, vutrisiran treatment led to a 30.6% reduction in the risk of all-cause mortality compared to placebo (hazard ratio: 0.694; 95% CI: 0.490, 0.982; P=0.0389) (Table 9 and Figure 16).

In the vutrisiran monotherapy subgroup, vutrisiran treatment led numerically to a 29.5% reduction in the risk of all-cause mortality compared to placebo (hazard ratio: 0.705; 95% CI: 0.467, 1.064; P=0.1179) (Table 9 and Figure 17).

Table 9. Component analysis of the primary endpoint: all-cause mortality during the DB period

Category	Overall Population		Vutrisiran Monotherapy Subgroup	
	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
All-cause mortality included in the analysis, n (%)	75 (22.9)	56 (17.2)	52 (26.1)	41 (20.9)
CV-related deaths	37 (11.3)	25 (7.7)	23 (11.6)	20 (10.2)
Indeterminate deaths	17 (5.2)	16 (4.9)	15 (7.5)	13 (6.6)
Non-CV-related deaths	17 (5.2)	12 (3.7)	13 (6.5)	8 (4.1)
Heart transplantations	4 (1.2)	3 (0.9)	1 (0.5)	0
LVAD placements	0	0	0	0
Hazard ratio from Cox PH model (vutrisiran/placebo) (95% CI)	0.694 (0.490, 0.982)		0.705 (0.467, 1.064)	
p-value	0.0389		0.1179	

Figure 16. Adjusted cumulative incidence rate plot of component analysis all-cause mortality during the DB period (overall population)

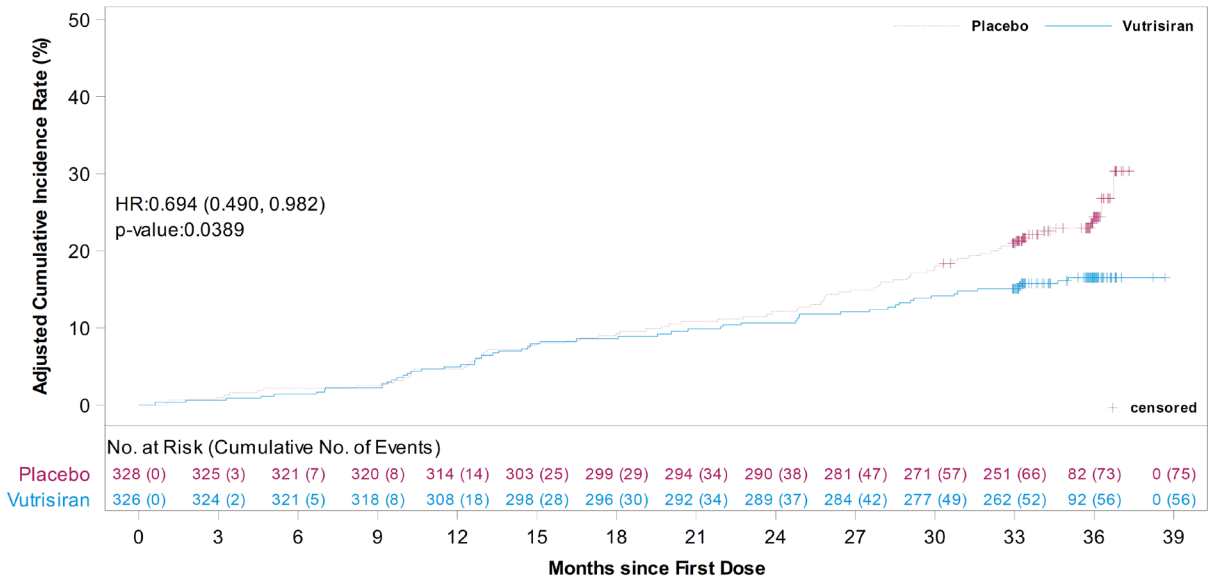
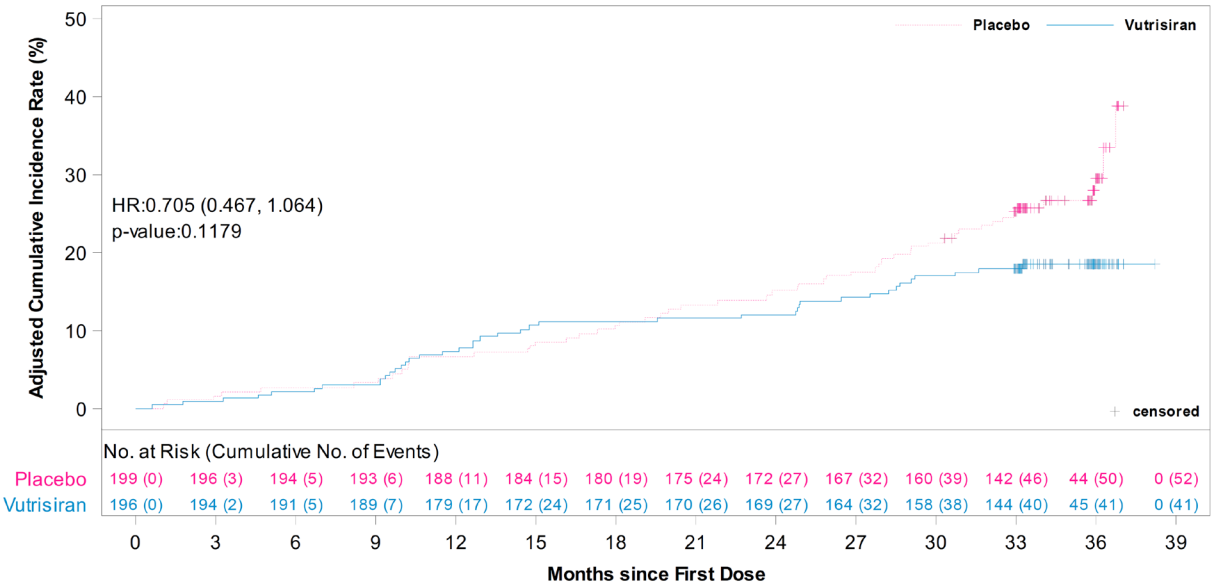


Figure 17. Adjusted cumulative incidence rate plot of component analysis all-cause mortality during the DB period (Vutrisiran monotherapy subgroup)



The prespecified sensitivity analysis of weighted log-rank FH (1,1) test, which allocates more weight to events that occurred at a later time period, also demonstrated a reduction in mortality in the vutrisiran group compared to placebo in both the overall population (P=0.0175) and the vutrisiran monotherapy subgroup (P=0.0327).

An additional analysis was performed to summarize CV-related mortality and resulted in a similar treatment effect as the all-cause mortality analyses in both the overall population and the vutrisiran monotherapy subgroup.

Component Analysis: Recurrent CV Events

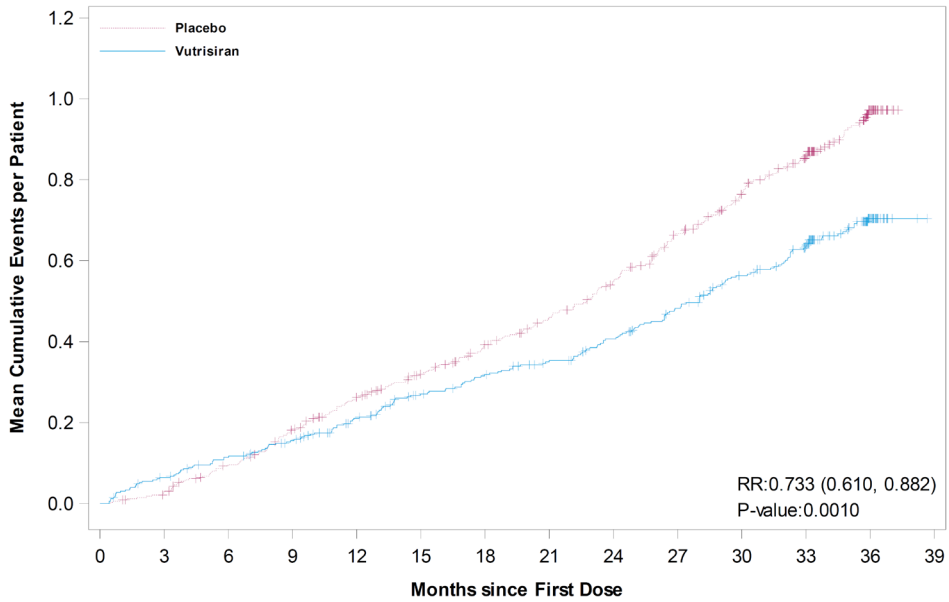
In the overall population, in the analysis of recurrent CV events, including CV hospitalizations and urgent HF visits, vutrisiran treatment led to a 26.7% reduction in the risk of CV events compared to placebo (relative rate ratio: 0.733; 95% CI: 0.610, 0.882; P=0.0010) (Table 10 and Figure 18).

In the vutrisiran monotherapy subgroup, vutrisiran led to a 32.4% reduction in the risk of CV events compared to placebo (relative rate ratio: 0.676; 95% CI: 0.533, 0.857; P=0.0012) (Table 10 and Figure 19).

Table 10. Component analysis of the primary endpoint: recurrent CV events during the DB period, Poisson regression model

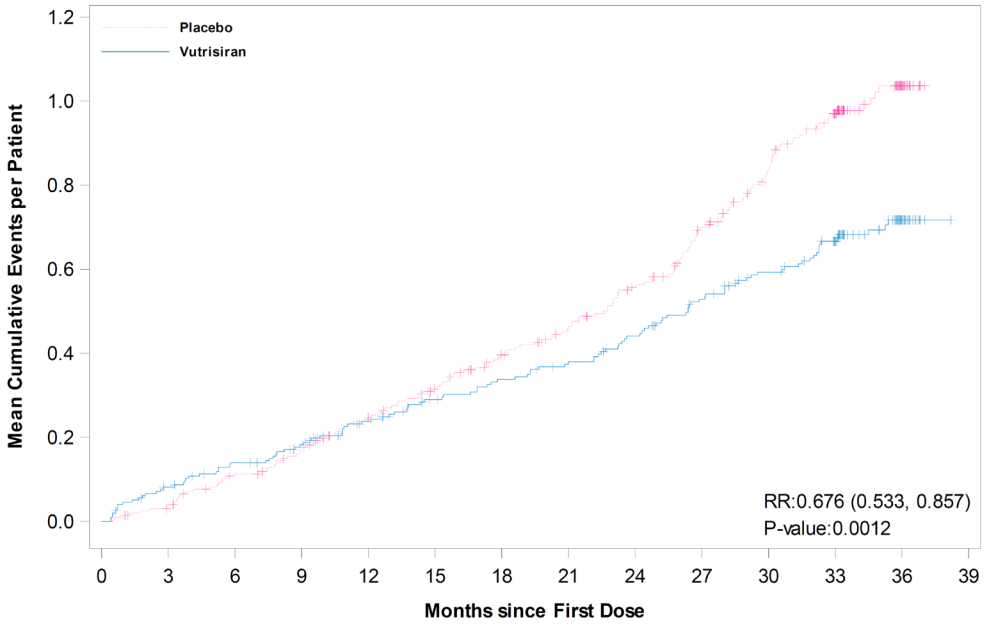
Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Observed event rate among all patients (total events/total follow-up years)	0.312	0.231	0.337	0.240
CV event rate	0.288	0.211	0.306	0.207
95% CI	0.253, 0.327	0.183, 0.244	0.260, 0.360	0.171, 0.250
Relative rate ratio (vutrisiran versus placebo)	0.733		0.676	
95% CI	(0.610, 0.882)		(0.533, 0.857)	
p-value	0.0010		0.0012	

Figure 18. Mean cumulative function plot of component analysis for recurrent CV events during the DB period (overall population)



Abbreviations: CV=cardiovascular; DB=double-blind; RR=rate ratio.
Source: Figure 14.2.3.1.4.1

Figure 19. Mean cumulative function plot of component analysis for recurrent CV events during the DB period (Vutrisiran monotherapy subgroup)



Abbreviations: CV=cardiovascular; DB=double-blind; RR=rate ratio.
Source: Figure 14.2.3.1.4.2

Recurrent CV events were also analyzed using a JFM as a sensitivity analysis. [Rondeau 2007] Consistent treatment effects were observed relative to the primary analysis in both populations.

Sensitivity and Additional Analyses for the Primary Endpoints

In the win ratio sensitivity analysis, the survival status collected after study discontinuation was included in the hierarchical comparisons. A win ratio of >1 represents a favorable outcome for vutrisiran. The win ratio in the overall population was 1.39 (P=0.0088), indicating a reduction in all-cause mortality and recurrent CV events in the vutrisiran group compared to placebo (Table 11). A consistent effect was observed in the vutrisiran monotherapy subgroup (win ratio: 1.51; P=0.0089). A numerically consistent but smaller effect was also observed for the Background Tafamidis Subgroup with a win ratio of 1.21; P= 0.3627 (Table 14.2.2.1.1, appendix of the study report). In patients with high NT-proBNP at baseline (NT-proBNP > 3000 ng/L) the win ratio was only 1.12 in the vutrisiran monotherapy group and even smaller than 1 (0.83) in the background Tafamidis groups.

Table 11. Sensitivity analysis of composite all-cause mortality, frequency of CV events during the DB period, stratified win ratio

Statistic	Overall Population Total (N=654)	Vutrisiran Monotherapy Subgroup Total (N=395)
Number of vutrisiran patients	326	196
Number of placebo patients	328	199
Number of vutrisiran-placebo pairs	32,697	21,777
All-cause mortality[a]		
Number (%) of pairs favoring vutrisiran	6090 (18.6)	4259 (19.6)
Number (%) of pairs favoring placebo	4028 (12.3)	3016 (13.8)
Number (%) of tied pairs	22,579 (69.1)	14,502 (66.6)
Frequency of CV events[a]		
Number (%) of pairs favoring vutrisiran	6239 (19.1)	4499 (20.7)
Number (%) of pairs favoring placebo	4018 (12.3)	2342 (10.8)
Number (%) of tied pairs	12,322 (37.7)	7661 (35.2)
Win ratio	1.39	1.51
95% CI	1.09, 1.78	1.11, 2.05
p-value	0.0088	0.0089

Abbreviations: CI=confidence interval; CV=cardiovascular; DB=double-blind.
[a] Percentages were based on the number of vutrisiran-placebo pairs.
Source: Table 14.2.2.1.1

Similarly, all other sensitivity and additional analyses performed for the primary endpoints were consistent and supported the primary analysis results of the vutrisiran treatment effect compared to placebo. This pertains to sensitivity analyses based on: - Data through 42 months, - Imputing CV events after study withdrawal, - Truncating outliers (For patients with more than 7 events, the first 7 most important events were kept for analysis, with importance ranked in the order of death, CV hospitalization and urgent HF visit), - HT/LVAD placement not treated as all cause mortality; data censored at the date of such procedure, - SGLT2 inhibitor drop-in due to cardiac disease progression treated as a CV event, and additional analyses based on: - Use of CV events per investigator assessment instead of CEC adjudication, - For the monotherapy subgroup, events beyond 9 months of initiation of tafamidis censored.

Subgroup Analysis: Composite Outcome of All-cause Mortality and Recurrent CV Events (CV Hospitalizations and Urgent HF Visits)

The effect of vutrisiran treatment on the composite outcome of all-cause mortality and recurrent CV events was consistent across allmost prespecified subgroups, including age, baseline tafamidis use (in the overall population), NYHA class, and baseline NT-proBNP in both the overall population (Figure 20) and the vutrisiran monotherapy subgroup (Figure 21). For patients with hATTR the analyses indicated efficacy of vutrisiran in the vutrisiran monotherapy subgroup but not in the overall population. The data suggest even a numerically negative effect of vutrisiran in patients with hATTR when pretreated with tafamidis.

Figure 20. Forest plot of prespecified subgroup analyses of composite all-cause mortality and recurrent CV events during the DB period, modified Andersen-Gill model (overall population)

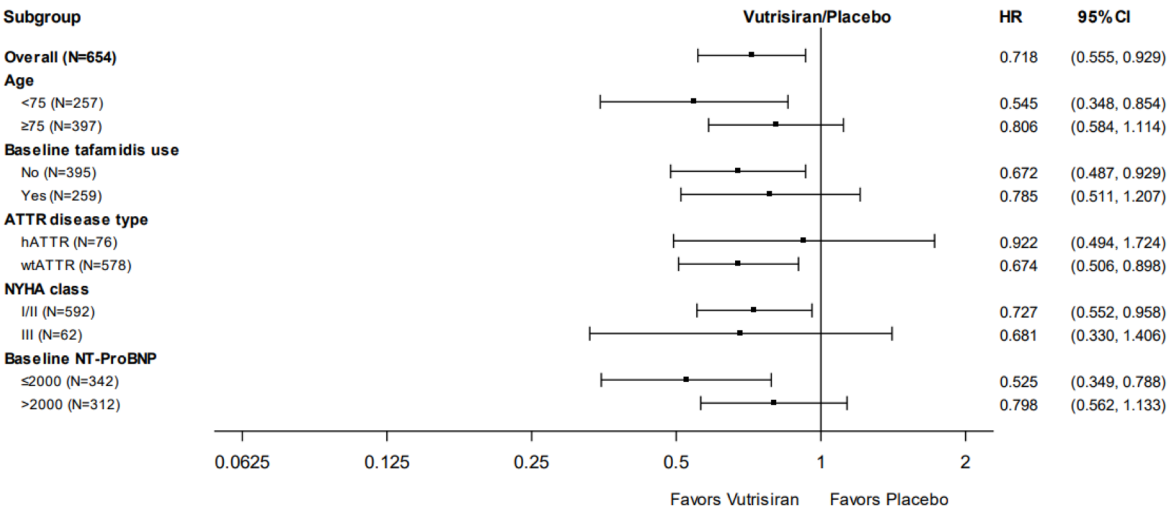
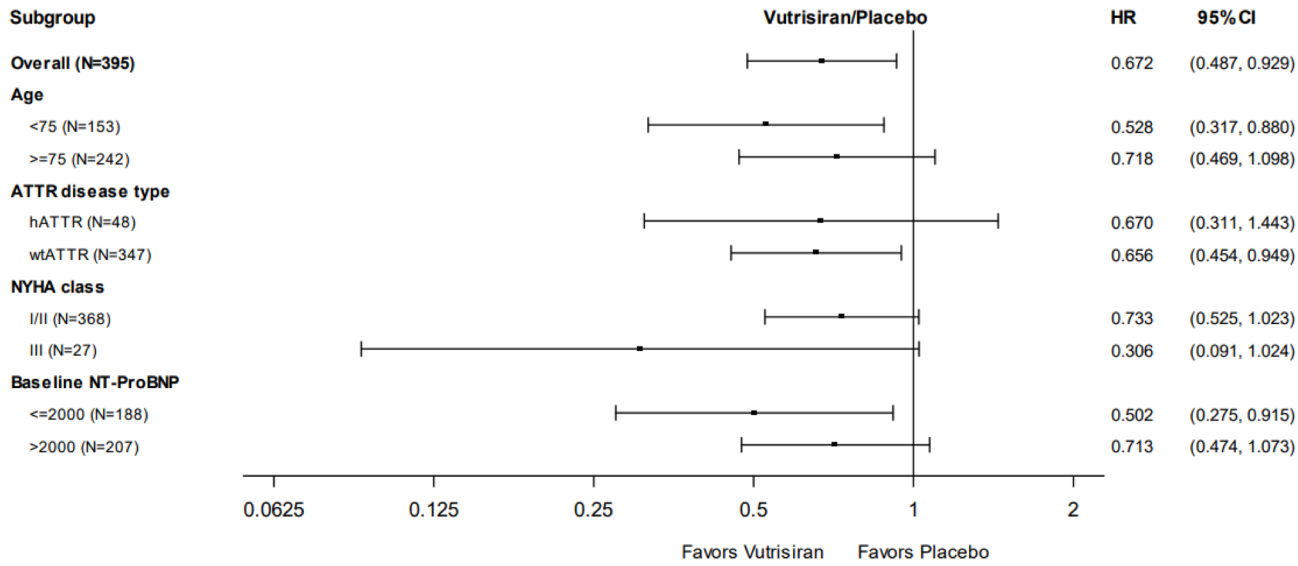
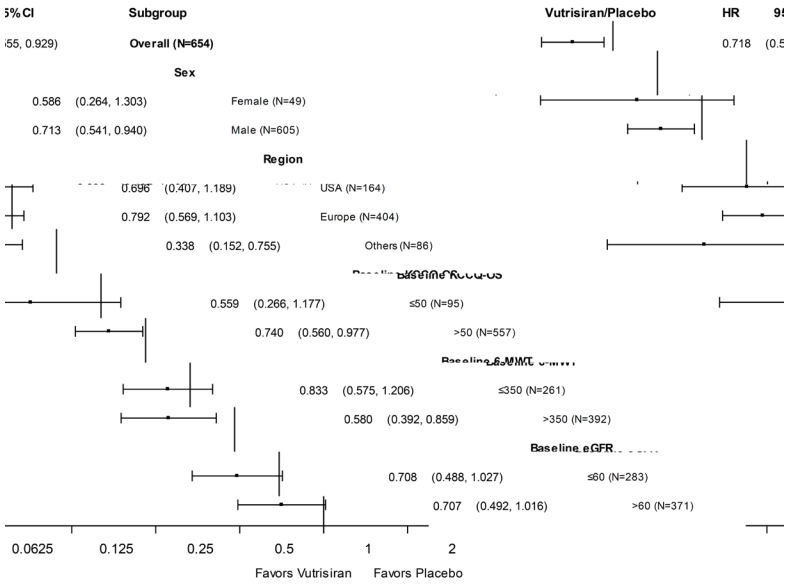


Figure 21. Forest plot of prespecified subgroup analyses of composite all-cause mortality and recurrent CV events during the DB period, modified Andersen-Gill model (Vutrisiran monotherapy subgroup)



Subgroup analyses including race, ethnicity, sex, region, baseline 6-MWT, KCCQ-OS, and eGFR are summarized in Table 14.5.3.1.1 and Table 14.5.3.1.3 and presented in Figure 14.5.3.1.1. below, In the vutrisiran monotherapy subgroup, additional subgroup analyses were also conducted for race, ethnicity, sex, baseline 6-MWT, KCCQ-OS, and eGFR.

Figure 14.5.3.1.1
Forest Plot of Subgroup Analyses of Composite All-cause Mortality and Recurrent CV Events During the Double-blind (DB) Period, Modified Andersen-Gill Model
Full Analysis Set



events as adjudicated by the Clinical Events Committee and determined by investigators. Detailed definition ided in SAP. All-cause mortality includes heart transplantation (HT) and left ventricular assist device (LVAD) nt.
ased on the modified Andersen-Gill model stratified by baseline tafamidis use, including treatment group and og-transformed NT-proBNP as covariates. Analysis is based on subgroup data only. For region subgroup analyses in SA and Others, baseline tafamidis use is removed from model.
Based or is inclu placeme E l U

Figure 14.5.3.1.2
Forest Plot of Subgroup Analyses of Composite All-cause Mortality and Recurrent CV Events During the Double-blind (DB) Period, Modified Andersen-Gill Model
Vutrisiran Monotherapy Subgroup FAS

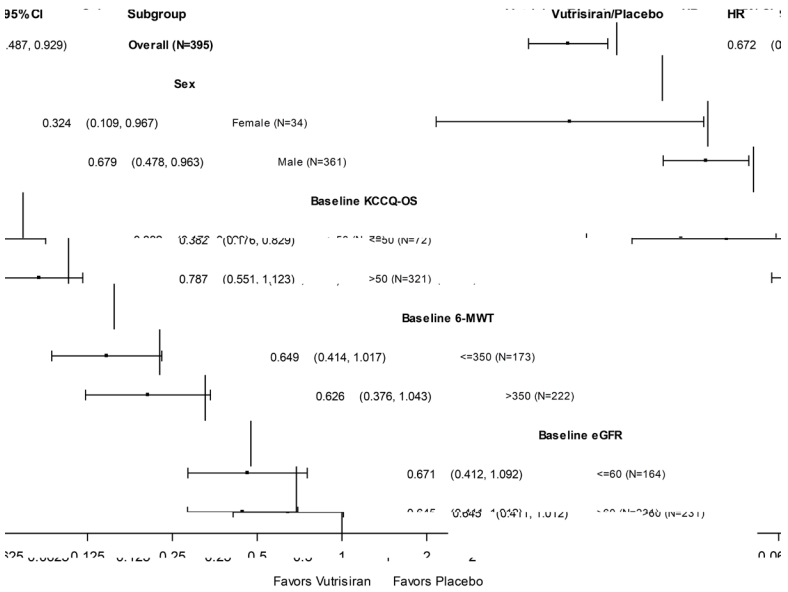


Figure 14.5.3.4.1
Forest Plot of Subgroup Analyses of All-cause Mortality During the DB and 6 Months of OLE Period
Full Analysis Set

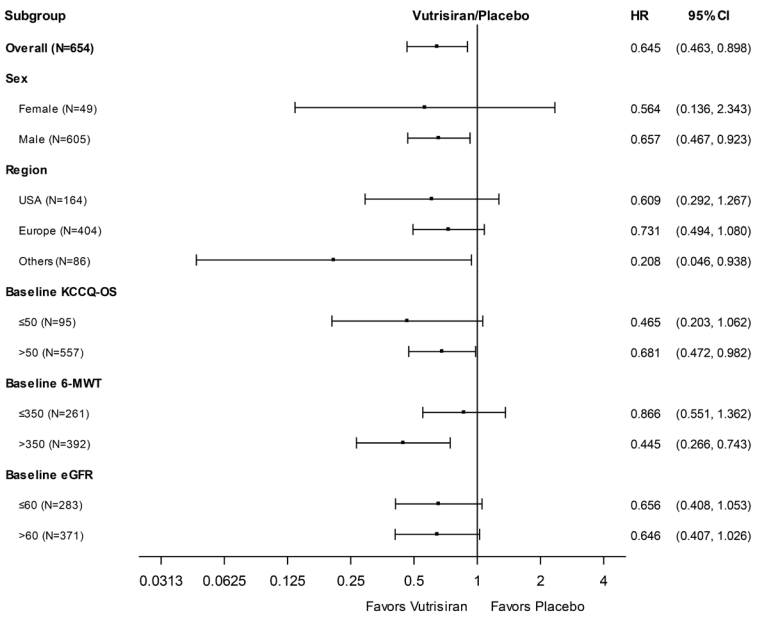
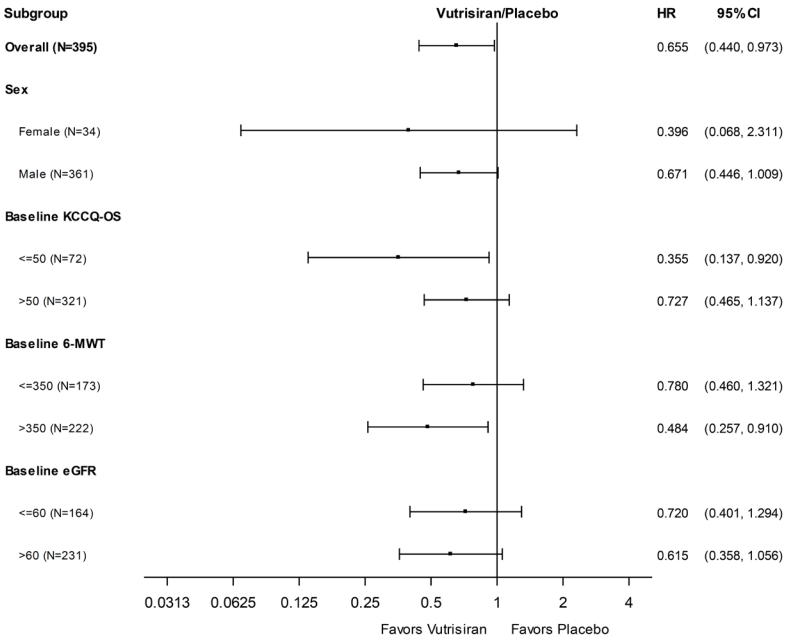


Figure 14.5.3.4.2
Forest Plot of Subgroup Analyses of All-cause Mortality During the DB and 6 Months of OLE Period
Vutrisiran Monotherapy Subgroup FAS



Secondary endpoints

6-MWT

Primary Analysis

In both the overall population and the vutrisiran monotherapy subgroup, baseline 6-MWT values were similar between treatment groups (Table 12). At Month 30, vutrisiran led to a statistically significant improvement in 6-MWT compared to placebo in the overall population (least square [LS] mean difference: 26.46 m; P=7.976E-05) (Figure 22), with consistent results observed in the vutrisiran monotherapy subgroup (32.09 m; P = 0.0005, Figure 23).

In the Background Tafamidis Subgroup the least square [LS] mean difference (SEM) at month 30 was 18.44 (9.15), P = 0.0450 (Table 14.2.1.2 of the study report).

6-MWT Binary Analysis

In the binary analysis in the overall population, 41.2% (95% CI: 34.9, 47.4) of patients in the vutrisiran group achieved improvement (≥0 m change from baseline) in 6-MWT at Month 30 compared to 27.8% (21.9, 33.7) of patients in the placebo group (Odds ratio (95% CI): 1.8 (1.2, 2.7), Adjusted difference (95% CI): 13.3 (4.7, 21.9), p-value 0.0024. Consistent results were observed in the vutrisiran monotherapy subgroup.

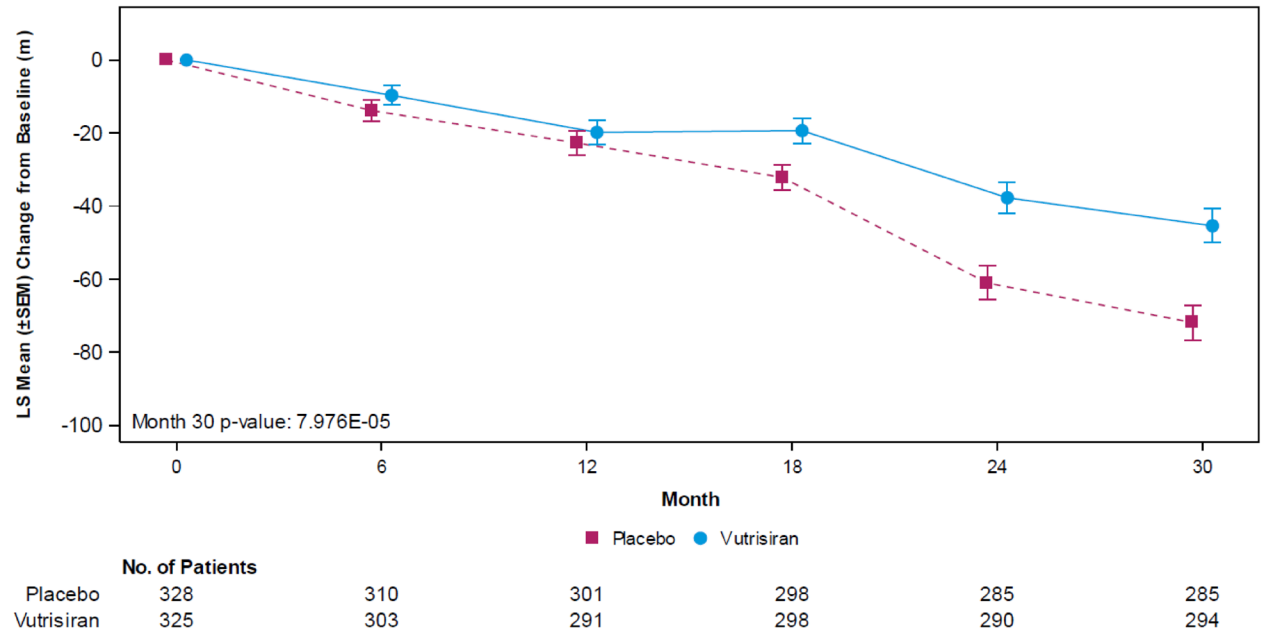
Prespecified sensitivity analyses indicated a consistent estimate of the treatment effect. The effect of vutrisiran treatment on 6-MWT was consistent across all prespecified subgroups in both the overall population (including baseline tafamidis use) and the vutrisiran monotherapy subgroup.

Table 12. Change from baseline to month 30 in 6-MWT, MMRM model

Visit Actual/Change	Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
		Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Baseline	n	328	325	199	196
	Mean (SD)	377.14 (96.29)	371.97 (103.71)	372.84 (98.08)	362.70 (102.74)
Observed change from baseline to Month 30	n	223	238	124	130
	Median	-30.65	-7.50	-47.33	-13.05
	Q1, Q3	-82.55, 4.77	-55.00, 18.00	-91.92, -2.35	-69.04, 17.41
Change from baseline to Month 30 with imputed values	n	285	294	166	170
	Mean (SD)	-68.00 (84.84)	-46.10 (82.67)	-86.56 (85.39)	-60.59 (89.91)
	LS mean (SEM)	-71.88 (4.79)	-45.42 (4.62)	-91.78 (6.39)	-59.69 (6.60)
	LS mean (SEM) difference (vutrisiran – placebo)	26.46 (6.66)		32.09 (9.19)	
	95% CI	13.38, 39.55		14.03, 50.15	
	p-value	7.976E-05		0.0005	

Abbreviations: 6-MWT=6-minute walk test; ATTR=transthyretin-mediated amyloidosis; CI=confidence interval;

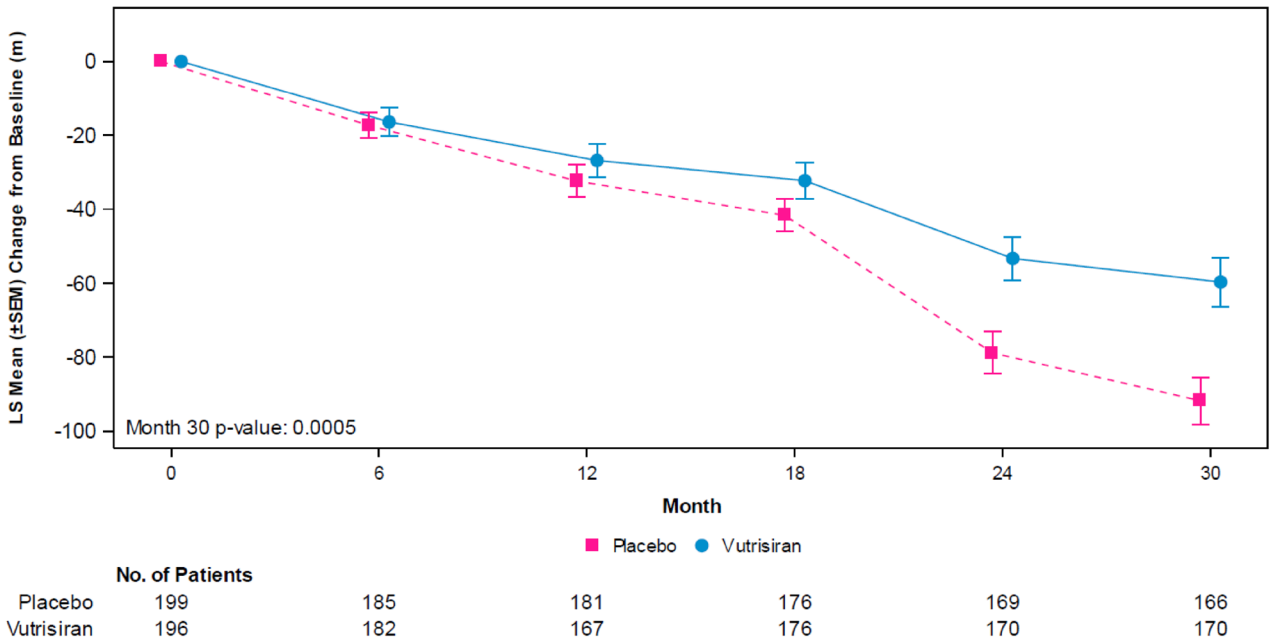
Figure 22. LS mean (±SEM) change from baseline in 6-MWT by visit during the DB period, MMRM (overall population)



No. of Patients						
Placebo	328	310	301	298	285	285
Vutrisiran	325	303	291	298	290	294

Abbreviations: 6-MWT=6-minute walk test; DB=double-blind; LS mean=least square mean; MMRM=mixed effects model repeated measures; SEM=standard error of the mean.
Source: Figure 14.2.1.2.1

Figure 23. LS mean (±SEM) change from baseline in 6-MWT by visit during the DB period, MMRM (Vutrisiran monotherapy subgroup)



No. of Patients						
Placebo	199	185	181	176	169	166
Vutrisiran	196	182	167	176	170	170

KCCQ-OS

The KCCQ is a self-administered questionnaire that measures patients' perception of health status, including HF symptoms, impact on physical and social function, and how their HF impacts quality of life within a 2-week recall period. Higher KCCQ scores indicate better health status.

In both the overall population and the vutrisiran monotherapy subgroup, baseline KCCQ-OS values were similar between treatment groups (Table 13). At Month 30, vutrisiran led to a statistically significant improvement in KCCQ-OS compared to placebo in the overall population (LS mean difference: 5.80 points; P=0.0008) (Figure 24), with consistent results observed in the vutrisiran monotherapy subgroup (Figure 25).

In the binary analysis in the overall population, 45.2% (95% CI: 39.1, 51.4) of patients in the vutrisiran group achieved improvement (≥0-point increase from baseline) in KCCQ-OS score at Month 30 compared to 32.1% (26.1, 38.0) of patients in the placebo group (p-value: 0.0028), Adjusted difference (vutrisiran placebo) (95% CI): 13.2 (4.6, 21.8).

Consistent results were observed in the vutrisiran monotherapy subgroup: 49.6 % (41.3, 58.0) vs. 26.7 % (19.1, 34.3) (p-value: 0.0002). Adjusted difference (vutrisiran placebo) (95% CI): 22.9 (11.7, 34.2).

Domains of the KCCQ-OS reflect the severity of physical and social limitations, the frequency and severity of symptoms, and the quality of life impacts associated with cardiomyopathy. Results across all KCCQ-OS domains were consistent with the primary analysis and showed a treatment effect in favor of vutrisiran compared to placebo in both the overall population and the vutrisiran monotherapy subgroup (not shown here).

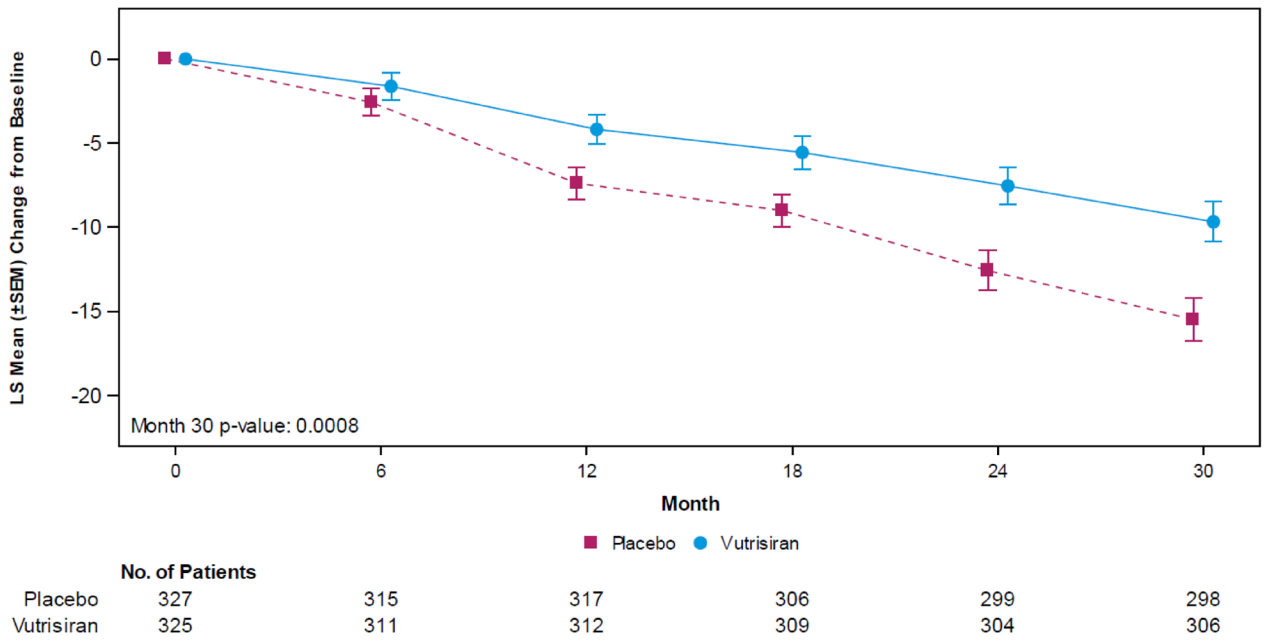
The effect of vutrisiran treatment on KCCQ-OS was largely consistent across all prespecified subgroups in both the overall population (including baseline tafamidis use) and the vutrisiran monotherapy subgroup but showed some variability (Figure 26 and Figure 27).

Table 13. Change from baseline to month 30 in KCCQ-QS score, MMRM model

Visit Actual/Change	Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
		Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Baseline	n	327	325	198	195
	Mean (SD)	72.26 (19.92)	72.96 (19.44)	69.93 (20.80)	70.29 (20.21)
Observed change from baseline to Month 30	n	234	252	131	139
	Median	-6.25	-1.30	-8.65	-0.26
	Q1, Q3	-17.71, 3.13	-11.07, 8.14	-20.05, 1.56	-13.80, 11.77
Change from baseline to Month 30 with imputed values	n	298	306	175	180
	Mean (SD)	-15.39 (22.15)	-9.34 (21.44)	-19.50 (23.37)	-10.25 (23.49)
	LS mean (SEM)	-15.49 (1.26)	-9.68 (1.19)	-19.47 (1.73)	-10.78 (1.66)
	LS mean (SEM) difference (vutrisiran – placebo)	5.80 (1.73)		8.69 (2.40)	
	95% CI	(2.40, 9.20)		(3.98, 13.40)	
	p-value	0.0008		0.0003	

Abbreviations: ATTR, ; CI, ; KCCQ-QS, Kansas City Cardiomyopathy

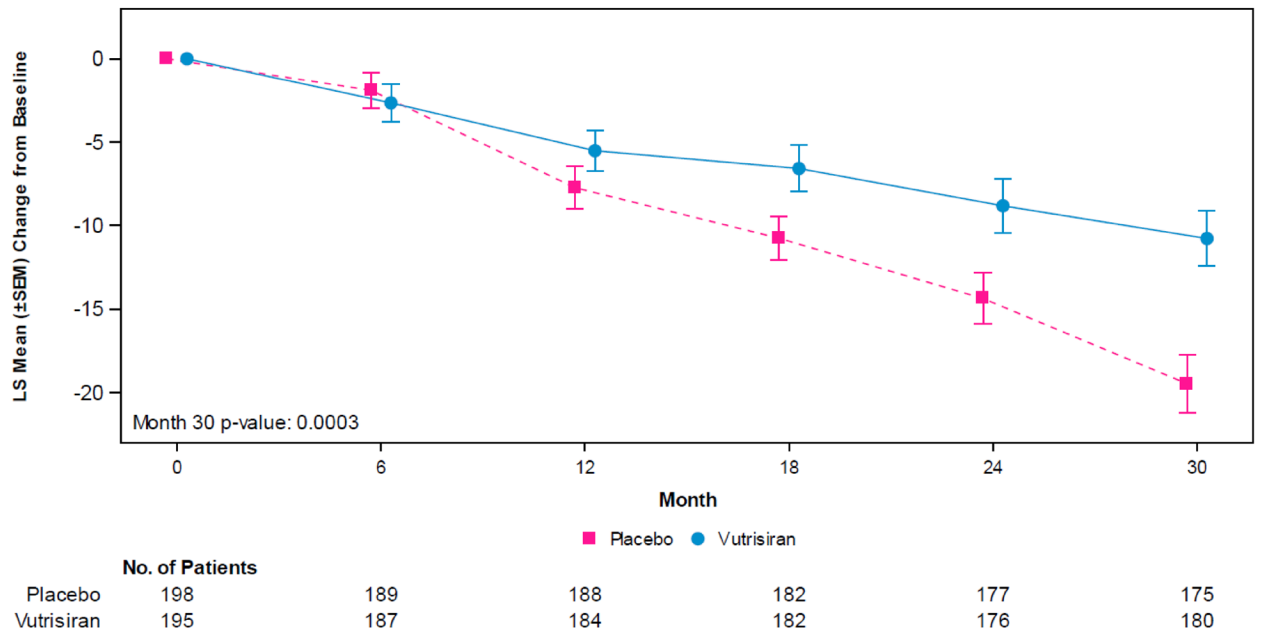
Figure 24. LS mean (±SEM) change from baseline in KCCQ-OS by visit during the DB period, MMRM (overall population)



No. of Patients						
Placebo	327	315	317	306	299	298
Vutrisiran	325	311	312	309	304	306

Abbreviations: DB=double-blind; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LS mean=least square mean; MMRM=mixed effects model repeated measures; SEM=standard error of the mean.
Source: Figure 14.2.1.3.1

Figure 25. LS mean (±SEM) change from baseline in KCCQ-OS score by visit during the DB period, MMRM model (Vutrisiran monotherapy subgroup)



No. of Patients						
Placebo	198	189	188	182	177	175
Vutrisiran	195	187	184	182	176	180

Figure 26. Forest plot of prespecified subgroup analyses of change from baseline to month 30 in KCCQ-OS score (overall population)

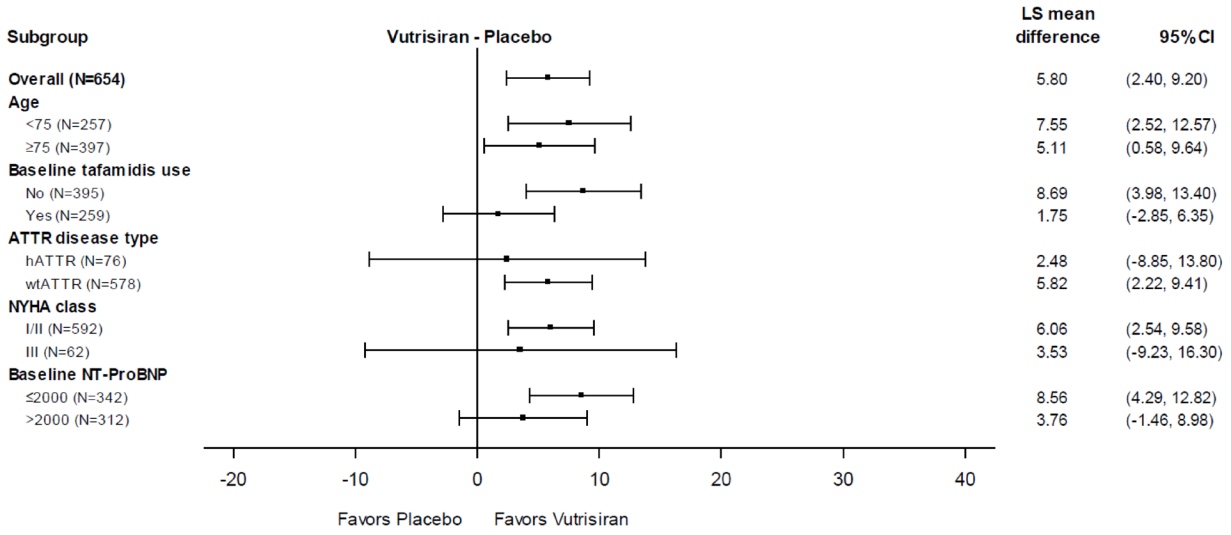
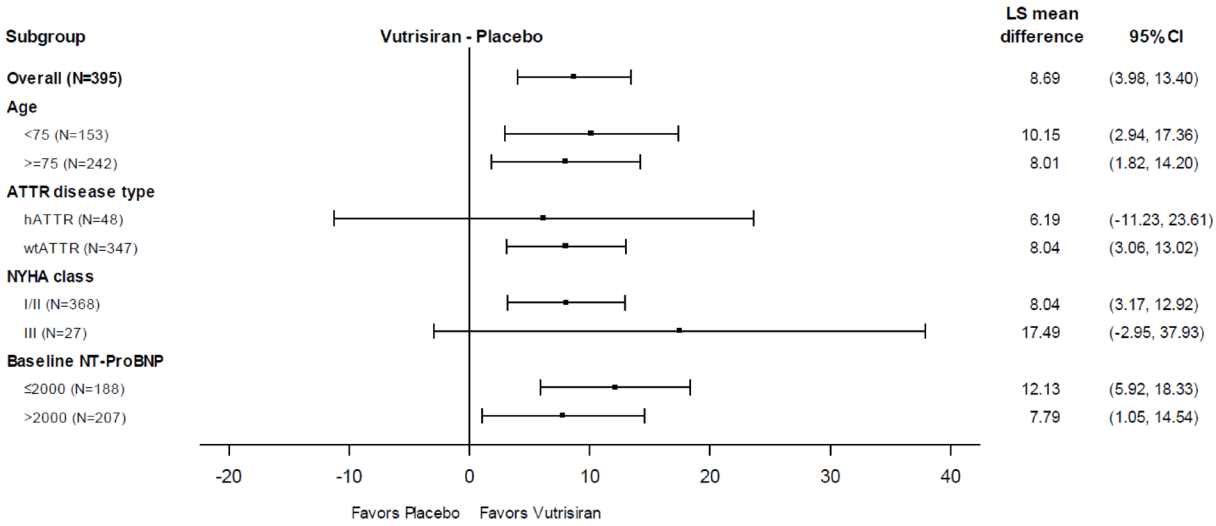


Figure 27. Forest plot of prespecified subgroup analyses of change from baseline to month 30 in KCCQ-OS (Vutrisiran monotherapy subgroup)



All-Cause Mortality

With the variable follow-up design of this study, patients enrolled in the OLE Period received their first OLE dose at either Month 33 or Month 36, depending on their enrollment time. The analysis of all-cause mortality as a secondary endpoint included all vital status collected through 42 months. Vital status collected after study withdrawal was also included in the analyses. Vital status was collected for all but 1 patient, who was censored at approximately 30 months. As of the data cutoff date of the primary analysis, patients who were alive but had not yet reached 42 months or completed 6 months of the OLE Period were censored at their last known alive date.

Vutrisiran patients had a statistically significant 35.5% reduction in the risk of all-cause mortality compared to placebo in the overall population (hazard ratio: 0.645; 95% CI: 0.463, 0.898; P=0.0098; 95% CI: 0.440, 0.973; P=0.0454) (Table 14).

Table 14. Analysis of all-cause mortality through 42 months

Category	Overall Population		Vutrisiran Monotherapy Subgroup	
	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
All-cause mortality included in the analysis, n (%)	85 (25.9)	60 (18.4)	58 (29.1)	43 (21.9)
CV-related deaths, n (%)	39 (11.9)	26 (8.0)	25 (12.6)	20 (10.2)
Indeterminate deaths, n (%)	21 (6.4)	19 (5.8)	18 (9.0)	15 (7.7)
Non-CV-related deaths, n (%)	21 (6.4)	12 (3.7)	14 (7.0)	8 (4.1)
Heart transplantation, n (%)	4 (1.2)	3 (0.9)	1 (0.5)	0
LVAD placement, n (%)	0	0	0	0
CV-related mortality, n (%)[a]	64 (75.3)	48 (80.0)	44 (75.9)	35 (81.4)
Hazard ratio from Cox PH model (vutrisiran/placebo) (95% CI)	0.645 (0.463, 0.898)		0.655 (0.440, 0.973)	
p-value	0.0098		0.0454	

The prespecified sensitivity analysis of weighted log-rank FH (1,1) test, which allocates more weight on events that occurred at a later time period, also demonstrated a reduction in mortality in both the overall population (P=0.0028) and the vutrisiran monotherapy subgroup (P=0.0079).

The analysis of CV-related mortality through 42 months showed a similar numerical treatment effect as all-cause mortality in both the overall population and the vutrisiran monotherapy subgroup (p > 0.05 for both groups, data not shown here).

All-Cause Mortality Subgroup Analysis

The effect of vutrisiran treatment on all-cause mortality was overall consistent across all prespecified subgroups in both the overall population (including baseline tafamidis use; and the vutrisiran monotherapy subgroup (data not shown here). Mortality was numerically only slightly reduced in hATTR patients in the overall population (HR (95% CI) 0.891 (0.390, 2.033) due to the difference in the vutrisiran monotherapy population (0.672 (0.254, 1780)).

NYHA Class

In both the overall population and the vutrisiran monotherapy subgroup, most patients had NYHA class II HF at baseline (Table 6). At Month 30, vutrisiran led to a statistically significantly greater proportion of patients who showed stability (no change in class) or improvement compared to placebo in the overall population (adjusted difference: 8.7%, 95% CI: 1.3, 16.1; P=0.0217), with consistent results observed in the vutrisiran monotherapy subgroup.

Table 15. Analysis of stable or improved NYHA class at month 30, CMH method with multiple imputation for missing data

Statistics at Month 30	Overall Population		Vutrisiran Monotherapy Subgroup	
	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Observed, n (%)				
Stable or improved from baseline	181 (55.2)	206 (63.2)	98 (49.2)	117 (59.7)
Worsened from baseline or death	118 (36.0)	100 (30.7)	78 (39.2)	62 (31.6)
Missing	29 (8.8)	20 (6.1)	23 (11.6)	17 (8.7)
With imputation				
% stable or improved from baseline	60.5	67.8	56.4	66.3
% worsened from baseline	39.5	32.2	43.6	33.7
Difference in % stable or improved (vutrisiran – placebo)	7.4		9.9	
Adjusted difference in % stable or improved (vutrisiran – placebo) (95% CI)	8.7 (1.3, 16.1)		12.5 (2.7, 22.2)	
p-value	0.0217		0.0121	

A sensitivity analysis of the change from baseline in NYHA class treated as a continuous variable and analyzed using MMRM model showed consistent results.

The effect of vutrisiran treatment on NYHA class was consistent across all prespecified subgroups in both the overall population (including baseline tafamidis use) and the vutrisiran monotherapy subgroup (data not shown here). Only a very small numerical difference favouring vutrisiran was observed in patients on tafamidis at baseline (% difference (95% CI): 3.0 (-8.4, 14.4)).

Exploratory endpoints

Time to First CV Event (including CV Hospitalizations and Urgent HF Visits) or All-Cause Mortality

Kaplan-Meier curves illustrating time to first CV event or all-cause mortality showed curves diverging after approximately 6 months of treatment in both the overall population (Figure 28) and in the vutrisiran monotherapy subgroup (Figure 29).

In the overall population, vutrisiran treatment led to a 28.4% reduction in the risk of first CV event or all-cause mortality compared to placebo (hazard ratio: 0.716; 95% CI: 0.566, 0.905; P=0.0062)

In the vutrisiran monotherapy subgroup, vutrisiran treatment led to a 35.6% reduction in the risk of first CV event or all-cause mortality compared to placebo (hazard ratio: 0.644; 95% CI: 0.479, 0.867; P=0.0043).

Figure 28. Adjusted Kaplan-Meier plot of time to first CV event or all-cause mortality during the DB period (overall population)

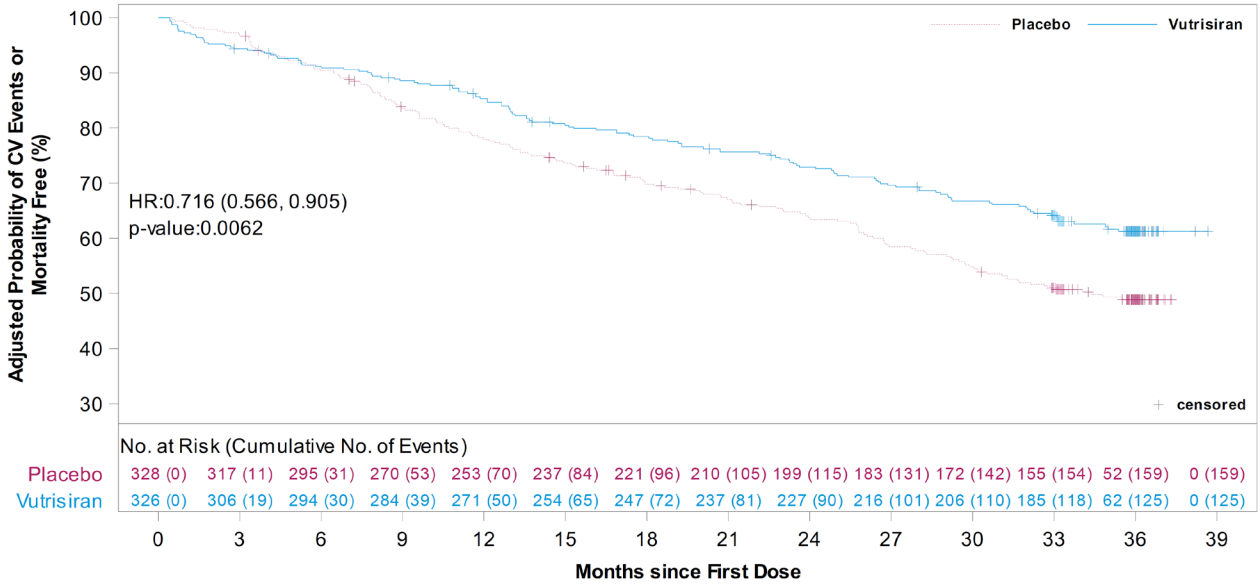
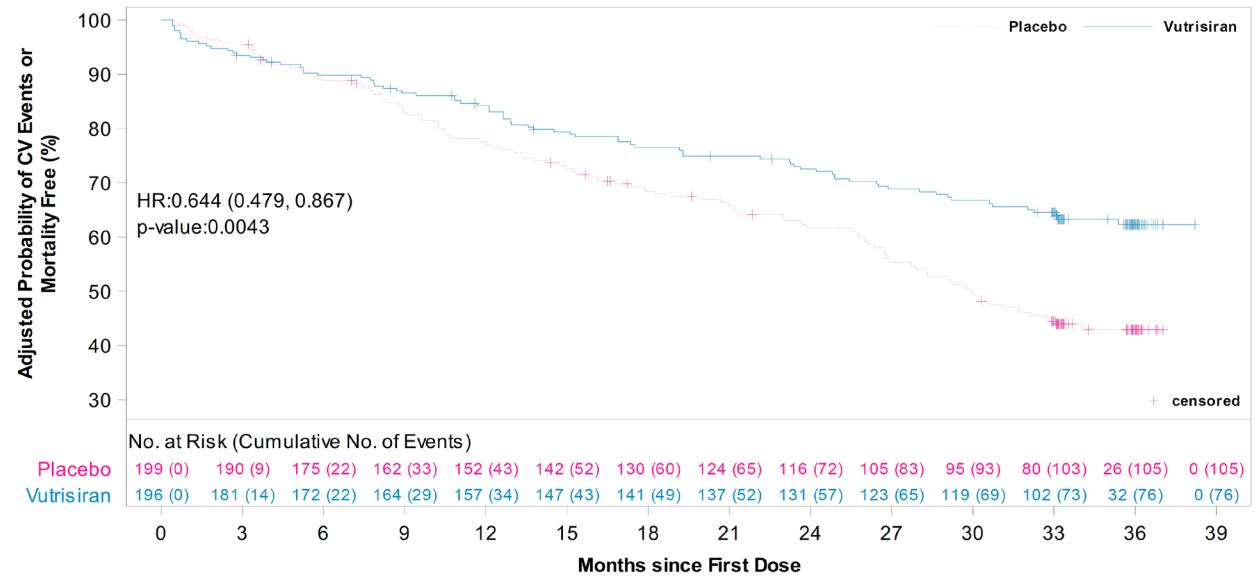


Figure 29. Adjusted Kaplan-Meier plot of time to first CV event or all-cause mortality during the DB period (Vutrisiran monotherapy subgroup)



Consistent results were also obtained for the following exploratory analyses (data not shown here):

- Time to First CV Event (including CV Hospitalization, Urgent HF Visit and Any Initiation of SGLT2 Inhibitor due to Cardiac Disease Progression), or All-Cause Mortality
- Time to First Oral Diuretic Intensification, First CV Event (including CV Hospitalization and Urgent HF Visit), or All-Cause Mortality
- Time to Second CV Event (including CV Hospitalizations and Urgent HF Visits) or All-Cause Mortality
- Composite Outcome of All-Cause Mortality and Recurrent All-Cause Hospitalizations and Urgent HF Visits.

- **Cardiac Biomarkers**

- NT-proBNP Change from Baseline

- Serum levels of NT-proBNP were measured during the DB Period.

- At Month 30, vutrisiran led to a 32% relative reduction in the fold increase in NT-proBNP compared to placebo in the overall population (adjusted geometric mean fold change ratio [vutrisiran/placebo]: 0.68; P=3.440E-12) (Table 16). Median change from baseline in NT-proBNP levels indicated relative stability in vutrisiran patients with an 8.98% increase while levels in placebo patients indicated worsening with a 51.62% increase.

- Vutrisiran led to a 43% relative reduction in the fold increase in NT-proBNP compared to placebo in the vutrisiran monotherapy subgroup (adjusted geometric mean fold change ratio [vutrisiran/placebo]: 0.57; P=4.339E-12) (Table 16).

- Adjusted median NT-proBNP values over time are shown in Figure 30 for the overall population and for the vutrisiran monotherapy group.

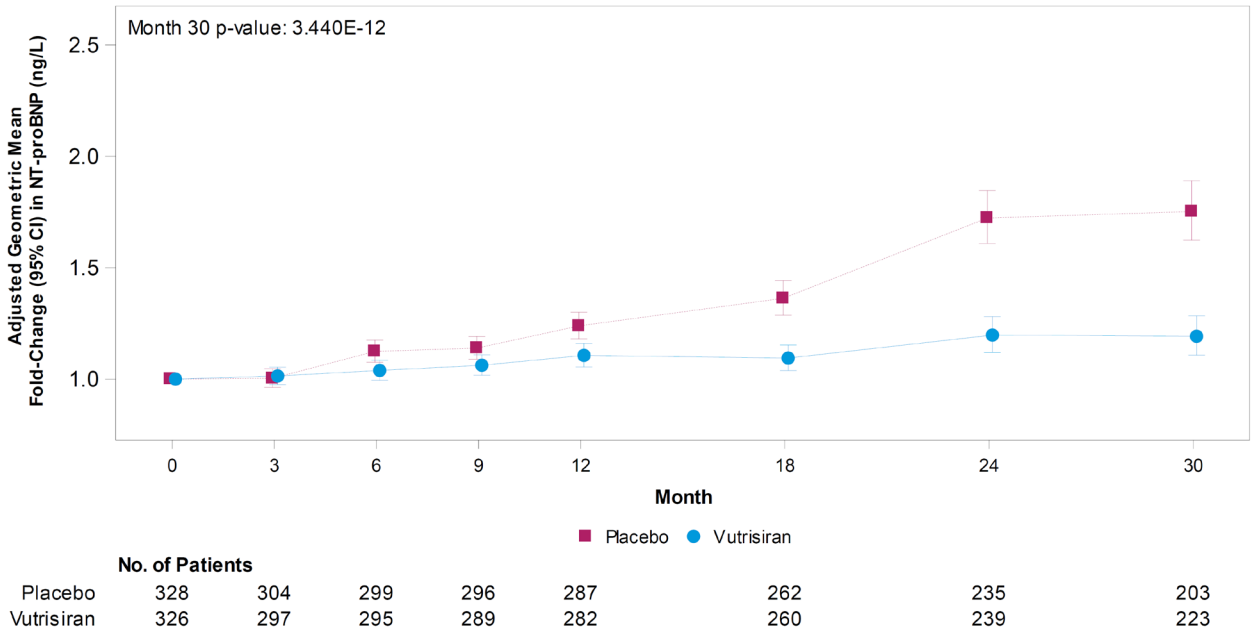
- In a binary analysis in the overall population, 41.6% of patients in the vutrisiran group remained stable or had decreases (≤0 ng/L change from baseline) in NT-proBNP levels at Month 30 compared to 24.9% in the placebo group (odds ratio: 2.2; 95% CI: 1.5, 3.3). In a binary analysis in the vutrisiran monotherapy subgroup, 36.4% of patients in the vutrisiran group remained stable or had decreases in NT-proBNP levels compared to 14.3% of patients in the placebo group (odds ratio: 3.4; 95% CI: 1.8, 6.6).

- The effect of vutrisiran treatment on NT-proBNP was consistent across most subgroups in both the overall population and the vutrisiran monotherapy population. However, only a small numerical difference was observed in patients with Tafamidis at baseline. At month 30 NT-proBNP values were similar (Mean (SD) placebo: 2753.22 (2522.64), n = 104 vs. vutrisiran 2521.62 (3472.60, n = 114), change in NT proBNP from baseline was 710.03 (1913.38) in the placebo arm vs. 579.45 (3039.67) in the vutrisiran arm, accounting for an adjusted geometric mean fold-change (95% CI) of 1.29 (1.18, 1.42) vs. 1.06 (0.94, 1.17). (Table 14.2.4.7.1. Appendix to the study report).

Table 16. Analysis of change from baseline to month 30 in NT-proBNP (ng/L), MMRM model

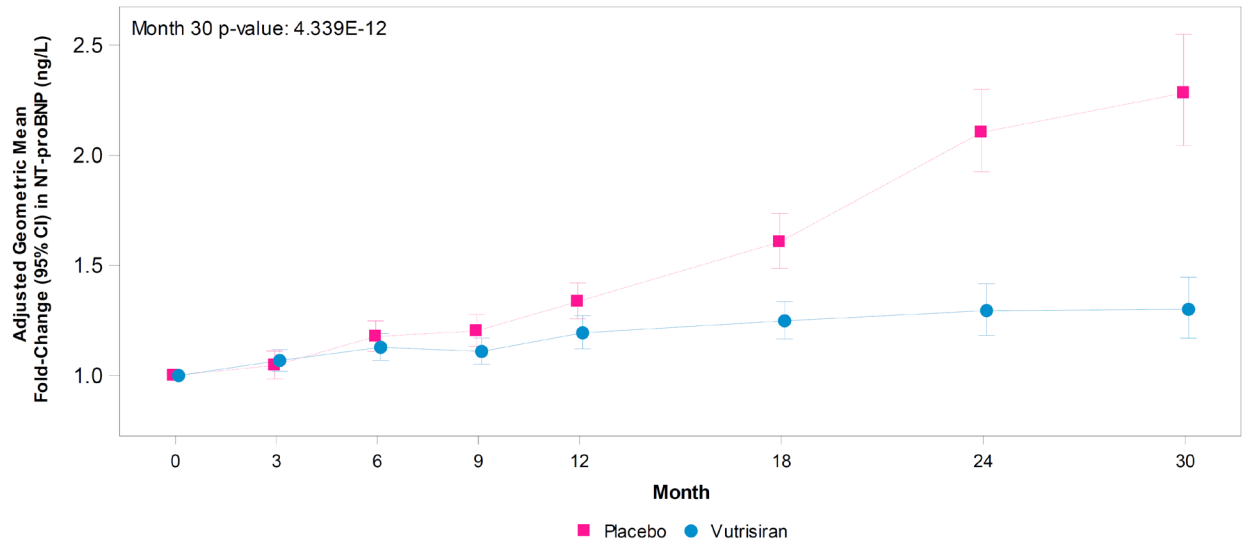
Visit Actual/Change	Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
		Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Baseline	n	328	326	199	196
	Median	1801.00	2020.50	1865.00	2402.00
	Geometric mean (SEM)[a]	1773.67 (72.59)	1979.81 (79.36)	1833.38 (98.61)	2213.21 (121.30)
Month 30	n	203	223	99	109
	Median	2846.00	1837.00	3778.00	2148.00
	Geometric mean (SEM)[a]	2697.60 (170.14)	1981.23 (125.47)	3707.84 (320.80)	2337.38 (228.48)
Change from baseline to Month 30	n	203	223	99	109
	Median change from baseline	753.00	118.00	1713.00	203.00
	Adjusted geometric mean fold-change[b]	1.75	1.19	2.28	1.30
	95% CI	1.62, 1.89	1.11, 1.28	2.04, 2.55	1.17, 1.45
	Ratio of adjusted geometric mean fold change (vutrisiran/placebo)[b]	0.68		0.57	
	95% CI	0.61, 0.76		0.49, 0.66	
	p-value	3.440E-12		4.339E-12	

Figure 30. Adjusted geometric mean fold-change of NT-proBNP (ng/L) during the DB period, MMRM model (overall population)



No. of Patients								
Placebo	328	304	299	296	287	262	235	203
Vutrisiran	326	297	295	289	282	260	239	223

Figure 31. Adjusted geometric mean fold-change of NT-proBNP (ng/L) during the DB period, MMRM model (Vutrisiran monotherapy subgroup)



No. of Patients								
Placebo	199	182	180	177	167	147	122	99
Vutrisiran	196	179	173	171	156	138	122	109

- <u>Troponin I</u>
- At Month 30, vutrisiran led to a 32% relative reduction in the fold increase in troponin I compared to placebo in the overall population (adjusted geometric mean fold change ratio [vutrisiran/placebo]: 0.68; P=1.566E-14). A median percent increase (worsening) in troponin I levels relative to baseline was observed for the placebo group (21.70%) compared to a median percent decrease (improving) for the vutrisiran group (-9.86%) (Table 14.2.4.8).

- Vutrisiran led to a 45% relative reduction in the fold increase in troponin I compared to placebo in the vutrisiran monotherapy subgroup (adjusted geometric mean fold change ratio [vutrisiran/placebo]: 0.55; P=9.684E-17). A median percent increase (worsening) in troponin I levels relative to baseline was observed for the placebo group (51.30%) compared to a median percent decrease (improving) for the vutrisiran group (-4.62%) stable or had decreases (≤0 ng/L change from baseline) in troponin I levels at Month 30 compared to 33.3% of patients in the placebo group (odds ratio: 2.9; 95% CI: 1.9, 4.2) (Table 14.2.4.8.3 of the study report, data not shown here).
- In a binary analysis in the vutrisiran monotherapy subgroup, 49.3% of patients in the vutrisiran group remained stable or had decreases in troponin I levels compared to 15.3% of patients in the placebo group (odds ratio: 5.4; 95% CI: 2.9, 10.2) (Table 14.2.4.8.3 of the study report, data not shown here).
- The effect of vutrisiran treatment on troponin I was consistent across most subgroups in both the overall population (including baseline tafamidis use; Table 14.2.4.8.1 and Figure 14.2.4.8.6) and the vutrisiran monotherapy subgroup.
- However, no notable difference was observed in patients with Tafamidis at baseline. At month 30 troponin values were similar (Mean (SD) placebo, n = 100: 73.26 (56.50) vs. vutrisiran, n = 114: 76.81 (94.60).
- At month 30 change in Troponin I from baseline was Mean (SD) -6.56 (64.09) vs. -7.94 (99.96) accounting for an adjusted geometric mean fold-change (95% CI) of 0.96 (0.88, 1.04) vs. 0.86 (0 0.79, 0.94) (Table 14.2.4.8.1. Appendix to the study report).

- <u>Echocardiographic parameters</u>
- Echocardiographic parameters were assessed during the study and analyzed by a central reader to evaluate changes in cardiac structure and function.
- In both the overall population and vutrisiran monotherapy subgroup some improvements were observed with vutrisiran compared to placebo for prespecified echocardiographic parameters of mean LV wall thickness and average peak longitudinal strain and additional parameters of cardiac structure (LV mass) and function (LV ejection fraction) at Month 30 as presented in Table 17.

Table 17. Analysis of change from baseline to month 30 in echocardiographic parameters, MMRM model

Visit Actual/Change	Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
		Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
Mean LV Wall Thickness (cm)					
Baseline	n	324	321	197	191
	Mean (SD)	1.82 (0.27)	1.82 (0.26)	1.83 (0.29)	1.82 (0.27)
Change from baseline to Month 30	n	219	236	120	127
	LS mean (SEM)	0.09 (0.01)	0.05 (0.01)	0.11 (0.02)	0.04 (0.02)
	LS mean (SEM) difference (vutrisiran–placebo)	-0.04 (0.02)		-0.08 (0.03)	
	95% CI	-0.08, -0.00		-0.14, -0.02	
	p-value	0.0343		0.0080	
Average Peak Longitudinal Strain (%)					
Baseline	n	328	324	199	194
	Mean (SD)	-13.96 (3.48)	-13.99 (3.46)	-14.25 (3.52)	-14.04 (3.44)
Change from baseline to Month 30	n	227	244	125	132
	LS mean (SEM)	2.18 (0.19)	0.95 (0.17)	2.37 (0.26)	1.07 (0.26)
	LS mean (SEM) difference (vutrisiran–placebo)	-1.23 (0.26)		-1.30 (0.36)	
	95% CI	-1.73, -0.73		-2.01, -0.59	
	p-value	2.021E-6		0.0004	
LV Mass, Estimated (g)					
Baseline	n	318	320	193	190
	Mean (SD)	350.64 (93.22)	351.83 (87.67)	356.17 (99.53)	355.06 (90.94)
Change from baseline to Month 30	n	207	228	112	123
	LS mean (SEM)	42.76 (5.41)	23.90 (4.72)	48.58 (7.80)	17.71 (7.00)
	LS mean (SEM) difference (vutrisiran – placebo)	-18.86 (7.17)		-30.87 (10.48)	

Visit Actual/Change	Statistic	Overall Population		Vutrisiran Monotherapy Subgroup	
		Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)
	95% CI	-32.96, -4.76		-51.50, -10.24	
	p-value	0.0088		0.0035	
LV Ejection Fraction (%)					
Baseline	n	318	309	192	182
	Mean (SD)	55.93 (12.35)	55.64 (12.74)	55.68 (12.05)	54.80 (12.64)
Change from baseline to Month 30	n	209	225	115	117
	LS mean (SEM)	-6.15 (0.66)	-4.12 (0.56)	-5.89 (0.93)	-3.62 (0.75)
	LS mean (SEM) difference (vutrisiran – placebo)	2.03 (0.86)		2.27 (1.19)	
	95% CI	0.34, 3.73		-0.07, 4.61	
	p-value	0.0190		0.0577	

Abbreviations: ATTR=transthyretin-mediated amyloidosis; CI=confidence interval; LS mean=least squares mean;

- eGFR
- Vutrisiran was associated with lower decline from baseline in eGFR compared to placebo (LS mean [SEM] difference: 2.2 [±1.3] mL/min/1.73m2, P=0.0876) in the overall population. Consistent results were observed in the vutrisiran monotherapy subgroup and in patients on background tafamidis therapy (LS mean [SEM] difference mL/min/1.73m2: 2.5 (1.8) p= 0.1654, and 2.0 (1.8), p= 0.2763 respectively).

- ATTR Amyloidosis Disease Stage
- ATTR amyloidosis disease staging is commonly used in clinical practice to stratify patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR.[Gillmore 2018] Stage 1 indicates lower risk, Stage 2 indicates intermediate risk, and Stage 3 indicates higher risk. More than half of patients in both treatment groups had ATTR amyloidosis disease Stage 1 (63.8%, vutrisiran group; 69.8%, placebo group) at baseline.
- In the overall population, 77.3% of patients in the vutrisiran group showed no progression in ATTR amyloidosis stage at Month 30 compared to 61.2% of patients in the placebo group (adjusted difference: 16.1; 95% CI: 8.1, 24.2; P=7.889E-05). Consistent results were observed in the vutrisiran monotherapy subgroup and in patients on background tafamidis therapy (adjusted difference: 14.8 (3.7, 26.0), p = 0.0112, and 17.8 (6.3, 29.3), p = 0.0030, respectively).

- Quality of Life

- EQ-5D-5L
- At Month 30, vutrisiran improved patients' self-reported general health-related quality of life, as assessed by the change from baseline in EQ-5D-5L index score, compared to placebo in the overall population (LS mean [SEM] difference: 0.0308 [±0.0111]; P=0.0056), with consistent results observed in the vutrisiran monotherapy subgroup. Consistent results were observed for the EQ-5D-5L visual analog scale.

Norfolk QoL-DN Questionnaire

At Month 30, vutrisiran improved patients' self-reported outcomes with respect to the impact of polyneuropathy on quality of life, as assessed by the Norfolk QoL-DN questionnaire, compared to placebo in the overall population (LS mean [SEM] difference: -5.3 (±1.4); P=0.0001, MMRM model). The effect size was larger in the vutrisiran monotherapy group (-7.5 (±1.9); P=0.0001) and smaller in the Background Tafamidis Group (-2.6 (±1.9); P= 0.1654). Baseline values for the vutrisiran monotherapy groups were 19.6 (19.5) and 19.2 (18.7) (vutrisiran and placebo (SD), in the background tafamidis group 14.3 (15.0) and 14.9 (15.2), and in 17.5 (18.0) and 17.5 (17.5), respectively in the overall population.

In a subset of patients with a history of neuropathy, vutrisiran also improved patients' self-reported outcomes with respect to the impact of polyneuropathy on quality of life compared to placebo in the overall population (LS mean [SEM] difference: -4.6 [±2.3]; P=0.0473). The effect size was larger in the vutrisiran monotherapy group (-9.5 (±3.5); P= 0.0089), No effect was observed in the Background Tafamidis Group (-0.8 (±3,1); P= 0. 8041)

- Baseline values for the vutrisiran monotherapy groups were 25.0 (19.9) and 27.5 (22.2) (vutrisiran and placebo (SD), in the background tafamidis group 17.5 (17.5) and 21.2 (16.5), and 21.1 (19.0) and 24.7 (20.0), respectively in the overall population.

Ancillary analyses

Regarding analyses for individual components, in subgroups and sensitivity analyses see above.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18. Summary of efficacy for HELIOS-B trial

Title: HELIOS-B: A Phase 3, Randomised, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)	
Study identifier	Study number: ALN-TTRSC02-003 EudraCT number: 2019-003153-28

Design	Phase 3, global, randomised (1:1), double-blind (DB), placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics (PK)/pharmacodynamics (PD) of vutrisiran in patients with hATTR and wtATTR amyloidosis with cardiomyopathy, who were either not on tafamidis at baseline (vutrisiran monotherapy subgroup) or were receiving concomitant tafamidis at baseline per the inclusion criteria (background tafamidis subgroup). Patients were stratified by baseline tafamidis use, ATTR disease type (hATTR vs wtATTR), and NYHA class I-II and age <75 years vs. all other.		
	Duration of main phase:		up to 36 months (completed)
	Duration of Run-in phase:		not applicable
	Duration of Open-label Extension phase:		up to 24 months (ongoing)
Hypothesis	Superiority of vutrisiran over placebo for clinical efficacy endpoints		
Treatments groups	Overall population		
	Vutrisiran		Treatment: vutrisiran SC injection 25 mg every 3 months (q3M) Duration: up to 36 months Number randomised: 326
	Placebo		Treatment: sodium chloride 0.9% w/v SC injection q3M Duration: up to 36 months Number randomised: 329
	Vutrisiran Monotherapy Subgroup (defined as the group of patients not on tafamidis at study baseline)		
	Vutrisiran		N=196
	Placebo		N=199
Endpoints and definitions	Primary endpoints	All-cause mortality and recurrent CV events	Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the overall population Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)
	Secondary endpoints (each defined in both the overall population and the vutrisiran monotherapy subgroup):	6-MWT	Change from baseline in 6-minute walk test (6-MWT) at Month 30
		KCCQ-OS	Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) at Month 30
		All-cause mortality	All-cause mortality through 42 months
		NYHA Class	Change from baseline in New York Heart Association (NYHA) class at Month 30

Database lock	Primary analysis database lock: 14 June 2024				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Full analysis set (FAS): all randomised patients who received any amount of study drug. Corresponds to "Overall population". Vutrisiran monotherapy subgroup full analysis set: All patients in the FAS who were not on tafamidis at the study baseline.				
Descriptive statistics and estimate variability	Treatment group	**Overall population**		**Vutrisiran Monotherapy Subgroup**	
		Placebo	Vutrisiran	Placebo	Vutrisiran
	Number of subjects	328	326	199	196
	Composite endpoint of All-cause mortality and recurrent CV events (total number of events)	332	251	211	155
	6-MWT (observed median change from baseline at Month 30, meters)	-30.65	-7.50	-47.33	-13.05
	Q1, Q3	-82.55, 4.77	-55.00, 18.00	-91.92, -2.35	-69.04, 17.41
	KCCQ-OS (observed median change from baseline at Month 30)	-6.25	-1.30	-8.65	-0.26
	Q1, Q3	-17.71, 3.13	-11.07, 8.14	-20.05, 1.56	-13.80, 11.77
	All-cause mortality (number of events [%])	85 (25.9%)	60 (18.4%)	58 (29.1%)	43 (21.9%)
	NYHA class (% stable or improved from baseline at Month 30)	60.5	67.8	56.4	66.3
Effect estimate per comparison	Primary endpoint All-cause mortality and recurrent CV events	**Overall population**			
		Comparison groups	Vutrisiran vs. placebo		
		Hazard ratio	0.718		

		95% CI	(0.555, 0.929)
		P-value (LWYY method)	0.0118
		Vutrisiran monotherapy subgroup	
		Comparison groups	Vutrisiran vs. placebo
		Hazard ratio	0.672
		95% CI	(0.487, 0.929)
		P-value (LWYY method)	0.0162
	Secondary endpoint 6-MWT	**Overall population**	
		Comparison groups	Vutrisiran vs. placebo
		LS mean difference at Month 30 (vutrisiran – placebo)	26.46
		95% CI	13.38, 39.55
		P-value (MMRM model)	7.976E-05
		Vutrisiran monotherapy subgroup	
		Comparison groups	Vutrisiran vs. placebo
		LS mean difference at Month 30 (vutrisiran – placebo)	32.09
		95% CI	14.03, 50.15
		P-value (MMRM model)	0.0005
	Secondary endpoint KCCQ-OS	**Overall population**	
		Comparison groups	Vutrisiran vs. placebo
		LS mean difference at Month 30 (vutrisiran – placebo)	5.80
		95% CI	(2.40, 9.20)
		P-value (MMRM model)	0.0008
		Vutrisiran monotherapy subgroup	
		Comparison groups	Vutrisiran vs. placebo
		LS mean difference at Month 30 (vutrisiran – placebo)	8.69
		95% CI	(3.98, 13.40)
		P-value (MMRM model)	0.0003
	Secondary endpoint All-cause mortality	**Overall population**	
		Comparison groups	Vutrisiran vs. placebo
		Hazard ratio (Cox PH model)	0.645
		95% CI	(0.463, 0.898)
		P-value (log-rank test)	0.0098

		Vutrisiran monotherapy subgroup	
		Comparison groups	Vutrisiran vs. placebo
		Hazard ratio (Cox PH model)	0.655
		95% CI	(0.440, 0.973)
		P-value (log-rank test)	0.0454
	Secondary endpoint NYHA Class	**Overall population**	
		Comparison groups	Vutrisiran vs. placebo
		Difference in % stable or improved at Month 30	8.7
		95% CI	(1.3, 16.1)
		P-value (Cochran-Mantel-Haenszel method with multiple imputation)	0.0217
		Vutrisiran monotherapy subgroup	
		Comparison groups	Vutrisiran vs. placebo
		Difference in % stable or improved at Month 30	12.5
		95% CI	(2.7, 22.2)
		P-value (Cochran-Mantel-Haenszel method with multiple imputation)	0.0121
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

The primary evidence for efficacy in this application is based on a single pivotal Phase 3 study in ATTR amyloidosis patients with cardiomyopathy.

No formal pooling or other comparisons of efficacy data across studies were performed to support this application.

Clinical studies in special populations

Table 19. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
HELIOS-B Study			
Overall	210/654 = 32.1%	367/654 = 56.1%	30/654 = 4.6%
Vutrisiran	96/326 = 29.4%	188/326 = 57.7%	15/326 = 4.6%
Placebo	114/328 = 34.8%	179/328 = 54.6%	15/328 = 4.6%
Non-Controlled trials	N/A	N/A	N/A

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Vutrisiran is an RNAi therapeutic comprised of a synthetic, chemically modified, double-stranded small interfering RNA (siRNA) that specifically targets variant and wtTTR and silences TTR messenger RNA (mRNA). This is accomplished by incorporation of vutrisiran siRNA into the cellular multiprotein enzyme cleavage complex known as the RNA induced silencing complex (RISC). Reduction of both variant and wild type TTR production in the liver, which are the fundamental pathogenic proteins causing hATTR amyloidosis, will reduce ongoing deposition of amyloid deposits and potentially allow for clearance of existing deposits and consequently, halting or reversing disease progression.

In amyloidosis with polyneuropathy previous clinical studies with mRNA silencing agents, such as patisiran, and the antisense oligonucleotide (ASO) inotersen, and with vutrisiran demonstrated that TTR reduction in patients with hATTR can have beneficial effects, measured by clinical endpoints evaluating disease manifestations and patient-reported outcomes. Amvuttra has been approved for the treatment of hATTR amyloidosis with in adult patients with stage 1 or stage 2 polyneuropathy.

Within this procedure the MAH applies for an extension of the indication as follows:

Amvuttra is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy (hATTR-PN).

Amvuttra is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

Design and conduct of clinical studies

The clinical development program of vutrisiran to support an indication for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) included one pivotal phase 3 trial, the study ALN-TTRSC02-003 (HELIOS B). It is an ongoing, Phase 3, multicenter, multinational,

randomized, double-blind, placebo-controlled study in hATTR amyloidosis patients with cardiomyopathy (Primary analysis completed, Data cutoff: 08 May 2024).

The clinical development program to support the indication and the design of the Phase 3 HELIOS-B study were discussed with the European Union (EU) European Medicines Agency EMA in June 2019 (EMEA/H/SA/3876/2/2019/PA/II), and subsequently advice was given in November 2023 in a pre-submission teleconference with the CHMP Rapporteur and Co-Rapporteur.

The data are assessed in the context of data submitted at the time of the initial MAA: A safety and clinical pharmacology study assessing PD in healthy subjects (Study 001) and an open-label on-going Phase 3 study in adult patients with hATTR amyloidosis with polyneuropathy (ALN-TTRSC02-002, HELIOS-A).

Design

HELIOS-B is an ongoing, global, Phase 3, randomized, double blind study designed to evaluate efficacy, safety, PK, and PD of vutrisiran in adult patients with hATTR amyloidosis with cardiomyopathy.

The study consisted of the following periods:

- Screening Period:

- Double blind (DB) treatment period

- Open-label treatment extension period up to 2 years

- Follow-up period up to 1 year after last dose of study drug (up to 18 months for women of child-bearing potential).

After screening, eligible patients were randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as an SC injection q3M (every 12 weeks ±7 days) for up to 36 months in the DB Period.

During the OLE Period, all patients received open-label doses of 25 mg q3M vutrisiran administered as SC injections.

Between Protocol Amendment 3 (13 May 2022, start) and Protocol Amendment 4 (22 March 2023, end) an Open-label Randomized Treatment Extension (RTE) Period was added wherein patients were randomized 1:1 to receive treatment with either 25 mg q3M vutrisiran or 50 mg once every 6 months (q6M) vutrisiran with all patients receiving 25 mg q3M vutrisiran thereafter.

Patients who were on tafamidis at baseline (background tafamidis subgroup) as per inclusion criteria were encouraged, if considered appropriate, to remain on tafamidis for the duration of the study. Initiating on-label use of tafamidis in previously naïve patients during the study (tafamidis drop-in) was allowed. In addition to study drug, all patients were instructed to take the recommended daily allowance of vitamin A during their DB, OLE, and Follow-up Periods.

Endpoints

Two **primary efficacy endpoints** were predefined:

• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the overall population

• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)

The following **(confirmatory) secondary endpoints** were defined in both the overall population and the vutrisiran monotherapy subgroup:

• Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • All-cause mortality • Change from baseline in NYHA class

Additional secondary endpoints covered among others

• Composite outcome of all-cause mortality and recurrent all-cause hospitalizations and urgent HF visits • Time to first CV event (including CV hospitalizations and urgent HF visits) or all-cause mortality

Change from baseline in • ECHO parameters, • NT-proBNP • Troponin I • eGFR • ATTR amyloidosis disease stage • EuroQoL-5 Dimensions-5 Levels questionnaire, and • Norfolk QoL-DN

In addition, assessment of **PD** (change from baseline in serum TTR levels) **plasma PK exposure** and frequency and **titers of ADA** was investigated.

The choice of the primary and secondary endpoint is overall acceptable

Conduct

The rate of reported protocol violations was within the expected range, partly related to COVID-19 pandemia. Quality control measures were in place. No serious GCP issues were identified with the potential to affect the integrity of the study or with an impact of the conclusions on the benefit risk balance. Analyses covering the impact of the COVID19-pandemic were provided. Overall treatment compliance was high.

- Via Amendment 1 the primary endpoint was amended in order to include not only CV hospitalizations but also urgent HF visits (UHV) without hospitalization. This is acceptable in case of stringent definition of the events, e.g., in line with Hicks et al 2018 and in case they are adjudicated.

- Via global amendment 5 (12 February 2024) an additional primary analysis in patients not on tafamidis at study baseline was added. Based on the information provided that Applicant had no information at that time point allowing a reasonable guess on treatment assignment at that stage.

Study size

Patients were randomized and treated at 87 study centers worldwide in 26 countries with a sufficient representation of patients from the EU. 799 patients were screened, 655 were randomized. Of the 326 patients in the vutrisiran group, 78 (23.9%) patients discontinued study drug during the DB Period. Of the 329 patients in the placebo group, 99 (30.1%) patients discontinued study drug during the DB Period. 241 (vutrisiran) and 221 patients (placebo) entered the OLE period, 4 and 8 patients, respectively discontinued vutrisiran therapy during the OLC period that was ongoing with 248 and 224 patients respectively at the time of the data base lock.

Study population

Subjects were well representative for patients with hATTRwt and hATTRv amyloidosis and mild to moderate symptomatic cardiomyopathy. Baseline disease characteristic were overall balanced between the groups. In the overall population, 578 (88.4%) patients had wtATTR amyloidosis and 76 (11.6%) patients had hATTR amyloidosis. The mean years since diagnosis of ATTR amyloidosis was 1.43 (range, 0.0 to 11.1) years. The mean age of patients at symptom onset was 73.3 (range, 35 to 85) years. Most (77.7%) patients had NYHA class II HF and were classified as having ATTR amyloidosis disease Stage 1 (66.8%) or Stage 2 (28.6%). In the overall population, baseline disease characteristics were generally similar between the vutrisiran and placebo groups, except for a higher median NT-proBNP level in the vutrisiran group (2020.50 ng/L) compared to the placebo group (1801.00 ng/L), which was primarily driven by an imbalance in the vutrisiran monotherapy subgroup. Baseline disease characteristics were indicative of somewhat greater disease

severity among patients not on tafamidis at baseline (vutrisiran monotherapy subgroup) compared with patients who were on tafamidis at baseline (background tafamidis subgroup).

Overall, 35.5% of patients also had a history of neuropathy/polyneuropathy.

Statistical methods

The definition of the analysis sets is overall appropriate. For the SAF Patients who were randomized to placebo group but received any amount of vutrisiran during the DB Period were grouped into the vutrisiran arm. This is not an issue if it happens to single patients. In a case where a larger group of patients in the placebo group receives single doses of vutrisiran, the AE rate may be diluted. This was not a relevant issue in HELIOS-B.

The primary efficacy analyses were prespecified for two populations, all patients included and patients on vutrisiran monotherapy (no tafamidis at baseline). This is endorsed. Analyses for patients on tafamidis background therapy are provided in the Attachment to the clinical study report separately. Reporting the results in this subgroup in the Body CSR and in the summary of efficacy/overview key documents also would have made the assessment of the data easier.

Estimands were specified in the SAP in alignment with the primary and key secondary objectives. Generally, as the study design and analysis should be aligned to the estimand, it is preferred when estimands are also specified in the protocol.

As part of the primary estimand definition, it was specified that the intercurrent events treatment discontinuation and initiation of alternative therapies (including tafamidis drop-in in the vutrisiran monotherapy subgroup) were to be accounted for by the treatment policy strategy, which is appropriate. Heart transplantation and LVAD placement were treated as CV-related death, i.e., accounted for by a composite strategy, which is also acceptable. Study discontinuation was considered as an intercurrent event by the applicant that was accounted for by the hypothetical strategy, however, it is not an intercurrent event in itself (see ICH E9 (R1)) but a reason for missing data.

For addressing the effect on 6-MWT and KCCQ-OS after 30 months of treatment, treatment discontinuation and initiation of alternative therapies was also accounted for by a treatment policy strategy. Death (including heart transplant and LVAD placement) was aimed to be accounted for by a composite strategy, which is in principle acceptable. However, it is not straightforward what is the appropriate implementation of a composite strategy, particularly whether the imputation based on 10% worst values in the respective treatment arm is appropriately aligned with considering a patient a treatment failure. Therefore, 1) an analysis assigning worst possible values to deaths (i.e., imputing a value of 0 for patients who die) and 2) a rank-based analysis in analogy to the sensitivity analysis for the primary endpoint (i.e., assigning worst ranks to patients with shortest survival time) was provided.

The randomisation stratification factors were appropriately taken into account in the analysis.

The analysis of the composite primary endpoint based on the modified Andersen-Gill model incorporating mortality as terminal event and hospitalisations as recurrent event may bear considerable problems with interpretation, as the two events included are of different severity, and mortality is a competing event for hospitalisation. However, it is acknowledged that a rank-based analysis was also provided as well as an analysis of the single components. Overall, the primary analysis in combination with these analyses are considered sufficient for providing a complete picture. In alignment with the treatment policy strategy, patients were aimed to be followed irrespectively of treatment discontinuation, which is appreciated. However, the analysis is based on the non-informative censoring assumption for patients who nevertheless discontinued the study, which is questionable as it assumes a continued benefit from treatment for patients in the active arm. It is acknowledged that a sensitivity analysis imputing CV events after discontinuation

was provided but as the imputation model considered treatment arm, it is still based on the assumption of similar CV risk for patients in the active arm who discontinued treatment than for patients on treatment. Additional analyses assuming a similar CV event rate as in the placebo arm were be provided showing robustness of the results

Included survival data collected within 6 months after the first dose during the OLE Period in the analysis of all-cause mortality is acceptable, as even if the assumption of no effect on mortality during this time was not fulfilled, it would be a conservative analysis.

For the continuous secondary endpoints 6-MWT and KCCQ-OS, the MMRM model that was primarily used may also not be plausible for patients who discontinued the study as it is based on the missing at random assumption. The pattern mixture model (copy reference) that was provided as sensitivity analysis may be in better alignment with the targeted estimand as it assumes similar outcomes than in patients who are not on active treatment and should be the basis for reporting results.

As a significant imbalance in baseline NT-proBNP and troponin I between treatment groups was observed after unblinding, adjusted Kaplan-Meier curves were generated for time to event endpoints, including all-cause mortality and time to first CV event or all-cause mortality. However, although the argument that the analysis models that were the basis for hypothesis tests and estimation of treatment effects are adjusted for these factors is acknowledged, results should still be primarily reported based on the pre-specified methods to avoid any data-driven decisions.

The multiplicity strategy ensured control of the study-wise type 1 error for the hypothesis tests for the primary and key secondary endpoints based on the overall population and the Vutrisiran Monotherapy Subgroup. However, as the effects in the overall population may be driven by the monotherapy subgroup, it is agreed that the analysis in the background tafamidis subgroup is also important.

Efficacy data and additional analyses

Primary Endpoint: Composite Outcome of All-cause Mortality and Recurrent CV Events (CV Hospitalizations and Urgent HF Visits)

In the overall population, vutrisiran patients had a statistically significant 28.2% reduction in the risk of all-cause mortality and recurrent CV events compared to placebo (hazard ratio: 0.718; 95% CI: 0.555, 0.929; P=0.0118).

In the vutrisiran monotherapy subgroup, vutrisiran patients had a statistically significant 32.8% reduction in the risk of all-cause mortality and recurrent CV events compared to placebo (hazard ratio: 0.672; 95% CI: 0.487, 0.929; P=0.0162).

There was a time delay of about 9 months and about 15 - 18 months before a treatment effect was observed for the overall population and the vutrisiran monotherapy population, respectively. Both, mortality events and HFH/UHVs events contributed consistently to the result. Heart transplant events added only to a minor degree to the mortality, consistent with “true” death events, no LVAD placement was noted. Inclusion of the letter two events did not have a relevant impact on the overall result.

A consistent numerical result was also noted in patients receiving background tafamidis therapy with a HR of 0.785, p = 0.27 favouring vutrisiran over placebo (not part of the primary analysis) with consistent numerical imbalances for both components of the composite endpoint. The data on the administration in combination with tafamidis are difficult to interpret. There may be some overlap in efficacy between onset of an effect of tafamidis after treatment initiation and onset of efficacy of vutrisiran. No conclusions are possible on whether there is benefit in coadministration of both drugs over administration of vutrisiran or

tafamidis alone. The data do also not provide information on whether efficacy of vutrisiran is higher than efficacy of tafamidis.

Individual Components of the Primary Endpoint

All-Cause Mortality

Events reported after study withdrawal were included for the component analysis of all-cause mortality. In the overall population, vutrisiran treatment led to a 30.6% reduction in the risk of all-cause mortality compared to placebo (hazard ratio: 0.694; 95% CI: 0.490, 0.982; P=0.0389).

In the vutrisiran monotherapy subgroup, vutrisiran treatment led numerically to a 29.5% reduction in the risk of all-cause mortality compared to placebo (hazard ratio: 0.705; 95% CI: 0.467, 1.064; P=0.1179).

There was a delay by about 18 – 24 months until an effect on mortality was observed. Of note, also the rate of non-CV deaths was lower in patients receiving vutrisiran.

Recurrent CV Events

In the overall population, in the analysis of recurrent CV events, including CV hospitalizations and urgent HF visits, vutrisiran treatment led to a 26.7% reduction in the risk of CV events compared to placebo (relative rate ratio: 0.733; 95% CI: 0.610, 0.882; P=0.0010).

In the vutrisiran monotherapy subgroup, vutrisiran led to a 32.4% reduction in the risk of CV events compared to placebo (relative rate ratio: 0.676; 95% CI: 0.533, 0.857; P=0.0012).

There was a delay by about 9 – 15 months for the treatment effect to emerge.

Sensitivity and Additional Analyses for the Primary Endpoints

In the win ratio sensitivity analysis, the survival status collected after study discontinuation was included in the hierarchical comparisons. A win ratio of >1 represents a favorable outcome for vutrisiran. The win ratio in the overall population was 1.39 (P=0.0088), indicating a reduction in all-cause mortality and recurrent CV events in the vutrisiran group compared to placebo. A consistent effect was observed in the vutrisiran monotherapy subgroup (win ratio: 1.51; P=0.0089).

All other sensitivity and additional analyses presented for the primary endpoints were consistent and supported the primary analysis results of the vutrisiran treatment effect compared to placebo. This pertains to sensitivity analyses based on: - Data through 42 months, - Imputing CV events after study withdrawal, - Truncating outliers (For patients with more than 7 events, the first 7 most important events were kept for analysis, with importance ranked in the order of death, CV hospitalization and urgent HF visit), - HT/LVAD placement not treated as all cause mortality; data censored at the date of such procedure, - SGLT2 inhibitor drop-in due to cardiac disease progression treated as a CV event, and additional analyses based on: - Use of CV events per investigator assessment instead of CEC adjudication, - For the monotherapy subgroup, events beyond 9 months of initiation of tafamidis censored.

Subgroup Analysis: Composite Outcome of All-cause Mortality and Recurrent CV Events (CV Hospitalizations and Urgent HF Visits)

The effect of vutrisiran treatment on the composite outcome of all-cause mortality and recurrent CV events was consistent across allmost prespecified subgroups, including age, baseline tafamidis use (in the overall population), NYHA class, and baseline NT-proBNP in both the overall population (Figure 20) and the vutrisiran monotherapy subgroup (Figure 20 and Figure 21). Analyses by Region showed consistent results for the EU population vs. other regions.

For patients with hATTR the analyses indicated efficacy of vutrisiran in the vutrisiran monotherapy subgroup but not in the overall population. The data suggest even a numerically negative effect of vutrisiran in patients with hATTR when pretreated with tafamidis. This was further clarified by the Applicant.

Secondary endpoints

6-MWT

At Month 30, vutrisiran led to a statistically significant improvement in 6-MWT compared to placebo in the overall population (least square [LS] mean difference: 26.46 m; P=7.976E-05), with consistent results observed in the vutrisiran monotherapy subgroup (32.09 m; P = 0.0005). In the Background Tafamidis Subgroup the least square [LS] mean difference (SEM) at month 30 was 18.44 (9.15), P = 0.0450. The difference by 32 and 26 m in the vutrisiran monotherapy and the overall group, respectively is at the threshold of what has been accepted in the past as being clinically relevant. There was a delay by about 12 – 18 months before a larger treatment effect was observed. This is consistent with published results for acoramidis (delay by about 12 months), but not for Tafamidis (no relevant delay, Gillmore et al., 2024; Maurer et al., 2018). Irrespectively, in the context of the totality of data, the result is supportive for the assumption of a clinically relevant efficacy.

KCCQ-OS

At Month 30, vutrisiran led to a statistically significant improvement in KCCQ-OS compared to placebo in the overall population (LS mean difference: 5.80 points; P=0.0008). The difference was larger (8.7 points (in the vutrisiran monotherapy group and small (LSMean difference 1.7) in the Background Tafamidis group.

The overall treatment effect can be considered a small but clinically relevant difference in the overall group and in the vutrisiran monotherapy group, whereas the difference in the background tafamidis group was below the generally accepted threshold of 5.

Results across all KCCQ-OS domains, reflecting the severity of physical and social limitations, the frequency and severity of symptoms, and the quality of life impacts associated with cardiomyopathy were consistent with the primary analysis and showed a treatment effect in favor of vutrisiran compared to placebo in both the overall population and the vutrisiran monotherapy subgroup.

The effect of vutrisiran treatment on KCCQ-OS was largely consistent across most prespecified subgroups in both the overall population (including baseline tafamidis use) and the vutrisiran monotherapy subgroup. Analyses for 6-MWD and KCCQ did not indicate athat an effect on polyneuropathy had a relevant impact on the overall results

All-Cause Mortality

The Applicant has counted death cases that occurred in the placebo arm after switching to open label vutrisiran treatment up to month 42 as death cases on placebo. The approach is based on the assumption of a time delay of more than 12 months until an effect of vutrisiran on mortality emerges. With the variable follow-up design of this study, patients enrolled in the OLE Period received their first OLE dose at either Month 33 or Month 36, depending on their enrollment time. The analysis of all-cause mortality as a secondary endpoint included all vital status collected through 42 months. The approach can be supported for exploratory but not for a confirmatory purpose. However, since the results are consistent with the component analysis of mortality during the DB phase, the acceptability of the approach is more of theoretical nature.

Vutrisiran patients had a statistically significant 35.5% reduction in the risk of all-cause mortality compared to placebo in the overall population (hazard ratio: 0.645; 95% CI: 0.463, 0.898; P=0.0098; 95% CI: 0.440, 0.973; P=0.0454.

The analysis of CV-related mortality through 42 months showed a similar numerical treatment effect as all-cause mortality in both the overall population and the vutrisiran monotherapy subgroup. ($p > 0.05$ for both groups. The effect of vutrisiran treatment on all-cause mortality was overall consistent across all prespecified subgroups in both the overall population and the vutrisiran monotherapy subgroup. Only a small effect on mortality was observed in patients with hATTR, mainly due to the result in the vutrisiran monotherapy population. An integrated discussion of the totality of data available for hATTR patients indicated efficacy of vutrisiran monotherapy also in this population whereas efficacy of vutrisiran in hATTR patients an tafamidis background therapy is in question.

NYHA Class

At Month 30, vutrisiran led to a statistically significantly greater proportion of patients who showed stability (no change in class) or improvement compared to placebo in the overall population (adjusted difference: 8.7%, 95% CI: 1.3, 16.1; P=0.0217), with consistent results observed in the vutrisiran monotherapy subgroup and only a smaller effect in patients at background tafamidis therapy.

Exploratory endpoints

Time to First CV Event (including CV Hospitalizations and Urgent HF Visits) or All-Cause Mortality

In the overall population, vutrisiran treatment led to a 28.4% reduction in the risk of first CV event or all-cause mortality compared to placebo (hazard ratio: 0.716; 95% CI: 0.566, 0.905; P=0.0062)

In the vutrisiran monotherapy subgroup, vutrisiran treatment led to a 35.6% reduction in the risk of first CV event or all-cause mortality compared to placebo (hazard ratio: 0.644; 95% CI: 0.479, 0.867; P=0.0043).

Kaplan-Meier curves illustrating time to first CV event or all-cause mortality showed curves diverging after approximately 6 months of treatment in both the overall population and in the vutrisiran monotherapy subgroup.

Consistent results were also obtained for the following exploratory analyses (data not shown here):

- Time to First CV Event (including CV Hospitalization, Urgent HF Visit and Any Initiation of SGLT2 Inhibitor due to Cardiac Disease Progression), or All-Cause Mortality
- Time to First Oral Diuretic Intensification, First CV Event (including CV Hospitalization and Urgent HF Visit), or All-Cause Mortality
- Time to Second CV Event (including CV Hospitalizations and Urgent HF Visits) or All-Cause Mortality
- Composite Outcome of All-Cause Mortality and Recurrent All-Cause Hospitalizations and Urgent HF Visits

Considering clinical and methodological issues hampering a straightforward interpretation of recurrent event analysis in diseases with high mortality, the first event analysis, even if only predefined as an exploratory analysis by the MAH, is considered of major importance. The results were consistent with the primary analysis and supported the robustness and assumption of the clinical relevance of the primary results in both main populations analysed.

Cardiac Biomarkers

NT-proBNP Change from Baseline

Serum levels of NT-proBNP were measured during the DB Period.

At Month 30, vutrisiran led to a 32% relative reduction in the fold increase in NT-proBNP compared to placebo in the overall population (adjusted geometric mean fold change ratio [vutrisiran/placebo]: 0.68; P=3.440E-12). Median change from baseline in NT-proBNP levels indicated relative stability in vutrisiran patients with an 8.98% increase while levels in placebo patients indicated worsening with a 51.62% increase.

Vutrisiran led to a 43% relative reduction in the fold increase in NT-proBNP compared to placebo in the vutrisiran monotherapy subgroup (adjusted geometric mean fold change ratio [vutrisiran/placebo]: 0.57; P=4.339E-12).

The effect of vutrisiran treatment on NT-proBNP was consistent across most subgroups in both the overall population and the vutrisiran monotherapy population. However, only a small numerical difference was observed in patients with Tafamidis at baseline.

Troponin I

Results for Troponin I were similar to the results as reported for NT-proBNP

Echocardiographic parameters

Echocardiographic parameters showed some improvement in change from baseline to month 30 when comparing vutrisiran and placebo. There was an LS mean (SEM) difference in mean LV wall thickness by 0.4 (0.2) mm and 0.8 (0.3) mm in the overall and the vutrisiran monotherapy population. Small differences were also seen for LV ejection fraction that decreased with placebo and with vutrisiran. There were LS mean (SEM) differences in the change of the ejection fraction by (absolute) 2.03 (0.86) and 2.27 (1.19) % (overall group and vutrisiran monotherapy group, respectively), in LV mass by -18.86 (7.17) and -30.87 (10.48) and in average peak longitudinal strain (%) by -1.23 (0.26) and -1.30 (0.36) respectively. Per se, these differences are considered at the most moderate.

eGFR

Vutrisiran was associated with lower decline from baseline in eGFR compared to placebo (LS mean [SEM] difference: 2.2 [±1.3] mL/min/1.73m2, P=0.0876) in the overall population. Consistent results were observed in the vutrisiran monotherapy subgroup and in patients on background tafamidis therapy (LS mean [SEM] difference mL/min/1.73m2: 2.5 (1.8) p= 0.1654, and 2.0 (1.8), p= 0.2763 respectively). The results are reassuring. Since the underlying form of amyloidosis has in impact on whether the kidney is a target organ of the disease, data on kidney function over time by differentiating between wtATTR and hATTR were requested. The data indicated a small numerical imbalance in favour of vutrisiran becoming visible after 24 months.

ATTR Amyloidosis Disease Stage

Categorizing patients by NAC stage is clinically in use for its prognostic value. In the overall population, 77.3% of patients in the vutrisiran group showed no progression in ATTR amyloidosis stage at Month 30 compared to 61.2% of patients in the placebo group (adjusted difference: 16.1; 95% CI: 8.1, 24.2; P=7.889E-05). Consistent results were observed in the vutrisiran monotherapy subgroup and in patients on background tafamidis therapy (adjusted difference: 14.8 (3.7, 26.0), p = 0.0112, and 17.8 (6.3, 29.3), p = 0.0030, respectively). The result of more patients showing no progression in ATTR NAC stage at month 30 are supportive for the overall conclusion on a beneficial treatment effect.

EQ-5D-5L

At Month 30, vutrisiran improved patients' self-reported general health-related quality of life, as assessed by the change from baseline in EQ-5D-5L index score, compared to placebo in the overall population (LS mean [SEM] difference: 0.0308 [±0.0111]; P=0.0056), with consistent results observed in the vutrisiran

monotherapy subgroup. The treatment effect is below of what has been described as a clinically MID values by simulations (Nathan S. McClure NS et al., Value in health 2017; 20: 644–650)

Norfolk QoL-DN Questionnaire

EMA has accepted the Norfolk QoL-DN as a validated tool to assess patients' self-reported outcomes with respect to the impact of polyneuropathy on quality of life to be used as a key secondary endpoint in the initial MAA for vutrisiran in patients with hATTR polyneuropathy and in other studies in hATTR with polyneuropathy.

At Month 30, vutrisiran the result in the Norfolk QoL-DN questionnaire, compared to placebo in the overall population (LS mean [SEM] difference: -5.3 (±1.4); P=0.0001, MMRM model). The effect size was larger in the vutrisiran monotherapy group (-7.5 (±1.9); P=0.0001) and smaller in the Background Tafamidis Group (-2.6 (±1.9); P= 0.1654).

In a subset of patients with a history of neuropathy, vutrisiran also improved the score with vutrisiran compared to placebo in the overall population (LS mean [SEM] difference: -4.6 [±2.3]; P=0.0473). The effect size was larger in the vutrisiran monotherapy group (-9.5 (±3.5); P= 0.0089). No effect was observed in the Background Tafamidis Group (-0.8 (±3,1); P= 0. 8041).

Considering the different patient population in HELIOS-A (ATTR amyloidosis with PN9 and HELIOS-B (ATTR amyloidosis with CM), it is expected that the effect size in HELIOS-B was smaller as compared to the effect size of -21.0 (3.1,8) in the indirect comparison between HELIOS A and APOLLO placebo. EPAR EMA/CHMP/689555/2022. Since no published values for an MID are known, the relevance of the finding is not entirely clear.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

No data in the paediatric population were submitted as part of the application.

A product-specific paediatric investigational plan waiver was granted by the EMA Paediatric Committee for vutrisiran (EMEA-002425-PIP01-18 – P/0015/2019), as ATTR amyloidosis occurs almost exclusively in adults. The waiver covers all subsets of the paediatric population (0 to 18 years).

2.4.4. Conclusions on the clinical efficacy

Transthyretin amyloidosis including hATTR and wtATTR is a rare, progressive and fatal disease which manifests as destabilization of the tetrameric structure of the TTR protein. Vutrisiran is an siRNA molecule that uses RNA interference mechanisms to target and silence the expression of wild type and variant TTR mRNA and inhibit the synthesis of the TTR protein.

Large reductions in TTR and a clinically relevant and statistically significant reduction in the primary composite endpoint of all-cause mortality and CV events (CV hospitalizations and UHVs) have been observed in the overall population and in patients not treated with tafamidis at baseline. The results are supported by clinically relevant and statistically significant improvements in the following confirmatory secondary endpoints: 6-MWT at month 30, KCCQ-OS at month 30, All-cause mortality by month 42 and

NYHA class at month 30 in both populations. The population reflects the target indication as proposed in the indication applied for.

2.5. Clinical safety

Introduction

The MAH is seeking to extend the indication for the medicinal product AMVUTTRA (vutrisiran) to include the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM), based on the results of the HELIOS-B study.

Patient exposure

During the DB period of the HELIOS-B study, 326 patients were treated with vutrisiran and 328 patients were treated with placebo. At the time of the primary analysis, all active patients had completed the DB period.

The median duration of treatment in the vutrisiran group was 35.78 months (range: 0.6 to 38.7 months), with a cumulative treatment exposure of 833.9 patient years (Table 20). Two hundred and fifty-seven (78.8%) patients had vutrisiran exposure ≥30 months, and 77 (23.6%) patients had vutrisiran exposure ≥ 36 months. The median duration of treatment in the placebo group was 33.77 months (range: 1.1 to 37.3 months), with a cumulative treatment exposure of 822.4 patient-years. The proportion of patients who received at least 12 doses was 75.8% and 69.5% in the vutrisiran and placebo groups, respectively. Overall, a total of 3601 doses of vutrisiran and 3573 doses of placebo were administered during the DB Period.

Table 20. Overall exposure to study drug during the DB period of the HELIOS-B study (safety analysis set)

Parameter	Placebo (N=328)	Vutrisiran (N=326)
Duration of study drug exposure (months)[a]		
Mean (SD)	30.09 (9.32)	30.70 (9.58)
Median (min, max)	33.77 (1.1, 37.3)	35.78 (0.6, 38.7)
Cumulative study drug exposure, patient-years[a]	822.4	833.9
Duration of study drug exposure (cumulative), n (%)		
≥1 day	328 (100.0)	326 (100.0)
≥6 months	314 (95.7)	312 (95.7)
≥12 months	301 (91.8)	293 (89.9)
≥18 months	279 (85.1)	278 (85.3)
≥24 months	262 (79.9)	267 (81.9)
≥30 months	241 (73.5)	257 (78.8)
≥36 months	63 (19.2)	77 (23.6)
Total number of doses received per patient		

Parameter	Placebo (N=328)	Vutrisiran (N=326)
Mean (SD)	10.9 (3.3)	11.0 (3.4)
Median (min, max)	12.0 (1, 13)	13.0 (1, 13)
Cumulative number of doses received	3573	3601
Total number of doses received, n (%)		
≥1	328 (100.0)	326 (100.0)
≥5	301 (91.8)	293 (89.9)
≥9	265 (80.8)	266 (81.6)
≥12	228 (69.5)	247 (75.8)

Abbreviations: DB=double-blind; max=maximum; min=minimum; SD=standard deviation.

[a] Individual duration of exposure (in days) was calculated as the earliest date of (the end of study, data cutoff date, 84 days after the last dose of study drug), minus the date of the first dose of study drug plus 1. Duration of exposure in months or years = duration of exposure (days) divided by 30.4375 and 365.25, respectively.

Adverse events

During the DB period of the HELIOS-B study, 322 (98.8%) patients in the vutrisiran group and 323 (98.5%) patients in the placebo group had at least 1 AE (Table 21). AEs considered related to study drug by the Investigator were reported in 41 (12.6%) patients in the vutrisiran group and 46 (14.0%) patients in the placebo group. The majority of the AEs were mild or moderate in intensity. Severe AEs were reported in 158 (48.5%) patients in the vutrisiran group and 194 (59.1%) patients in the placebo group. The proportion of patients with severe AEs considered related to study drug by the Investigator was low in the 2 groups (1 [0.3%] vutrisiran; 2 [0.6%] placebo).

Serious adverse events (SAEs) were reported in 201 (61.7%) patients in the vutrisiran group and 220 (67.1%) patients in the placebo group. The percentage of patients with SAEs considered related to study drug by the Investigator was low in both groups (2 [0.6%] vutrisiran; 1 [0.3%] placebo). AEs leading to discontinuation of study drug were reported in 10 (3.1%) patients in the vutrisiran group and 13 (4.0%) patients in the placebo group. No AEs leading to discontinuation of study drug were considered related to study drug in the vutrisiran group.

Fatal AEs were reported in 49 (15.0%) patients in the vutrisiran group and 63 (19.2%) patients in the placebo group. No deaths were assessed as related to study drug by the Investigator.

Table 21. Overview of AEs during the DB period of the HELIOS-B study (safety analysis set)

Category	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
	n (%)	Events/ER	n (%)	Events/ER
At least 1 AE	323 (98.5)	4549/553.1	322 (98.8)	3542/424.7
Related to study drug	46 (14.0)	77/9.4	41 (12.6)	57/6.8
At least 1 serious AE	220 (67.1)	629/76.5	201 (61.7)	528/63.3
Related to study drug	1 (0.3)	1/0.1	2 (0.6)	2/0.2
At least 1 severe AE	194 (59.1)	515/62.6	158 (48.5)	366/43.9

Category	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
	n (%)	Events/ER	n (%)	Events/ER
Related to study drug	2 (0.6)	3/0.4	1 (0.3)	1/0.1
At least 1 AE leading to study drug interruption	8 (2.4)	9/1.1	8 (2.5)	10/1.2
Related to study drug	0	0	2 (0.6)	2/0.2
At least 1 AE leading to discontinuation from study drug	13 (4.0)	18/2.2	10 (3.1)	10/1.2
Related to study drug	1 (0.3)	1/0.1	0	0
Deaths[a]	63 (19.2)	NA	49 (15.0)	NA

Abbreviations: AE=adverse event; DB=double-blind; ER=exposure-adjusted event rate per 100 patient-years, calculated as events/PY*100; NA=not applicable; PY=patient-years; SAE=serious adverse event.

[a] All fatal SAEs are summarized regardless of treatment-emergent classification. Deaths that occurred after the end of study visit or after the data cutoff date are not included.

Common Adverse Events

AEs that were reported in ≥10% of patients during the DB period of the HELIOS-B study in any group are presented by Preferred Term in Table 22. The most commonly reported AEs (≥20% of patients) in the Placebo and Vutrisiran group were cardiac failure (39.0% vs. 31.0%), COVID-19 (30.2% vs. 26.7%), and atrial fibrillation (20.7% vs. 21.2%). The majority of AEs in the vutrisiran group occurred at a similar or lower frequency than in the placebo group. No AE had an incidence of ≥3% higher in the vutrisiran group compared to the placebo group.

Table 22. AEs in ≥10% of patients in the placebo and Vutrisiran group by preferred term during the DB period of the HELIOS-B study (safety analysis set)

Preferred Term	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
	n (%)	Events/ER	n (%)	Events/ER
At least 1 AE	323 (98.5)	4549/553.1	322 (98.8)	3542/424.7
Cardiac failure	128 (39.0)	255/31.0	101 (31.0)	173/20.7
COVID-19	99 (30.2)	109/13.3	87 (26.7)	93/11.2
Atrial fibrillation	68 (20.7)	92/11.2	69 (21.2)	107/12.8
Gout	51 (15.5)	77/9.4	48 (14.7)	81/9.7
Dyspnoea	51 (15.5)	66/8.0	43 (13.2)	49/5.9
Fall	69 (21.0)	111/13.5	42 (12.9)	64/7.7
Back pain	32 (9.8)	38/4.6	39 (12.0)	45/5.4
Arthralgia	39 (11.9)	46/5.6	33 (10.1)	49/5.9
Constipation	43 (13.1)	55/6.7	33 (10.1)	35/4.2
Oedema peripheral	25 (7.6)	28/3.4	33 (10.1)	41/4.9
Urinary tract infection	38 (11.6)	49/6.0	33 (10.1)	46/5.5

Preferred Term	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
	n (%)	Events/ER	n (%)	Events/ER
Dizziness	43 (13.1)	52/6.3	32 (9.8)	36/4.3
Fatigue	45 (13.7)	58/7.1	28 (8.6)	33/4.0

Abbreviations: AE=adverse event; COVID-19=Coronavirus disease 2019; DB=double-blind; ER=exposure-adjusted event rate per 100 patient-years, calculated as number of events/PY*100; MedDRA=Medical Dictionary for Regulatory Activities; PY=patient-years. Note: Adverse events were coded using MedDRA version 23.0. Preferred terms are ordered by descending frequency in vutrisiran column.

Adverse Events Related to Study Drug

Related AEs were reported in 41 (12.6%) patients in the vutrisiran group and 46 (14.0%) patients in the placebo group during the DB period of the HELIOS-B study. The only related AE reported in ≥1% of patients in either group was injection site reaction (ISR; 7 [2.1%] patients in the vutrisiran group and 8 [2.4%] patients in the placebo group). None of the related ISRs were severe or serious or led to discontinuation of study drug.

Serious adverse event/deaths/other significant events

Deaths

Deaths were reported in 49 patients (15.0%) in the vutrisiran group and 63 patients (19.2%) in the placebo group during the DB period of the HELIOS-B study. None of the deaths were considered related to study drug by the Investigator. The majority of deaths were CV in nature and consistent with those expected in this patient population.

Serious Adverse Events (SAEs)

The most frequently reported SAEs (≥5%) in either treatment group were cardiac failure (11.7% vutrisiran, 17.4% placebo), atrial fibrillation (8.0% vutrisiran, 6.1% placebo), and cardiac failure acute (4.0% vutrisiran, 5.5% placebo).

Only 2 (0.6%) patients in the vutrisiran group (PT: hematuria and cough in 1 patient each) and 1 (0.3%) patient in the placebo group (PT: syncope) had SAEs assessed as related to study drug by the Investigator. All of these events resolved during the study.

Table 23. SAEs in ≥2% of patients in the placebo and Vutrisiran group by preferred term during the DB period of the HELIOS-B study (safety analysis set)

Preferred Term	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
	n (%)	Events/ER	n (%)	Events/ER
At least 1 SAE	220 (67.1)	629/76.5	201 (61.7)	528/63.3
Cardiac failure	57 (17.4)	94/11.4	38 (11.7)	70/8.4
Atrial fibrillation	20 (6.1)	27/3.3	26 (8.0)	29/3.5
Cardiac failure acute	18 (5.5)	21/2.6	13 (4.0)	16/1.9
Pneumonia	10 (3.0)	11/1.3	12 (3.7)	13/1.6
Acute kidney injury	10 (3.0)	13/1.6	11 (3.4)	12/1.4

Preferred Term	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
	n (%)	Events/ER	n (%)	Events/ER
Osteoarthritis	8 (2.4)	10/1.2	10 (3.1)	10/1.2
Atrial flutter	9 (2.7)	9/1.1	9 (2.8)	10/1.2
Syncope	7 (2.1)	8/1.0	8 (2.5)	10/1.2
Ventricular tachycardia	8 (2.4)	9/1.1	8 (2.5)	9/1.1
Fall	8 (2.4)	8/1.0	6 (1.8)	6/0.7
Cardiac failure congestive	15 (4.6)	21/2.6	4 (1.2)	4/0.5
Cardiogenic shock	7 (2.1)	8/1.0	4 (1.2)	4/0.5
Chest pain	7 (2.1)	8/1.0	4 (1.2)	5/0.6
Bradycardia	7 (2.1)	8/1.0	3 (0.9)	3/0.4
Hyponatraemia	7 (2.1)	7/0.9	3 (0.9)	3/0.4

Abbreviations: DB=double-blind; ER=exposure-adjusted event rate per 100 patient-years, calculated as number of events/PY*100; MedDRA=Medical Dictionary for Regulatory Activities; PY=patient-years; SAE=serious adverse event.
Note: Adverse events were coded using MedDRA version 23.0. Preferred terms are ordered by descending frequency in vutrisiran column.

Adverse Events of Special Interest

Injection site reactions (ISRs)

Treatment-related ISRs were reported in 7 (2.1%) patients in the vutrisiran group and 8 (2.4%) patients in the placebo group (Table 24). All ISRs were non-serious, transient, and considered mild in severity; no ISR led to study drug discontinuation.

Table 24. Treatment related ISRs during the DB period (safety analysis set)

Category	Placebo (N=328, PY=822.4)		Vutrisiran (N=326, PY=833.9)	
Preferred Term	n (%)	Events/ER	n (%)	Events/ER
Number of patients with at least 1 ISR[a]	8 (2.4)	9/1.1	7 (2.1)	7/0.8
Total number of doses	3573	N/A	3601	N/A
Total number (%) of doses with ISRs[b]	9 (0.3)	N/A	7 (0.2)	N/A
ISR signs and symptoms[c]				
Injection site erythema	1 (0.3)	2/0.2	2 (0.6)	2/0.2
Injection site haematoma	0	0	1 (0.3)	1/0.1
Injection site induration	0	0	1 (0.3)	1/0.1
Injection site pain	3 (0.9)	3/0.4	3 (0.9)	3/0.4
Injection site paraesthesia	1 (0.3)	1/0.1	0	0
Injection site pruritus	2 (0.6)	2/0.2	0	0
Injection site rash	0	0	1 (0.3)	1/0.1
Injection site swelling	1 (0.3)	1/0.1	0	0

Abbreviations: AE=adverse event; CRF=case report form; DB=double blind; ER=exposure adjusted event rate per 100 patient years; HLT=high level term; ISR=injection site reactions; MedDRA=Medical Dictionary for Regulatory Activities; N/A=not applicable; PY=patient years.

[a] Includes related AEs considered as injection site reactions by the Investigator (with sign/symptoms collected on a separate CRF page). The subject is counted once for the event if a patient experienced more than 1 event from the same injection.

[b] % of doses with ISRs=(Total number of doses with ISRs/Total number of doses)×100.

[c] The number of AEs under this section counts individual sign/symptom. AEs mapped to the MedDRA HLT of injection site reactions (sign/symptom not collected) are summarized according to their preferred terms. An ISR may consist of 1 or more signs or symptoms. Thus, sum of ISR signs and symptoms in this section may be larger than number of ISRs.

Cardiac Events

As patients with ATTR amyloidosis commonly have cardiomyopathy and other cardiac manifestations, the proportion of patients reporting cardiac events was evaluated, including a summary of patients with AEs and SAEs in the Cardiac disorders SOC and the Cardiac arrhythmia high-level group term (HLGT) and high-level terms (HLTs), and by performing an analysis of AEs mapping to the SMQs.

Overall, the type and nature of cardiac events reported in the vutrisiran group were consistent with those expected in the patient population and consistent with the underlying disease.

AEs in the Cardiac disorders SOC were reported during the DB period of the HELIOS-B study in 227 (69.6%) patients of the vutrisiran group and in 242 (73.8%) patients of the placebo group (Table 25).

The percentage of patients with SAEs in the Cardiac disorders SOC was similar between the two treatment groups (35.6% vutrisiran, 37.8% placebo). None of the SAEs were considered related to the study drug.

The percentage of patients with AEs within the Cardiac failure SMQ was lower in the vutrisiran group compared to the placebo group when using narrow terms (39.0% vutrisiran, 51.5% placebo) and when using both broad and narrow terms (49.4% vutrisiran, 59.8% placebo). The percentage of patients with AEs within the Cardiac arrythmia HLGT was lower in the vutrisiran group (42.9%) compared to the placebo group (46.3%). The percentage of patients with AEs within the Torsade de pointes/QT prolongation SMQ was

similar between the vutrisiran (16.9%) and placebo (17.7%) groups (Table 25). No confirmed events of Torsade de pointes were reported.

Table 25. Summary of cardiac events during the DB period (safety analysis set)

	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
Category	**n (%)**	**Events/ER**	**n (%)**	**Events/ER**
AEs in the Cardiac disorders SOC	242 (73.8)	687/83.5	227 (69.6)	535/64.2
SAEs in the Cardiac disorders SOC	124 (37.8)	259/31.5	116 (35.6)	196/23.5
Cardiac Failure SMQ (narrow) AEs	169 (51.5)	353/42.9	127 (39.0)	232/27.8
Cardiac Failure SMQ (broad and narrow) AEs	196 (59.8)	424/51.6	161 (49.4)	299/35.9
Cardiac arrhythmia HLGT AEs	152 (46.3)	271/33.0	140 (42.9)	253/30.3
Cardiac conduction disorders	34 (10.4)	37/4.5	18 (5.5)	24/2.9
Rate and rhythm disorders NEC	34 (10.4)	41/5.0	25 (7.7)	27/3.2
Supraventricular arrhythmias	98 (29.9)	156/19.0	96 (29.4)	162/19.4
Ventricular arrhythmias and cardiac arrest	30 (9.1)	37/4.5	31 (9.5)	40/4.8
Torsade de Pointes/QT Prolongation SMQ AEs	58 (17.7)	82/10.0	55 (16.9)	69/8.3

Abbreviations: AE=adverse event; DB=double-blind; ER=exposure-adjusted event rate per 100 patient-years, calculated as number of events/PY*100; HLGT=high level group term; HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term; PY=patient-years; SAE=serious adverse event; SMQ=standardized MedDRA queries; SOC=system organ class.
Notes: If a patient had more than 1 event in a given SOC, HLGT, HLT, or SMQ, that patient is counted once for the SOC, HLGT, HLT, or SMQ. If a patient had more than 1 event with a given PT, that patient is counted only once for that PT. For the total number of events, a patient can be counted more than once if the patient has multiple events. Adverse events were coded using MedDRA version 23.0.

Hepatic Events

As vutrisiran is directed to the liver, the frequency of hepatic events was evaluated by performing an analysis of AEs mapping to the Standardized MedDRA Query (SMQ) Drug-related Hepatic Disorders.

The proportion of hepatic AEs during the DB period of the HELIOS-B study was similar between the vutrisiran (56 [17.2%] patients) and placebo group (62 [18.6%] patients) (. Most of the hepatic AEs were within the Investigations SOC and occurred at a similar frequency between the vutrisiran and placebo group.

The majority of the hepatic AEs were mild or moderate in severity and considered not related to study drug. Hepatic SAEs were reported in 2 patients in the vutrisiran group (hepatic failure and alanine aminotransferase [ALT] increased [1 patient each]) and 5 patients in the placebo group (hepatic function abnormal, hepatic encephalopathy, ischaemic hepatitis, hepatic enzyme increased [1 patient each]; ascites and hepatocellular carcinoma, both in the same patient). All SAEs were considered severe except for the event of ascites. No hepatic SAE was considered related to the study drug. The only SAE (PT: hepatocellular carcinoma) leading to discontinuation of study drug was reported in 1 patient in the placebo group.

Overall, the frequency of hepatic AEs was low, with no imbalances between vutrisiran and placebo groups in the HELIOS-B study.

Table 26. Drug-related hepatic disorders (SMQ) in ≥1% of patients in either group during the DB period (safety analysis set)

SOC	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY=833.9)	
Preferred Term	n (%)	Events/ER	n (%)	Events/ER
At least 1 Drug-related Hepatic Disorder (SMQ) AE	62 (18.6)	90/10.9	56 (17.2)	87/10.4
Hepatobiliary disorders	21 (6.4)	21/2.6	19 (5.8)	22/2.6
Hepatic function abnormal	5 (1.5)	5/0.6	3 (0.9)	4/0.5
Investigations	41 (12.5)	58/7.1	40 (12.3)	61/7.3
Aspartate aminotransferase increased	5 (1.5)	5/0.6	4 (1.2)	9/1.1
Blood alkaline phosphatase increased	6 (1.8)	7/0.9	6 (1.8)	6/0.7
Blood bilirubin increased	5 (1.5)	5/0.6	4 (1.2)	4/0.5
Gamma-glutamyltransferase increased	11 (3.4)	12/1.5	10 (3.1)	12/1.4
Hepatic enzyme increased	7 (2.1)	7/0.9	3 (0.9)	3/0.4
Liver function test abnormal	8 (2.4)	8/1.0	6 (1.8)	6/0.7
Liver function test increased	3 (0.9)	3/0.4	7 (2.1)	7/0.8
Transaminases increased	5 (1.5)	5/0.6	5 (1.5)	5/0.6
Gastrointestinal disorder	8 (2.4)	8/1.0	3 (0.9)	3/0.4
Ascites	8 (2.4)	8/1.0	2 (0.6)	2/0.2

Abbreviations: AE=adverse event; DB=double-blind; MedDRA=Medical Dictionary for Regulatory Activities; PY=patient-years; SMQ=standardized MedDRA queries; SOC=system organ class.

Liver Function Parameters

Table 27 summarizes central and local laboratory results for worst post-baseline liver function tests (LFT) for vutrisiran and placebo patients. The majority of patients, 72.6% in the placebo group and 66.0% in the vutrisiran treatment group had liver function tests (LFT) within normal ranges.

The proportion of patients with ALT elevations (>ULN and ≤3×ULN) during the DB period of the HELIOS B study was higher in the vutrisiran group 97 patients (29.8%) compared with 78 patients (23.8%) in the placebo group. The potential risk for ALT increase is currently not reflected in the SPC. The MAH was asked and agreed to include this information in section 4.4 or 4.8 of the SPC.

In addition, 3 (0.9%) patients in the vutrisiran group and 0 patients in the placebo group met biochemical Hy's law criteria (ALT or AST >3×ULN and concurrent total bilirubin >2×ULN) based on central and local laboratory results (Table 27 and refer to Study 003 CSR 1, Section 12.3.3.2). All elevations were attributed to concurrent conditions and the applicant just referred to full narratives for these patients (Study 003 CSR 1, Section 14.3.3) without providing further explanation. In the view of CHMP involvement of vutrisiran on elevated liver function tests (LFT) cannot be excluded with certainty and therefore this was adequately reflected in the SPC.

Table 27. Summary of worst post-baseline LFT results during the DB period (central and local laboratories, safety analysis set)

Parameter	Criterion	n (%)	
		Placebo (N=328)	Vutrisiran (N=326)
ALT	≤ULN	238 (72.6)	215 (66.0)
	>ULN and ≤3×ULN	78 (23.8)	97 (29.8)
	>3×ULN and ≤5×ULN	4 (1.2)	5 (1.5)
	>5×ULN and ≤10×ULN	3 (0.9)	3 (0.9)
	>10×ULN and ≤20×ULN	1 (0.3)	2 (0.6)
	>20×ULN	1 (0.3)	0
	Missing	3 (0.9)	4 (1.2)
AST	≤ULN	204 (62.2)	198 (60.7)
	>ULN and ≤3×ULN	109(33.2)	114 (35.0)
	>3×ULN and ≤5×ULN	7 (2.1)	5 (1.5)
	>5×ULN and ≤10×ULN	3 (0.9)	3 (0.9)
	>10×ULN and ≤20×ULN	1 (0.3)	1 (0.3)
	>20×ULN	1 (0.3)	1 (0.3)
	Missing	3 (0.9)	4 (1.2)
ALT or AST	≤ULN	180 (54.9)	169 (51.8)
	>ULN and ≤3×ULN	131 (39.9)	142 (43.6)
	>3×ULN and ≤5×ULN	8 (2.4)	5 (1.5)
	>5×ULN and ≤10×ULN	3 (0.9)	3 (0.9)
	>10×ULN and ≤20×ULN	2 (0.6)	2 (0.6)
	>20×ULN	1 (0.3)	1 (0.3)
	Missing	3 (0.9)	4 (1.2)
Total bilirubin	≤ULN	190 (57.9)	201 (61.7)
	>ULN and ≤1.5×ULN	77 (23.5)	82 (25.2)
	>1.5×ULN and ≤2×ULN	39 (11.9)	18 (5.5)
	>2×ULN and ≤3×ULN	15 (4.6)	18 (5.5)
	>3×ULN and ≤5×ULN	4 (1.2)	3 (0.9)
	>5×ULN	0	0
	Missing	3 (0.9)	4 (1.2)
ALP	>1.5×ULN	88 (26.8)	77 (23.6)
ALT or AST and concurrent total bilirubin	ALT or AST >3×ULN and total bilirubin >2×ULN	0	3 (0.9)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DB=double-blind; LFT=liver function test; OLE=open-label extension; ULN=upper limit of normal.
Note: Includes central lab assessments from the scheduled and unscheduled visits through the first dose in the OLE Period for patients who entered OLE, or the earlier of (84 days after the last dose of study drug, early study discontinuation) for patients who discontinued DB treatment.

Source: Study 003 CSR 1, Table 36.

Renal Events

As patients with ATTR amyloidosis often have renal involvement and/or heart failure that can result in renal failure and end stage renal disease, the frequency of patients with AEs mapping to the Acute renal failure SMQ was evaluated.

Overall, the types of renal AEs reported were consistent with those expected in patients with ATTR amyloidosis, and there were no safety concerns considered related to vutrisiran.

The proportion of patients with renal AEs during the DB period of the HELIOS-B study was similar between the vutrisiran (55 [16.9%] patients) and placebo group (57 [17.4%] patients) (Table 28).

Most of the AEs occurred at a similar frequency in the vutrisiran and placebo groups. Renal events reported in ≥2% of patients in either group included acute kidney injury (32 [9.8%] vutrisiran, 27 [8.2%] placebo) followed by renal impairment (7 [2.1%] vutrisiran, 18 [5.5%] placebo). The majority of AEs were mild or moderate in severity. One patient in the vutrisiran group (renal impairment) and 3 patients in the placebo group (renal impairment, albuminuria, and protein urine present [1 patient each]) had renal AEs that were considered related to study drug; all were non-serious and mild/moderate in severity.

Renal SAEs were reported in a similar proportion of patients in the placebo and vutrisiran groups. No renal SAE was considered related to the study drug.

Table 28. Renal AEs during the DB period of the HELIOS-B study (safety analysis set)

SOC	Placebo (N=328; PY=822.4)		Vutrisiran (N=326; PY-833.9)	
Preferred Term	n (%)	Events/ER	n (%)	Events/ER
At least 1 AE in the Acute Renal Failure SMQ	57 (17.4)	80/9.7	55 (16.9)	66/7.9
Investigations	9 (2.7)	11/1.3	6 (1.8)	8/1.0
Creatinine renal clearance decreased	2 (0.6)	2/0.2	3 (0.9)	4/0.5
Blood creatinine increased	2 (0.6)	2/0.2	2 (0.6)	2/0.2
Glomerular filtration rate decreased	5 (1.5)	5/0.6	1 (0.3)	1/0.1
Protein urine present	1 (0.3)	1/0.1	1 (0.3)	1/0.1
Blood urea increased	1 (0.3)	1/0.1	0	0
Renal and urinary disorders	53 (16.2)	69/8.4	50 (15.3)	58/7.0
Acute kidney injury	27 (8.2)	36/4.4	32 (9.8)	37/4.4
Renal impairment	18 (5.5)	21/2.6	7 (2.1)	7/0.8
Proteinuria	2 (0.6)	2/0.2	5 (1.5)	5/0.6
Renal failure	5 (1.5)	5/0.6	5 (1.5)	5/0.6
Albuminuria	5 (1.5)	5/0.6	2 (0.6)	2/0.2
Renal tubular dysfunction	0	0	2 (0.6)	2/0.2

Abbreviations: AE=adverse event; DB=double-blind; ER=exposure adjusted event rate per 100 years; MedDRA=Medical Dictionary for Regulatory Activities; PY=patient years; PY=patient years; SMQ=standardized MedDRA queries; SOC=system organ class.
Adverse events were coded using MedDRA version 23.0.

Note: Preferred terms are sorted by decreasing frequency in the vutrisiran column.

Malignancies

Overall, the malignancies observed across studies showed no pattern and were similar in the nature and types of malignancies reported in the general population of this age. During the DB period of the HELIOS-B study, a total of 30 (9.2%) patients in the vutrisiran group reported any AE of malignant or unspecified tumors SMQ compared to 45 (13.7%) patients in the placebo group; none were considered related to the study drug.

Laboratory findings

There were no clinically relevant differences between vutrisiran and placebo regarding changes over time in laboratory parameters (including hematologic measures and blood-chemistry evaluations) except for alanine aminotransferase (ALT) elevations.

The proportion of patients with ALT elevations (>ULN and ≤3×ULN) during the DB period of the HELIOS B study was higher in the vutrisiran group 97 patients (29.8%) compared with 78 patients (23.8%) in the placebo group. The potential risk for ALT increase is currently not reflected in the SPC. The MAH was asked to include this information in section 4.8 of the SPC.

In addition, 3 (0.9%) patients in the vutrisiran group and 0 patients in the placebo group met biochemical Hy's law criteria (ALT or AST >3×ULN and concurrent total bilirubin >2×ULN) based on central and local laboratory results (Table 20 and refer to Study 003 CSR 1, Section 12.3.3.2). The involvement of vutrisiran on elevated liver function tests (LFT) cannot be excluded with certainty and therefore this was adequately reflected in the SPC. The information in 4.8. of the SmPC is under 'Description of selected adverse reactions, Liver function tests'.

Vital Signs, Physical Examination and ECG

No clinically relevant changes in vital signs, physical examination or electrocardiograms were observed in either group, and the percentage of patients with abnormalities was similar between the vutrisiran and placebo groups in the HELIOS-B study

Safety in special populations

The safety profile of vutrisiran in HELIOS-B was consistent with the safety profile characterized in HELIOS-A and in subsequent post-marketing use. With regard to special populations please refer to current product information (SmPC/PL) of commercial vutrisiran (AMVUTTRA®).

Elderly

Section 4.2:
No dose adjustment is required in patients ≥ 65 years of age (see section 5.2).

Section 5.2:
There were no significant differences in steady state pharmacokinetic parameters or TTR reduction between patients < 65 years old and ≥ 65 years old.

Renal impairment

Section 4.2:

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 90 mL/min/1.73 m2). Vutrisiran has not been studied in patients with severe renal impairment or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Section 5.2:
Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73 m2) on vutrisiran exposure or TTR reduction compared to subjects with normal renal function. Vutrisiran has not been studied in patients with severe renal impairment or end-stage renal disease.

Hepatic impairment

Section 4.2:
No dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤ 1 x upper limit of normal (ULN) and aspartate aminotransferase (AST) > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST). Vutrisiran has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Section 5.2:
Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild hepatic impairment (total bilirubin ≤ 1 x ULN and AST > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST) on vutrisiran exposure or TTR reduction compared to patients with normal hepatic function. Vutrisiran has not been studied in patients with moderate or severe hepatic impairment.

Paediatric population

Section 4.2:
The safety and efficacy of Amvuttra in children or adolescents < 18 years of age have not been established. No data are available.

A product-specific paediatric investigational plan waiver was granted by the EMA Paediatric Committee for vutrisiran (EMEA-002425-PIP01-18 – P/0015/2019), as ATTR amyloidosis occurs almost exclusively in adults. The waiver covers all subsets of the paediatric population (0 to 18 years)

Safety related to drug-drug interactions and other interactions

For interaction with other medicinal products and other forms of interaction, see section 4.5 of the SmPC (attached in the ANNEX 3 below).

Discontinuation due to adverse events

The percentage of patients with an AE leading to discontinuation of study drug was 3.1% in the vutrisiran group and 4.0% in the placebo group. No AEs leading to discontinuation of study drug were considered related to study drug in the vutrisiran group.

Post marketing experience

According to the 4th Periodic Benefit-Risk Evaluation Report (PBRER) for AMVUTTRA (vutrisiran), covering the reporting interval 13 June 2023 through 12 June 2024 (i.e., the data lock point [DLP] of this report), cumulatively, 13,387 prefilled syringes of AMVUTTRA have been sold worldwide, corresponding to an estimated 3346.5 patient-years exposure, and it was estimated that 3034 patients had been treated with

AMVUTTRA. Based on the evaluation of the post-marketing safety data received, the benefit-risk profile of AMVUTTRA in its approved indication remained positive. Also, based on the evaluation of the cumulative safety data and the benefit-risk analysis, no additional changes to the vutrisiran CCDS, the AMVUTTRA EU RMP, or other product documents were warranted. No change in the PSUR frequency, which is 1 year, has been proposed.

2.5.1. Discussion on clinical safety

The safety profile of vutrisiran in HELIOS-B was consistent with the profile characterized in HELIOS-A and in subsequent post-marketing use.

- In general, the treatment emergent AEs and SAEs observed were consistent with those expected in the patient population and underlying disease.
- The percentage of patients with treatment-related AEs (12.6% vutrisiran, 14.0% placebo) or AEs leading to study drug discontinuation (3.1% vutrisiran, 4.0% placebo) tended to be lower in the vutrisiran group than in the placebo group. The percentage of patients with SAEs considered related to study drug by the Investigator was low in both groups (2 [0.6%] vutrisiran; 1 [0.3%] placebo).
- Fewer cases of deaths were reported in the vutrisiran group (15.0%) than in the placebo group (19.2%) during the DB period of the HELIOS-B study. None of the deaths were considered related to study drug by the Investigator.
- Overall, no safety concerns regarding cardiac events were observed. The type and nature of cardiac events reported in the vutrisiran group were consistent with those expected in the patient population and underlying disease. Compared to placebo, fewer patients in the vutrisiran group reported AEs within the Cardiac disorders SOC (69.6% vutrisiran, 73.8% placebo), the Cardiac failure SMQ (49.4% vutrisiran, 59.8% placebo), and the Cardiac arrhythmia HLGT (42.9% vutrisiran, 46.3% placebo). The percentage of patients with AEs within the Torsade de pointes/QT prolongation SMQ was similar between treatment groups (16.9% vutrisiran, 17.7% placebo). No confirmed events of Torsade de pointes were reported.
- Regarding hepatic events, the proportion of hepatic AEs during the DB period of the HELIOS-B study was similar between the vutrisiran (56 [17.2%] patients) and placebo group (62 [18.6%] patients). Most of the hepatic AEs were within the Investigations SOC and occurred at a similar frequency between the vutrisiran and placebo group.

  The proportion of patients with ALT elevations (>ULN and ≤3×ULN) during the DB period of the HELIOS B study was higher in the vutrisiran group 97 patients (29.8%) compared with 78 patients (23.8%) in the placebo group. The potential risk for ALT increase was included in section 4.8 of the SmPC.
- Regarding renal events, overall, the types of renal AEs reported were consistent with those expected in patients with ATTR amyloidosis, and there were no safety concerns considered related to vutrisiran. Renal SAEs were reported in a similar proportion of patients in the placebo and vutrisiran groups. No renal SAE was considered related to the study drug.

  The MAH proposed to delete the following AEs (from SmPC section 4.8) that were initially included based on results of HELIOS A: Dyspnoea, arthralgia, Blood Alkaline Phosphatase increased and pain in extremity. Regarding dyspnoea, pain in extremity and arthralgia the proposal can be followed. Since the data from HELIOS-B are not considered sufficient to overrule the signal identified in HELIOS-A, ALP increases should not be deleted from section 4.8 of the SmPC.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

A product-specific paediatric investigational plan waiver was granted by the EMA Paediatric Committee for vutrisiran (EMEA-002425-PIP01-18 – P/0015/2019), as ATTR amyloidosis occurs almost exclusively in adults. The waiver covers all subsets of the paediatric population (0 to 18 years).

2.5.2. Conclusions on clinical safety

In general, the safety profile of vutrisiran in the HELIOS-B study was similar with the HELIOS-A safety profile and consistent with the profile to that demonstrated in the post-marketing exposure. Based on the results of the HELIOS-B study, the overall safety profile of vutrisiran (AMVUTTRA®) for the proposed new additional wild-type or hereditary ATTR-CM indication is positive.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

According to the EURD list the current PSUR frequency is 1 year. In the last PSUSA (EMEA/H/C/PSUSA/00011021/202406) no change has been proposed.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version1.2 with this application.

The (main) proposed RMP changes were the following:

Reference is made to the PRAC Rapp RMP assessment report regarding RMP part I. T

Safety concerns

A summary of the safety concerns is provided in Table 29.

Table 29. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risk	• Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions
Missing information	• Longer-term safety (>2 years) • Use in patients with moderate or severe hepatic impairment • Use in pregnant women and effects on pregnancy outcomes

Pharmacovigilance plan

The MAH did not propose changes to the current routine pharmacovigilance activities.

A targeted follow-up questionnaire will be implemented for reports of vitamin A deficiency/ocular toxicity in order to collect additional information on these events; these data will be analysed and presented in the Periodic Safety Update Reports (PSURs) to further characterise the clinical consequences, noted as important potential risk in the RMP.

The MAH did not propose new additional pharmacovigilance activities.

The MAH proposed some further changes to the information of the two post-approval studies:

Ongoing and Planned Additional Pharmacovigilance Activities

Study Number Short Name Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones (required by regulators)**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
• Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
• Not applicable				
Category 3 - Required additional pharmacovigilance activities				
HELIOS-A Randomised Treatment Extension The HELIOS-A-RTE[a] study is a Phase 3 global, open-label study to evaluate the safety and efficacy of ALN-TTRSC02 in patients with hATTR Amyloidosis. (Ongoing)	The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.	• Longer-term safety (>2 years)[a] • Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions	Final CSR (planned)	**31/12/**2025
ALN-TTRSC02-005 Study 005: Prospective observational study to monitor and assess the safety of Amvuttra® [vutrisiran] in a real-world cohort of ~~hATTR~~ **ATTR** amyloidosis patients ~~(Planned; protocol to be submitted)~~ **(Ongoing)**	The primary objective of this study is to characterise the long-term (>2 years) safety of vutrisiran under real-world conditions, including determining the incidence of selected events (eg, hypersensitivity reactions and clinical consequences of vitamin A deficiency, including delayed	• Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity ~~Reactions~~ **reactions** • Longer term safety (>2 years) • Use in patients with moderate or severe hepatic impairment • Use in pregnancy and pregnancy and	Final Protocol	~~Final protocol submission date: *XX June 2023*~~ **Submitted on 19/12/2022** **Protocol Amendment Submission: After regulatory approval of type II variation to expand Amvuttra indication.**
			Start of vutrisiran data collection	~~As soon as the Study 005 protocol is agreed by regulatory authorities~~ **Actual Start of Data Collection:**

Study Number Short Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones (required by regulators)	Due Dates
	symptoms) in ~~hATTR~~ **ATTR** amyloidosis patients exposed to vutrisiran, as well as provide comparative safety data from patients including untreated patients and patients treated with other therapies for ~~hATTR~~ **ATTR** amyloidosis excluding patisiran, following local standard of care.	infant outcomes •		**10/04/2024**
			Interim updates	Interim Report 1: ~~Q4~~ **31/12/**2025 Interim Report 2: ~~Q4~~ **31/12/**2027 Interim Report 3: ~~Q4~~ **31/12/**2029 Interim Report 4: ~~Q4~~ **31/12/**2031 Interim Report 5 & End of data Collection: ~~Q4~~ **31/12/**2033~~Report of Study Results:~~ Study progress ~~reports~~ **reports** will be provided with each PBRER
			Final Report	Final study report: ~~Q4~~ **31/12/**2034

Abbreviations: **ATTR=hereditary or wild-type Transthyretin amyloidosis**; CSR=clinical study report; EC=European Commission; hATTR amyloidosis=hereditary transthyretin ~~mediated~~ amyloidosis; **NYHA=New York Heart Association**; PAM=post-authorisation measure; PBRER=periodic benefit risk evaluation report; RTE=Randomised Treatment Extension; ~~TBD=to be determined~~.

[a] HELIOS-A Protocol Amendment 3, in place ~~at the time of database lock for this document~~ **as of 17 July 2020** included an 18-month extension period (for a total study duration of 36 months~~); as of 19 February 2021,~~). Protocol Amendment 4 lengthened the extension period to a maximum of 36 months (for a total study duration of up to 54 months**). Protocol Amendment 5 further lengthened the extension period to a maximum of 42 months extension period (for a total study duration of up to 78 months).**

The MAH submitted a separate document entitled:
"ABSTRACT for Study ALN-TTRSC02-005 Protocol Amendment 1"

Summary as provided by the MAH of key changes in the proposed protocol amendment 1 compared to current protocol:

- Inclusion of patients with wild-type ATTR amyloidosis so that the patient population studied is expanded from hATTR amyloidosis to ATTR (including both hATTR and wtATTR) amyloidosis.
- Expansion of planned sample size to account for patients with ATTR-CM.
- Addition of sub-population of interest 'Patients with NYHA Class IV heart failure'.
- Addition of data analysis for patients with ATTR-CM including descriptive and comparative analysis if feasible, e.g., overlapping propensity score.
- Addition of milestones of submission of protocol amendment 1 and of start of data collection in patients with ATTR-CM. Addition of option to end data collection earlier if accrual target is met.

The PRAC having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Routine risk minimisation activities as described in RMP Part V.1 are considered sufficient to to minimise the risks of the medicinal product. No additional risk minimisation measures are proposed.

A summary of PV activities and risk minimisation activities is provided in Table 30.

Table 30. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risk:		
Clinical consequences of vitamin A deficiency, including delayed symptoms	Routine risk minimisation measures: • The secondary pharmacologic effect on serum vitamin A levels is described in SmPC sections 4.4, 4.6, 5.1, and 5.3, and PIL Section 2. • Legal status: Prescription-only Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • Specific targeted follow-up of vitamin A deficiency/ocular toxicity Additional PV activities: • Evaluation of data from the HELIOS-A Randomised Treatment Extension (HELIOS-A RTE) • Evaluation of data from Study 005
Hypersensitivity reactions	Routine risk minimisation measures: • SmPC Section 4.3 and PIL Section 2 • Legal status: Prescription-only Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the HELIOS-A RTE • Evaluation of data from Study 005
Missing Information:		
Longer-term safety (>2 years)	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the HELIOS-A RTE • Evaluation of data from Study 005

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from Study 005
Use in pregnant women and effects on pregnancy outcomes	Routine risk minimisation measures: • SmPC sections 4.4, 4.6, and 5.3, and PIL Section 2- Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from Study 005

Abbreviations: PIL=Patient Information Leaflet; PV=Pharmacovigilance; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.

Overall conclusion on the RMP

The PRAC considered that the risk management plan version 1.5 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. One additional administrative change has been made and the last submitted version of the RMP was 2.0.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

As requested, the MAH reverted the proposed amendments of the milestones for end of data collection and final study report or study 005 (ALN-TTRSC02-005).

The changes to the RMP are acceptable.

The CHMP endorsed the PRAC recommendation with no comments.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to user testing from the initial Marketing Authorisation

Application (MAA, procedure EMEA/H/C/0005852/0000) .The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Vutrisiran (AMVUTTRA®) is a ribonucleic acid interference (RNAi) therapeutic designed to suppress production of both variant and wild-type TTR in the liver and was approved by the European Commission on 15 September 2022 for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

Current approved therapeutic indication:

"Amvuttra is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy."

Proposed new additional ATTR-CM indication:

Within this procedure the MAH applies for an extension of the indication as follows:

Amvuttra is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy (hATTR-PN).

Amvuttra is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

*Note: The Applicant does not propose any changes to the dosage form, route of administration, or

dosing regimen via this application. The drug product for the proposed additional ATTR-CM indication has the same formulation and presentation as commercial vutrisiran (AMVUTTRA®).

3.1.1. Disease or condition

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease resulting from the deposition of misfolded TTR as amyloid fibrils in various organs, predominantly the nerves and heart (Castaño and Maurer, 2019; Ruberg et al., 2019). The most clinically important manifestations are the result of involvement of the peripheral nervous system and the heart. Accumulation of amyloid fibrils in the heart causes an infiltrative, restrictive cardiomyopathy (ATTR-CM) resulting in progressive clinical heart failure associated with high mortality and morbidity. Patients with ATTR-CM typically experience frequent hospitalizations for heart failure, irreversible loss of physical function, and worsening health status and QoL. Advanced ATTR-CM causes some of the most deleterious adverse clinical outcomes in ATTR (Castaño and Maurer, 2019; Ioannou et al., 2023; Ruberg et al., 2019).

In hATTR amyloidosis, inherited variants in the TTR gene lead to destabilization of the tetrameric protein. The phenotypic expression varies depending on the predominant site of deposition of the amyloid fibrils; however, most patients with hATTR amyloidosis experience both cardiomyopathy and polyneuropathy over the course of their disease. Wild-type TTR alone can also be amyloidogenic; this is the basis for the nonhereditary, wtATTR amyloidosis. There is no known genetic cause of wtATTR amyloidosis, and it is presumed to be the result of age-related mechanisms associated with alteration in TTR physiological processing and clearance. [Dharmarajan 2012; Ruberg 2012a] In patients with wtATTR amyloidosis,

amyloid deposits are typically found primarily in heart tissue. These patients have cardiomyopathy as their primary manifestation but commonly have non-cardiac manifestations.

In ATTR amyloidosis patients with cardiomyopathy, cardiac infiltration of the extracellular matrix by TTR amyloid fibrils causes ventricular wall thickening, a marked increase in chamber stiffness, and diastolic dysfunction. Systolic function is also impaired, as characterized by abnormal longitudinal strain. The ejection fraction typically remains normal until late stages of the disease.[Castano 2015; Dungu 2012; Mohty 2013; Ruberg 2012b] Patients suffer from typical symptoms of congestive heart failure, including dyspnea and fatigue, resulting in decreased functional capacity.[Brito 2023; Maurer 2019] Amyloid infiltration can also disrupt cardiac conduction and cause arrhythmias or sudden death due to severe conduction disorders.[Adams 2016; Ando 2013; Benson 2007; Connors 2004] These progressive manifestations of heart failure (HF), in addition to necessitating hospitalizations or urgent interventions, progressively impact patients' daily activities and can markedly diminish quality of life.

Natural history studies depict a progression of HF resulting in hospitalizations and death 2.5 to 5 years after diagnosis.[Antonopoulos 2022; Castano 2015; Damy 2015; Dungu 2012; Hawkins 2015] The rate of mortality and cardiovascular (CV) hospitalizations among untreated patients with ATTR cardiomyopathy is high. In the Phase 3 study (ATTR-ACT) with the TTR stabilizer tafamidis, which recruited wtATTR and hATTR amyloidosis patients with cardiomyopathy, the mortality rate in the tafamidis arm was 30% and in the placebo arm was 43% at Month 30. [Maurer 2018]. Recently, with the advent of non-invasive technetium scintigraphy imaging for diagnosing amyloidosis with cardiomyopathy,[Gillmore 2016] growing disease awareness and improvements in standard of care, there has been a shift in the global ATTR disease landscape with patients being diagnosed earlier in the course of their disease and generally presenting with milder disease stage.[Ioannou 2022].

3.1.2. Available therapies and unmet medical need

Historically, the treatment of ATTR amyloidosis with cardiomyopathy has focused on palliative therapies directed at symptoms, such as diuretics for congestive symptoms and antiarrhythmic drugs, pacemakers, and automatic implantable cardioverter defibrillators for arrhythmias and conduction defects.

Center-based studies suggest that heart transplantation in ATTR amyloidosis with cardiomyopathy can be an effective option with outcomes similar to those transplanted for other causes of HF. [Barrett 2020; Razvi 2022] However, cardiac transplantation continues to be a less pursued option due to the need for lifelong immunosuppression and long waiting times associated with transplantation.

In regions such as the United States (US) and the European Union (EU), the only approved treatments for cardiomyopathy in adult patients with wtATTR or hATTR amyloidosis are Transthyretin Stabilizers which act by stabilising the tetrameric TTR protein and reducing its rate of dissociation into amyloidogenic monomers. Tafamidis, and Acoramidis have been approved in the US and the EU.

Despite important therapeutic advances, a substantial medical need persists. In the phase 3 study with tafamidis (ATTR-ACT, Maurer MS et al., N Engl J Med 2018;379:1007-101), about 29.5% of patients died in the combined active treatment arms during the 30 months observation period, and the annualized rate of CV-related hospitalization remained high at 0.48/year. In the ATTRibute-CM study (Gillmore JD et al., N Engl J Med 2024;390:132-142) patients on acoramidis had a 80.7% observed 30-month survival while on acoramidis.

3.1.3. Main clinical studies

Vutrisiran (AMVUTTRA®) was approved by the European Commission on 15 September 2022 for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

The pivotal trial for this application is HELIOS-B (ALN-TTRSC02-003). It is an ongoing, Phase 3, multicenter, multinational, randomized, double-bind, placebo-controlled study in hATTR amyloidosis patients with cardiomyopathy (Primary analysis completed, Data cutoff: 08 May 2024) designed to evaluate efficacy, safety, PK, and PD of vutrisiran in adult patients with hATTR amyloidosis with cardiomyopathy. Patients were either not on tafamidis at baseline (vutrisiran monotherapy subgroup) or were receiving concomitant tafamidis at baseline per the inclusion criteria (background tafamidis subgroup). Randomization was stratified by baseline tafamidis use.

The study consisted of the following periods: - Screening Period: - Double blind (DB) treatment period - Open-label treatment extension period up to 2 years - Follow-up period up to 1 year after last dose of study drug (up to 18 months for women of child-bearing potential). After screening, eligible patients were randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as an SC injection q3M (every 12 weeks ±7 days) for up to 36 months in the DB Period. During the OLE Period, all patients received open-label doses of 25 mg q3M vutrisiran administered as SC injections. An Open-label Randomized Treatment Extension (RTE) Period was added wherein patients were randomized 1:1 to receive treatment with either 25 mg q3M vutrisiran or 50 mg once every 6 months (q6M) vutrisiran with all patients receiving 25 mg q3M vutrisiran thereafter between 13 May 2022 and 22 March 2023.

The study was performed in 77 centers in 26 countries. Subjects were well representative for patients with hATTRwt and hATTRv amyloidosis and mild to moderate symptomatic cardiomyopathy. Baseline disease characteristic were overall balanced between the groups. In the overall population, 578 (88.4%) patients had wtATTR amyloidosis and 76 (11.6%) patients had hATTR amyloidosis. The mean years since diagnosis of ATTR amyloidosis was 1.43 (range, 0.0 to 11.1) years. The mean age of patients at symptom onset was 73.3 (range, 35 to 85) years. Most (77.7%) patients had NYHA class II HF and were classified as having ATTR amyloidosis disease Stage 1 (66.8%) or Stage 2 (28.6%).

799 patients were screened, 655 were randomized. Of the 326 patients in the vutrisiran group, 78 (23.9%) patients discontinued study drug during the DB Period. Of the 329 patients in the placebo group, 99 (30.1%) patients discontinued study drug during the DB Period. 241 (vutrisiran) and 221 patients (placebo) entered the OLE period, 4 and 8 patients, respectively discontinued vutrisiran therapy during the OLC period that was ongoing with 248 and 224 patients respectively at the time of the data base lock.

Two primary efficacy endpoints were predefined:

• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the overall population

• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)

The following (confirmatory) secondary endpoints were defined in both the overall population and the vutrisiran monotherapy subgroup:

• Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • All-cause mortality • Change from baseline in NYHA class

Additional secondary and exploratory endpoints covered among others

• Composite outcome of all-cause mortality and recurrent all-cause hospitalizations and urgent HF visits • Time to first CV event (including CV hospitalizations and urgent HF visits) or all-cause mortality

Change from baseline in • ECHO parameters, • NT-proBNP • Troponin I • eGFR • ATTR amyloidosis disease stage • EuroQoL-5 Dimensions-5 Levels questionnaire, and • Norfolk QoL-DN

The results from the completed double-blind period and the ongoing open-label extension (OLE) period of HELIOS-B comprise the primary focus of this type II variation. The safety of vutrisiran has been established in HELIOS-B and across the vutrisiran clinical development program.

3.2. Favourable effects

Primary endpoints

In the overall population, vutrisiran patients had a statistically significant 28.2% reduction in the risk of all-cause mortality and recurrent CV events compared to placebo (hazard ratio: 0.718; 95% CI: 0.555, 0.929; P=0.0118).

In the vutrisiran monotherapy subgroup, vutrisiran patients had a statistically significant 32.8% reduction in the risk of all-cause mortality and recurrent CV events compared to placebo (hazard ratio: 0.672; 95% CI: 0.487, 0.929; P=0.0162).

Confirmatory secondary endpoints

At Month 30, vutrisiran led to a statistically significant improvement in 6-MWT compared to placebo in the overall population (least square [LS] mean difference: 26.46 m; P=7.976E-05), with consistent results observed in the vutrisiran monotherapy subgroup (32.09 m; P = 0.0005).

At Month 30, vutrisiran led to a statistically significant improvement in KCCQ-OS compared to placebo in the overall population (LS mean difference: 5.80 points; P=0.0008). The difference was larger (8.7 points) in the vutrisiran monotherapy group.

Vutrisiran patients had a statistically significant 35.5% reduction in the risk of all-cause mortality compared to placebo in the overall population (hazard ratio: 0.645; 95% CI: 0.463, 0.898; P=0.0098; 95% CI: 0.440, 0.973; P=0.0454 and a statistically significant 34.5% reduction in the vutrisiran monotherapy subgroup (hazard ratio: 0.655; 95% CI: 0.440, 0.973; P=0.0454).

At Month 30, vutrisiran led to a statistically significantly greater proportion of patients who showed stability (no change in class) or improvement compared to placebo in the overall population (adjusted difference: 8.7%, 95% CI: 1.3, 16.1; P=0.0217), with consistent results observed in the vutrisiran monotherapy subgroup (adjusted difference: 12.5%, 95% CI: 2.7, 22.2; P=0.0121).

Other secondary and exploratory endpoints

In the overall population, in the analysis of recurrent CV events, including CV hospitalizations and urgent HF visits, vutrisiran treatment led to a 26.7% reduction in the risk of CV events compared to placebo (relative rate ratio: 0.733; 95% CI: 0.610, 0.882; P=0.0010).

In the vutrisiran monotherapy subgroup, vutrisiran led to a 32.4% reduction in the risk of CV events compared to placebo (relative rate ratio: 0.676; 95% CI: 0.533, 0.857; P=0.0012).

In the overall population, vutrisiran treatment led to a 28.4% reduction in the risk of first CV event or all-cause mortality compared to placebo (hazard ratio: 0.716; 95% CI: 0.566, 0.905; P=0.0062)

In the vutrisiran monotherapy subgroup, vutrisiran treatment led to a 35.6% reduction in the risk of first CV event or all-cause mortality compared to placebo (hazard ratio: 0.644; 95% CI: 0.479, 0.867; P=0.0043).

In the overall population, 77.3% of patients in the vutrisiran group showed no progression in NAC ATTR amyloidosis stage at Month 30 compared to 61.2% of patients in the placebo group (adjusted difference: 16.1; 95% CI: 8.1, 24.2; P=7.889E-05). Consistent results were observed in the vutrisiran monotherapy subgroup (adjusted difference: 14.8 (3.7, 26.0), p = 0.0112).

At Month 30, vutrisiran improved patients' self-reported general health-related quality of life, as assessed by the change from baseline in EQ-5D-5L index score, compared to placebo in the overall population (LS mean [SEM] difference: 0.0308 [±0.0111]; P=0.0056), with consistent results observed in the vutrisiran monotherapy subgroup.

At Month 30, the result for the Norfolk QoL-DN questionnaire improved vutrisiran compared to placebo in the overall population (LS mean [SEM] difference: -5.3 (±1.4); P=0.0001, MMRM model). The effect size was larger in the vutrisiran monotherapy group (-7.5 (±1.9); P=0.0001).

3.3. Uncertainties and limitations about favourable effects

Patients with mild to moderate CM were included. Most patients were in NYHA stage II. Patients in NYHA stage III were excluded if they were also in NAC stage 3. Therefore, information is limited regarding efficacy and safety in patients at an advanced stage of the disease. Some information on the safety of patients at advanced stage were generated from patients deteriorating during the course of the study. The preliminary data did not raise safety concerns when treatment was continued. Currently, extrapolation of the results to patients with advanced stages of heart failure is not considered justified and the SmPC should better reflect absence on information on initiating vutrisiran in those patients at these advances stages of the disease and reflect the preliminary data on maintenance of vutrisiran treatment in patients deterioration on therapy.

There is uncertainty on the interpretation of the results in patients receiving tafamidis background therapy and how to place vutrisiran. Tafamidis has an established benefit in the target group of patients with ATTR amyloidosis regarding mortality and CV hospitalization rate. In the subgroup of patients receiving tafamidis background therapy results for efficacy of vutrisiran vs. placebo were numerically consistent with the results in the complementary vutrisiran monotherapy subgroup for most efficacy endpoints analysed but as a rule, effect sizes were smaller and nominal significance or clinical relevance could not be demonstrated for all of the primary, secondary and exploratory endpoints. Analyses in this subgroup were not predefined in a confirmatory testing strategy and superiority of efficacy in this subgroup was not a hypothesis to be tested separately. It is therefore not possible to conclude on a statistically significant and clinically relevant superiority of efficacy of vutrisiran in the add-on setting to tafamidis. But even when assuming that the numerically better results with vutrisiran for almost all efficacy endpoints investigated in this group indicated somewhat improved efficacy, it is still not possible to decide whether vutrisiran alone had a tendency to better efficacy than tafamidis, or whether the combination of both medicinal products exerted an add-on/potentiated effect when combined. A comparison to efficacy in the vutrisiran monotherapy subgroup is not meaningful in this regard due to relevant differences in baseline characteristics between the vutrisiran monotherapy subgroup and the background tafamidis subgroup. The uncertainty related particularly to patients with hATTR already receiving tafamidis. In this small subgroup results were even numerically in favour of placebo over vutrisiran for a number of endpoints evaluate. The same holds true for patients at NYHA stage III at baseline. Due to the low number the results in these subgroups should be interpreted with caution, no conclusions are possible whether these patients have a benefit of administering vutrisiran on top of tafamidis.

Currently it is therefore not possible to draw final conclusions as to whether patients on tafamidis background therapy should receive add-on vutrisiran or should receive vutrisiran in exchange of tafamidis. Post hoc analyses indicated that patients deteriorating on tafamidis tended to have more of a benefit than those that appeared to be clinically stable. However, no firm conclusions can be drawn in this regard. Irrespectively, the results in the overall population and in the vutrisiran monotherapy population sufficiently provide evidence of a clinically relevant efficacy of vutrisiran.

Efficacy in patients with wtATTR was convincing, whereas subgroup analyses in patients with hATTR indicated potentially lower efficacy in the overall population. This was particularly relevant for patients on background tafamidis. Due to low numbers it is currently also not possible to come to final conclusions as to whether patients in NYHA stage III on tafamidis background therapy can expect a clinically relevant benefit of adding vutrisiran.

Secondary endpoints pertaining to quality of life and exercise capacity depend on both, cardiovascular and neurological effects Additional analyses provided did not indicate that efficacy on polyneuropathy had a relevant impact on the overall results.

3.4. Unfavourable effects

In general, the treatment emergent AEs and SAEs observed were similar between treatment groups and consistent with those expected in the patient population and underlying disease.

The percentage of patients with treatment-related AEs (12.6% vutrisiran, 14.0% placebo) or AEs leading to study drug discontinuation (3.1% vutrisiran, 4.0% placebo) tended to be lower in the vutrisiran group than in the placebo group. The percentage of patients with SAEs considered related to study drug by the Investigator was low in both groups (2 [0.6%] vutrisiran; 1 [0.3%] placebo).

Fewer cases of deaths were reported in the vutrisiran group (15.0%) than in the placebo group (19.2%) during the DB period of the HELIOS-B study. None of the deaths were considered related to study drug by the Investigator.

Overall, no safety concerns regarding cardiac events were observed. Compared to placebo, fewer patients in the vutrisiran group reported AEs within the Cardiac disorders SOC (69.6% vutrisiran, 73.8% placebo), the Cardiac failure SMQ (49.4% vutrisiran, 59.8% placebo), and the Cardiac arrhythmia HLGT (42.9% vutrisiran, 46.3% placebo). The percentage of patients with AEs within the Torsade de pointes/QT prolongation SMQ was similar between treatment groups (16.9% vutrisiran, 17.7% placebo). No confirmed events of Torsade de pointes were reported.

3.5. Uncertainties and limitations about unfavourable effects

3.6. Effects Table

Table 31. Effects table for Vutrisiran and treatment of ATTR amyloidosis with CM

Effect	Short description	Unit	Vutrisiran N=326 Overall population; N=196 Vutrisiran Monotherapy Subgroup	Placebo N=328 Overall population; N=199 Vutrisiran Monotherapy Subgroup	Uncertainties Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Vutrisiran N=326 Overall population; N=196 Vutrisiran Monotherapy Subgroup	Placebo N=328 Overall population; N=199 Vutrisiran Monotherapy Subgroup	Uncertainties Strength of evidence	References
All-cause mortality and recurrent CV events	Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the overall population	n	251	332	Hazard ratio 0.718 95% CI (0.555, 0.929) P = 0.0118	DB Period of the HELIOS-B Study
All-cause mortality and recurrent CV events	Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)	n	155	211	Hazard ratio 0.672 95% CI (0.487, 0.929) P = 0.0162	DB Period of the HELIOS-B Study
6-MWT	Change from baseline in 6-minute walk test (6-MWT) at Month 30 in the overall population	meters, (observed median, Q1, Q3)	-7.50 (-55.00, 18.00)	-30.65 (-82.55, 4.77)	LS mean difference 26.46 95% CI 13.38, 39.55 P = 7.976E-05	DB Period of the HELIOS-B Study
6-MWT	Change from baseline in 6-minute walk test (6-MWT) at Month 30 in the monotherapy subgroup	meters, (observed median, Q1, Q3)	-13.05 (-69.04, 17.41)	-47.33 (-91.92, -2.35)	LS mean difference 32.09 95% CI 14.03, 50.15 P = 0.0005	DB Period of the HELIOS-B Study
KCCQ-OS	Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) at	observed median (Q1, Q3)	-1.30 (-11.07, 8.14)	-6.25 (-17.71, 3.13)	LS mean difference 5.80 95% CI (2.40, 9.20)	DB Period of the HELIOS-B Study

Effect	Short description	Unit	Vutrisiran N=326 Overall population; N=196 Vutrisiran Monotherapy Subgroup	Placebo N=328 Overall population; N=199 Vutrisiran Monotherapy Subgroup	Uncertainties Strength of evidence	References
	Month 30 in the overall population				P = 0.0008	
KCCQ-OS	Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) at Month 30 in the monotherapy subgroup	observed median (Q1, Q3)	-0.26 (-13.80, 11.77)	-8.65 (-20.05, 1.56)	LS mean difference 8.69 95% CI (3.98, 13.40) P = 0.0003	DB Period of the HELIOS-B Study
All-cause mortality	All-cause mortality through 42 months in the overall population	n (%)	60 (18.4%)	85 (25.9%)	Hazard ratio 0.645 95% CI (0.463, 0.898) P = 0.0098 Uncertainty: OLE period in placebo arm on treatment. Strength: Approach rather conservative. Consistent with results in DB period	DB Period of the HELIOS-B Study + extension phase
All-cause mortality	All-cause mortality through 42 months in the monotherapy subgroup	n (%)	43 (21.9%)	58 (29.1%)	Hazard ratio 0.655 95% CI (0.440, 0.973) P = 0.0454 Uncertainty: OLE period in placebo arm on treatment. Strength: Approach rather conservative. Consistent with results in DB period	DB Period of the HELIOS-B Study + extension phase
NYHA Class	Change from baseline in	% stable or	67.8	60.5	Difference in % stable or	DB Period of the

Effect	Short description	Unit	Vutrisiran N=326 Overall population; N=196 Vutrisiran Monotherapy Subgroup	Placebo N=328 Overall population; N=199 Vutrisiran Monotherapy Subgroup	Uncertainties Strength of evidence	References
	New York Heart Association (NYHA) class at Month 30 in the overall population	improved			improved 8.7 95% CI (1.3, 16.1) P = 0.0217	HELIOS-B Study
NYHA Class	Change from baseline in New York Heart Association (NYHA) class at Month 30 in the monotherapy subgroup	% stable or improved	66.3	56.4	Difference in % stable or improved 12.5 95% CI (2.7, 22.2) P = 0.0121	DB Period of the HELIOS-B Study
Unfavourable Effects						
Adverse events related to study drug	Treatment-related AE	n (%)	41 (12.6%)	46 (14.0%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
Serious adverse events related to study drug	Treatment-related SAE	n (%)	2 (0.6%)	1 (0.3%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
At least 1 AE leading to discontinuation from study drug	Treatment-emergent AE	n (%)	10 (3.1%)	13 (4.0%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
Deaths	Treatment-emergent SAE	n (%)	49 (15.0%)	63 (19.2%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
Deaths related to study drug as assessed by the Investigator	Treatment-related SAE	n (%)	0 (0%)	0 (0%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
Cardiac disorders SOC AEs	AEs of Special Interest	n (%)	227 (69.6%)	242 (73.8%)	DB Period of the HELIOS-B Study (Safety	HELIOS-B Phase 3 study

Effect	Short description	Unit	Vutrisiran N=326 Overall population; N=196 Vutrisiran Monotherapy Subgroup	Placebo N=328 Overall population; N=199 Vutrisiran Monotherapy Subgroup	Uncertainties Strength of evidence	References
					Analysis Set)	
AEs in the Acute Renal Failure SMQ	AEs of Special Interest	n (%)	55 (16.9%)	57 (17.4%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
Drug-related Hepatic Disorders (SMQ)	AEs of Special Interest	n (%)	56 (17.2%)	62 (18.6%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study
ALT elevations (>ULN and ⩽ 3×ULN)	AEs of Special Interest	n (%)	97 (29.8%)	78 (23.8%)	DB Period of the HELIOS-B Study (Safety Analysis Set	HELIOS-B Phase 3 study
Treatment-related injection site reaction (ISR)	AE of Special Interest	n (%)	7 (2.1%)	8 (2.4%)	DB Period of the HELIOS-B Study (Safety Analysis Set)	HELIOS-B Phase 3 study

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the European Union (EU), the only approved treatment for cardiomyopathy in adult patients with wtATTR or hATTR amyloidosis is tafamidis, which acts by stabilising the tetrameric TTR protein and reducing its rate of dissociation into amyloidogenic monomers. For Acoramids with the same mechanism of action EMA has issued a positive opinion on 12 December 2024.

Thus, there is an important need for additional approved agents to treat wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) which are safe, effective, and convenient to use.

Vutrisiran showed statistically significant and clinically relevant effects on the composite primary endpoint of all-cause mortality and CV hospitalization/urgent heart failure visits, on all-cause mortality and on Quality of life as measured by KCCQ-OS. In addition, a statistically significant effect was demonstrated on exercise capacity as assessed by the 6-MWT and on the NYHA class. For all of these confirmatory endpoints statistical significance was demonstrated in vutrisiran monotherapy and in the overall population including patients with and without background tafamidis therapy. Considering the increasing number of patients being diagnosed, the limited number of therapeutic options available and the still high morbidity and mortality in the target group of patents there is an unmet medical need and the favourable effects are of high clinical relevance.

3.7.2. Balance of benefits and risks

Transthyretin amyloidosis with cardiomyopathy (wt ATTR and hATTR) is progressive and eventually fatal disease which manifests as destabilization of the tetrameric structure of the TTR protein. Vutrisiran is a siRNA molecule that uses RNA interference mechanisms to target and silence the expression of wild type and variant TTR mRNA and inhibit the synthesis of the TTR protein.

A large reduction in TTR and large, statistically significant and clinically meaningful improvements in morbidity, mortality and quality of life and statistically significant improvements regarding NYHA stage and exercise capacity have been observed with vutrisiran in a pivotal randomized phase 3 study (HELIOS-B) as compared to placebo in the overall population and in patients on vutrisiran monotherapy. The safety profile of vutrisiran as derived from the presented safety data is considered acceptable and manageable with appropriate labelling in the product information.

Therefore, the benefits of vutrisiran in the proposed target population outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of vutrisiran (AMVUTTRA®) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by a majority the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of wild-type or hereditary transthyretin-mediated amyloidosis in adult patients with cardiomyopathy (ATTR-CM), based on primary analysis results from study HELIOS-B (ALN-TTRSC02-003); a Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. An updated version 1.5, dated 10 April 2025. and a final update version 2.0. of the RMP have also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that AMVUTTRA (vutrisiran) is not similar to Vyndaqel (tafamidis), Tegsedi (inotersen) and Onpattro (patisiran) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Amvuttra-H-C-005852-II-0015'.