Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Alnylam Pharmaceuticals:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Amyloidosis UK
   b. Cardiomyopathy UK
   c. British Cardiovascular Society – written by clinical expert, Dr William Moody
   d. NHS England

4. **Expert personal perspectives** from:
   a. Professor Julian Gillmore – clinical expert, nominated by Alnylam Pharmaceuticals
   b. Dr William Moody – clinical expert, nominated by Alnylam Pharmaceuticals & British Cardiovascular Society

5. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Company evidence submission

March 2025

File name	Version	Contains confidential information	Date
ID6470_Vutrisiran_Company Evidence Submission_[CON+DPD]	**2**	**Yes**	**14 March 2025**

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Abbreviations

Term	Definition
6-MWT	6-minute walk test
ACC	American College of Cardiology
ACM	all-cause mortality
AE	adverse event
AHA	American Heart Association
ALT	Alanine transaminase
ARC	Amyloidosis Research Consortium
AST	Aspartate transaminase
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloidosis with cardiomyopathy
ATTR-PN	transthyretin amyloidosis with polyneuropathy
BID	twice per day
BNF	British National Formulary
BNP	B-type natriuretic peptide
BOI	burden of illness
CDSR	Cochrane Database of Systematic Reviews
CEC	clinical events committee
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CNS	central nervous system
CPCI-S	Conference Proceedings Citation Index-Science
CV	cardiovascular
DPD-Tc	^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid
DSU	Decision Support Unit
EEPRU	Economic Methods of Evaluation in Health and Social Care Policy Research Unit
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
FAS	full analysis set
FDA	Food and Drug Administration
GalNAc	3 N-acetylgalactosamine
GI	gastrointestinal
hATTR	hereditary transthyretin amyloidosis
hATTR-CM	hereditary transthyretin amyloidosis with cardiomyopathy
hATTR-PN	hereditary transthyretin amyloidosis with polyneuropathy
HCRU	healthcare resource utilisation
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HMDP	99Tchydroxymethylene diphosphonate

Term	Definition
HR	hazard ratio
HRG	healthcare resource group
HRQoL	health-related quality of life
HTA	health technology assessment
I68L	Isoleucine to leucine substitution at amino acid position 68
ICD-10	International Classification of Diseases version 10
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment Database
INR	international normalised ratio
IQR	interquartile range
ISA	International Symposium on Amyloidosis
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire – Overall Summary
KM	Kaplan–Meier
KPS	Karnofsky performance status
L111M	leucine to methionine transition at amino acid position 111
LMEM	linear mixed-effects model
LS	least squares
LV	left ventricle
LVAD	left ventricular assistance device
LVEF	left ventricular ejection fraction
LY	life year
MAIC	matching-adjusted indirect comparison
mBMI	modified body mass index
MCID	minimal clinically important difference
MCMC	Markov Chain Monte Carlo
MDI	Major Depression Inventory
MGUS	monoclonal gammopathy of unknown significance
MHRA	Medicines and Healthcare Regulatory Agency
MMRM	mixed effects model repeated measures
NA	not applicable
NAC	National Amyloidosis Centre
NICE	National Institute for Health and Care Excellence
NIS	Neuropathy Impairment Score
NHS	National Health Service
NMB	net monetary benefit
NT-proBNP	N-terminal pro-brain natriuretic peptide

Term	Definition
NYHA	New York Heart Association
ODI	oral diuretic intensification
OLE	open-label extension
PH	proportional hazards
PICOS	Population, Intervention, Comparator, Outcome, and Study design
PMM	pattern mixture model
PND	polyneuropathy disability
PROACT	Patient-Reported Outcomes in Transthyretin Amyloid Cardiomyopathy
PSS	personal social services
PWT	posterior wall thickness
PYP-Tc	^{99m}Tc-pyrophosphate; subcutaneous
Q3M	every 3 months
QALY	quality-adjusted life year
QD	every day
QoL	quality of life
RNAi	RNA interference
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SEE	structured expert elicitation
SGLT2	sodium-glucose cotransporter-2
siRNA	small interfering RNA
SLR	systematic literature review
SMC	Scottish Medicines Consortium
STA	Single Technology Appraisal
T60A	threonine to alanine substitution at amino acid position 60
THOAS	Transthyretin Amyloidosis Outcomes Survey
TTR	transthyretin
UK	United Kingdom
ULN	upper limit of normal
UTI	urinary tract infection
V122I	valine to isoleucine substitution at amino acid position 122
wtATTR	wild-type transthyretin amyloidosis
wtATTR-CM	wild-type transthyretin amyloidosis with cardiomyopathy
WTP	willingness-to-pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Vutrisiran is anticipated to be indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy.

[redacted]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)	People with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)	NA
Intervention	Vutrisiran	Vutrisiran monotherapy	The company submission considers that vutrisiran will be positioned as a monotherapy at launch. This is based on anticipated lack of cost-effectiveness of combination use of two branded medicines (i.e., vutrisiran and tafamidis) given current NICE STA cost-effectiveness thresholds and clinician intentions for the use of vutrisiran once it is available.
Comparator(s)	• Tafamidis • Established clinical management without vutrisiran	• Tafamidis	Alnylam understands that all treatment-eligible patients for vutrisiran would otherwise be treated with tafamidis, the current SOC. Therefore, it is the only comparator considered in the company cost-effectiveness analysis.
Outcomes	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as global longitudinal strain BNP level) • cardiovascular-related hospitalisation	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as global longitudinal strain or BNP level) • cardiovascular-related hospitalisation	Alnylam regards the outcomes to be appropriate; however, given the role of loop diuretics for symptomatic management of worsening heart failure, loop diuretic dose has also emerged as a useful indicator of disease severity in ATTR-CM.[1] Specifically, longitudinal changes in daily loop diuretic dose have shown prognostic value in patients with ATTR-CM, as patients seen at the NAC (n=1,598) experiencing ODI (defined as initiation of oral loop diuretics or any increase in loop diuretic dose [furosemide equivalent]) from diagnosis to 1 year post-diagnosis, had a 1.9-fold increase (vs. patients without

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients and carers).	• functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients and carers) • ODI	ODI) in mortality risk from 1 year post-diagnosis onward.[2] Therefore, Alnylam has included results from outcomes that incorporate ODI in patients with ATTR-CM in the submission.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the NICE scope.	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	• Severity of heart failure (such as by New York Heart classification class) • Wild type or hereditary ATTR-CM	No subgroup analyses were performed.	Subgroup analyses were not performed. Alnylam regards it reasonable that subgroups defined by level of heart failure severity (via NYHA classification) and disease type (hATTR-CM vs wtATTR-CM) may be of potential interest to assess clinical effectiveness and cost effectiveness. However, there were very few patients within these subgroups in the vutrisiran and tafamidis monotherapy groups in HELIOS-B, meaning that reliable estimates of cost-effectiveness could not be generated. Further, vutrisiran demonstrated consistent efficacy across all predefined subgroups in HELIOS-B,[3] which included patients in NYHA I/II versus NYHA III, and in patients with wtATTR-CM versus hATTR-CM.

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; BNP, brain natriuretic peptide; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; NA, not applicable, NAC, National Amyloidosis Centre; NHS, National Health System; NYHA, New York Heart Association; ODI, outpatient diuretic intensification; SOC, standard of care; STA, single technology appraisal; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy.

1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Vutrisiran (AMVUTTRA®)
Mechanism of action	Vutrisiran is a chemically stabilised double-stranded siRNA that specifically targets variant and wild-type TTR mRNA. It is covalently linked to a ligand containing three GalNAc residues to enable targeted delivery of the siRNA to hepatocytes.[4] Through a natural process called RNAi, vutrisiran causes the catalytic degradation of TTR mRNA in the liver thus silencing the expression of the TTR gene, resulting in the reduction of variant and wild-type serum TTR protein levels.[4]
Marketing authorisation/CE mark status	**hATTR-PN**: MHRA approval of vutrisiran was granted on 16 September, 2022.[5] **ATTR-CM**: Vutrisiran is anticipated to receive market authorisation from the MHRA in August 2025.[6]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**MHRA SmPC indications:** **hATTR-PN: AMVUTTRA** (vutrisiran) is indicated for the treatment of hATTR in adult patients with stage 1 or stage 2 polyneuropathy.[5] **ATTR-CM:** The proposed indication is: "AMVUTTRA (vutrisiran) is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy." This is aligned with the indication in this appraisal.
Method of administration and dosage	The recommended dose of vutrisiran is 25 mg administered via SC injection Q3M.[6]
Additional tests or investigations	None required
List price and average cost of a course of treatment	**List price:** £95,862.36 per pre-filled syringe of vutrisiran (25 mg in 0.5 mL solution for injection) **Annual price:** £383,449.44 per patient at the list price
Patient access scheme (if applicable)	There is a confidential PAS currently in place for vutrisiran. PAS price: £[redacted]

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; GalNAc, *N*-acetylgalactosamine; hATTR, hereditary transthyretin amyloidosis; hATTR-PN, transthyretin amyloidosis with polyneuropathy; MHRA, Medicines and Healthcare products Regulatory Agency; mRNA, messenger ribonucleic acid; NHS, National Health Service; PAS, patient access scheme; Q3M, quarterly; RNAi, ribonucleic acid interference; SmPC, Summary of Product Characteristics; SC, subcutaneous; siRNA, small interfering ribonucleic acid; TTR, transthyretin.

1.3 Health condition and position of the technology in the treatment pathway

ATTR-CM, is a rare, fatal, and rapidly progressive condition.

- There are two predominant clinical manifestations associated with transthyretin (ATTR) amyloidosis, hereafter referred to as ATTR: ATTR with cardiomyopathy (ATTR-CM), which may be non-hereditary (i.e., wild-type [wtATTR]) or hereditary (hATTR) in origin and ATTR with polyneuropathy (ATTR-PN), which is most often seen in patients with hATTR.
  - Vutrisiran received positive NICE guidance for the treatment of hATTR-PN (TA868),[7] and is the current standard of care for hATTR-PN in the UK.
- **The current appraisal for vutrisiran is for ATTR-CM [ID6470], a rare, rapidly progressive, and ultimately fatal condition,** which is characterised by the deposition of amyloid fibrils in the myocardium.[8,9]
- When untreated, **ATTR-CM causes progressive heart failure**, which leads to:

  1) Symptoms that drive rapid, irreversible progression of impairment in physical capacity and health-related quality of life (HRQoL), resulting in substantial clinical and humanistic burden, and

  2) Premature death.[10-24]
    - Median survival from ATTR-CM diagnosis is 2.1 to 5.8 years.[14-24]
- As a result of its clinical and functional impacts, ATTR-CM also causes considerable economic burden to the health system in the form of increased healthcare resource utilisation (HCRU), along with diminished social participation and labour productivity for patients and their informal caregivers (family and friends of the ATTR-CM patient).[25-29]
- As of 2024, there were an estimated 1,300 treated patients with ATTR-CM in the UK.

Despite the availability of tafamidis 61mg in the UK, patients with ATTR-CM currently have substantial unmet treatment-related needs.

- Tafamidis 61 mg is currently the only Medicines and Healthcare products Regulatory Agency (MHRA)-approved therapy for ATTR-CM, which requires daily oral dosing.[30]
- Tafamidis is a TTR stabiliser, which works by binding to unstable TTR at thyroxine binding sites but does not target the source of pathogenic TTR protein production.
- Patients treated with tafamidis continue to experience worsening of physical capacity, HRQoL, and cardiac injury level from their pretreatment baseline, as well as excess mortality, with uncertain efficacy in some patient types (including patients in New York Heart Association [NYHA] III).[10,31,32]
  - The limitations of tafamidis in patients with ATTR-CM in NYHA III have been noted by the EMA, NICE, and the European Society of Cardiology.[33-35]
- A targeted literature review demonstrated that the majority (~40–70%) of tafamidis-treated patients worsen in disease within 6–12 months from initiation, and that mortality remains high in real-world contemporary ATTR-CM patient populations treated with tafamidis.[36]
- New treatment options that further slow or halt disease progression, preserve HRQoL and physical capacity, and reduce excess mortality in all patient types, with a convenient administration profile, are therefore needed.

Rapid and sustained knockdown of TTR by vutrisiran, a novel RNAi therapy, leads to disease modification with reduced morbidity and mortality, addressing the unmet needs of patients with ATTR-CM. Vutrisiran is anticipated to be a new standard-of-care treatment option for ATTR-CM in the UK.

- Vutrisiran acts upstream of TTR stabilisers such as tafamidis (which do not inhibit production of toxic TTR) by mediating catalytic degradation of TTR messenger RNA,[37] resulting in rapid knockdown of the toxic TTR protein, thus preventing amyloid deposition in vital organs including the myocardium.
    - Therefore, vutrisiran modifies the disease trajectory in ATTR-CM via a novel mechanism of action that directly addresses production of toxic TTR, the driver of the disease process, at its source.
    - The rapid and sustained knockdown of serum TTR by vutrisiran leads to disease stabilisation.
- Vutrisiran addresses the unmet clinical needs associated with tafamidis, by significantly improving survival versus placebo and potentially restoring survival to that of the age-matched healthy general population,[38] preserving pre-treatment baseline levels of physical capacity, HRQoL, and cardiac well-being, and providing consistent efficacy across all patient types.[3]
    - In patients in NYHA III, vutrisiran demonstrated numerically favourable results in mortality and cardiovascular (CV) events versus placebo (Alnylam, data on file).
- Vutrisiran has a convenient administration profile catered towards providing benefits for patients and the healthcare system, with a fixed-dose subcutaneous (SC) injection every 3 months (Q3M).
- Vutrisiran therefore represents a new standard-of-care treatment option for all patients with ATTR-CM in the UK, including those patients currently treated with tafamidis with inadequate response.
- Based on the anticipated lack of cost-effectiveness of combination use of two branded medicines (i.e., vutrisiran and tafamidis), and in view of current NICE STA cost-effectiveness thresholds and clinician intentions for the use of vutrisiran, vutrisiran is anticipated to be positioned as a monotherapy at launch.

1.3.1 Overview of ATTR

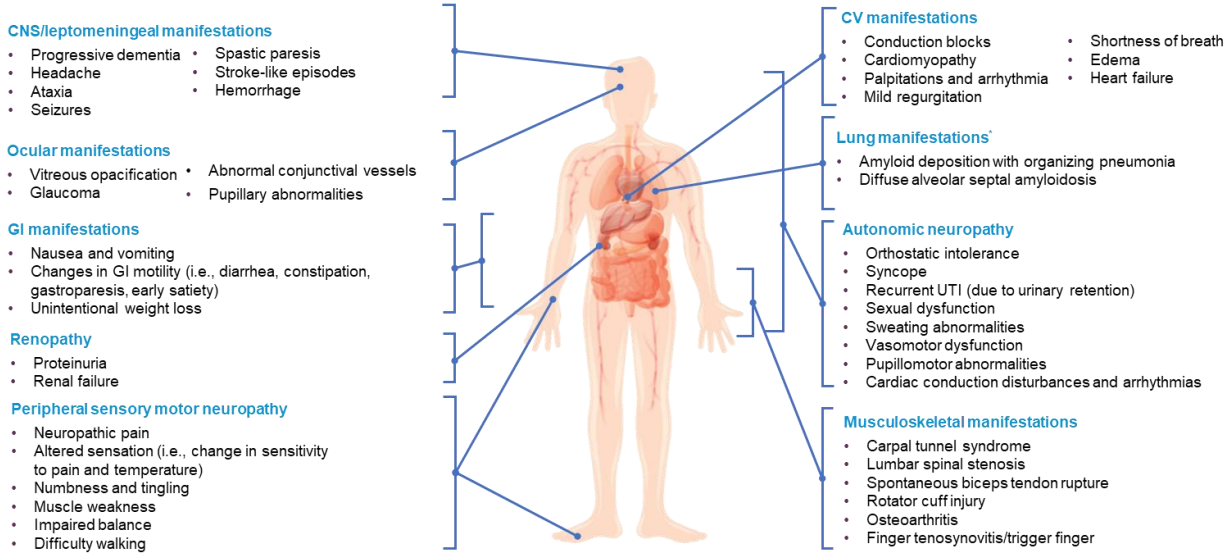
ATTR is a rare, rapidly progressive, and fatal condition, which is characterised by the deposition of amyloid fibrils derived from toxic TTR protein in multiple organs and tissues (e.g., heart, nerves, gastrointestinal [GI] tract, and kidneys), with corresponding clinical manifestations.[39] TTR is primarily produced in the liver. In its normal configuration, it is a tetrameric protein composed of four monomers, and it functions as a transport protein for thyroxine and vitamin A.[18,39,40]

ATTR may be nonhereditary (wtATTR) or hereditary (hATTR) in origin.[8,9]

- **wtATTR**: patients express normal, wild-type TTR protein (i.e., no pathogenic TTR gene variant is present), and the pathological formation of amyloid from this wild-type TTR protein appears to be associated with aging.[41-43]
- **hATTR**: the pathological process is driven by the presence of an inherited pathogenic TTR gene variant, which encodes TTR protein with an increased propensity for amyloid formation.[8,9]

The potential clinical manifestations of ATTR are varied (Figure 1).[39,44-46] In any given patient, the manifestations of ATTR may be predominantly limited to a single organ or tissue type, or they may be multisystemic in nature.[39,44-47]

Figure 1: Symptoms of ATTR



ATTR, transthyretin amyloidosis; CNS, central nervous system; GI, gastrointestinal; UTI, urinary tract infection. *Based on individual case reports. Sources: Conceicao et al. 2016[44]; Gonzalez-Duarte 2019[45]; Sekijima et al. 2015[47]; Carr et al. 2019[48]; Campbell et al. 2020[49]; Aus Dem Siepen et al. 2019[50]; Arevalo et al. 2020[51]; Ando et al. 1994[52]; Lui et al. 2012[53]; Agarwal et al. 2017[54]; Shen and Zipes 2014[55]; Uotani et al. 2007[56]; Maurer et al. 2016[46]; Khella et al. 2018[57]; Garcia-Pavia et al. 2019[58]; Gonzalez-Lopez et al. 2015[59]; Nakagawa et al. 2016[60]; Sekijima et al. 2018[61]; Witteles et al. 2019[62]; Visser and Klein 2017[63]; Zivkovic et al. 2019[64]; Ruberg et al. 2019[8]; M'bappe et al. 2012[65]; Geller et al. 2017[66]; Castano et al. 2020[67]; Hara et al. 2020[68]; Takashio et al. 2020[69]; Eldhagen et al. 2021[70]; George et al. 2020[71]; Milandri et al. 2020[72]; Triguero et al. 2021[73]; Tsukada et al. 2020[74]; Yamada et al. 2020[75]; Nakao et al. 2017[76]; Tomita et al. 2019[77]; Damy et al. 2022[13]; Rapezzi et al. 2013[78]; Coelho et al. 2013[79]

There are two predominant phenotypes of ATTR, and most patients present with either one, while some present with both:

ATTR with polyneuropathy (ATTR-PN):

- Polyneuropathy results from the deposition of TTR amyloid fibrils in the nerves, causing sensory neuropathy, motor dysfunction, and autonomic dysfunction (including gastrointestinal and cardiac autonomic dysfunction).[53,80]

- Vutrisiran received positive NICE guidance for the treatment of hATTR-PN (TA868),[7] and is the current standard of care for hATTR-PN in the UK.

ATTR with cardiomyopathy (ATTR-CM):

- Cardiomyopathy resulting from accumulation of TTR-derived amyloid fibrils in the heart is referred to as ATTR-CM. The buildup of amyloid fibrils in the myocardial tissue in the heart causes progressive loss of cardiac function, ultimately resulting in heart failure (inability to pump an adequate supply of blood to body systems) and premature death.[8,9,14-24]

ATTR with cardiomyopathy and polyneuropathy (i.e., mixed phenotype):

- A mixed phenotype of cardiomyopathy and polyneuropathy is seen in some patients due to the systemic deposition of TTR amyloid in both the myocardium and the peripheral and autonomic nerves (see Figure 1).[39,44-47] For example, an analysis of the medical histories of patients with ATTR-CM enrolled in a phase 3 clinical trial (n=359) showed that polyneuropathy manifestations occurred in 21.7% of analysed patients, with these manifestations occurring a median of 40.5 months before diagnosis with ATTR-CM.[81] Further, the analysis demonstrated similar distribution of polyneuropathy manifestations in patients with hATTR-CM (25.4%) and wtATTR-CM (20.8%).[81]

This submission [ID6470] is solely intended for the appraisal of vutrisiran as a treatment of ATTR-CM in patients with wild-type (wtATTR) or hereditary (hATTR) disease.

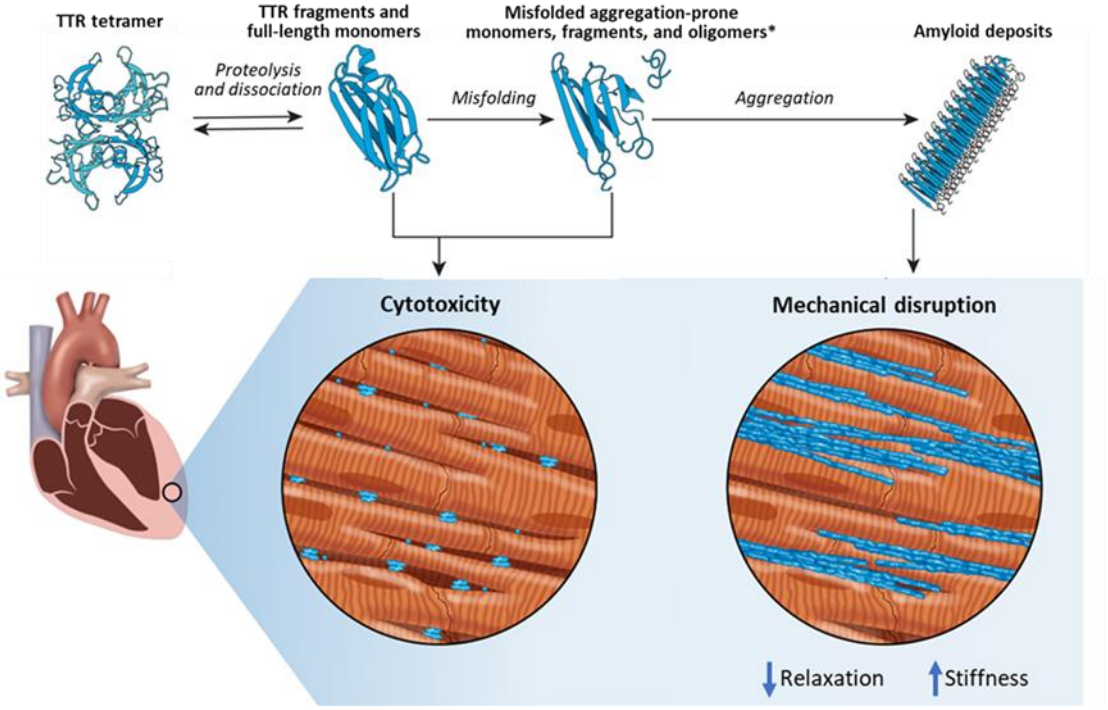
1.3.2 Description of ATTR-CM

1.3.2.1 Pathophysiology

ATTR-CM results from the deposition of TTR-derived amyloid fibrils in the interstitial tissue of the myocardium, leading to progressive heart failure and, potentially, cardiac conduction disorders.

In ATTR-CM, the deposition of TTR amyloid fibrils in the interstitial space in the myocardium results in thickening of the ventricular walls, causing myocardial tissue to become rigid, preventing normal physiological function of the heart (Figure 2).[18,42] Cardiac TTR amyloid deposition may also disrupt electrical signalling within the heart. Such disturbances of cardiac conduction may occur when conductive heart tissues, the blood vessels that supply these tissues, and/or (as has been reported in hATTR) autonomic nerves involved in regulating heart rhythm are impacted by TTR amyloid deposition.[82-84] These TTR amyloid-driven processes lead to progressive heart failure—the core clinical manifestation of ATTR-CM—and potentially, conduction disorders, leading to substantial morbidity and premature mortality.

Figure 2: Pathophysiology of ATTR-CM



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; TTR, transthyretin. **In vitro* studies have shown that unstable TTR monomers and short oligomers (smaller than 100 kDa) also damage cardiac cells in a manner that leads to cell death and thus further contributes to cardiac dysfunction.[34,75] Source: Griffin et al, 2021[42]

1.3.2.2 Epidemiology

ATTR-CM is a rare disease, with an estimated 1,300 treated patients in the UK.

Global epidemiology

ATTR-CM is a rare disease.[18] Globally, the estimated number of patients with ATTR-CM is [redacted]. ATTR-CM is more commonly of wild-type origin than of variant (hereditary) origin. There are an estimated 40,000 patients with hATTR-CM,[39] and Alnylam estimates [redacted] patients with wtATTR-CM (Alnylam data on file).

Studies in cohorts with existing heart failure have consistently found that patients with ATTR-CM are disproportionately male.[19,59,85-87]

Disease onset in hATTR-CM typically occurs by around 60 years of age,[15] but it can occur in as early as the third decade of life.[42] Due to the age-associated factors in wtATTR-CM, patients are typically relatively older at disease onset, often in their seventh decade of life or later.[42]

The four mutations most commonly associated with hATTR-CM are V122I, T60A, L111M, and I68L.[46,78,88] The V122I variant is the most studied and most common, likely originating in West Africa,[88,89] while the T60A mutation originated in Donegal, Republic of Ireland, and is endemic to northwest Ireland.[90,91]

UK epidemiology

Based on discussions with experts at the UK National Amyloidosis Centre (NAC), Alnylam understands there were approximately 1,300 diagnosed and treated patients with ATTR-CM in the UK at the end of 2024.

1.3.2.3 Clinical presentation and clinical burden

Premature mortality

Without disease-modifying treatment, ATTR-CM results in premature death, with analyses of UK patients showing median survival from diagnosis of only ~2.6 years.[19,20]

Based on natural history studies, estimated median survival from diagnosis in patients with ATTR-CM ranges from 2.1 to 5.8 years.[14-24] Natural history studies have shown a tendency toward shorter survival in patients with the V122I or the T60A TTR gene variant compared to other forms of ATTR-CM (i.e., wtATTR-CM/hATTR-CM due to other TTR gene variants; Table 3).[15,19]

Table 3: Median survival from diagnosis in different ATTR-CM patient types

Disease subtype	Authors	Study design	Median survival from diagnosis
ATTR-CM	Cheng et al. (2020)[22]	Retrospective study of 309 patients (66% wtATTR) in a care centre in New York, USA	4.0 years
	Gillmore et al. (2018)[14]	Retrospective study of 869 patients attending the NAC in the UK	4.8 years
	Damy et al. (2023)[24]	Retrospective analysis of 8,481 patients in France	3.5 years
wtATTR-CM	Ruberg et al. (2012)[21]	Prospective study of 18 patients attending US medical centres	3.6 years
	Lane et al. (2019)[19]	Prospective study of 711 patients attending the NAC in the UK	4.8 years
	Pinney et al. (2013)[20]	Prospective study of 102 patients attending the NAC in the UK	2.7 years
	Grogan et al. (2016)[16]	Retrospective study of 360 patients diagnosed at the Mayo Clinic in Rochester, USA	3.6 years
	Connors et al. (2015)[17]	Prospective study of 121 patients diagnosed at the Boston University Amyloidosis Centre, USA	3.9 years
hATTR-CM	Ruberg et al. (2012)[21]	Prospective study of 11 V122I patients attending US medical centres	2.1 years
	Lane et al. (2019)[19]	Prospective study of 323 patients (non-V122I, n=118; V122I, n=205) attending the NAC in the UK	V122I: 2.6 years Non-V122I: 5.8 years
	Swiecicki et al. (2015)[15]	*Retrospective study including patients with cardiomyopathy-related TTR gene mutations (T60A, n=68 patients; V122I, n=28 patients) at the Mayo Clinic in Rochester, USA	V122I: 2.1 years T60A: 3.2 years

ATTR, transthyretin amyloidosis; hATTR, hereditary transthyretin amyloidosis; NAC, National Amyloidosis Centre; T60A, threonine to alanine substitution at amino acid position 60; UK, United Kingdom; USA, United States of America; V122I, valine to isoleucine substitution at amino acid position 122; wtATTR, wild-type transthyretin amyloidosis. *Among patients with the T60 TTR gene variant, 82.4% of patients had cardiomyopathy, while all V122I patients had cardiomyopathy.

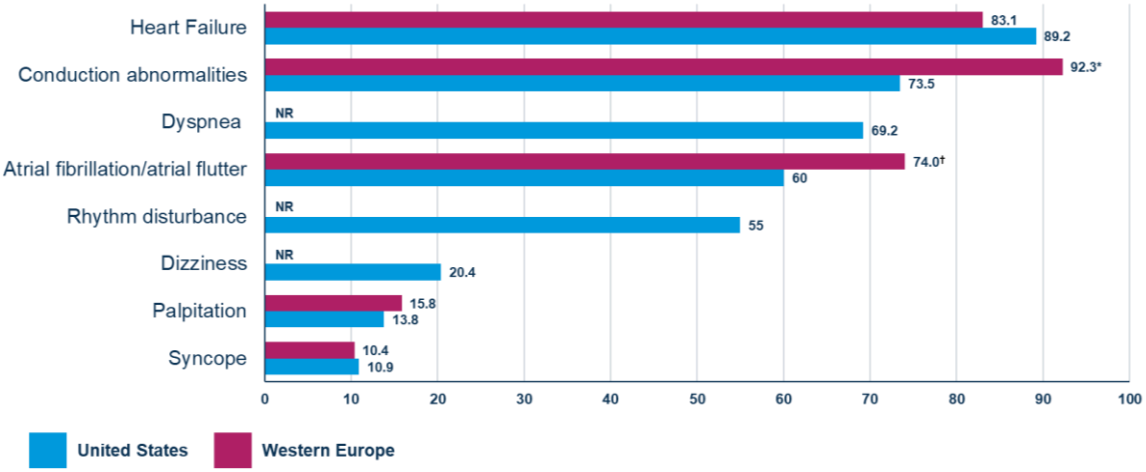
Symptom burden

Patients with ATTR-CM have compromised heart function, which results in numerous debilitating cardiac-related signs and symptoms.

In addition to having a shortened life expectancy, patients with ATTR-CM experience multiple cardiac abnormalities that adversely impact their quality of life. Patients can develop both left- and right-sided heart failure,[17,90,92] conduction disorders and arrythmias, as well as embolisms and intracardiac thrombotic events.[18,92-95]

These cardiac abnormalities lead to a range of debilitating symptoms, including irregular heartbeat, heart palpitations, fatigue/exercise intolerance, oedema in the lower extremities, ascites, early satiety, nausea, dyspnoea, and syncope.[18,19,79,92,96] Burdensome symptoms such as these are common, as seen by their high frequencies in patients from the United States (US) and Western Europe at enrolment in the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry, a global, multicentre, longitudinal, observational survey of patients with ATTR (Figure 3).

Figure 3: Frequency (%) of signs and symptoms among patients with ATTR-CM in the THAOS registry



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy NR, not reported; THAOS, Transthyretin Amyloidosis Outcomes Survey; V122I, valine to isoleucine substitution at amino acid position 122; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy. Note: Data are pooled from patients with hATTR-CM and wtATTR-CM. All United states patients with hATTR-CM had the V122I variant. *Based on having an abnormal electrocardiogram result. †Only representative of patients with atrial fibrillation. Sources: Maurer et al. 2016[46]; Damy et al. 2022[97]

As noted in Section 1.3.1 (Figure 1), patients with ATTR-CM can also experience a wide range of burdensome extracardiac symptoms due to the systemic nature of ATTR, and the potential for TTR amyloid deposits in other tissues.[39,44-47]

Impairment of physical capacity

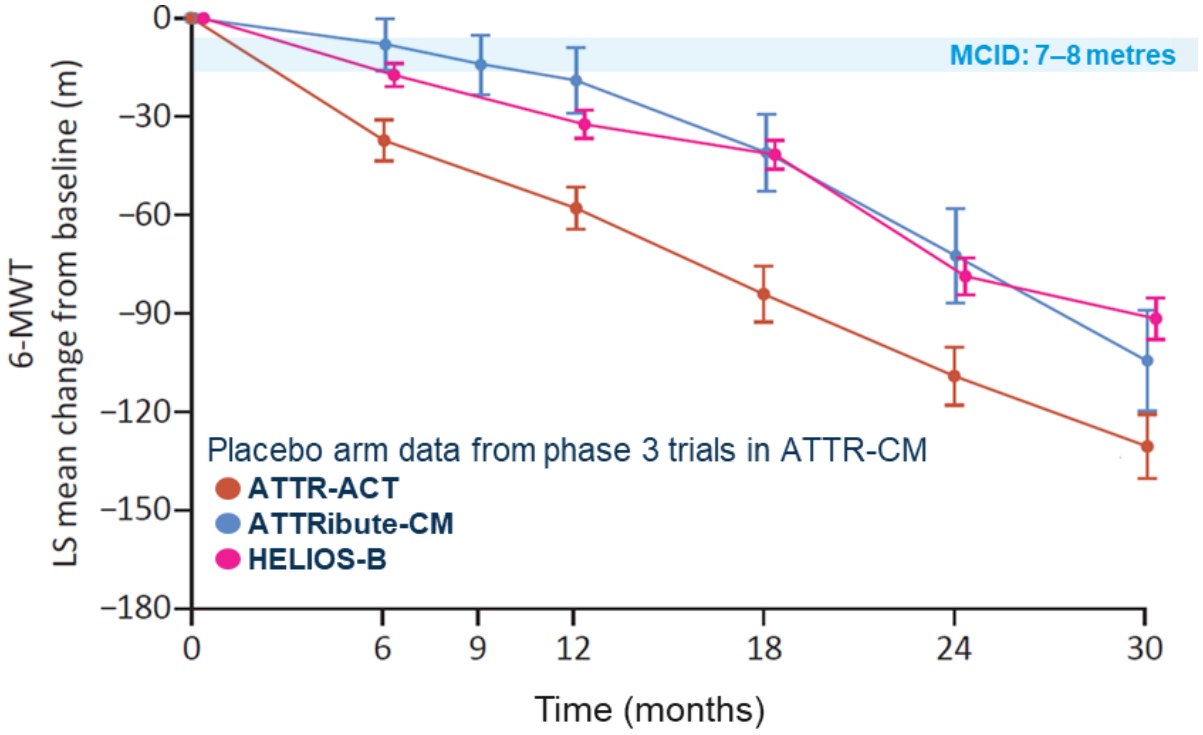
Progressive cardiomyopathy leads to patients experiencing ongoing, irreversible worsening of physical capacity, fatigue and loss of ability to perform everyday activities.

Impairment of physical capacity in ATTR-CM, driven by symptoms such as exercise intolerance and fatigue, is a prominent element of disease burden. Studies that evaluated physical capacity using the 6-minute walk test (6-MWT)—a common measure of physical capacity in patients with heart failure—have shown that the impairment of physical capacity seen in ATTR-CM is not only substantial, but also worsens over time:

- In a prospective study of patients with ATTR-CM being treated at the NAC in the UK (N=382; wtATTR, n=289; hATTR, n=93), a statistically significant mean reduction in 6-MWT distance of approximately 100 metres from baseline to 36 months was observed.[19]
- In phase 3 trials of patients with ATTR-CM, placebo-administered patients have demonstrated substantial declines (up to a least square [LS] mean reduction of 131 metres) in 6-MWT over 30 months (Figure 4).[3,10,11]

Considering that the minimal clinically important difference (MCID) for the 6-MWT in ATTR-CM has been shown to be 7–8 metres,[98] the natural decline in physical capacity in patients with ATTR-CM is clinically substantial.

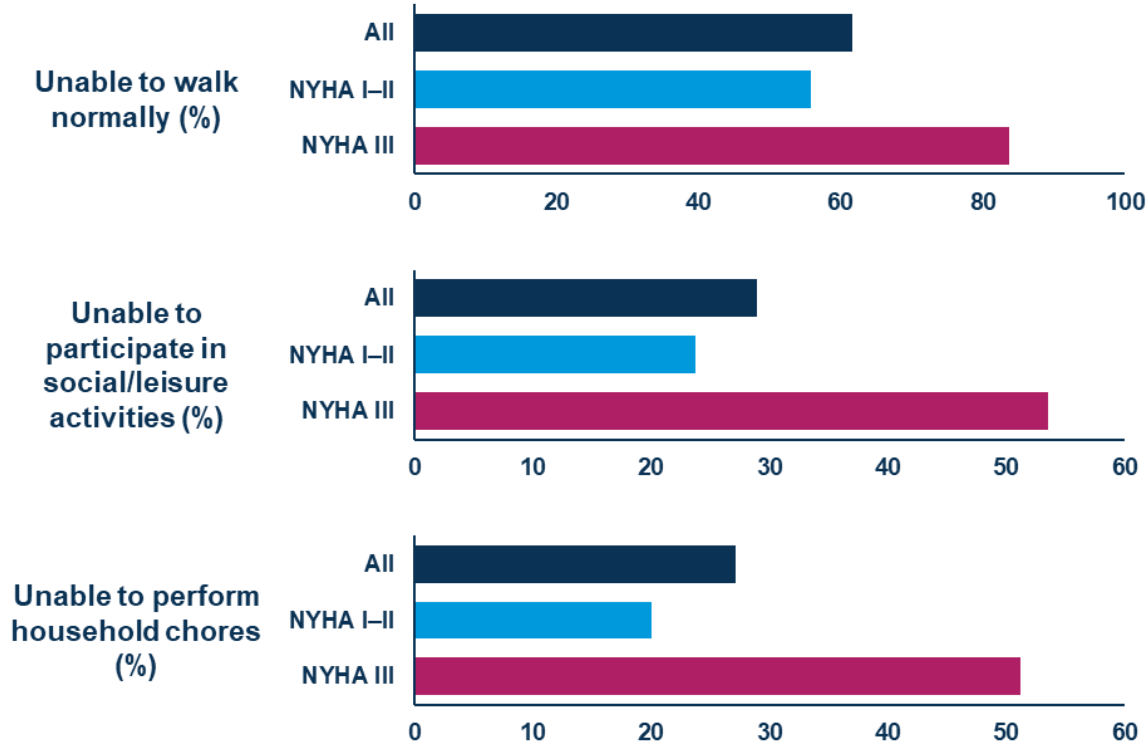
Figure 4: LS mean change in 6-MWT distance in placebo-administered patients in Phase 3 ATTR-CM clinical trials



6-MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; LS, least square; MCID, minimal clinically important difference. Note: Data are from placebo-administered patients from ATTR-ACT, ATTRibute-CM, and HELIOS-B (phase 3 clinical trials of tafamidis, acoramidis, and vutrisiran, respectively). 6-MWT measures the distance a patient walks in 6 minutes Source: Fontana et al. 2024[3]; Gillmore et al. 2024[11]; Maurer et al. 2018[10]

The decline in physical capacity leads to limitations in daily activities (e.g., walking, social/leisure activities, chores), which become more prevalent as the disease progresses (Figure 5).[12]

Figure 5: Effects of ATTR-CM on patients' daily activities



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; NYHA, New York Heart Association. Data from an international, multicentre, cross-sectional study of patients with ATTR-CM (n=208). Source: Ponti et al. 2023[12]

1.3.2.4 HRQoL burden

Patients with ATTR-CM experience substantial and irreversible declines in HRQoL and other detrimental humanistic impacts due to the loss of physical capacity and the ability to carry out everyday activities.

HRQoL of patients with ATTR-CM has been assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated, 23-item self-administered questionnaire designed to assess symptoms, function, and quality of life in patients with heart failure (Figure 6).[99,100]

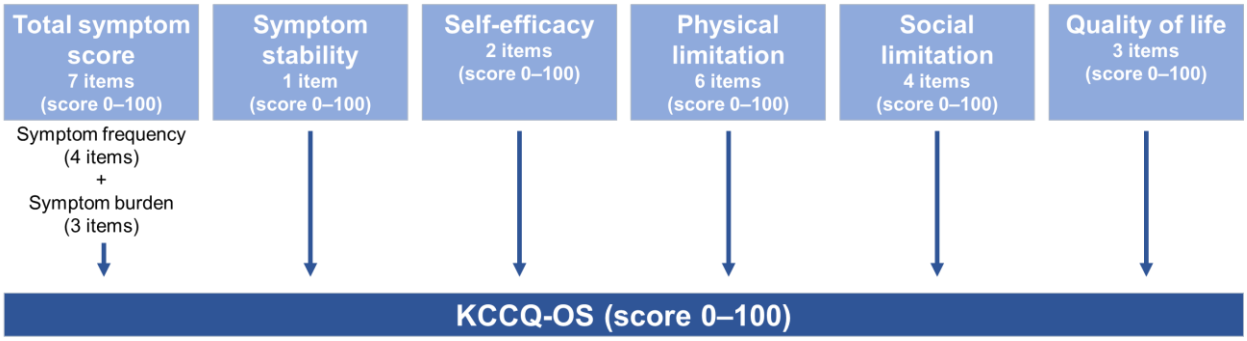
The KCCQ assesses multiple domains, namely:[99,100]

- Total symptom score (comprising symptom frequency and symptom burden)
- Symptom stability
- Physical limitations
- Social limitations
- Quality of life (QoL)
- Self-efficacy (the patient's understanding of how to manage their heart failure)

The KCCQ – Overall Summary (KCCQ-OS) score ranges from 0–100, with lower scores representing a worse outcome, and provides a global measure of cardiomyopathy-related HRQoL across all domains.[99,100] The MCID for the KCCQ-OS score is 5 points, while differences in KCCQ-OS score of 10 and 20 points represent moderate-to-large and large-to-very large clinical changes, respectively.[100]

Furthermore, in patients with heart failure, KCCQ-OS scores have shown to be an independent prognostic factor, as patients with lower KCCQ-OS scores show higher rates of mortality and heart failure hospitalisations.[101]

Figure 6: Summary of KCCQ domains



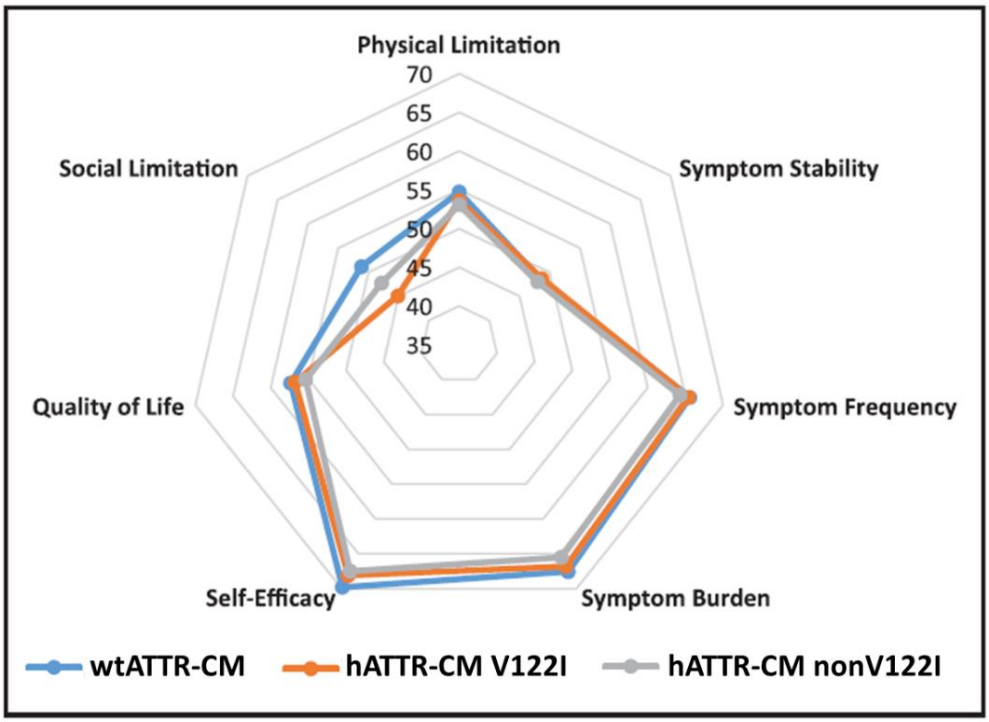
KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary. Source: Spertus et al. 2020[100]; Green et al. 2000[99]

In a cross-sectional study of 169 patients with ATTR-CM from Denmark, Sweden, Norway, and Finland, a mean KCCQ-OS score of 64.8 points (SD: 20.9 points) was observed.[102] Notably, this is lower than the mean baseline KCCQ-OS scores of 70 or greater (indicating better HRQoL) that have been reported in clinical trials and observational studies for the following cardiac conditions:[102]

- Heart failure with preserved ejection fraction (HFpEF)
- Heart failure with reduced ejection fraction (HFrEF)
- Obstructive hypertrophic cardiomyopathy

Even lower mean KCCQ-OS scores of 55–58 points were observed at 12 months after diagnosis in a prospective study of UK patients with ATTR-CM (N=158).[19] This study also showed that specific domains of the KCCQ were impacted differentially in ATTR-CM, with physical limitation, social limitation, and symptom stability domains showing the greatest impairment (Figure 7).[19]

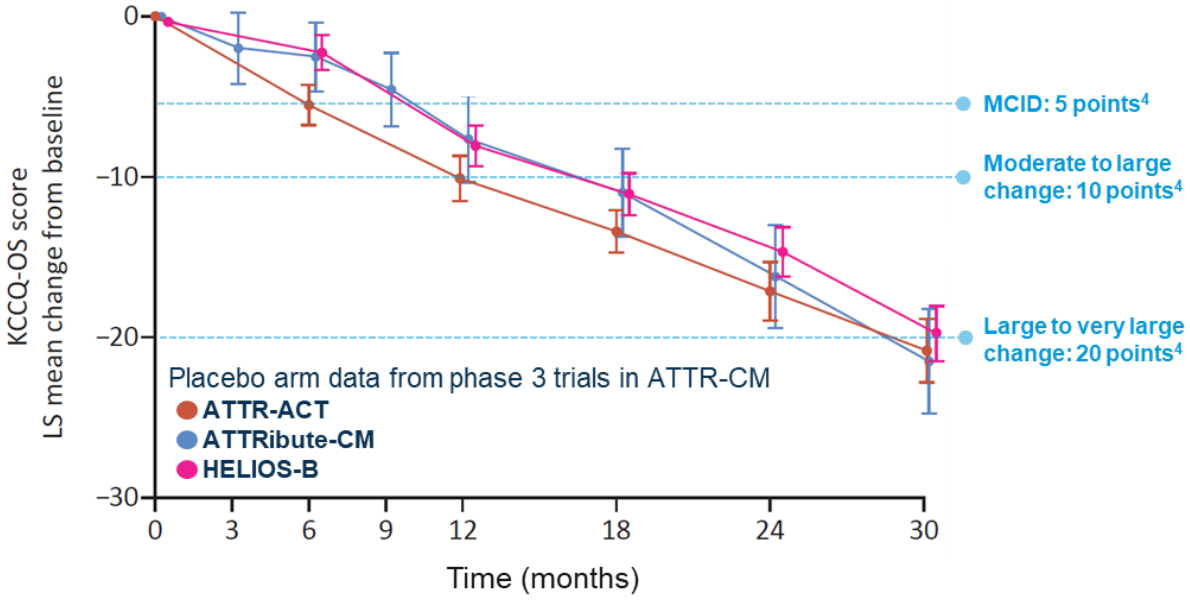
Figure 7: KCCQ scores at diagnosis* in 158 patients with ATTR-CM



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; KCCQ, Kansas City Cardiomyopathy Questionnaire; V122I, valine to isoleucine substitution at amino acid position 122; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy. *KCCQ scores were measured within 12 months of diagnosis. Source: Lane et al. 2021[19]

In addition to being substantial, the HRQoL burden of ATTR-CM worsens over time. Substantial, clinically significant worsening (decrease) in KCCQ-OS score (LS mean reductions of ~20 points) have been observed in placebo-administered patients over 30 months in phase 3 trials in ATTR-CM (Figure 8).[3,10,11]

Figure 8: LS mean change in KCCQ-OS score in placebo-administered patients with ATTR-CM in Phase 3 trials



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least square; MCID, minimal clinically important difference. Note: Data are from placebo-

administered patients from ATTR-ACT, ATTRibute-CM, and HELIOS-B (Phase 3 clinical trials of tafamidis, acoramidis, and vutrisiran, respectively). Source: Fontana et al. 2024[3]; Gillmore et al. 2024[11]; Maurer et al. 2018[10]

A study of French patients with ATTR-CM has also demonstrated the substantial burden of the condition on HRQoL related to specific emotional and social impairments.[13] In that study, patients self-reported the following impacts of their condition:

- Anger or anxiousness (≥50% of patients)
- Worry about their future (>65%)
- Perturbation in their relationship with their partner (≥50%)
- Fear of being a burden on their family and friends (>50%).

From the same study, EuroQol 5-dimension (EQ-5D) domain scores also revealed that in each EQ-5D domain, a large proportion of patients had moderate or severe impairment, which was most substantial in the domains of mobility, usual activities, and pain and discomfort (Table 4).[13]

Table 4: Frequency of moderate or severe impairment by EQ-5D domain in French patients with ATTR-CM

Patient type	Severity of impairment	EQ-5D domain				
		Mobility n (%)	Self-care n (%)	Usual Activities n (%)	Pain or discomfort n (%)	Anxiety/ Depression n (%)
hATTR-CM (n=92)	Moderate	38 (41)	16 (17)	44 (48)	62 (67)	54 (59)
	Severe	26 (28)	12 (13)	20 (22)	19 (21)	7 (8)
wtATTR-CM (n=100)	Moderate	31 (31)	31 (31)	47 (47)	43 (43)	48 (48)
	Severe	41 (41)	1 (1)	21 (21)	28 (28)	5 (5)

EQ-5D, EuroQol 5-dimension; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; wtATTR-CM, wild-type transthryetin amyloidosis with cardiomyopathy. Source: Damy et al. 2022[13]

1.3.2.5 Economic burden

Patients with ATTR-CM require resource-intensive care, suffer productivity losses due to their physical impairment, and frequently need the assistance of caregivers, who themselves face a substantial burden in terms of caregiving time and emotional distress.

HCRU in ATTR-CM

The clinical morbidity resulting from the progressive loss of cardiac function in ATTR-CM has important economic consequences,[25] as patients with ATTR-CM require resource-intensive care, placing a heavy burden on healthcare systems.

Notably, ATTR-CM has a significantly greater burden on healthcare services compared to other forms of heart failure.

- For example, in a retrospective study of healthcare resource utilisation (HCRU) among patients with ATTR-CM and a matched cohort of patients with heart failure due to other causes (n=1,831 in both cohorts; based on healthcare registry data from Denmark, Finland, Norway, and Sweden), over the 3-year period prior to diagnosis and in the first year after diagnosis, patients with ATTR-CM had a higher mean number of:[26]
    - Outpatient visits

    - Hospitalisations
    - Hospitalisation days
    - Surgical procedures
- This trend of increased HCRU in ATTR-CM relative to other forms of heart failure was also observed when the analysis was limited to patients who were alive in the final year of study (2018, including patients diagnosed before 2018 and during 2018).[26]

HCRU in the 3 years prior to diagnosis and in the first year following diagnosis of ATTR-CM has also been characterised in UK patients via a prospective study (Table 5).[19]

Table 5: HCRU in UK patients with ATTR-CM

HCRU Item	Median (IQR)
HCRU over the entire 3-year period prior to diagnosis (n=534)	
Hospital visits*	17 (9, 27)
Inpatient hospitalisations*	3 (1, 5)
HCRU in the year after diagnosis (n=364)	
Outpatient visits	8 (5, 13)
Inpatient hospitalisations	2 (1, 5)
Emergency department attendances	1 (1, 2)

ATTR, transthyretin amyloidosis; HCRU; healthcare resource utilisation; IQR, interquartile range. *Inpatient hospitalisations were also counted as hospital visits. Source: Lane et al. 2019[19]

A retrospective UK study reported costs associated with ATTR-CM (based on patients referred to the King's Health Partners Centre from 2010 to 2018) from symptom onset to diagnosis, and from diagnosis to the end of the data collection period (i.e., 2018).[25] Costs associated with ATTR-CM were substantial both before and after diagnosis and were increased in patients in more severe disease stages at symptom onset and diagnosis, as indicated by the NYHA class (Table 6).[25]

Table 6: Average monthly costs associated with HCRU for UK patients with ATTR-CM based on NYHA class at symptom onset and diagnosis

	NYHA I	NYHA II	NYHA III	NYHA IV
Costs from symptom onset to diagnosis (NYHA class at time of symptom onset)				
Number of patients analysed	7	21	5	1
Mean days from symptom onset to diagnosis	839	817	407	194
Mean cost/patient/month over this period	£130	£334	£571	£4,451

	NYHA I	NYHA II	NYHA III	NYHA IV
Costs from diagnosis to end of the data collection period (NYHA class at time of diagnosis)				
Number of patients analysed	6	14	10	6
Mean days from diagnosis to end of data collection period	657	770	458	909
Mean cost/patient/month over this period	£92	£345	£575	£621

NYHA, New York Heart Association. Note: Costs categories included echocardiogram, new and follow-up cardiology outpatient visit, accident and emergency, heart failure community nurse visit, inpatient admission, and excess hospital bed days. Source: Asher et al. 2022[25]

Caregiver burden

The progressive clinical deterioration and loss of physical capacity that occur in ATTR-CM also limit the autonomy of affected patients. As a result, patients with ATTR-CM frequently need extensive caregiver assistance, which can bear a physical and emotional burden on informal caregivers, thus resulting in deterioration in their HRQoL.

- In a study of patients with ATTR-CM in France, approximately half of the patients required assistance from a family member for caregiving.[13]
- Caregivers for patients with ATTR report increased rates of anxiety and depression.[28,29]
- Caregiver time requirements increase substantially as patients progress in disease.
    - In an international observational study, the median time required per week to provide care for patients with ATTR-CM was 2 hours for caregivers of patients in NYHA class I/II, and 17.5 hours for caregivers of patients in NYHA class III.[12]

Diminished productivity

In addition to requiring high levels of HCRU, patients with ATTR-CM also experience substantial declines in productivity due to the impact of CV-related functional impairments. Notably, physical capacity is strongly impaired in patients with ATTR-CM,[19] and patients have reported physical exertion and fatigue resulting from activities of daily living are severely burdensome.[96] The ability to perform work duties is substantially impaired as a result, and cross-sectional online surveys have demonstrated this decreased work productivity in patients with ATTR-CM:

Findings from a study of 33 patients with ATTR in the US:[27,28]

- 60% of patients with ATTR-CM reported being unemployed.
- 71.4% of patients with cardiomyopathy and polyneuropathy reported being unemployed.
- 50.1% of planned work hours were missed in working patients with ATTR.

Findings from a survey of working-age Spanish patients (n=16) with ATTR (mean age of 49.3 years [SD: 12.5]):[28]

- Only 25% of patients surveyed reported being employed.

1.3.2.6 Assessment of disease severity and monitoring of progression

Due to the progressive and fatal nature of ATTR-CM, establishing an accurate prognosis and monitoring disease progression are crucial for informing decisions regarding disease management.

Due to the progressive and fatal nature of ATTR-CM, assessment of disease severity at diagnosis and subsequent monitoring of disease progression are critical for informing decisions to use interventions that aim to limit disease progression and mortality risk. The initial severity and ongoing progression of ATTR-CM are typically assessed using measures related to:[103-105]

Clinical and functional status:

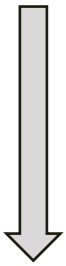
- CV hospitalisation rate, loop diuretic dose intensification, 6-MWT distance, HRQoL (e.g., KCCQ-OS score), and NYHA class (Table 7)

Cardiac morbidity:

- Laboratory biomarkers (including serum N-terminal prohormone of brain natriuretic peptide [NT-proBNP], troponin T, and NAC stage [Table 8])
- Imaging and electrocardiography (ECG) parameters (including left ventricular wall thickness, stroke volume, ejection fraction, global longitudinal strain, diastolic functioning grade, and identification of conduction disturbances).

NYHA class (which assesses patients' functional status based on the level of physical activity that gives rise to heart failure symptoms) is a mainstay measure of disease severity in the initial assessment and ongoing monitoring of patients with heart failure (Table 7),[106] including heart failure due to ATTR-CM, and it is predictive of both HRQoL and mortality in patients with ATTR-CM (i.e., higher classes are associated with worse survival prognosis and worse HRQoL).[22,102,107]

Table 7: NYHA functional classification of heart failure

NYHA class	Criteria	
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or shortness of breath.	**Worsening disease** 
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath, or chest pain.	
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath, or chest pain.	
IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort.	

NYHA, New York Heart Association. Source: American Heart Association[106]

NAC staging, which is based on patients' serum NT-proBNP level and estimated glomerular filtration rate (eGFR), is also used for initial assessment and ongoing monitoring of patients, as it is also predictive of both HRQoL and mortality in patients with ATTR-CM (i.e., higher stages are associated with worse survival prognosis and worse HRQoL; Table 8).[14,102]

Table 8: NAC staging of ATTR-CM

Stage	Criteria	
I	NT-proBNP ≤3,000 ng/L AND eGFR ≥45 ml/min	**Worsening disease** 
II	Remainder of patients not in stage I or III	
III	NT-proBNP >3,000 ng/L AND eGFR <45 ml/min	

ATTR, transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide. Note: Both specified criteria (i.e., for NT-proBNP and eGFR) need to be met for a patient to be categorised in stage I or III. Source: Gillmore et al. 2018[14]

Serum NT-proBNP, a component of the NAC staging system for ATTR-CM, is itself a strong independent prognostic indicator of mortality when assessed either as a static, cross-sectional measure of disease severity or as a longitudinal measure of change in disease severity over time.

Analyses from the THAOS registry in patients with ATTR-CM demonstrated:

- In patients with NT-proBNP (n=550) and BNP (n=1,079) levels available at study enrolment, there was a statistically significant difference in 3-year survival rate according to NT-proBNP/BNP levels:[108]
    - NT-proBNP/BNP <325 ng/L: 3-year survival = 98.1%
    - NT-proBNP/BNP >325 ng/L: 3-year survival = 70.1%
- Serum NT-proBNP level at the time of study enrolment was an independent predictor of survival.[108]
    - In a multivariate analysis, after controlling for all other independent predictors of survival, patients in the top quartile with respect to serum NT-proBNP levels at enrolment had an approximately 50% relative reduction in survival probability versus all other patients in the analysis cohort.[108]

In regards to longitudinal changes in NT-proBNP, in an analysis of patients with ATTR-CM seen at the NAC (n=1,598), those who showed worsening of serum NT-proBNP levels (defined as an increase of >700 ng/L in absolute terms and >30% in relative terms) from diagnosis to 1 year post-diagnosis, versus those who did not experience such worsening, showed an approximately 1.8-fold increase in mortality risk from 1 year post-diagnosis onward.[2]

Given the role of loop diuretics for symptomatic management of worsening heart failure, loop diuretic dose has also emerged as a useful indicator of disease severity in ATTR-CM.[1] For example:

- In one analysis of data from the French National Health Data System (SNDS), it was found that patients with ATTR-CM receiving a lower daily dose of loop diuretics (furosemide <20 mg or bumetanide <0.5 mg) had a median survival of 5 years, while those receiving a higher daily dose (furosemide ≥120 mg or bumetanide ≥3 mg) had a median survival of 1.2 years.[1]
- In a single-centre study of 309 patients with ATTR-CM, daily dose of furosemide at baseline (first clinical visit of the study) was also found be a strong predictor of mortality, with a 1.43-fold increase in mortality hazard (adjusted HR: 1.43 [95% CI: 1.06, 1.93]; P=0.02) observed for every 1-mg/kg increase in daily furosemide dose.[22]

Longitudinal changes in daily loop diuretic dose also have prognostic value in patients with ATTR-CM, as demonstrated in a retrospective multinational analysis.[2] Specifically:

- It was found that patients (seen at the NAC; n=1,598) experiencing outpatient diuretic intensification (ODI; defined as any increase in loop diuretic dose [furosemide equivalent]) from diagnosis to one year post-diagnosis, had a 1.88-fold increase (vs. patients without ODI) in risk of mortality from one year post-diagnosis onward.[2]
- In a validation cohort of patients with ATTR-CM (n=677) from six other specialist centres (one in the US, one in Austria, and four in Italy) assessing the same parameters regarding longitudinal change in ODI as described above, a similar 2.05-fold increase in mortality risk was observed.[2]

1.3.2.7 Diagnosis

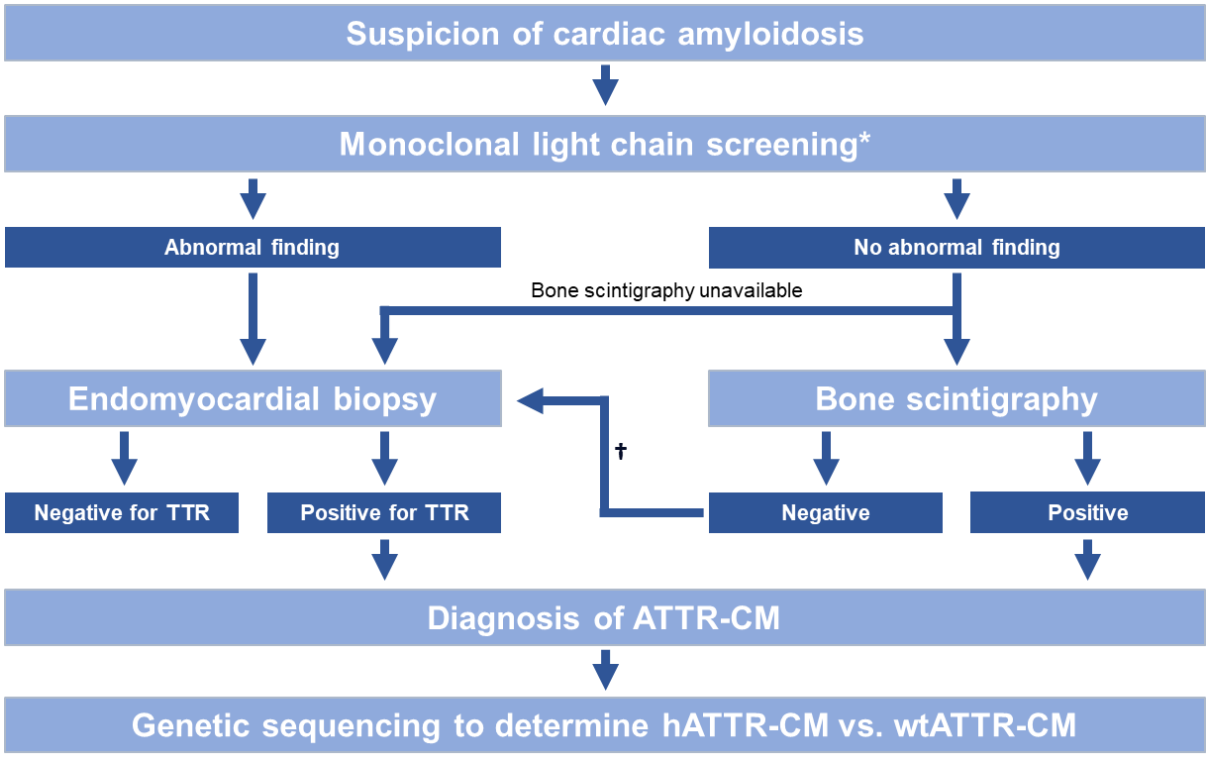
Consensus recommendations regarding a diagnostic algorithm for ATTR-CM were published by the Amyloidosis Research Consortium in 2019.[104] In addition, the 2023 American College of Cardiology (ACC) guidelines for cardiac amyloidosis align with the diagnostic recommendations presented by the Amyloidosis Research Consortium.[109]

Both guidelines note that diagnosis of ATTR-CM is often delayed and that clinical suspicion is important in the diagnostic process.[109] The ACC and Amyloidosis Research Consortium diagnostic guidelines agree to such an extent that they can both be summarised in one schematic (Figure 9), highlighting the current consensus in the diagnosis of ATTR-CM.

In summary:

- After observing signs and symptoms that lead to clinical suspicion of ATTR-CM and excluding a diagnosis of light chain amyloidosis via monoclonal protein testing, bone scintigraphy should be performed if the procedure is available.[104,109]
    - If bone scintigraphy reveals the presence of amyloid deposits in the heart, this (together with a negative screen for light chain amyloidosis) confirms a diagnosis of ATTR-CM.[104,109]
- If results of monoclonal protein testing do not reject the possibility of light chain amyloidosis, if bone scintigraphy is not available, or if scintigraphy is negative but cardiac amyloidosis is still suspected, endomyocardial biopsy must be performed to assess for the presence of amyloid deposits (and identify the amyloidogenic protein present, whether TTR or light-chain) in the heart.
    - If endomyocardial biopsy is performed, a positive biopsy result for TTR confirms ATTR-CM, irrespective of prior findings (e.g., even when monoclonal protein testing does not yield a negative result).
    - In the case of endomyocardial biopsy, Congo Red staining is the gold standard for diagnosis and can exhibit specificity of up to 100% for the detection of amyloid deposits,[18,104,109] noting that amyloid deposits must be further tested (via immunofluorescence or mass spectrometry) to confirm their origin (TTR or light chain).[104,109]
- After ATTR-CM is confirmed, genetic testing can be performed to assess whether the condition is of hereditary (hATTR) or wild-type (wtATTR) origin.

Figure 9: Diagnostic algorithm for suspected ATTR-CM



ATTR, transthyretin amyloidosis; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy; TTR, transthyretin. *A negative monoclonal light chain screen excludes light chain amyloidosis. †Biopsy can be performed after a negative result from bone scintigraphy if clinical suspicion of ATTR-CM is still high. Sources: Kittleson et al. 2023[109]; Maurer et al. 2019[104]

Pathway to diagnosis and subsequent treatment for ATTR-CM in the UK

A Highly Specialised Service (HSS) is in place for amyloidosis management in the UK.[110] The NAC at the Royal Free Hospital has led innovation in diagnostic testing and treatment internationally. Initial consultations, diagnosis, and the prescription of therapies for patients with ATTR-CM are overseen by the NAC. Similarly, patients with ATTR-CM are also seen for follow-up care at the NAC.

From 2025 onwards, NHS England is considering an amyloidosis service networked model of care (i.e., the UK Amyloidosis Network [UKAN]),[111] which is proposed to consist of the NAC plus four regional centres. If the UKAN is established, it is anticipated that prescribing and routine follow-up may occur at any one of these centres, providing greater convenience for patients and improved efficiency of coordinated care.

1.3.3 ATTR-CM treatment landscape in the UK

1.3.3.1 Current treatments

Currently, tafamidis 61 mg is the only MHRA-approved treatment option available for patients with ATTR-CM. Additional medicines used for the management of heart failure-related symptoms are also available.

Tafamidis is currently the only MHRA-approved option available for treating ATTR-CM, while certain other conventional therapies may be used as background treatments for the management of heart failure-related symptoms. Limitations with tafamidis are discussed further in Section 1.3.3.2.

Tafamidis

Tafamidis 61 mg (equivalent to 80 mg [4x20 mg] tafamidis meglumine), commercialised as VYNDAQEL, is a TTR stabiliser that acts by binding to the thyroxine-binding site on TTR, thereby stabilising TTR and slowing the dissociation of TTR tetramers into monomers.[10] As a result of its mechanism of action, tafamidis increases concentrations of serum TTR.[112] Tafamidis is administered orally once per day.[30]

Tafamidis was evaluated in the multicentre, international, double-blind, placebo-controlled, phase 3 trial ATTR-ACT.[10] ATTR-ACT enrolled 441 patients with ATTR-CM, who were randomised to receive daily tafamidis meglumine 80 mg (n=176), daily tafamidis meglumine 20 mg (n=88), or placebo (n=177) for 30 months.[10] Compared to patients in the placebo arm, patients receiving tafamidis (pooled analysis of tafamidis meglumine 20 mg and 80 mg doses) had more favourable outcomes on a composite endpoint of all-cause mortality and frequency of CV-related hospitalisation (primary endpoint), as well as on other secondary endpoints, namely 6-MWT distance and KCCQ-OS score. Over 30 months, tafamidis use led to a significant decrease in all-cause mortality compared to placebo (HR: 0.70; 95% CI: 0.51, 0.96). Nonetheless, despite the benefit demonstrated versus placebo in ATTR-ACT, efficacy limitations associated with tafamidis currently leave patients with ATTR-CM with unmet treatment-related needs (described in Section 1.3.3.2). Furthermore, ATTR-ACT was completed in 2018,[113] meaning the patient population in ATTR-ACT is not representative of the contemporary ATTR-CM population that exists currently, as greater disease awareness and improved supportive care have led to patients being healthier at the time of diagnosis in the present day, with less advanced disease progression. For these reasons, results from the ATTR-ACT trial are less generalisable to current clinical practice than results from trials conducted in contemporary ATTR-CM patient populations. There is therefore increased uncertainty regarding real-world therapeutic outcomes with tafamidis.[114]

Conventional background medication for symptomatic relief

Various approaches to alleviate general cardiac symptoms may also be used in the context of ATTR-CM, including:[91,109,115,116]

- Diuretics (e.g., aldosterone antagonists and loop diuretics (e.g., furosemide)
- Anticoagulants for patients who also have atrial fibrillation
- Non-drug approaches (i.e., dietary salt reduction and compression stockings for oedema).

Due to the TTR amyloid deposits in the myocardium, however, many other conventional medications used for heart failure symptoms and arrhythmia are not tolerated by patients with ATTR-CM.[91]

- Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers are not well tolerated due to the low blood pressure often preexisting in patients with ATTR-CM, as these therapies can exacerbate hypotension.[91,115]
- Calcium channel blockers and digoxin are also generally contraindicated in patients with ATTR-CM, due to effects that likely arise from the affinity of these therapies for amyloid fibrils.[91] Specifically, increased binding of calcium channel blockers to amyloid fibrils is thought to promote high-degree heart block and have negative inotropic effects that may result in shock, whereas digoxin has been shown to have affinity for amyloid deposits *in vitro*, which could explain observations of abrupt cardiac rhythm disturbance and death in patients with cardiac amyloidosis treated with digoxin.[91]

1.3.3.2 Limitations associated with tafamidis

Patients treated with tafamidis continue to experience worsening in physical capacity and HRQoL relative to their respective pre-treatment baseline levels, as well as excess mortality, with limited treatment benefit in some patient types.[10]

A targeted literature review demonstrated that the majority (~40–70%) of tafamidis-treated patients worsen in disease within 6–12 months from initiation and that mortality remains high in real-world contemporary ATTR-CM patient populations currently treated with tafamidis.[36]

Efficacy limitations in ATTR-ACT

Tafamidis is a TTR stabiliser and acts downstream of hepatic TTR production in the ATTR-CM disease pathway.

In ATTR-ACT, patients with ATTR-CM treated with tafamidis continued to experience worsening in physical capacity, HRQoL, and cardiac injury relative to their pretreatment baseline, as well as substantial rates of mortality. Additionally, the benefits of tafamidis treatment in some patient types were limited.

Progressive, irreversible worsening in disease relative to baseline:

- On average, patients treated with tafamidis consistently declined in 6-MWT distance over 30 months relative to pretreatment baseline (LS mean reduction of 55 metres),[117] representing clinically relevant loss of physical capacity.[10]
- On average, patients treated with tafamidis consistently declined in KCCQ-OS score over 30 months relative to pretreatment baseline (LS mean decrease of 7 points),[117] representing a clinically relevant decline in HRQoL.[10]
- On average, NT-proBNP levels increased over 30 months relative to pretreatment baseline in tafamidis-treated patients (mean increase in NT-proBNP: tafamidis 20 mg=2,542.2 ng/L; tafamidis 80 mg=1,371 ng/L), meaning cardiac injury continued to worsen.[31]

Substantial mortality:

- In tafamidis-treated patients, mortality at Month 30 remained high (29.5%), despite the survival advantage shown versus placebo.[10]

Limited benefit from treatment in some patient types:

- Tafamidis-treated patients in NYHA III had a significantly higher rate of CV-related hospitalisations compared to placebo-administered patients, and decreased magnitude of treatment effect on mortality compared to patients in NYHA I/II.[10]
- In patients with the worst levels of physical capacity at baseline (quartile of NYHA III patients with the lowest 6-MWT distance [<269 metres]), tafamidis treatment was associated with a higher frequency of CV-related hospitalisations per year compared to placebo (tafamidis: 0.93; placebo: 0.73).[118]

Efficacy limitations in in real-world use

A targeted literature review demonstrated that the majority (~40–70%) of tafamidis-treated patients worsen in disease within 6–12 months from initiation, and that mortality remains high in real-world contemporary ATTR-CM patient populations currently treated with tafamidis.[36]

Patients with ATTR-CM treated with tafamidis in real-world clinical practice continue to experience clinically evident cardiac worsening (reflected by CV events, CV hospitalisations,

mortality, and increased rates of diuretic initiation) in addition to showing biochemical signals of disease progression (reflected by elevated NT-proBNP levels and decreased eGFR).[119]

Specifically, a real-world analysis of a United States electronic health records database, in which outcomes were evaluated in 813 tafamidis-treated patients with ATTR-CM (median follow-up: 354 days), showed the following:[119]

- Substantial rates of diuretic initiation in the follow-up period in patients not on diuretics at the start of tafamidis treatment (23.4% of patients who were not on diuretics in the 365-day baseline period prior to initiating treatment with tafamidis).
- Cardiac worsening in the follow-up period in a substantial proportion of patients (52.6% of patients; 793.9 cardiac worsening events per 1,000 person years).
    - Cardiac worsening was defined as having occurred if a patient experienced any of the following: myocardial infarction, deep vein thrombosis, pulmonary embolism, stroke, transition to a worse heart failure stage (based on NYHA, National Amyloidosis Centre [NAC], or ACC/American Heart Association [AHA] staging systems), CV-related hospitalisation, aortic valve replacement, aortic stenosis, revascularisation, or arrhythmia.
    - Among cardiac worsening events, CV hospitalisation occurred in 36.2% of patients, with an incidence rate of 418.5 hospitalisations per 1,000 person years.
- Substantial mortality in the follow-up period (7.1% of patients; 63.4 deaths per 1,000 person years, which is 10 times higher than the mortality rate seen in >65-year-olds with heart failure [not specifically due to ATTR-CM] in the US[120]).
- Worsening biomarkers indicative of cardiac injury, as demonstrated by a mean increase of 1,612 ng/L in NT-proBNP from pretreatment baseline up to 1 year after tafamidis treatment initiation. Among patients with available data, 61% worsened (i.e., had increased NT-proBNP) over this period.
- Decreased kidney function, as demonstrated by a mean decrease of 4.5 mL/min/1.73m^2 in estimated glomerular filtration rate (eGFR) from pretreatment baseline up to 1 year after tafamidis treatment initiation. Among patients with available data, 62% worsened (i.e., had decreased kidney function) over this period.

Non-clinical limitations of tafamidis use

Risks related to the supply of tafamidis have been noted, as the availability of tafamidis has previously been impacted by supply disruptions in France (lasting for >1 year and necessitating importation from other countries) and in Korea.[121,122]

1.3.3.3 Unmet therapeutic needs

Considering the limitations of tafamidis, which include remaining excess mortality in tafamidis-treated patients, continued worsening in physical capacity, HRQoL, and cardiac injury from pretreatment baseline, and limited efficacy in some patient types, there is a need for additional therapies for ATTR-CM.

Considering the limitations of tafamidis (Section 1.3.3.2), there is a need for therapies that:

- Have a novel mechanism of action that targets the underlying cause of disease by rapidly limiting TTR protein production,
- Halt or significantly reduce disease-related worsening in HRQoL, physical capacity, and cardiac injury,
- Address excess mortality by improving survival,

- Are consistently efficacious across all patient types, and
- Have a nonburdensome, infrequent method of administration that is easily adhered to by older, polymedicated adults.

1.3.3.4 Place of vutrisiran in therapy

Vutrisiran is anticipated to be a new standard-of-care treatment for all patients with ATTR-CM in the UK, including those patients currently treated with tafamidis with inadequate response

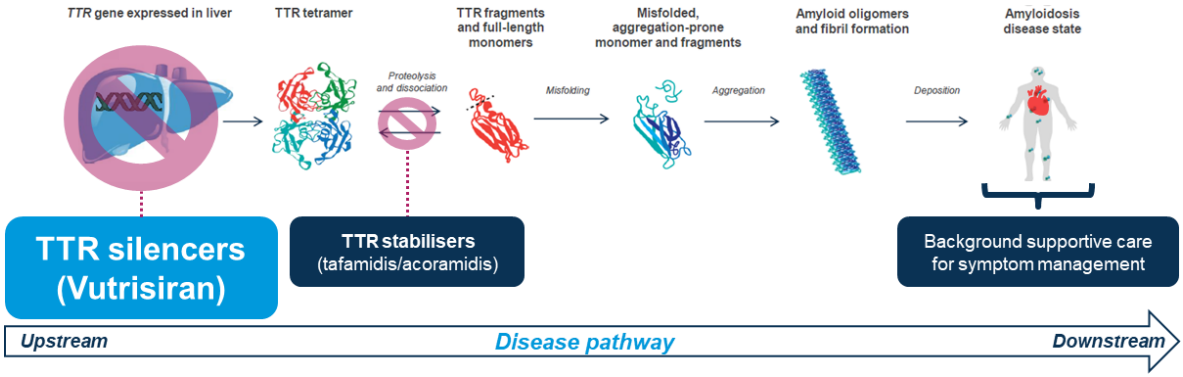
By virtue of the rapid and sustained knockdown of TTR resulting from vutrisiran treatment, vutrisiran is anticipated to halt or significantly slow disease progression and reduce morbidity and mortality in all ATTR-CM patient types.

Vutrisiran, an RNA interference (RNAi) therapeutic that is administered subcutaneously Q3M, rapidly reduces serum TTR levels by promoting catalytic degradation of RNA that encodes for variant and wild-type TTR protein (the cause of amyloid deposits in ATTR-CM).[4]

As vutrisiran targets the expression of the TTR gene in the liver—the main source of TTR production—it acts upstream from TTR stabilisers, which do not impact TTR production (Figure 10).[37]

The rapid and sustained knockdown of serum TTR by vutrisiran is anticipated to lead to disease modification, resulting in reduced morbidity and mortality.

Figure 10: Comparison of vutrisiran versus TTR stabilisers in ATTR



ATTR, transthyretin amyloidosis; TTR, transthyretin.

An overview of the current UK treatment landscape in ATTR (including hATTR-PN and ATTR-CM), and the proposed treatment landscape after introduction of vutrisiran, is depicted in Figure 11.

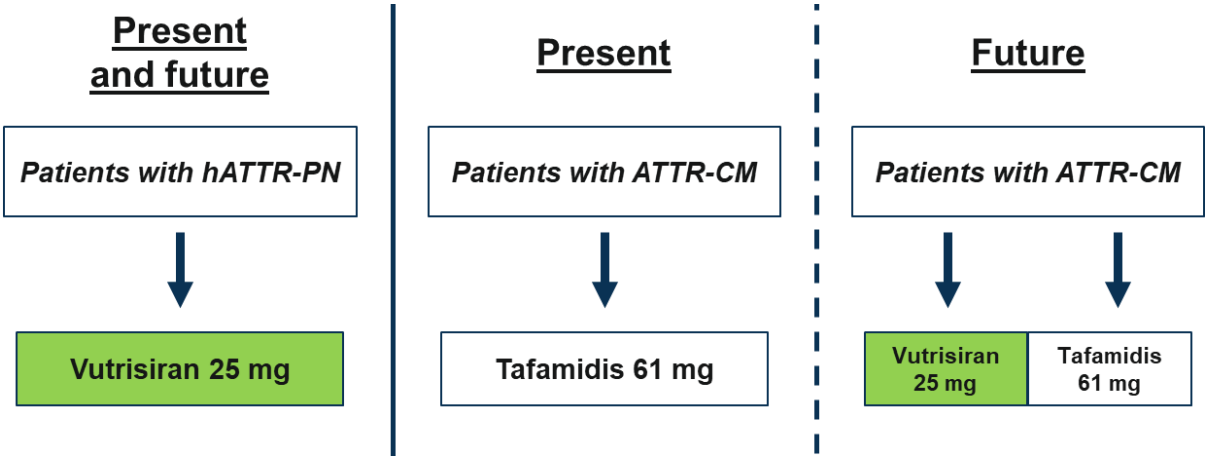
In ATTR-CM, tafamidis is currently the only MHRA-approved and NICE-recommended therapy, and is thus by default the current standard-of-care therapy in the UK; however, as described in Section 1.3.3.2, there are a number of limitations associated with tafamidis.

As detailed in Section 2, vutrisiran addresses the unmet needs in patients with ATTR-CM, including those unmet needs presented by tafamidis, namely, continued worsening in physical capacity, HRQoL, and cardiac injury, remaining excess mortality, and limited treatment benefit in some patient types (Section 1.3.3.2).

The anticipated position of vutrisiran in the ATTR-CM treatment landscape is as a new standard-of-care treatment for all patients with ATTR-CM in the UK, including those patients currently treated with tafamidis with inadequate response.

Based on the anticipated lack of cost-effectiveness of combination use of two branded medicines (i.e., vutrisiran and tafamidis), in view of current NICE STA cost-effectiveness thresholds and clinician intentions for the use of vutrisiran once it is available, vutrisiran is anticipated to be positioned as a monotherapy at launch.

Figure 11: Current and anticipated ATTR treatment landscape in the UK



ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; MHRA, Medicine and Healthcare Regulatory Agency; NICE, National Institute for Health and Care Excellent. Note: Patisiran and inotersen are also MHRA-approved and NICE-recommended for hATTR-PN.[123-126]

1.4 Equality considerations

Health inequalities exist among patients with ATTR-CM, as the V122I TTR gene variant disproportionately affects individuals of African descent, and is associated with higher mortality than other forms of ATTR-CM (Section 1.3.2.3).

The V122I TTR gene variant is understood to have originated in West Africa,[88,89] and a high proportion of current carriers of this variant are of African descent. For example, an analysis of genotypes from the UK Biobank from 2006–2010 (487,327 genotyped participants) revealed that out of 387 identified carriers of the V122I TTR gene variant, 80.6% were of self-reported African descent.[127]

Given the disproportionate prevalence of the V122I TTR gene variant, and given that this variant often expresses as ATTR-CM, the burden of ATTR-CM is notable in populations of African descent.

2 Clinical effectiveness

In the phase 3 HELIOS-B trial in patients with ATTR-CM, vutrisiran treatment led to statistically significant and clinically meaningful benefits versus placebo across all primary and secondary endpoints in both the overall population and the monotherapy population, including the:

- Primary endpoint of the composite outcome of all-cause mortality (ACM) and recurrent CV events over up to 36 months.[3]
- Secondary endpoints of change from baseline to Month 30 in 6-MWT and KCCQ-OS score, ACM up to Month 42, and percentage of patients stable/improved in NYHA class from baseline to Month 30.[3]

Patients treated with vutrisiran maintained their baseline HRQoL and physical capacity (via analyses of observed values), in addition to preserving baseline cardiac well-being over 30 months.[3]

Vutrisiran demonstrated consistent efficacy versus placebo across all predefined subgroups.[3]

2.1 Identification and selection of relevant studies

See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

HELIOS-B was a phase 3, randomised, double-blind, placebo-controlled, multicentre study that evaluated the efficacy and safety of vutrisiran in patients with ATTR-CM (Table 9).[128,129] It is the only study used to inform the economic analysis in Section 3.

Table 9: Clinical effectiveness evidence

Item	Description
Study	HELIOS-B: a study to evaluate vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy (NCT04153149)[129]
Study design	Randomised, double-blind, placebo-controlled, multicentre study
Population	Patients with ATTR-CM (N=654)
Intervention(s)	Vutrisiran
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes

Item	Description
Reported outcomes specified in the decision problem	The outcome measures to be considered include: • Overall survival • Cardiovascular-related mortality • Cardiac function (such as global longitudinal strain BNP level) • Cardiovascular-related hospitalisation • Functional exercise capacity • Signs and symptoms of heart failure (such as breathlessness) • Adverse effects of treatment • Health-related quality of life (of patients and carers).
All other reported outcomes	As described in Table 1, results from outcomes that incorporate ODI have been included in the submission.

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ODI, oral diuretic intensification.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

HELIOS-B methodology is summarised in Table 10, and described in further detail below.

Table 10: HELIOS-B methodology overview

Item	Description
Trial number	HELIOS-B (NCT04153149)[129]
Location	HELIOS-B was conducted at 87 sites across 26 countries. Countries with ≥10 patients included the US (n=165 [25.2%]), United Kingdom (n=151 [23.1%]), Spain (n=64 [9.8%]), Germany (n=37 [5.6%]), France (n=29 [4.4%]), Australia (n=28 [4.3%]), Japan (n=25 [3.8%]), Netherlands (n=22 [3.4%]), Portugal (n=17 [2.6%]), Argentina (n=16 [2.4%]), Sweden (n=15 [2.3%]), Norway (n=14 [2.1%]), Denmark (n=12 [1.8%]), Belgium (n=11 [1.7%]), and Austria (n=10 [1.5%]).[130]
Trial design	Phase 3 randomised, placebo-controlled study. Patients were randomised 1:1 to receive vutrisiran or placebo. Primary and secondary endpoint analyses were conducted in the overall population (which included a proportion of patients receiving background tafamidis at baseline) and separately in the monotherapy population (those patients in the overall population who were not receiving tafamidis at baseline).

Item	Description
Eligibility criteria for participants	**Key inclusion criteria:** • Diagnosis of ATTR-CM (hATTR or wtATTR) • Medical history of HF, with ≥ 1 prior hospitalisation for HF OR clinical evidence of HF **Key exclusion criteria:** • NYHA Class IV • NYHA Class III AND at high risk (NAC stage III*) • PND score IIIA, IIIB, or IV
Trial drugs	**Overall population (i.e., including patients receiving background tafamidis at baseline):** • Vutrisiran: n=326 • Placebo: n=328 **Monotherapy population (i.e., no background tafamidis at baseline):** • Vutrisiran: n=196 • Placebo: n=199
Primary outcome	**The composite outcome of ACM and recurrent CV events over up to 36 months, in the overall population and monotherapy population considered separately.** • ACM includes death, heart transplantation, and receipt of a ventricular assist device. • CV events include CV hospitalisations and urgent heart failure visits.
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints (in the overall population and monotherapy population considered separately):** • Change from baseline to Month 30 in 6-MWT • Change from baseline to Month 30 in KCCQ-OS • ACM over up to 42 months • Proportion of patients who are stabilised or improved in NYHA class from baseline to Month 30.
Preplanned subgroups	• Age (<75 vs. ≥75 years) • Tafamidis use at baseline (yes vs. no; only in the overall population) • ATTR disease type (hATTR vs. wtATTR) • NYHA class (I/II vs. III) • Baseline NT-proBNP (≤2,000 ng/L vs. >2,000 ng/L)

6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; hATTR, hereditary transthyretin amyloidosis; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; wtATTR, wild-type transthyretin amyloidosis; *NAC stage III is classified as NT-proBNP >3000 ng/L and eGFR <45 ml/min/1.73m^2.

2.3.1 Study design

HELIOS-B was a phase 3, randomised, double-blind, placebo-controlled, multicentre study that evaluated the efficacy and safety of vutrisiran in patients with ATTR-CM.[128,129] In HELIOS-B, a total of 655 participants were randomised 1:1 to receive 25 mg of vutrisiran (n=326) or placebo (n=329; one patient was randomised to placebo but did not receive a dose due to withdrawal by patient) Q3M via subcutaneous (SC) injection.[128,129]

Randomisation was stratified by:[128]

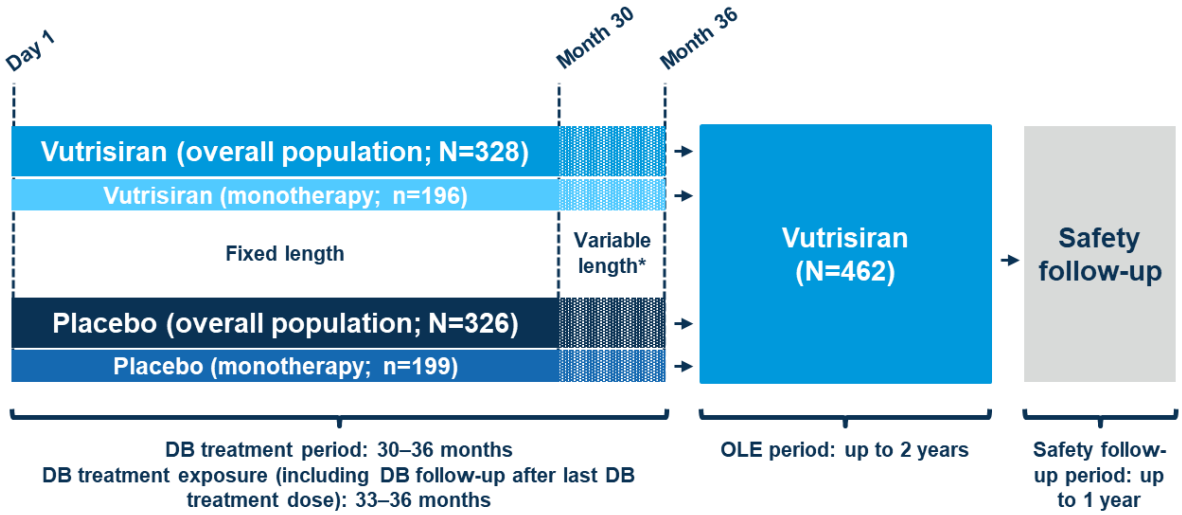
- Baseline tafamidis use (yes vs. no)
- ATTR type (hATTR vs. wtATTR)
- NYHA class and age (class I/II and <75 years old versus all other patients [i.e., all patients in NYHA class III and patients in NYHA class I/II who were >75 years old])

The double-blind period of HELIOS-B was up to 36 months in duration; specifically, patients were to receive double-blind treatment (vutrisiran or placebo) for 30 months after the last enrolled patient in the study was randomised or for 33 months after their own randomisation, whichever occurred first, and then undergo an additional 3 months of double-blind follow-up after their last double-blind treatment dose. Thereafter, patients were eligible to enter the open-label extension (OLE) portion of the study, during which all patients (regardless of original randomisation) were to receive treatment with vutrisiran every 3 months for up to 2 years, beginning immediately at the conclusion of double-blind follow-up.

The 654 patients randomised to vutrisiran or placebo made up the overall population. This population included both patients receiving background tafamidis at baseline and patients not receiving background tafamidis at baseline within each treatment arm. Within the overall population, a separate monotherapy population (N=395; vutrisiran: n=196; placebo: n=199) was defined, comprising patients in the overall population who were not receiving tafamidis at baseline. Tafamidis drop-in use was allowed in the monotherapy population, which is described further in Section 2.6.9. As described in Section 2.3.5, all primary and secondary endpoints were assessed in the overall population and also separately in the monotherapy population.

An overview of the HELIOS-B trial design is provided in Figure 12.

Figure 12: HELIOS-B trial design



DB, double blind; OLE, open-label extension. *Patients were to receive double-blind treatment for 30 months after the last enrolled patient in the study was randomised or for 33 months after their own randomisation, whichever occurred first, and then undergo an additional 3 months of double-blind follow-up after their last double-blind treatment dose, such that the duration of DB exposure ranged from 33–36 months.

2.3.1.1 Overview of comparator choice in HELIOS-B

A formal comparison of vutrisiran versus tafamidis within HELIOS-B was deemed to be infeasible, due to the timing of the trial and the availability of tafamidis. HELIOS-B started on November 26, 2019,[129] prior to the approval of tafamidis in multiple countries and regions such as Canada,[131] Australia,[132], and the EU,[33,133] and only shortly after its approval in the US.[117] Thus, from a global perspective, the comparison of vutrisiran versus tafamidis was not relevant for informing real-world treatment decisions at the time of HELIOS-B initiation, given the limited worldwide availability of tafamidis in real-world practice at that time.

[redacted] Additionally, the number of patients required for a powered head-to-head comparison to assess the non-inferiority of vutrisiran versus tafamidis on the primary endpoint used in HELIOS-B (the composite of ACM and recurrent CV events) was estimated to exceed 7,000, under the assumption of equivalent efficacy between vutrisiran and tafamidis, and specifying that non-inferiority could be declared if the upper bound of the 95% CI of the hazard ratio (vutrisiran vs. tafamidis) for the primary endpoint was less than 1.1. A study cohort of this size would not have been feasible to recruit, considering the low prevalence of ATTR-CM. For example, it took approximately 5.5 years to recruit the 655 patients who participated in HELIOS-B and complete the double-blind portion of the trial (November 2019 to June 2024).[129] During this time period, recruitment of a larger study cohort for a powered comparison of vutrisiran versus tafamidis would have been hindered by competing recruitment efforts for other ongoing clinical trials, including ATTRibute-CM, with 632 patients and a study duration of approximately 4 years (March 2019 to May 2023),[136] Cardio-TTRansform, with 1,438 patients and a duration of approximately 5 years (March 2020 to June 2025 [estimated completion]),[137] and APOLLO-B, with 360 patients and a duration of approximately 3 years (September 2019 to June 2022).[138] Notably, like HELIOS-B, all three of these other randomised trials were designed with placebo as the comparator.

2.3.2 Patient eligibility

Eligibility criteria for HELIOS-B are presented in Table 11.

Table 11: Eligibility criteria for HELIOS-B

Inclusion criteria

• 18–85 years of age
• Documented diagnosis of ATTR-CM, classified as either hATTR-CM or wtATTR-CM:
  ○ hATTR-CM was diagnosed based on meeting all the following criteria:
  ▪ Documentation of a TTR pathogenic mutation consistent with hATTR.
  ▪ Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
  ▪ 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 by technetium (^{99m}Tc) scintigraphy (DPD-Tc, PYP-Tc, or HMDP) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
  ▪ If evidence of an MGUS based on serum and urine protein electrophoresis and serum free light chain presented, documentation of TTR protein in tissue with immunohistochemistry or mass spectrometry was required.
  ○ wtATTR-CM was diagnosed based on meeting all the following criteria:
  ▪ Documentation of absence of pathogenic TTR mutation.

- Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
- Amyloid deposits in cardiac tissue with TTR protein identification by immunohistochemistry OR by mass spectrometry OR by technetium (^{99m}Tc) scintigraphy (DPD-Tc, PYP-Tc, or HMDP) with Grade 2 or 3 cardiac uptake, if MGUS had been excluded.
- If evidence of an MGUS based on serum and urine protein electrophoresis and serum free light chains presented, the following was required: documentation of TTR protein in cardiac tissue with immunohistochemistry or mass spectrometry; OR documentation of TTR protein in noncardiac tissue (e.g., fat pad aspirate, salivary gland, median nerve connective sheath) with immunohistochemistry or mass spectrometry and Grade 2 or 3 cardiac uptake on technetium scintigraphy.

- One prior hospitalisation for heart failure (not due to arrythmia or conduction disturbance treated with a permanent pacemaker) or clinical evidence of heart failure manifested by signs and symptoms of volume overload or elevated intracardiac pressure that currently requires treatment with a diuretic.
- If naïve to tafamidis at screening, must not be planning to take tafamidis in the 12 months following randomisation.
- In stable clinical status with no CV-related hospitalisation in the 6 weeks prior to randomisation.
- NT-proBNP levels of >300 ng/L and <8500 ng/L (>600 ng/L and <8500 ng/L for patients with permanent or persistent atrial fibrillation).
- Able to walk 150 metres or more on the 6-MWT at screening.
- KPS ≥60%.

Exclusion criteria

Disease-specific conditions

- Primary amyloidosis (AL amyloidosis) or leptomeningeal amyloidosis.
- NYHA class IV heart failure OR NYHA class III heart failure and NAC stage III.
- PND score of IIIA/IIIB/IV (required a cane or stick to walk or was in a wheelchair due to polyneuropathy).

Laboratory assessments

- Any of the following laboratory values at screening: AST or ALT >2.0 x ULN, total bilirubin >2.0 x ULN, INR >1.5 [INR >3.5 for patients on anticoagulants]).
- eGFR of <30 mL/min/1.73 m^2.
- HIV infection or a current chronic infection with hepatitis B or C viruses.

Prior/concomitant therapy

- Naïve to tafamidis and was planned or anticipated to begin taking tafamidis during screening or in the first 12 months after randomisation.
- Previously received revusiran, patisiran, or inotersen or was participating in a gene therapy trial for hATTR.
- Currently receiving diflunisal, doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid (a 30-day washout period for these agents permits inclusion).
- Unwilling to avoid concurrent treatment with diflunisal, doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid or other TTR-lowering agents (excluding study treatment).
- Currently taking part or planning to take part in another study for an investigational device or drug or had received an investigational agent within 30 days or 5 half-lives of the investigational agent (whichever was longer). For investigational TTR stabilisers, the washout period required was 3 months.
- Required treatment with or unwilling to avoid any concurrent treatment with non-dihydropyridine calcium channel blockers.

Medical conditions

- Any of the following medical conditions: other non-TTR cardiomyopathy, unstable congestive heart failure, acute coronary syndrome or unstable angina within the past 3 months, history of sustained ventricular tachycardia or aborted ventricular fibrillation, history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed, persistent elevation of systolic (>170 mmHg) or diastolic (>100 mmHg) blood pressure that is considered uncontrolled by a physician, untreated hypo- or hyperthyroidism, active infection

requiring systemic antiviral, antiparasitic, or antimicrobial therapy that will not be completed prior to study dosing.
- Previously received or was anticipated to receive (in the first 12 months after randomisation) a heart, liver, or other organ transplant or implantation of left-ventricular assist device.
- History of multiple drug allergies or historic allergic reactions to any excipient in the study drug formulation.
- History of intolerance to SC injections.
- Any other medical condition or comorbidity which interfered with study compliance or data interpretation, based on the opinion of the investigator.

Contraception, pregnancy, and breastfeeding
- Pregnant, planning to be pregnant, breast-feeding, or was not willing to comply with contraceptive requirements during the study period.

Alcohol use
- Unwilling to limit alcohol consumption, or in the opinion of the investigator, had a history of alcohol abuse within the 12 months prior to screening or a history of illicit drug abuse within the last 5 years that would interfere with study compliance.

6-MWT, 6-minute walk test; ALT, Alanine transaminase; AST, Aspartate transaminase; ATTR, transthyretin amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild-type transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; DPD-Tc, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; HIV, human immunodeficiency virus; HMDP, ^{99}Tc-hydroxymethylene diphosphonate; INR, international normalised ratio; IVSd, interventricular septal wall thickness; KPS, Karnofsky performance status; MGUS, monoclonal gammopathy of undetermined significance; PND, polyneuropathy disability; PYP-Tc, ^{99m}Tc-pyrophosphate; subcutaneous; TTR, transthyretin; ULN, upper limit of normal.
Source: HELIOS-B Clinical Study Protocol[128]

2.3.3 Baseline patient characteristics

A summary of the baseline patient characteristics from HELIOS-B is provided in Table 12. Characteristics were generally comparable between vutrisiran and placebo groups in both the overall population and monotherapy population; however, measures related to disease severity (NAC stage and NT-proBNP) suggest that within the monotherapy population, vutrisiran-treated patients had more severe disease and worse cardiac injury at baseline compared to placebo.[3] In the overall population, 259 patients (39.6%) were receiving tafamidis at baseline.[3]

Table 12: Baseline patient characteristics in HELIOS-B (full analysis set)

	Overall population (N=654)		Monotherapy population (N=395)	
Parameter at baseline	**Vutrisiran (n=326)**	**Placebo (n=328)**	**Vutrisiran (n=196)**	**Placebo (n=199)**
Age at randomisation, median, years (range)	77.0 (45.0–85.0)	76.0 (46.0–85.0)	77.5 (46.0–85.0)	76.0 (53.0–85.0)
Male, n (%)	299 (91.7)	306 (93.3)	178 (90.8)	183 (92.0)
Race				
White	277 (85.0)	275 (83.8)	169 (86.2)	169 (84.9)
Asian	18 (5.5)	19 (5.8)	12 (6.1)	15 (7.5)
Black/African American	23 (7.1)	24 (7.3)	10 (5.1)	11 (5.5)
Other/not reported	8 (2.5)	10 (3.0)	5 (2.6)	4 (2.0)
Disease type				
hATTR, n (%)	37 (11.3)	39 (11.9)	23 (11.7)	25 (12.6)
V122I, n (%)	24 (7.4)	25 (7.6)	13 (6.7)	16 (8.0)
wtATTR, n (%)	289 (88.7)	289 (88.1)	173 (88.3)	174 (87.4)
Time since diagnosis, median, years (range)	0.9 (0–11.1)	1.0 (0–10.8)	0.5 (0–8.3)	0.6 (0–6.2)

Parameter at baseline	Overall population (N=654)		Monotherapy population (N=395)	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
Tafamidis baseline use, n (%)	130 (39.9)	129 (39.3)	–	–
Time on tafamidis prior to start of study, median, months (range)	9.2 (1.1–65.3)	11.3 (1.1–65.5)	–	–
NYHA class				
I, n (%)	49 (15.0)	35 (10.7)	15 (7.7)	12 (6.0)
II, n (%)	250 (76.7)	258 (78.7)	172 (87.8)	169 (84.9)
III, n (%)	27 (8.3)	35 (10.7)	9 (4.6)	18 (9.0)
NAC stage				
1, n (%)	208 (63.8)	229 (69.8)	113 (57.7)	138 (69.3)
2, n (%)	100 (30.7)	87 (26.5)	68 (34.7)	55 (27.6)
3, n (%)	18 (5.5)	12 (3.7)	15 (7.7)	6 (3.0)
6-MWT, mean, metres (SD)*	372.0 (103.7)	377.1 (96.3)	362.7 (102.7)	372.8 (98.1)
KCCQ-OS score, mean, points (SD)*	73.0 (19.4)	72.3 (19.9)	70.3 (20.2)	69.9 (20.8)
NT-proBNP, median, ng/L (IQR)	2021 (1138, 3312)	1801 (1042, 3081)	2402 (1321, 3867)	1865 (1067, 3099)
Troponin I, median, ng/L (IQR)	71.9 (44.9, 115.9)	65.2 (41.0, 105.5)	76.3 (48.4, 138.8)	62.2 (39.2, 105.6)
eGFR, median, mL/min/1.73m^2 (IQR)	64 (50, 81)	65 (53, 81)	64 (50, 81)	65 (54.0, 81)

6-MWT, 6-minute walk test; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP; N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; V122I, valine to isoleucine substitution at amino acid position 122; wtATTR, wild-type transthyretin amyloidosis. *Baseline 6-MWT and KCCQ-OS values were assigned in 325 patients in the vutrisiran arm of the overall population, and baseline KCCQ-OS values were assigned in 327 patients in the placebo arm of the overall population. Source: Fontana et al. 2024[3]

2.3.4 Patient disposition

A summary of patient disposition is provided in Table 13.[3] A total of 655 patients with ATTR-CM were randomised to vutrisiran (n=326) or placebo (n=329), with one patient who was assigned to placebo withdrawing from the trial prior to receiving a dose of randomised treatment. Over the double-blind period, 78 (23.9%) patients in the vutrisiran arm and 99 (30.1%) patients in the placebo arm discontinued treatment. As of the 8 May 2024 data cutoff, 450 patients were being treated with vutrisiran in the OLE, including 237 vutrisiran-treated and 213 placebo-administered patients in the double-blind period.

Table 13: Patient disposition in HELIOS-B

Patient disposition	Vutrisiran	Placebo
Screened, N	**799**	
Screening failure, n (%)	**144 (18)**	
Randomised, n (%)	**655* (82)**	
Randomised, N	**326**	**328***

Patient disposition	Vutrisiran	Placebo
Discontinued treatment during DB period, n (%)	**78 (24)**	**99 (30)**
Death, n	37	48
Withdrawal by participant, n	23	23
Adverse event, n	13	13
Physician decision, n	2	8
Lost to follow-up, n	1	2
Non-compliance with study drug, n	1	0
Other, n	1	5
Stopped study participation during DB period, n (%)	**69 (21)**	**93 (28)**
Death, n	49	63
Withdrawal by participant, n	11	15
Adverse event, n	2	6
Physician decision, n	0	2
Lost to follow-up, n	1	2
Withdrawal by guardian, n	2	0
Other, n	4	5
Entered OLE, n (%)	**241 (74)**	**221 (67)**
OLE treatment ongoing, n (%)	**237 (73)**	**213 (65)**
Discontinued treatment during OLE, n (%)	**4 (1)**	**8 (2)**
Death, n	3	6
Withdrawal by participant, n	1	0
Adverse event, n	0	1
Withdrawal by guardian, n	0	1
Stopped study participation during OLE, n (%)	**3 (1)**	**8 (2)**
Death, n	3	7
Withdrawal by guardian, n	0	1

DB, double blind; OLE, open-label extension. *One subject who was randomised to placebo but did not receive a dose of study drug was not included in the randomised population. Source: HELIOS-B CSR 1 2024[130]

2.3.5 Endpoints

Endpoints in HELIOS-B were designed to assess the efficacy of vutrisiran versus placebo across a wide range of clinically relevant endpoints in patients with ATTR-CM. These included endpoints assessing mortality, CV events, physical capacity, HRQoL, and heart failure severity.[128] The endpoints in HELIOS-B effectively capture multiple elements of disease progression in ATTR-CM, in line with consensus recommendations from a panel of experts in ATTR-CM.[105]

In addition to assessment in the overall population (as was originally planned), a HELIOS-B protocol amendment in February 2024 specified the assessment of all endpoints in the monotherapy population.[128] The analyses in the monotherapy population were included to determine the clinical benefit of vutrisiran in ATTR-CM independent from the effect of background tafamidis use at baseline (present in 39.6% of patients in HELIOS-B).[128] In the same protocol amendment, an additional exploratory endpoint was included that assessed the time to first diuretic intensification, first CV event, or ACM.[128] This endpoint was added considering recent emerging evidence that diuretic intensification is predictive of increased

mortality risk in ATTR-CM and thus could be considered together with CV events and mortality as an indicator of worsening in patients' clinical status.[2]

2.3.5.1 Primary endpoint

The primary endpoints of HELIOS-B were 1) a composite endpoint of ACM and recurrent CV events (comprising CV hospitalisations and urgent heart failure visits) observed among all patients (overall population [with and without background tafamidis use at baseline]) and 2) the same composite endpoint observed among patients not on tafamidis at baseline (monotherapy population), over a follow-up duration of up to 36 months (i.e., the entirety of double-blind follow-up).[128,129]

[redacted] For this analysis, heart transplantation and/or receipt of a ventricular assist device were categorised as deaths.

2.3.5.2 Secondary endpoints

Secondary endpoints included change from baseline in physical capacity as measured by 6-MWT distance at 30 months, change from baseline in HRQoL as measured by KCCQ-OS at 30 months, ACM up to 42 months (including up to the first 6 months of the OLE period following the double-blind period), and change from baseline in heart failure severity as measured by NYHA class changes at 30 months.[128] Each of these secondary endpoints was assessed among all patients (overall population), and among patients not on tafamidis at baseline (monotherapy population).[128]

6-MWT

The difference between vutrisiran and placebo in change from baseline to Month 30 in 6-MWT was assessed as a secondary endpoint in HELIOS-B for the overall population and separately for the monotherapy population.[128] The 6-MWT is an assessment of functional exercise capacity as reflected by the distance a patient can walk in 6 minutes,[128,139] which reflects patients' overall physical capacity. Increases in distance indicate improvement in physical capacity. In patients with heart failure, decreased 6-MWT distances are associated with increased rates of mortality, non-fatal CV events, and heart failure hospitalisations.[139] Age-associated declines in 6-MWT distance of approximately 5–6 metres per year have been demonstrated in healthy adults aged 40–80 years.[140]

A wide range of MCIDs have been reported for the 6-MWT. For example, a systematic review conducted across a range of different conditions (e.g., chronic obstructive pulmonary disease, lung cancer, coronary artery disease, diffuse parenchymal lung disease, and non-cystic fibrosis bronchiectasis) identified an MCID range of 14.0 to 30.5 metres.[141] Similarly, in general heart failure populations, MCIDs have been reported in two separate studies, which estimated MCIDs of 14–15 metres and 30.1 metres, respectively.[142,143] In ATTR-CM, the MCID for 6-MWT distance has been shown to be 7–8 metres.[98]

KCCQ-OS

To assess the effects of vutrisiran on HRQoL in patients with ATTR-CM, the difference between vutrisiran and placebo in change from baseline to Month 30 in KCCQ-OS was assessed; separate analyses of this endpoint were performed for the overall trial population and for the monotherapy population.[128] The KCCQ is described in detail in Section 1.3.2.4. The MCID for KCCQ-OS is 5 points, while differences in KCCQ-OS scores of 10 and 20 points represent moderate-to-large and large-to-very large clinical changes, respectively.[100]

ACM

Comparisons of vutrisiran versus placebo with respect to the occurrence of ACM as a stand-alone outcome, in the overall trial population and separately in the monotherapy population, were conducted as secondary endpoint assessments.[128] These comparisons considered all vital status data collected during double-blind follow-up (up to 36 months) and from up to the first 6 months of the OLE period.[128] Thus, secondary endpoint analyses of stand-alone ACM reflected patient outcomes over a follow-up duration of up to 42 months.

The decision to include vital status data from up to the first 6 months of the OLE period in this analysis was made to improve the precision of treatment estimates and to increase the power to detect a treatment difference versus placebo.

NYHA class

To assess the effects of vutrisiran on heart failure severity in patients with ATTR-CM, the HELIOS-B trial evaluated change in NYHA class as a secondary endpoint, with separate analyses of the overall population and the monotherapy population.[128] For these analyses, the outcome of change from baseline in NYHA class at Month 30 was dichotomised as "stable/improved" or "worsened", and the proportion of patients in whom NYHA class was stable/improved was compared between the vutrisiran and placebo arms. Stabilisation or improvement of a patient's NYHA class (i.e., avoiding worsening of NYHA class) is of clear clinical value, as the normal natural history of ATTR-CM is marked by progressive heart failure, and each change in NYHA class represents a frank change in functional status and symptom burden as it relates to heart failure.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Statistical analysis of primary and secondary endpoints

A summary of statistical analysis methods used for primary and secondary endpoints in HELIOS-B is provided in Table 14.

Table 14: Statistical analysis methods for primary and secondary endpoints in HELIOS-B

Endpoint	Statistical method
Primary endpoint	
Composite of ACM and recurrent CV events	*Overall population analysis* • Modified Andersen-Gill model – Stratified by baseline tafamidis use – Covariates included treatment (vutrisiran vs. placebo), ATTR disease type (hATTR vs. wtATTR), NYHA class (I/II vs. III), age group (<75 vs. ≥75 years), and baseline NT-proBNP (continuous variable with logarithmic transformation) *Monotherapy population analysis* • Same as overall population analysis, but without stratification by baseline tafamidis use *Missing data* • No imputation for early dropouts • Deaths ascertained after study discontinuation were not included in the composite analysis but were included in the ACM component analysis of the primary endpoint

Endpoint	Statistical method
Secondary endpoints	
6-MWT	*Overall population analysis* • MMRM which included baseline 6-MWT distance as a covariate and treatment (vutrisiran vs. placebo), visit, treatment-by-visit interaction, ATTR disease type (hATTR vs. wtATTR), age group (<75 vs. ≥75 years), baseline tafamidis use (yes vs. no), and treatment-by-baseline tafamidis use interaction as fixed-effect terms *Monotherapy population analysis* • Same as overall population analysis, but without inclusion of baseline tafamidis use and treatment-by-baseline tafamidis use interaction as fixed-effect terms in model *Missing data* • For patients with missing data at a given time point due to death or the inability to walk due to disease progression, data at that time point were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline value for the patient with the missing data] • For all other instances of missing data, MMRM implicitly imputes missing values assuming these values are missing at random
KCCQ-OS	*Overall population analysis* • MMRM which included baseline KCCQ-OS score as a covariate and treatment (vutrisiran vs. placebo), visit, treatment-by-visit interaction, ATTR disease type (hATTR vs. wtATTR), age group (<75 vs. ≥75 years), baseline tafamidis use (yes vs. no), and treatment-by-baseline tafamidis use interaction as fixed-effect terms *Monotherapy population analysis* • Same as overall population analysis, but without inclusion of baseline tafamidis use and treatment-by-baseline tafamidis use interaction as fixed-effect terms in model *Missing data* • For patients with missing data at a given time point due to death, data at that time point were derived from imputed domain change scores; domain change scores were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline domain score for the patient with the missing data] • For all other instances of missing data, MMRM implicitly imputes missing values assuming these values are missing at random
ACM	*Overall population analysis* • Log-rank test stratified by baseline tafamidis use (yes vs. no) and baseline NT-proBNP group (≤3000 ng/L vs. >3000 ng/L) used to test the difference between vutrisiran and placebo • Cox proportional hazards model with treatment (vutrisiran vs. placebo), ATTR disease type (hATTR vs. wtATTR), NYHA Class (I/II vs. III), age group (<75 vs. ≥75 years), and baseline NT-proBNP (continuous variable with

Endpoint	Statistical method
	logarithmic transformation) as covariates used to estimate the overall HR and 95% CI *Monotherapy population analysis* • Same as overall population analysis, but without stratification by baseline tafamidis use in log-rank test *Missing data* • All deaths collected were included in the analysis, including deaths after treatment and study discontinuation
NYHA class	*Overall population analysis* • CMH method applied, with stratification by baseline NT-proBNP (continuous variable with logarithmic transformation) and baseline tafamidis use (yes vs. no), to 100 data sets generated via multiple imputation of missing NYHA class data (as described below) • Results combined across all datasets using Rubin's rule to obtain overall estimate of treatment effect, 95% CI, and P value *Monotherapy population analysis* • Same as overall population analysis, but without stratification by baseline tafamidis use in CMH method *Missing data* • Missing NYHA class data due to death imputed as Class IV; other missing NYHA class data assumed to be missing at random and multiply imputed using an MCMC approach with baseline NYHA class (I/II vs. III), ATTR disease type (hATTR vs. wtATTR), age group (<75 vs. ≥75), baseline NT-proBNP (continuous variable with logarithmic transformation), and all non-missing postbaseline NYHA class assessments at scheduled study visits as covariates

6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; hATTR, hereditary transthyretin amyloidosis; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; MCMC, Markov Chain Monte Carlo; MMRM, mixed effects model repeated measures; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; wtATTR, wild-type transthyretin amyloidosis. Source: HELIOS-B Statistical Analysis Plan[144]

2.4.2 Prespecified multiplicity testing procedure for primary and secondary endpoints

The overall Type I error rate for the primary and secondary endpoints was controlled at a 2-sided 0.05 significance level using a prespecified multiplicity testing procedure.[144] For the purposes of this procedure, five distinct endpoint families were defined, each comprising 1) a given outcome evaluated in the overall population of HELIOS-B and 2) the same outcome evaluated in the monotherapy population of HELIOS-B.[144] Thus, the endpoint families (presented in order of their appearance in the HELIOS-B endpoint hierarchy, starting with the primary endpoint family) were as follows:

- Composite primary endpoint family: composite outcome of ACM and recurrent CV events assessed up to Month 36 in the 1) overall population and 2) monotherapy population
- 6-MWT endpoint family: change from baseline to Month 30 in 6-MWT distance assessed in the 1) overall population and 2) monotherapy population
- KCCQ-OS score endpoint family: change from baseline to Month 30 in KCCQ-OS score assessed in the 1) overall population and 2) monotherapy population

- ACM endpoint family: stand-alone ACM assessed up to Month 42 in the 1) overall population and 2) monotherapy population
- NYHA class endpoint family: Percentage of patients with stable/improved NYHA class from baseline to Month 30 assessed in the 1) overall population and 2) monotherapy population

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. This Hochberg-based gatekeeping procedure was based on an extension of the general mixture methodology.[145,146] This multiple testing procedure was implemented in HELIOS-B as follows:

Step 1: Testing of composite primary endpoint family

- Perform statistical testing for both endpoints in family
    - *If larger P value and smaller P value from testing in endpoint family are both ≤0.049*
        - Reject null hypotheses for both endpoints in family
        - Advance to version 'a' of next step in testing procedure (testing of next endpoint in endpoint hierarchy in both the overall and monotherapy populations)
    - *If larger P value from testing in endpoint family is >0.049 and smaller P value is ≤0.025*
        - Reject null hypothesis corresponding to smaller *P* value, and accept null hypothesis corresponding to larger *P* value
        - Advance to version 'b' of next step in testing procedure (testing of next endpoint in endpoint hierarchy only in the population for which the null hypothesis was rejected here)
    - *If larger P value from testing in endpoint family is >0.049 and smaller P value is >0.025*
        - Accept null hypotheses for both endpoints in family
        - Do not advance further in testing procedure

Step 2: Testing of 6-MWT endpoint family

- *Step 2a:* Perform statistical testing for both endpoints in family
    - Follow same rules as used in step 1 for rejection/acceptance of null hypotheses and determination of next step in testing procedure
- *Step 2b:* Perform statistical testing of endpoint only in the population for which the null hypothesis was rejected in Step 1
    - *If P value is ≤0.001*
        - Reject null hypothesis
        - Advance to version 'b' of next step in testing procedure (testing of next endpoint in endpoint hierarchy only in the population for which the null hypothesis was rejected here)
    - *If P value is >0.001*
        - Accept null hypothesis
        - Do not advance further in testing procedure

Step 3: Testing of KCCQ-OS endpoint family

- *Step 3a:* Perform statistical testing for both endpoints in family
    - Follow same rules as used in step 1 for rejection/acceptance of null hypotheses and determination of next step in testing procedure
- *Step 3b:* Perform statistical testing of endpoint only in the population for which the null hypothesis was rejected in Step 2
    - Follow same rules as used in step 2b for rejection/acceptance of null hypothesis and determination of next step in testing procedure

Step 4: Testing of ACM endpoint family

- *Step 4a:* Perform statistical testing for both endpoints in family
    - Follow same rules as used in step 1 for rejection/acceptance of null hypotheses and determination of next step in testing procedure
- *Step 4b:* Perform statistical testing of endpoint only in the population for which the null hypothesis was rejected in Step 3
    - Follow same rules as used in step 2b for rejection/acceptance of null hypothesis and determination of next step in testing procedure

Step 5: Testing of NYHA class endpoint family

- *Step 5a:* Perform statistical testing for both endpoints in family
    - *If larger P value and smaller P value from testing in endpoint family are both ≤0.05:* Reject null hypotheses for both endpoints in family
    - *If larger P value from testing in endpoint family is >0.05 and smaller P value is ≤0.025:* Reject null hypothesis corresponding to smaller *P* value, and accept null hypothesis corresponding to larger *P* value
    - *If larger P value from testing in endpoint family is >0.05 and smaller P value is >0.025:* Accept null hypotheses for both endpoints in family
- *Step 5b:* Perform statistical testing of endpoint only in the population for which the null hypothesis was rejected in Step 4
    - *If P value is ≤0.001:* Reject null hypothesis
    - *If P value is >0.001:* Accept null hypothesis

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality appraisal of the HELIOS-B trial is provided in Appendix B.

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Summary of efficacy results

Results from HELIOS-B demonstrated that vutrisiran is an efficacious therapy for patients with ATTR-CM, as vutrisiran showed statistically and clinically significant benefit versus placebo across all primary and secondary endpoints in both the overall population and the monotherapy population.[3]

The findings from HELIOS-B translate to substantial clinical benefit in the form of reduced mortality and CV hospitalisations, as well as stabilisation of physical capacity, HRQoL, and heart failure severity, with consistent efficacy across all patient types. A summary of results from HELIOS-B for all primary and secondary endpoints is provided in Table 15.[3]

Table 15: Summary of results from HELIOS-B for primary and secondary endpoints

Measure	Overall population (N=654)		Monotherapy population (N=395)	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
Primary endpoint: composite of ACM and recurrent CV events over up to 36 months				
Patients with at least one event, n (%)	125 (38.3)	159 (48.5)	76 (38.8)	105 (52.8)
HR (vutrisiran/placebo) (95% CI)	0.72 (0.56, 0.93) P=0.01		0.67 (0.49, 0.93) P=0.02	
Secondary endpoint: change in 6-MWT over 30 months*				
LS mean change over 30 months, metres (95% CI)	–45.4 (–54.5, –36.3)	−71.9 (−81.3, −62.4)	−59.7 (−72.7, −46.7)	−91.8 (−104.4, −79.2)
LS mean difference (vutrisiran – placebo), metres (95% CI)	26.5 (13.4, 39.6) P<0.001		32.1 (14.0, 50.2) P<0.001	
Secondary endpoint: change in KCCQ-OS score over 30 months†				
LS mean change over 30 months, points (95% CI)	−9.7 (−12.0, −7.4)	−15.5 (−18.0, −13.0)	−10.8 (−14.1, −7.5)	−19.5 (−22.9, −16.1)
LS mean difference (vutrisiran – placebo), points (95% CI)	5.8 (2.4, 9.2) P<0.001		8.7 (4.0, 13.4) P<0.001	
Secondary endpoint: ACM over up to 42 months				
Deaths, n (%)	60 (18.4)	85 (25.9)	43 (21.9)	58 (29.1)
HR (vutrisiran/placebo) (95% CI)	0.65 (0.46, 0.90) P=0.01		0.66 (0.44, 0.97) P=0.045	
Secondary endpoint: change in NYHA class over 30 months‡				
Stable/improved over 30 months, %	67.8	60.5	66.3	56,4
Adjusted difference (vutrisiran – placebo), % (95% CI)	8.7 (1.3, 16.1) P=0.02		12.5 (2.7, 22.2) P=0.01	

6-MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire; LS, least square; NYHA, New York Heart Association. *Missing values at a given visit due to death or inability to walk because of disease progression were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit from the same treatment arm and baseline tafamidis use group, with imputed values capped by [0 – baseline value for the patient with the missing data]. †Missing change values at a given visit due to death were derived from imputed domain change scores; domain change scores were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline domain score for the patient with the missing data]. ‡Missing change values at Month 30 due to death, heart transplantation, or left ventricular assist device placement were imputed as NYHA class IV; all other missing values were imputed via a probabilistic approach (Markov Chain Monte Carlo method) that predicts NYHA class at Month 30 from patients' baseline characteristics and pre-Month 30 NYHA class assessments. Source: Fontana et al. 2024[3]; HELIOS-B CSR 1[130]

2.6.2 HELIOS-B primary endpoint: composite outcome of ACM and recurrent CV events over up to 36 months (double-blind follow-up period)

Patients treated with vutrisiran were significantly less likely to experience clinical morbidity and mortality compared to patients who received placebo.

Vutrisiran treatment led to 28% and 33% reductions in the risk of mortality and recurrent CV events in the overall population and the monotherapy population, respectively, versus placebo.

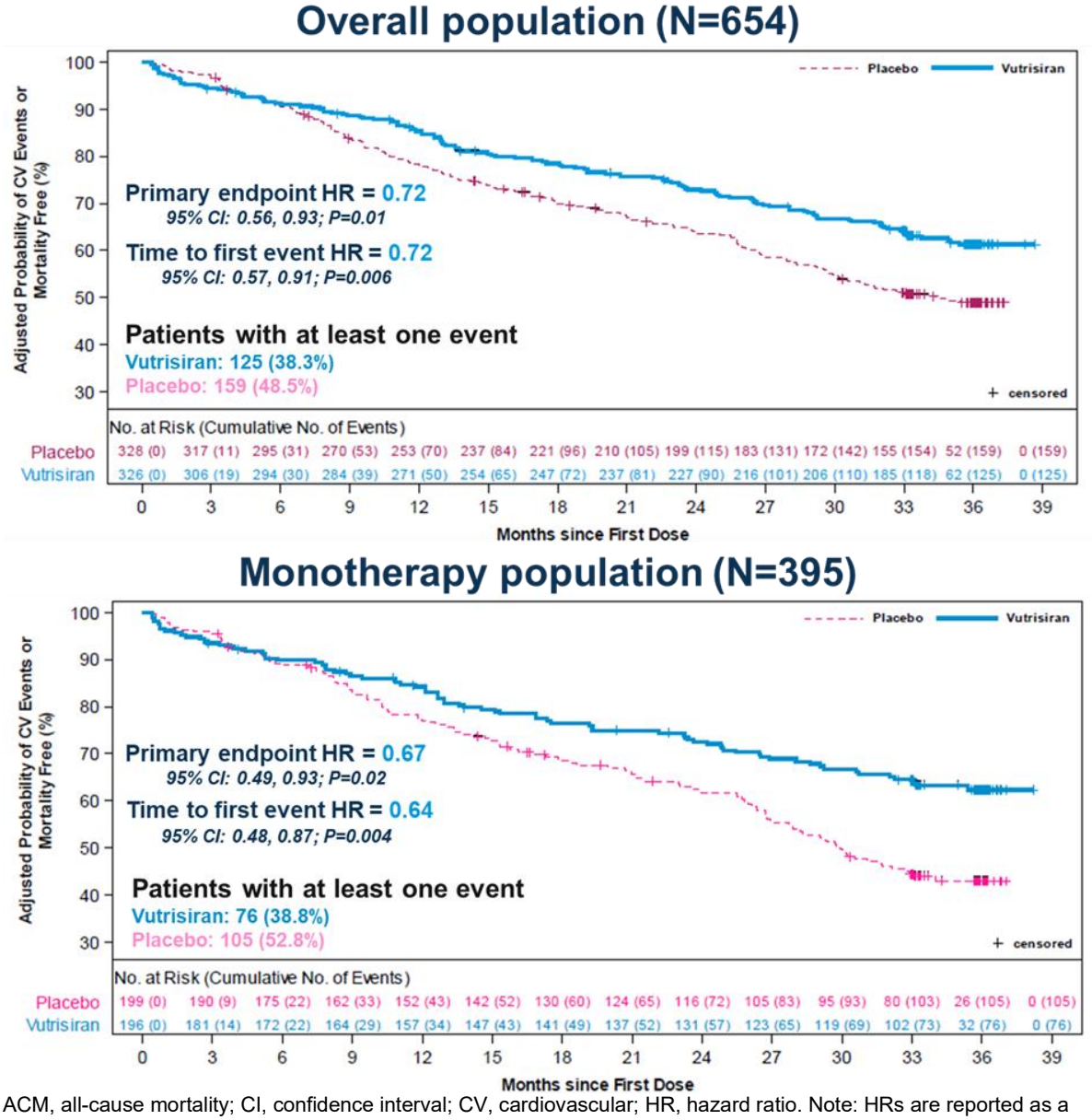
Vutrisiran treatment resulted in a significant reduction in the risk of mortality and recurrent CV events (considered together as a composite endpoint) in both the overall population (HR=0.72 [95% CI: 0.56, 0.93]; P=0.01) and in the monotherapy population (HR=0.67 [95% CI: 0.49, 0.93]; P=0.02).[3]

This means that, compared to patients in the placebo group, patients in the vutrisiran group had a significantly reduced risk of mortality, CV hospitalisation, and urgent heart failure hospital visits (considered collectively). Notably, these benefits of vutrisiran over placebo were observed both in the overall population (including patients who were and patients who were not receiving background tafamidis) and in the monotherapy population (patients not receiving background tafamidis).

The observed HR values indicate that the magnitude of relative reduction in the risk of these events with vutrisiran (calculated as: 100% x [1 – HR]) was 28% in the overall population and 33% in the monotherapy population.

Kaplan–Meier plots of time to death or first CV event (whichever occurred first) also show a significant benefit for vutrisiran in both populations, with divergence of curves at approximately 6 months (Figure 13).[3]

Figure 13: HELIOS-B primary endpoint additional analysis: time to ACM or first CV event (whichever occurred first) in the overall population and monotherapy population



ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio. Note: HRs are reported as a comparison of the vutrisiran arm versus the placebo arm within the specified population (overall population or monotherapy population). Source: HELIOS-B CSR 1[130]

2.6.3 HELIOS-B secondary endpoint: change from baseline to Month 30 in 6-MWT

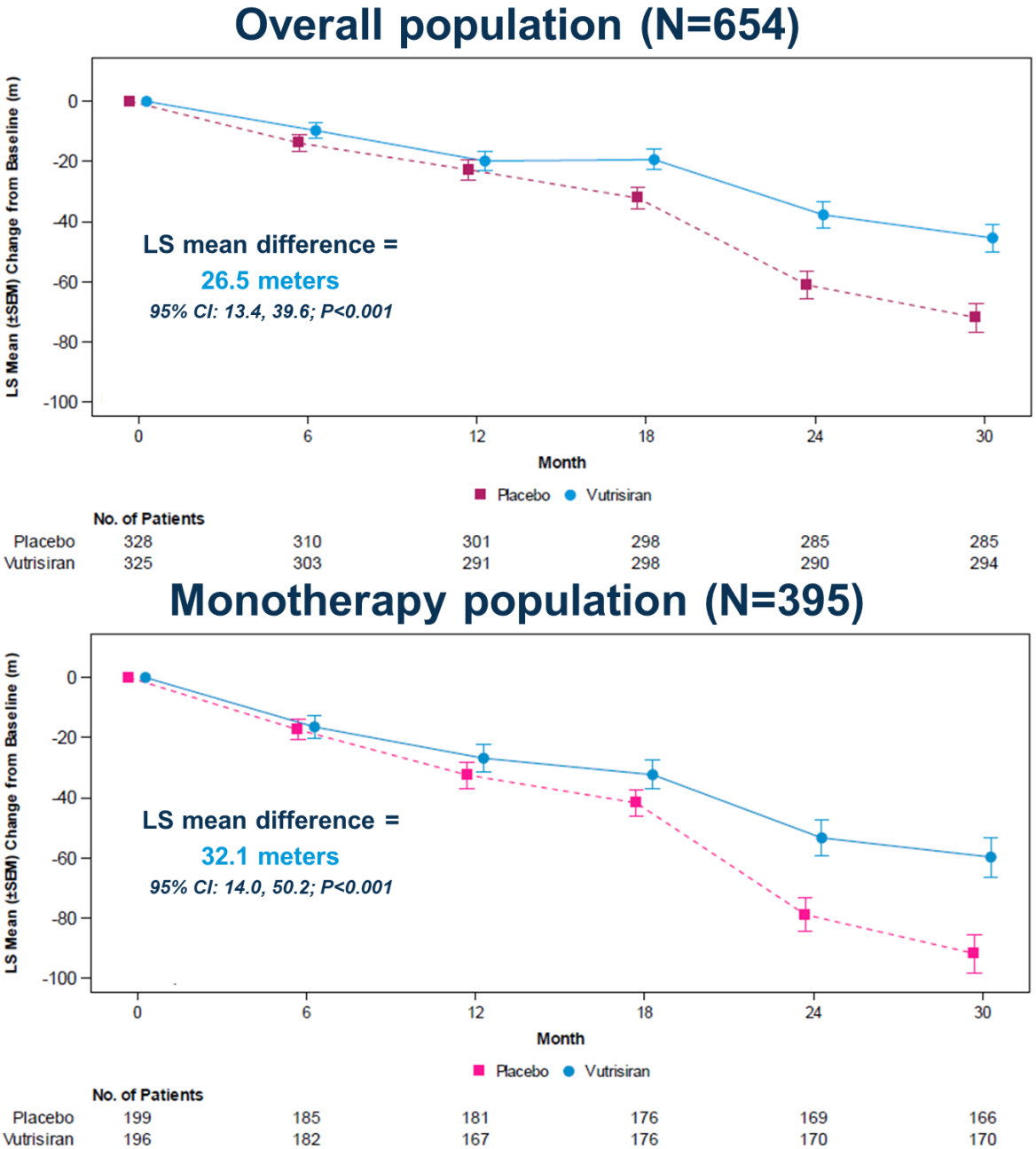
Patients treated with vutrisiran exhibited statistically significant and clinically meaningful preservation of physical capacity compared to patients who received placebo over 30 months. Notably, preservation of baseline physical capacity in in vutrisiran-treated patients was observed in an analysis where missing data were not imputed.

Vutrisiran treatment led to a significant benefit in terms of 6-MWT distance compared to placebo. Treatment differences in favour of vutrisiran (LS mean difference vutrisiran – placebo) of 26.5 metres (95% CI: 13.4, 39.6; P<0.001) in the overall population and 32.1

metres (95% CI: 14.0, 50.2; P<0.001) in the monotherapy population were observed for 6-MWT distance, based on analyses that involved imputation of data missing not at random (i.e., missing because of death or because of the inability to walk in association with disease progression; Figure 14).[3]

These treatment differences exceed the established MCID for 6-MWT in patients with ATTR-CM (7–8 metres) and thus represent a clinically meaningful effect of vutrisiran on physical capacity.[98]

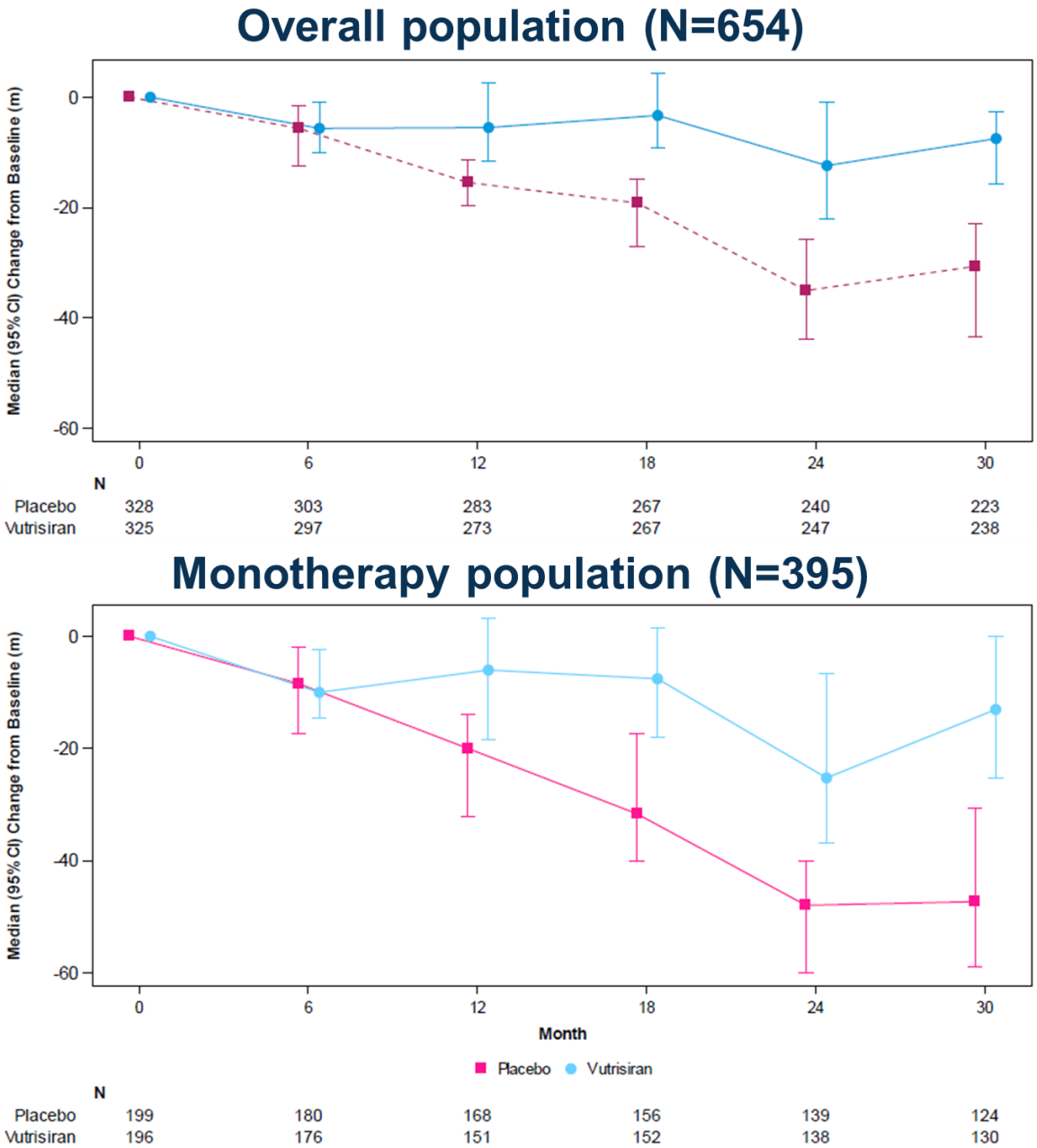
Figure 14: HELIOS-B secondary endpoint: LS mean change from baseline to Month 30 in 6-MWT distance in the overall population and monotherapy population



6-MWT, 6-minute walk test; CI, confidence interval; LS, least square; SEM, standard error of the mean. Note: LS mean difference is calculated as vutrisiran – placebo within the specified population (overall population or monotherapy population). For patients with missing data at a given time point due to death or inability to walk because of disease progression, data at that time point were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline value for the patient with the missing data]. Source: HELIOS-B CSR 1[130]

Importantly, in an analysis that included only observed values, without imputation of missing data, patients treated with vutrisiran showed preservation of their physical capacity over 30 months relative to pretreatment baseline, as demonstrated in Figure 15. This finding suggests the halting of disease-related declines in physical capacity, on average, relative to pretreatment baseline in patients with available data.

Figure 15: HELIOS-B secondary endpoint: median change from baseline to Month 30 in 6-MWT distance in the overall population and monotherapy population, observed values



6-MWT, 6-minute walk test; CI, confidence interval. Note: Median changes reflect the observed results from surviving patients with available data. Source: HELIOS-B CSR 1[130]

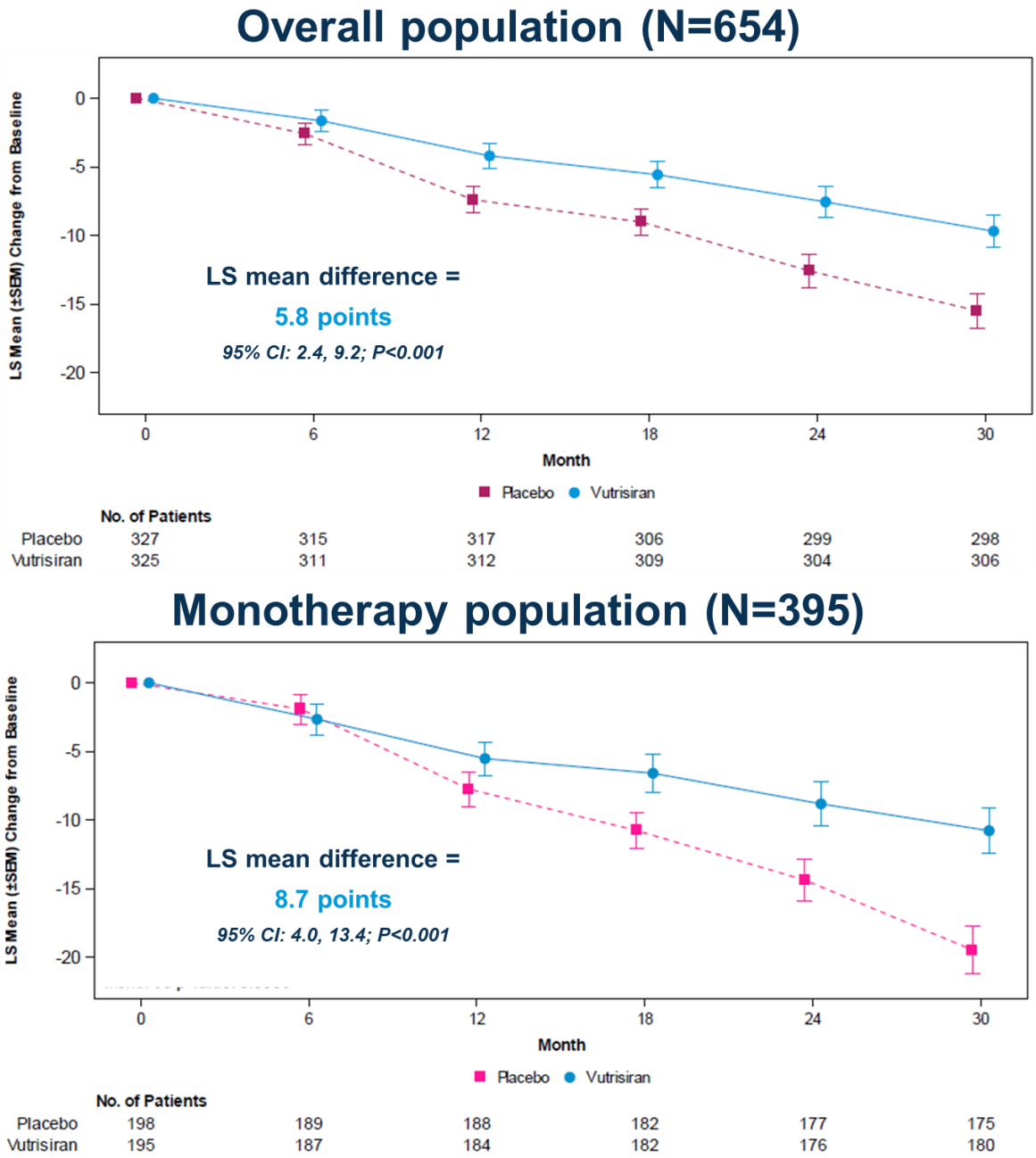
2.6.4 HELIOS-B secondary endpoint: change from baseline to Month 30 in KCCQ-OS score

Patients treated with vutrisiran exhibited statistically significant and clinically meaningful preservation of HRQoL compared to patients who received placebo over 30 months. Notably, baseline HRQoL was preserved in vutrisiran-treated patients in an analysis where missing data were not imputed.

Vutrisiran treatment led to a significant benefit in terms of KCCQ-OS score over 30 months compared to placebo. Treatment differences in favour of vutrisiran (LS mean difference vutrisiran – placebo) of 5.8 points (95% CI: 2.4, 9.2; P<0.001) in the overall population and 8.7 points (95% CI: 4.0, 13.4; P<0.001) in the monotherapy population were observed for KCCQ-OS score, based on analyses with imputation of data missing due to death (Figure 16).[3]

These findings demonstrate that treatment with vutrisiran yielded clinically relevant benefits in terms of HRQoL, given that the magnitude of the treatment effect exceeded the established MCID of 5 points for KCCQ-OS score.[100]

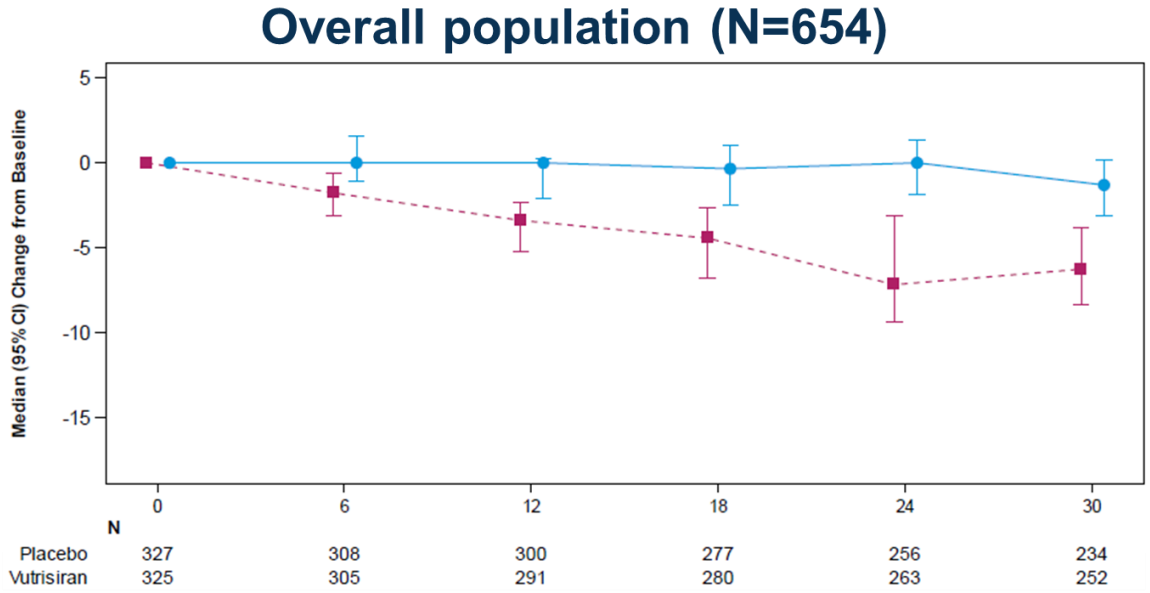
Figure 16: HELIOS-B secondary endpoint: LS mean change from baseline to Month 30 in KCCQ-OS score in the overall population and monotherapy population

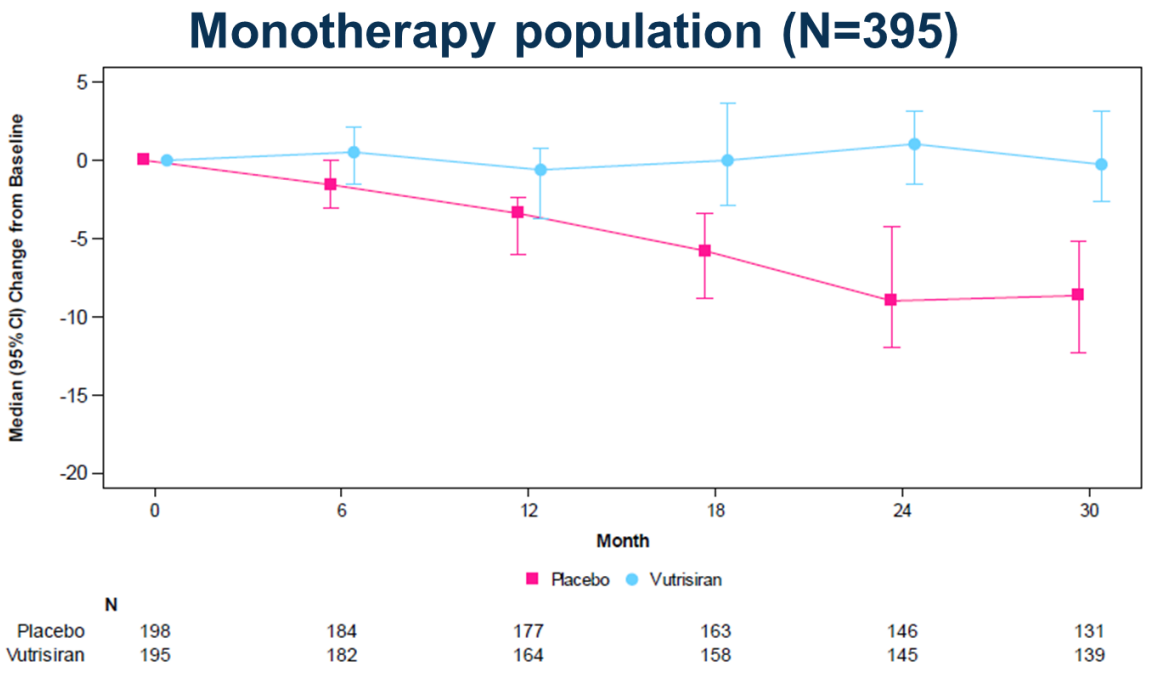


CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least square; SEM, standard error of the mean. Note: LS mean difference is calculated as vutrisiran – placebo within the specified population (overall population or monotherapy population). For patients with missing data at a given time point due to death, data at that time point were derived from imputed domain change scores; domain change scores were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline domain score for the patient with the missing data]. Source: HELIOS-B CSR 1[130]

As with 6-MWT, analysis of observed values without imputation showed preservation of HRQoL relative to pretreatment baseline in patients receiving vutrisiran, as demonstrated in Figure 17. This finding suggests the halting of disease-related declines in HRQoL on average over 30 months of treatment with vutrisiran, parallelling the observed halting of disease-related declines in physical capacity (6-MWT), in patients with available data.

Figure 17: HELIOS-B secondary endpoint: median change from baseline to Month 30 in KCCQ-OS score in the overall population and monotherapy population, observed values





CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary. Note: Median changes reflect the observed results from surviving patients with available data. Source: HELIOS-B CSR 1[130]

2.6.5 HELIOS-B secondary endpoint: ACM up to Month 42

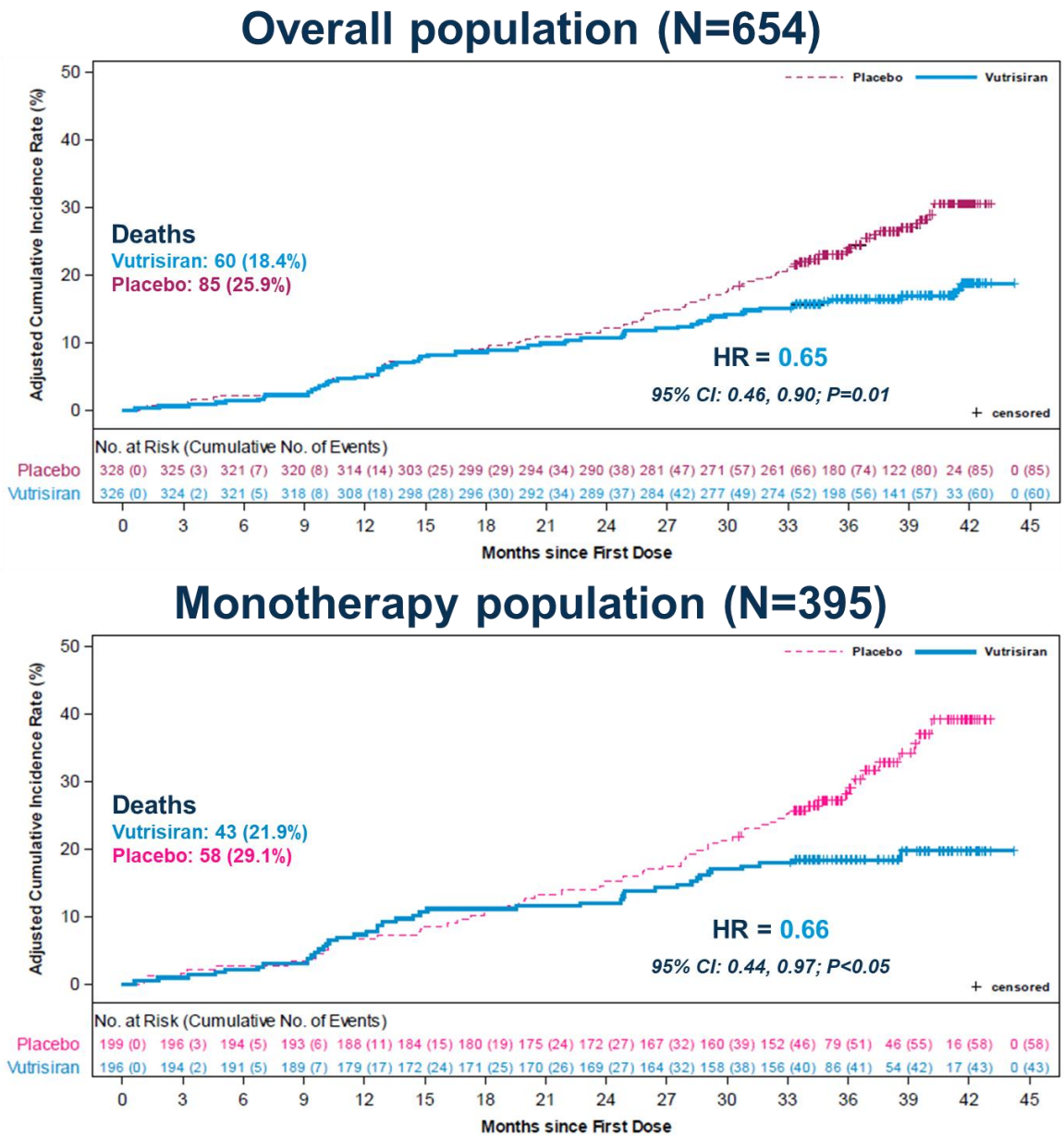
Vutrisiran treatment led to a statistically significant reduction in mortality over up to 42 months of treatment compared to placebo, with 35% and 34% reductions in mortality risk in the overall population and the monotherapy population, respectively.

Patients treated with vutrisiran in HELIOS-B showed a statistically significant reduction in ACM over up to 42 months (Figure 18).

In the overall population, 60 patients (18.4%) in the vutrisiran arm and 85 patients (25.9%) in the placebo arm died from any cause during the follow-up period for the ACM endpoint. In the monotherapy population, 43 patients (21.9%) in the vutrisiran arm and 58 patients (29.1%) in the placebo arm died from any cause over this same period.[3]

The reduction in mortality rate for vutrisiran versus placebo was statistically significant in both the overall population (HR=0.65 [95% CI: 0.46, 0.90]; P=0.01) and in the monotherapy population (HR=0.66 [95% CI: 0.44, 0.97]; P=0.05).[3] The observed HR values indicate that the magnitude of relative reduction in mortality risk was 35% in the overall population and 34% in the monotherapy population.

Figure 18: HELIOS-B secondary endpoint: ACM over up to 42 months in the overall population and monotherapy population



ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio. Note: HRs are reported as a comparison of the vutrisiran arm versus the placebo arm within the specified population (overall population or monotherapy population). This analysis included vital status data collection through up to Month 6 of the OLE. Source: HELIOS-B CSR 1[130]

2.6.6 HELIOS-B secondary endpoint: change from baseline to Month 30 in NYHA class

Vutrisiran treatment provided a significant benefit in preventing worsening in heart failure severity, as the percentage of patients who had stabilised or improved NYHA class over 30 months was significantly higher with vutrisiran compared to placebo.

Compared to placebo, treatment with vutrisiran led to a significantly greater proportion of patients maintaining or improving (i.e., avoiding worsening of) NYHA class over 30 months, indicating a significant benefit for vutrisiran in preventing the worsening of heart failure severity.

In the overall population, 68% of patients treated with vutrisiran remained stable or improved in NYHA class, compared to 61% of patients who received placebo (adjusted difference: 8.7% [95% CI: 1.3, 16.1]; P=0.02). In the monotherapy population, 66% of patients in the vutrisiran group remained stable or improved in NYHA class, compared to 56% of patients in the placebo group (adjusted difference: 12.5% [95% CI: 2.7, 12.2]; P=0.01).[3]

2.6.7 HELIOS-B exploratory endpoint: change from baseline to Month 30 in serum NT-proBNP level

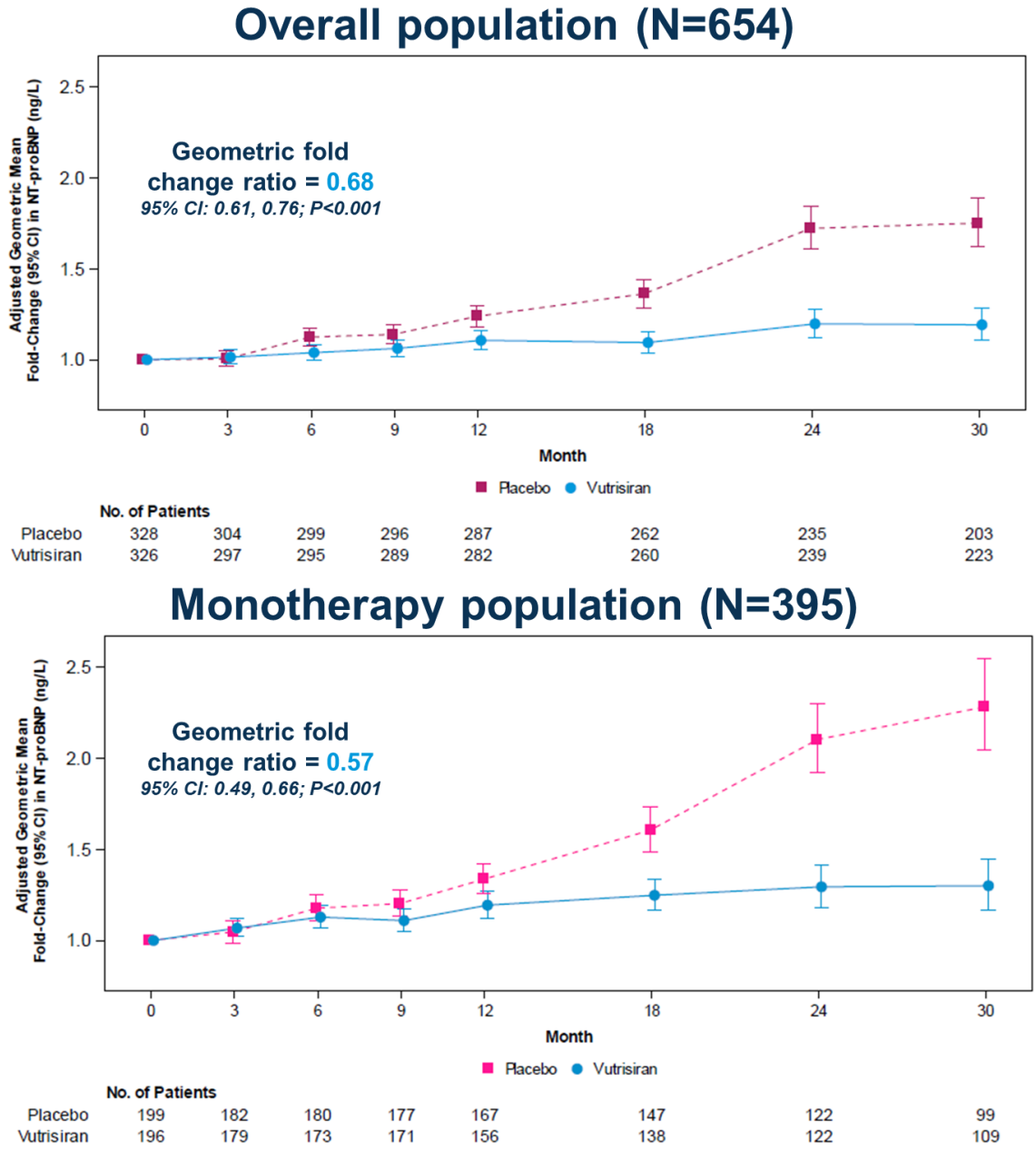
Patients treated with vutrisiran exhibited statistically significant and clinically meaningful prevention of worsening in cardiac injury levels (via serum NT-proBNP levels) compared to patients who received placebo over 30 months.

Over 30 months, vutrisiran treatment showed a significant benefit versus placebo on the outcome of cardiac injury as indicated by changes in serum NT-proBNP, with consistent results in both the overall population and the monotherapy population (Figure 19).

Over 30 months of treatment, in the overall population, adjusted geometric mean fold change in NT-proBNP was 1.75 in the placebo group, and 1.19 in the vutrisiran group, corresponding to a 32% relative reduction in the fold change in NT-proBNP with vutrisiran compared to placebo (adjusted geometric mean fold change ratio for vutrisiran vs. placebo: 0.68 [95% CI: 0.61, 0.76]; P<0.001).

In the monotherapy population, over the same time period, adjusted geometric mean fold change in serum NT-proBNP was 2.28 in the placebo arm and 1.30 in the vutrisiran arm, corresponding to a 43% relative reduction in the fold change in NT-proBNP with vutrisiran compared to placebo (adjusted geometric mean fold change ratio for vutrisiran vs. placebo: 0.57 [95% CI: 0.49, 0.66]; P<0.001).[3]

Figure 19: HELIOS-B exploratory endpoint: adjusted geometric mean fold change from baseline to Month 30 in serum NT-proBNP in the overall population and monotherapy population



6-MWT, 6-minute walk test; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; MMRM, mixed models for repeated measures; NT-proBNP, N-terminal pro-brain natriuretic peptide. Note: Analyses were carried out using the same MMRM model used for 6-MWT and KCCQ-OS score, but with baseline log-transformed NT-proBNP values as a covariate instead of baseline 6-MWT/KCCQ-OS score. Data collected after tafamidis drop-in were excluded from the analysis. Source: HELIOS-B CSR 1[130]

Analyses of median change from baseline in NT-proBNP levels showed prevention of substantial worsening in cardiac injury beyond the level observed at pretreatment baseline in patients receiving vutrisiran.

In the overall population, the median change from baseline in NT-proBNP levels in the vutrisiran arm was a [redacted]% increase, reflecting relative stability, while the median change in the placebo arm was a [redacted]% increase, reflecting worsening of cardiac injury.[130]

Similarly, in the monotherapy population, the median change from baseline in NT-proBNP levels in the vutrisiran arm was a [redacted]% increase, reflecting relative stability, while the median change in the placebo arm was a [redacted]% increase, reflecting worsening of cardiac injury.[130]

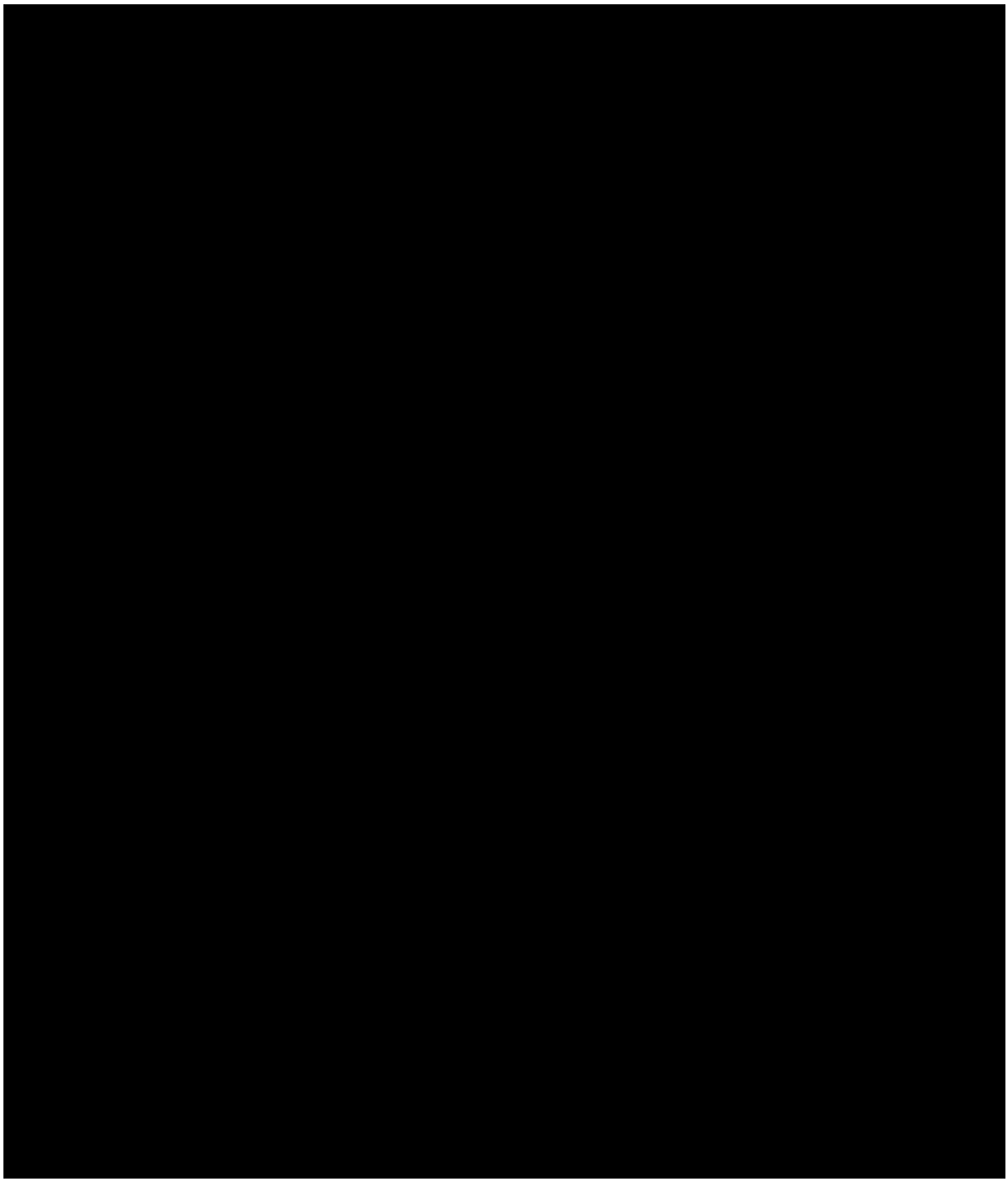
2.6.8 HELIOS-B exploratory endpoint: time to first oral loop diuretic intensification, first CV event, or ACM

Vutrisiran treatment led to a significant decrease in the risk of first oral loop diuretic intensification, first CV event, or ACM, compared to placebo.

An analysis of time to first oral loop diuretic intensification (including loop diuretic initiation in patients not previously on loop diuretics), first CV event, or ACM over the double-blind period demonstrated a statistically significant [redacted]% reduction in the risk of a first event (out of these three event types) for vutrisiran-treated patients compared to placebo-administered patients in the overall population ([redacted]; Figure 20).[130]

Similarly, in the monotherapy population, vutrisiran-treated patients had a [redacted]% risk reduction compared to placebo-administered patients ([redacted]; Figure 22) with regard to occurrence of a first event.[130] Considering that initiation or intensification of oral loop diuretic dose in patients with ATTR-CM is associated with significantly worse survival prognosis,[2] findings from this exploratory analysis (where oral diuretic intensification was additionally included in a composite outcome together with other clinically relevant outcomes from the composite primary endpoint) further demonstrate that vutrisiran treatment leads to clinically relevant benefits in patients with ATTR-CM.

Figure 20: HELIOS-B exploratory endpoint: time to first oral loop diuretic intensification, first CV event, or ACM (whichever occurred first) in the overall population and monotherapy population



ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; ODI, oral diuretic intensification; PH, proportional hazards. Note: HRs are reported as a comparison of the vutrisiran arm versus the placebo arm within the specified population (overall population or monotherapy population). This endpoint was assessed over the double-blind period (up to 36 months from baseline) via log-rank test and Cox PH model, including the same stratification factors and covariates as those used in the ACM secondary endpoint analysis. Source: HELIOS-B CSR 1 2024[130]

2.6.9 Drop-in use of tafamidis in the monotherapy population

Within the monotherapy population, a similar number of patients, 44 patients (22.4%) in the vutrisiran arm and 41 patients in the placebo arm (20.6%), started treatment with tafamidis (tafamidis drop-in) during HELIOS-B.[3] Among these patients, the timing of tafamidis initiation relative to HELIOS-B baseline was similar when comparing the vutrisiran and placebo arms

(vutrisiran, median: 17.7 months [range: 6.4–39.1]; placebo, median: 17.0 months [range: 1.5–33.8]).[3]

[redacted] In cases in which the reason for drop-in was categorised as “potential clinical benefit”, patients were not progressing in disease, but rather, the decision to initiate treatment with tafamidis was based on a lack of expectation of potential negative repercussions from doing so, with potential for clinical benefit. Note that during HELIOS-B, tafamidis received regulatory approval in multiple countries and regions such as Canada,[131] Australia,[132] and the EU.[33,133] Within these regions, which contained many HELIOS-B trial sites,[130] the regulatory approval of tafamidis, resulting in the availability of a new, potentially beneficial treatment option, likely contributed to the occurrence of tafamidis drop-in for “potential clinical benefit" during the trial.

Of note, tafamidis drop-in rates were similar in the vutrisiran and placebo groups within the monotherapy population; however, drop-in use for “potential clinical benefit” (i.e., not in situations where patients were progressing in disease) was more common in vutrisiran-treated patients, while drop-in use for disease progression was more common in placebo-administered patients.

2.6.10 Overview of efficacy results from within-trial comparison of vutrisiran and tafamidis monotherapy arms

The cost-effectiveness model described in Section 3 compares vutrisiran and tafamidis for the treatment of patients with ATTR-CM. Clinical inputs for the vutrisiran and tafamidis arms in this analysis were informed by results in HELIOS-B, via data from patients receiving vutrisiran monotherapy (i.e., patients in the vutrisiran arm within the monotherapy population; n=196) and patients receiving tafamidis monotherapy (i.e., patients in the placebo arm who were on background tafamidis at baseline; n=129).

Stabilised inverse probability of treatment weighting (IPTW) was used to balance baseline differences between the vutrisiran and tafamidis monotherapy groups, given these groups were not randomised within HELIOS-B. Another point to note regarding differences between these two groups is that patients in the tafamidis monotherapy group had been receiving treatment with tafamidis for a median of 11.3 months (range: 1.1, 65.5) at baseline, meaning that these patients were already deriving some degree of efficacy benefit from tafamidis at baseline of HELIOS-B. In contrast, patients in the vutrisiran group were not receiving vutrisiran until entry into HELIOS-B, and thus did not derive efficacy benefit from vutrisiran until after HELIOS-B baseline.

Outcomes from HELIOS-B that informed the cost-effectiveness model include ACM, recurrent CV events, NYHA class, and HRQoL (EQ-5D 5-level [EQ-5D-5L] index score). A summary of results for these outcomes is provided in Table 16.

Table 16: Summary of results from HELIOS-B for the vutrisiran and tafamidis monotherapy arms

Measure	Vutrisiran monotherapy (n=196)	Tafamidis monotherapy (n=129)
Composite of ACM and recurrent CV events over up to 36 months*		
Patients with at least one event, n (%) ***Note: Results not adjusted for baseline differences between treatment groups.***	[redacted]	[redacted]
HR (vutrisiran/tafamidis) (95% CI)	0.83 (0.54, 1.29)	
ACM over up to 42 months†		
Deaths, n (%) ***Note: Results not adjusted for baseline differences between treatment groups.***	[redacted]	[redacted]
HR (vutrisiran/tafamidis) (95% CI)	0.81 (0.50, 1.34)	
Recurrent CV events over up to 36 months‡		
Total CV events ***Note: Results not adjusted for baseline differences between treatment groups.***	[redacted]	[redacted]
CV event rate, (95% CI)	[redacted]	[redacted]
Relative rate ratio, (95% CI)	0.82 (0.62, 1.08)	
Change in NYHA class over 30 months§		
Stable/improved over 30 months, %	[redacted]	[redacted]
Adjusted difference (vutrisiran – tafamidis)	[redacted]	
Odds ratio at Month 30 (vutrisiran vs. tafamidis) (95% CI)	[redacted]	
Change in EQ-5D-5L index score over 30 months#		
LS mean change over 30 months, (95% CI)	[redacted]	[redacted]
LS mean difference (vutrisiran – tafamidis), (95% CI)	[redacted]	

6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-dimension 5-level; HR, hazard ratio; IPTW, inverse probability of treatment weighting; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire; LS, least square; MMRM, mixed effects model repeated measures; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; SEM, standard error of the mean. Note: These comparisons used stabilised inverse probability of treatment weighting based on propensity scores, calculated through a logistic regression model of the odds of being in the vutrisiran monotherapy vs. tafamidis monotherapy group, conditional on patients' baseline characteristics. The following parameters were included as covariates: age category, ATTR disease type, NYHA class, log-transformed troponin I, log-transformed NT-proBNP, KCCQ-OS score, average peak longitudinal strain, eGFR, sex, race category, history of antithrombotic agents, PND score, and 6-MWT. *Hazard ratios are based on the modified Andersen-Gill model and include treatment, log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT as covariates. †Analysed using a Cox proportional hazards model with treatment group, log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT as covariates. Proportional hazards assumptions were not met. ‡CV event rate and relative rate ratio were determined via a Poisson regression model that included treatment group, log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT as covariates, with logarithm of the follow-up time as an offset variable. §Adjusted difference and 95% CI were derived from multiple imputation procedure by combining estimates per Rubin's rules based on 100 datasets where missing NYHA class

values due to death, heart transplantation, and left ventricular assist device placement are imputed as class IV, and the other missing NYHA class values are imputed using a Markov chain Monte Carlo procedure including selected baseline variables and postbaseline NYHA class assessments. For each imputed dataset, adjusted proportions, odds ratios, and 95% CI are based on a logistic regression model including treatment group, log-transformed NT-proBNP, log-transformed troponin I, 6-MWT, and baseline NYHA as covariates. ¶For patients with missing KCCQ-OS score data at a given time point due to death, data at that time point were derived from imputed domain change scores; domain change scores were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline domain score for the patient with the missing data]. LS means are based on an MMRM model including baseline KCCQ-OS score, treatment group, visit, log-transformed NT-proBNP, log-transformed troponin I, 6-MWT and treatment-by-visit as covariates. #LS means are based on an MMRM model including baseline EQ-5D-5L index score, treatment group, visit, log-transformed NT-proBNP, log-transformed troponin I, 6-MWT, and treatment-by-visit as covariates. Source: Alnylam data on file

2.7 Subsequent treatments used in the relevant studies

During HELIOS-B, only tafamidis was approved globally for the treatment of ATTR-CM. Following discontinuation of vutrisiran in HELIOS-B, subsequent use of tafamidis was not monitored.

2.8 Subgroup analysis

Subgroup analyses were preplanned for all primary and secondary endpoints in both the overall population and monotherapy population.[128] Subgroups assessed included age (<75 and ≥75 years old), tafamidis use at baseline (yes and no; only in the overall population), ATTR disease type (hATTR and wtATTR), baseline NYHA class (I/II and III), and baseline serum NT-proBNP (≤2,000 ng/L and >2,000 ng/L).

Due to the importance of the primary endpoint (composite of ACM and recurrent CV events) and secondary endpoint of ACM over up to 42 months as measures of the impact of treatment on the most severe consequences of ATTR-CM, statistical methods and results of the subgroup analyses for these two endpoints in both the overall population and monotherapy population are presented in this submission.

Subgroup analyses for the primary endpoint were conducted using a modified Andersen-Gill model with a robust variance estimator (referred to as the LWYY model), including treatment (vutrisiran vs. placebo) and baseline NT-proBNP (continuous variable with logarithmic transformation) as covariates.

Subgroup analyses for the secondary endpoint of ACM were analysed using a Cox model including treatment (vutrisiran vs. placebo) and baseline NT-proBNP (continuous variable with logarithmic transformation) as covariates.

For subgroup analyses in the overall population for both endpoints, models were also stratified by baseline tafamidis use.

Results of subgroup analyses of the primary endpoint and secondary endpoint of ACM are presented in Appendix C. Results of all subgroup analyses (not limited to the primary endpoint and secondary endpoint of ACM) demonstrated consistent clinical benefit for vutrisiran in all subgroups, with point estimates of treatment effect consistently favouring vutrisiran.[130]

2.9 Meta-analysis

As there are no further phase 3 randomised trials studying the efficacy and safety of vutrisiran in ATTR-CM, no meta-analysis was conducted.

2.10 Indirect and mixed treatment comparisons

In HELIOS-B, 40% of patients were receiving background tafamidis at baseline. For an indirect comparison of vutrisiran versus tafamidis, the HELIOS-B population included in the

comparison would need to be limited to the monotherapy population (i.e., patients not on tafamidis at baseline), to minimise any confounding of results due to background tafamidis use.

A feasibility assessment for an indirect treatment comparison (ITC) of vutrisiran (from HELIOS-B in the monotherapy population) versus tafamidis (from ATTR-ACT, the phase 3 trial of tafamidis described in Section 1.3.3.1) concluded that it was not feasible to conduct a cross-trial comparison of the two treatments in an unbiased manner.

The lack of feasibility was due to imbalances in the patient populations assessed in HELIOS-B and ATTR-ACT, which were driven by recent advancements in the ATTR-CM management landscape. This resulted in patient populations with vastly different baseline characteristics—including multiple parameters that could not be adjusted for, such as the use of supportive care interventions concomitantly with study treatment.

Differences in baseline characteristics in HELIOS-B and ATTR-ACT

Due to the evolution of clinical practice over time, patients diagnosed with ATTR-CM in the present benefit from recent advances in supportive care that have improved baseline prognosis for all patients with ATTR-CM. In recent years, patients with ATTR-CM have increasingly been diagnosed earlier, with less severe disease, due to increased disease awareness within the clinician community and improved diagnostic techniques (e.g., more widespread availability of technetium scintigraphy as a non-invasive alternative to cardiac biopsy).[104,109]

For these reasons, baseline disease characteristics were broadly different between patients in HELIOS-B and ATTR-ACT, due to the differing time periods in which these trials were conducted (Table 17). Even with propensity score reweighting of patient data from HELIOS-B, performed as part of the feasibility assessment for a matching-adjusted indirect treatment comparison (MAIC), significant differences in baseline characteristics remained between the HELIOS-B monotherapy population patients and patients in ATTR-ACT, specifically with respect to race, geographic region (US vs. ex-US), percentage of patients with troponin I level greater than the median value observed in ATTR-ACT, global longitudinal strain, left ventricular ejection fraction (LVEF), modified body mass index (mBMI), and percentage of patients with diabetes (Table 17).

These parameters represent potential confounding factors in a comparison of vutrisiran and tafamidis. For example, troponin I, global longitudinal strain, LVEF, and mBMI have all been shown to have statistically significant associations with mortality risk in patients with ATTR-CM,[16,17,19] while the presence of diabetes is understood to increase the risk of morbidity and mortality in patients with heart disease.[147]

Furthermore, only 2.6% of patients in the monotherapy subgroup of HELIOS-B were recruited from the US (Alnylam, data on file), and the majority were recruited from other geographies. In contrast, the ATTR-ACT population was recruited primarily from the US (63.3%),[10] creating an additional, substantial geographic imbalance between the HELIOS-B and ATTR-ACT populations that may have an important impact on treatment outcomes (e.g., due to geographic differences in medical practice regarding what clinical situations necessitate CV hospitalisation), and that cannot be fully resolved via adjustment methods.

Table 17: Baseline characteristics in HELIOS-B and ATTR-ACT before and after propensity score weighting to balance characteristics between trial populations

Characteristic	HELIOS-B monotherapy population*		ATTR-ACT†		P value	
	Vutrisiran (N=195)	Placebo (N=198)	Tafamidis 80mg (N=176)	Placebo (N=177)	Vutrisiran vs. tafamidis	Placebo vs. placebo
Before MAIC weighting						
Age, mean, years (SD)	76.27 (6.83)	75.48 (6.41)	75.20 (7.20)	74.10 (6.70)	[redacted]	[redacted]
Male, n (%)	177 (90.77)	182 (91.92)	158 (89.80)	157 (88.70)	[redacted]	[redacted]
Race, White, n (%)	168 (86.15)	168 (84.85)	136 (77.30)	146 (82.50)	[redacted]	[redacted]
Race, Black, n (%)	10 (5.13)	11 (5.56)	26 (14.80)	26 (14.70)	[redacted]	[redacted]
Race, Asian, n (%)	12 (6.15)	15 (7.58)	11 (6.30)	5 (2.80)	[redacted]	[redacted]
Race, other, n (%)	5 (2.56)	4 (2.02)	3 (1.70)	0 (00)	[redacted]	[redacted]
NYHA I/II, n (%)	186 (95.38)	180 (90.91)	121 (68.80)	114 (64.40)	[redacted]	[redacted]
NYHA III, n (%)	9 (4.62)	18 (9.09)	55 (31.30)	63 (35.60)	[redacted]	[redacted]
hATTR, n (%)	23 (11.79)	25 (12.63)	42 (23.90)	43 (24.30)	[redacted]	[redacted]
wtATTR, n (%)	172 (88.21)	173 (87.37)	134 (76.10)	134 (75.70)	[redacted]	[redacted]
USA, n (%)	[redacted]	[redacted]	108 (61.40)	108 (61.00)	[redacted]	[redacted]
Ex-USA, n (%)	[redacted]	[redacted]	68 (38.60)	69 (39.00)	[redacted]	[redacted]
6-MWT, mean, metres (SD)	362.94 (102.95)	373.13 (98.25)	344.80 (120.30)	353.30 (126.00)	[redacted]	[redacted]
KCCQ-OS score mean, points (SD)	70.29 (20.21)	69.93 (20.80)	67.10 (21.30)	65.90 (21.70)	[redacted]	[redacted]
NT-proBNP, mean, pg/mL (SD)	2883.12 (2048.45)	2413.88 (1850.75)	3941.10 (3090.00)	3845.50 (2971.50)	[redacted]	[redacted]
NT-proBNP > median observed in ATTR-ACT, n (%)	[redacted]	[redacted]	88 (50.00)	88 (50.00)	[redacted]	[redacted]
Troponin I, mean, ng/mL (SD)	0.15 (0.28)	0.25 (2.19)	0.26 (0.94)	0.18 (0.18)	[redacted]	[redacted]
Troponin I > median observed in ATTR-ACT, n (%)	[redacted]	[redacted]	88 (50.00)	88 (50.00)	[redacted]	[redacted]

Characteristic	HELIOS-B monotherapy population*		ATTR-ACT†		P value	
	Vutrisiran (N=195)	Placebo (N=198)	Tafamidis 80mg (N=176)	Placebo (N=177)	Vutrisiran vs. tafamidis	Placebo vs. placebo
Global longitudinal strain, % (SD)	[redacted]	[redacted]	–9.30 (3.70)	–9.40 (3.60)	[redacted]	[redacted]
LVEF, % (SD)	[redacted]	[redacted]	48.00 (10.50)	48.60 (9.50)	[redacted]	[redacted]
Years since diagnosis (SD)	1.03 (1.28)	1.17 (1.28)	0.93 (1.18)	1.23 (1.44)	[redacted]	[redacted]
Implanted cardiac defibrillator, n (%)	[redacted]	[redacted]	11 (6.10)	9 (5.10)	[redacted]	[redacted]
Permanent pacemaker, n (%)	[redacted]	[redacted]	9 (4.90)	12 (6.80)	[redacted]	[redacted]
mBMI, mean, kg/m^2 x g/L (SD)	1224.62 (190.68)	1220.76 (184.34)	1064.50 (172.50)	1066.40 (194.40)	[redacted]	[redacted]
Atrial fibrillation, n (%)	114 (58.46)	110 (55.56)	93 (52.80)	89 (50.30)	[redacted]	[redacted]
Diabetes, n (%)	4 (2.05)	6 (3.03)	14 (8.00)	13 (7.30)	[redacted]	[redacted]
Hypertension, n (%)	101 (51.79)	107 (54.04)	90 (51.10)	84 (47.50)	[redacted]	[redacted]
NAC I, n (%)	11 (57.95)	137 (69.19)	79 (45.10)	71 (40.10)	[redacted]	[redacted]
NAC II, n (%)	67 (34.36)	55 (27.78)	63 (36.00)	72 (40.70)	[redacted]	[redacted]
NAC III, n (%)	15 (7.69)	6 (3.03)	33 (18.90)	34 (19.20)	[redacted]	[redacted]
eGFR, mean, mL/min/1.73m^2, (SD)	67.27 (23.19)	69.90 (20.64)	57.50 (17.30)	55.60 (16.80)	[redacted]	[redacted]
After MAIC weighting						
Age, mean, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	–	–
Male, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, White, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, Black, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, Asian, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, other, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA I/II, %	[redacted]	[redacted]	[redacted]	[redacted]	–	–
NYHA III, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hATTR, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
wtATTR, %	[redacted]	[redacted]	[redacted]	[redacted]	–	–
USA, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ex-USA, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-MWT, mean, metres (SD)	[redacted]	[redacted]	[redacted]	[redacted]	–	–

Characteristic	HELIOS-B monotherapy population*		ATTR-ACT†		P value	
	Vutrisiran (N=195)	Placebo (N=198)	Tafamidis 80mg (N=176)	Placebo (N=177)	Vutrisiran vs. tafamidis	Placebo vs. placebo
KCCQ-OS score mean, points (SD)	[redacted]	[redacted]	[redacted]	[redacted]	–	–
NT-proBNP, mean, pg/mL (SD)	[redacted]	[redacted]	[redacted]	[redacted]	–	–
NT-proBNP > median observed in ATTR-ACT, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Troponin I, mean, ng/mL (SD)	[redacted]	[redacted]	[redacted]	[redacted]	–	–
Troponin I > median observed in ATTR-ACT, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global longitudinal strain, % (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LVEF, % (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Years since diagnosis (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Implanted cardiac defibrillator, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Permanent pacemaker, %	[redacted]	[redacted]	[redacted]	[redacted]	–	–
mBMI, mean, kg/m^2 x g/L (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAC I, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	–	–
NAC II, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	–	–
NAC III, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mean, $mL/min/1.73m^2$, (SD)	[redacted]	[redacted]	[redacted]	[redacted]	–	–

6-MWT, 6-minute walk test; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LVEF, left ventricular ejection fraction; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; wtATTR, wild-type transthyretin amyloidosis. *In HELIOS-B, propensity score adjustment was conducted for patients not on tafamidis at baseline in the full analysis set. Among these patients (vutrisiran, N=196; placebo, N=199), one patient in the vutrisiran group and one patient in the placebo group were missing the baseline KCCQ-OS score assessment and were excluded from the analysis. †Data are from the tafamidis 80 mg group in ATTR-ACT, except for data on the following parameters, which were only available from the pooled tafamidis group (20 mg + 80 mg) in ATTR-ACT: patients with an implanted cardiac defibrillator or permanent pacemaker, eGFR, and NAC stage. Note: Baseline characteristics from ATTR-ACT were sourced from the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) report for tafamidis,[148] the Centre for Drug Evaluation and Research (United States FDA) Clinical Review of tafamidis,[149] Damy et al. (2021),[31] Shah et al. (2024),[150] and Vong et al. (2021).[151] P-values for continuous variables were calculated using the Wald test. P-values for categorical variables were calculated using the chi-square test. The Fisher exact test was used for categorical variables with small frequency (i.e., n <5).

Differences in supportive care in patients in HELIOS-B and ATTR-ACT

Advancements in general management of heart failure have improved the baseline prognosis of patients with ATTR-CM in a way that may modify the magnitude of effect of an active disease-modifying treatment and that cannot be accounted for using propensity score adjustment.[152]

For example, sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have recently been shown to provide benefit by better managing underlying fluid imbalance resulting from heart failure in patients with ATTR-CM,[152] were used by 237 patients (36.2%) in HELIOS-B, including 216 patients who initiated an SGLT2 inhibitor post-baseline. This highlights the recent inclusion of SGLT2 inhibitors in the supportive management of patients with ATTR-CM. However, complete data regarding the use of supportive care interventions are not readily available from ATTR-ACT, meaning they cannot be accounted for in an ITC of vutrisiran and tafamidis. This imbalance is anticipated to have potentially important impacts that would confound assessment of the relative efficacy of vutrisiran and tafamidis in an ITC.

Differences in clinical outcomes in placebo-administered patients in HELIOS-B and ATTR-ACT

As a result of the above-described differences in the contemporary patient population in HELIOS-B and the historical population in ATTR-ACT, clinical outcomes in the placebo groups of these trials differed substantially. As outlined in Table 18, even after propensity score matching, patients in the placebo group in ATTR-ACT had higher mortality risk, increased occurrence of CV events, and greater declines in physical capacity (via 6-MWT) and HRQoL (via KCCQ-OS), when compared patients in the placebo group in HELIOS-B. This is likely due to baseline parameters that were still significantly different after propensity score matching, and due to differences (which could not be adjusted for due to data availability) in supportive care that was available during the time periods in which these trials took place. These results exemplify the bias that would be present in an ITC of vutrisiran and tafamidis, making it infeasible to perform.

Table 18: Outcomes in placebo-administered patients from HELIOS-B and ATTR-ACT after propensity score matching

Outcome	HELIOS-B monotherapy population, placebo (n=198)	ATTR-ACT, placebo (n=177)
ACM, HELIOS-B placebo vs. ATTR-ACT placebo, HR (95% CI)	[redacted]	
Frequency of CV events, incidence rate per patient-year (95% CI)	[redacted]	[redacted]
6-MWT, LS mean change at Month 30, metres (95% CI)	[redacted]	[redacted]
KCCQ-OS, LS mean change at Month 30, points (95% CI)	[redacted]	[redacted]

6-MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least square. Source: Alnylam data on file.

2.11 Adverse reactions

Vutrisiran had an acceptable safety profile in HELIOS-B (Table 19). Almost all patients in the vutrisiran and placebo groups had at least one adverse event (AE), with higher proportions of patients in the placebo group compared to the vutrisiran group experiencing a serious AE (SAE), severe AE, cardiac AE, cardiac SAE, and an AE leading to treatment discontinuation or death. These findings support observations from a previous phase 3 trial of vutrisiran (HELIOS-A, included in NICE's appraisal of vutrisiran for hATTR-PN) which demonstrated vutrisiran to have an acceptable safety profile.[7,153]

Table 19: Adverse event profile of vutrisiran and placebo in HELIOS-B

Event, n (%)	Vutrisiran (N=326)	Placebo (N=328)
At least 1 AE	322 (99)	323 (98)
AEs occurring in ≥15% of patients in either arm		
Cardiac failure	101 (31)	128 (39)
Covid-19	87 (27)	99 (30)
Atrial fibrillation	69 (21)	68 (21)
Gout	48 (15)	51 (16)
Dyspnoea	43 (13)	51 (16)
Fall	42 (13)	69 (21)
Any SAE	201 (62)	220 (67)
SAEs occurring in ≥5% of patients in either arm		
Cardiac failure	38 (12)	57 (17)
Atrial fibrillation	26 (8)	20 (6)
Cardiac failure acute	13 (4)	18 (5)
Any severe AE	158 (48)	194 (59)
Cardiac AEs	227 (70)	242 (74)
Cardiac SAEs	116 (36)	124 (38)
AEs leading to discontinuation	10 (3)	13 (4)
AEs leading to death	49 (15)	63 (19)

AE, adverse event; SAE, serious adverse event. Source: Fontana et al. 2024[3]

Appendix D describes searches for additional studies that reported AEs incurred in patients with ATTR-CM treated with vutrisiran.

2.12 Ongoing studies

The OLE phase of HELIOS-B is currently ongoing, in which patients are treated with vutrisiran SC Q3M for up to 2 years. Results from this phase of HELIOS-B will provide data regarding the long-term efficacy and safety of vutrisiran in patients with ATTR-CM. It is not expected that there will be any interim analyses available within the next 12 months.

2.13 Interpretation of clinical effectiveness and safety evidence

Vutrisiran modifies the disease trajectory in ATTR-CM and addresses key needs of patients by reducing excess morbidity and mortality, preserving physical function and HRQoL, and preventing worsening of cardiac injury, with consistent efficacy across all patient types.

Results from HELIOS-B suggest that vutrisiran can potentially restore survival in patients with ATTR-CM to that of the age-matched general population.[38]

ATTR-CM is a burdensome, rapidly progressive, and fatal disease. Tafamidis is currently the only approved therapy available for patients with ATTR-CM in the UK.[30] Tafamidis acts downstream from the source of the disease-causing TTR protein by stabilising unstable TTR tetramers.

Although tafamidis demonstrated the slowing of disease progression in the ATTR-ACT trial, tafamidis-treated patients showed substantial rates of mortality and morbidity, as well as ongoing worsening of physical capacity, HRQoL, and cardiac injury relative to their pretreatment baseline, with limited therapeutic benefit in some patient types (described in Section 1.3.3.2).[10] Furthermore, the population in ATTR-ACT was vastly different from the contemporary ATTR-CM population in HELIOS-B. Considering the progress made in recent years in disease awareness, diagnosis, and supportive care strategies, the contemporary ATTR-CM population in HELIOS-B was generally healthier than the historical population in ATTR-ACT at baseline, and received better supportive care throughout the trial. This suggests that results from ATTR-ACT may not be generalisable to the contemporary ATTR-CM population.

Vutrisiran is a novel RNAi therapy that acts upstream of tafamidis in modifying the ATTR-CM disease pathway,[37] with a mechanism of action that inhibits TTR gene expression by promoting catalytic degradation of TTR mRNA, resulting in rapid and sustained reduction in TTR protein production in the liver and subsequently, rapid and sustained knockdown of circulating serum TTR protein, the underlying cause of ATTR-CM (Section 1.3.3.4). In HELIOS-B, when compared to patients who received placebo, treatment with vutrisiran led to statistically significant and clinically meaningful benefits in patients with ATTR-CM across all primary and secondary endpoints in the overall population and the monotherapy population. Vutrisiran-treated patients had significant reductions (28% risk reduction overall and 33% risk reduction in patients not on background tafamidis at baseline) in the composite risk of ACM and recurrent CV events, in addition to a significant reduction (35% risk reduction overall and 34% risk reduction in patients not on background tafamidis at baseline) in ACM as a stand-alone endpoint. Results from HELIOS-B demonstrate that vutrisiran can potentially restore mortality rates in patients with ATTR-CM to those of the age-matched general population.[38] Notably, the efficacy observed on these key measures was consistent across all prespecified subgroups, including age, baseline tafamidis use, ATTR disease type, NYHA class, and baseline NT-proBNP.

Beyond the benefits demonstrated on the primary composite endpoint and on the secondary endpoint of ACM, vutrisiran also provided statistically significant and clinically meaningful benefits over placebo in terms of heart failure severity (via NYHA class), physical capacity (via 6-MWT), and HRQoL (via KCCQ-OS). Median observed changes from baseline in 6-MWT and KCCQ-OS, respectively, showed the relative stabilisation of (i.e., halting of worsening in) physical capacity and HRQoL at pretreatment baseline levels in vutrisiran-treated patients. In addition, a similar pattern of stabilisation was noted on the exploratory endpoint of NT-proBNP, a prognostic factor in ATTR-CM and key marker of cardiac injury (described in Section 1.3.2.6). Stabilisation of the disease is a notable and highly relevant

treatment benefit provided by vutrisiran, considering that the natural history of ATTR-CM is characterised by rapid disease progression leading to irreversible loss of physical function and HRQoL. These results show that vutrisiran addresses the current unmet clinical needs of patients with ATTR-CM.

The benefits demonstrated by vutrisiran are even more notable when considering that HELIOS-B included a contemporary population of patients with ATTR-CM. Due to the evolution of clinical practice over time, patients in HELIOS-B had less severe disease at baseline compared to patients in previous phase 3 trials of therapies for ATTR-CM (i.e., ATTR-ACT), and are likely to have benefited from recent advances in supportive care that have improved baseline prognosis for all patients with ATTR-CM. Improved outcomes in placebo-administered patients in HELIOS-B as a result of this evolution could have been expected to limit the opportunity to demonstrate benefit over placebo with active treatment, and thus reduce relative treatment effect sizes. Despite these considerations, vutrisiran demonstrated statistically and clinically significant benefit versus placebo across all primary and secondary endpoints, including an approximate 30% relative reduction in the composite risk of death and recurrent CV events and an approximate 35% relative reduction in ACM.[3] As noted above, this increases the relevancy of the present results, as treatment outcomes in the contemporary patient population in HELIOS-B (versus the population studied in ATTR-ACT) are more generalisable to current patients with ATTR-CM in the UK.

In this regard, the October 2024 Institute for Clinical and Economic Review's (ICER) report on ATTR-CM concluded with high certainty that vutrisiran provides a substantial net health benefit when compared to no disease-specific therapy (such that vutrisiran received an "A" grade for comparative clinical effectiveness), whereas it was concluded (due to the historical nature of the ATTR-ACT trial population) that there was only moderate certainty that tafamidis provides a substantial net health benefit compared to no disease-specific therapy (such that tafamidis received a "B+" grade for comparative clinical effectiveness).[114]

Aside from showing efficacy across the full range of endpoints and patient subgroups in HELIOS-B, vutrisiran demonstrated an acceptable safety profile in patients with ATTR-CM, with AEs occurring at a similar or lower rate compared to placebo. Further, the administration profile of vutrisiran provides a valuable and convenient alternative for patients in whom daily oral treatment with tafamidis may pose challenges.

In summary, vutrisiran addresses the current unmet needs associated with the treatment of ATTR-CM with tafamidis, by stabilising cardiac well-being and physical capacity, thereby preserving HRQoL, and ultimately, significantly reducing morbidity and mortality, with consistent efficacy in all ATTR-CM patient types.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

An SLR was conducted to identify published cost-effectiveness studies in ATTR-CM (described in Appendix E). A total of 12 records were identified, including one published journal article, one conference abstract, one Institute for Clinical and Economic Review report, and nine health technology assessment (HTA) reports, which are summarised in Table 20.

Table 20: Summary of published cost-effectiveness studies in ATTR-CM

Study	Year	Summary of model	Population	QALYs	Costs	ICER (Cost per QALY)
Kazi et al.[154]	2020	**Model Type:** Markov **Health states**: event-based, with modelled events including hospitalisation from CV causes and death from CV or non-CV causes. **Intervention**: Tafamidis **Comparator:** Usual care (no disease-specific treatment)	Adult patients with ATTR-CM. **Age at model entry:** 74.5 years	**Tafamidis**: 3.48 **BSC:** 2.19	**Tafamidis:** US$1,262,000 **BSC:** US$126,000	US$880,000
Sebastião et al.[155]	2023	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 74 years	**Tafamidis**: 5.86 **BSC:** 2.59	**Tafamidis:** R$1,220,718 **BSC:** R$11,668 *(Costs in Brazilian Reals)*	R$473,458 *(Costs in Brazilian Reals)*
CDA appraisal of tafamidis[156]	2020	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 75 years	**Tafamidis**: 5.21 **BSC:** 2.01	**Tafamidis:** CAD$833,282 **BSC:** CAD$42,903	CAD$247,069
NICE first appraisal of tafamidis (TA696)[157]	2021	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 74.3 years	*Redacted*	*Redacted*	**Submitted by company:** <£30,000 **NICE committee:** “Substantially above £30,000”

Study	Year	Summary of model	Population	QALYs	Costs	ICER (Cost per QALY)
NICE second appraisal of tafamidis (TA984)[157]	2024	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 74.3 years	*Redacted*	*Redacted*	**Submitted by company:** Within acceptable range (£20,000–£30,000) **NICE committee:** Agreed
SMC first appraisal of tafamidis	2021	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 74.3 years	*Redacted*	**Tafamidis:** Intervention cost per year based on list price: £129,645	*Redacted*
SMC second appraisal of tafamidis[158]	2023	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 74.3 years	*Redacted*	**Tafamidis:** Intervention cost per year based on list price: £129,645	*Redacted*
PBAC first appraisal of tafamidis[159]	2020	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM. **Age at model entry:** 74 years	**Tafamidis**: 3.80 **BSC:** 1.83	*Redacted*	>AU$200,000
PBAC final appraisal of tafamidis[160]	2023	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM in NYHA I/II. **Age at model entry:** 74 years	**Tafamidis**: 4.16 **BSC:** 3.19	**Tafamidis:** Between AU$155,000 and AU$255,000 **BSC:** AU$51,684	Between AU$135,000 and AU$155,000
TLV appraisal of tafamidis[161]	2020	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM in NYHA I/II. **Age at model entry:** 74 years	*Redacted*	*Redacted*	*Redacted*

Study	Year	Summary of model	Population	QALYs	Costs	ICER (Cost per QALY)
HAS appraisal of tafamidis[162]	2019	**Model type:** Markov **Health states:** NYHA classes **Intervention:** Tafamidis **Comparator:** BSC	Adult patients with ATTR-CM in NYHA I–III and <90 years of age. **Age at model entry:** 74.3 years	**Tafamidis**: 3.28 **BSC:** 1.83	**Tafamidis:** €367,337 **BSC:** €31,064	€231,568
Institute for Clinical and Economic Review appraisal on ATTR-CM therapies[114]	2024	**Model type:** Markov **Health states:** NYHA classes **Intervention:** TTR stabilising agents (tafamidis or acoramidis) **Comparator:** BSC	Adult patients with ATTR-CM **Age at model entry:** 77 years	**TTR stabilising agents**: 2.9 **BSC:** 2.0	**TTR stabilising agents:** US$858,000 **BSC:** US$76,000	US$873,000

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; BSC, best supportive care; CDA, Canada's Drug Agency; CV, cardiovascular; HAS, Haute Autorité de Sante; HF, heart failure; ICER, incremental cost-effectiveness analysis; IVS, interventricular septal; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PBAC, Pharmaceutical Benefits Advisory Committee; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; TLV, The Swedish Dental and Pharmaceutical Benefits Agency; TTR, transthyretin.

3.2 Economic analysis

This pharmacoeconomic analysis (cost-effectiveness analysis [CEA]) compares costs and clinical outcomes of vutrisiran versus tafamidis for the treatment of ATTR-CM. The model for this analysis estimates costs associated with the treatment of ATTR-CM using either vutrisiran or tafamidis and converts clinical outcomes observed over time in the target patient population of patients with ATTR-CM into life-years (LYs) and quality-adjusted life-years (QALYs). The results of the model are expressed in terms of cumulative costs and LYs and QALYs for vutrisiran and tafamidis, and incremental cost per clinical outcome, including incremental costs per LY gained and incremental costs per QALY gained (i.e., incremental cost-effectiveness ratio [ICER]), with vutrisiran relative to tafamidis.

The studies described in Table 20 were used to inform the model where appropriate. Specific approaches in this analysis that align with published studies are noted.

3.2.1 Patient population

The CEA evaluates the overall ATTR-CM patient population, in line with the product label and final NICE scope.

3.2.2 Model structure

A Markov cohort model was developed in Microsoft Excel® to assess the cost effectiveness of vutrisiran for the treatment of ATTR-CM. The model simulates the clinical course of ATTR-CM and traces the movement of the patient cohort through the stages of the disease using health states defined by the NYHA classification of heart failure.

NYHA functional classification is a commonly used staging system for heart failure (Section 1.3.2.6), including that resulting from ATTR-CM (Table 21).[106]

Table 21: NYHA functional classification of heart failure

NYHA class	Criteria	
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or shortness of breath.	**Worsening disease** 
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath, or chest pain.	
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath, or chest pain.	
IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort.	

NYHA, New York Heart Association. Source: American Heart Association[106]

3.2.2.1 Use of NYHA classes to model ATTR-CM disease progression

NYHA classification was selected to model disease progression (health states) in patients with ATTR-CM in this CEA for several reasons, which are outlined below.

Widespread use

The NYHA classification system has emerged as the preferred tool for heart failure classification in economic analyses in ATTR-CM, as seen in the recent HTA appraisals of tafamidis in the UK (NICE),[163] France (Haute Autorité de Sante [HAS]),[162] Canada (Canada's Drug Agency [CDA]),[156] the US (Institute for Clinical and Economic Review),[114] Australia

(Pharmaceutical Benefits Advisory Committee [PBAC]),[159,160] Scotland (Scottish Medicines Consortium [SMC]),[158,164] and Sweden (The Swedish Dental and Pharmaceutical Benefits Agency [TLV]).[161] The NYHA classification system is a universal system for defining severity of heart failure resulting from different cardiac pathologies. Its ease of implementation (via clinician assessment) makes it a readily available and accessible tool.

Prognostic value and association with HRQoL and healthcare resource use

The NYHA classification system has been shown to be predictive of mortality, HRQoL, and HCRU in patients with ATTR-CM. For example, a retrospective study of patients with ATTR-CM (N=309) demonstrated that NYHA class at baseline (first clinical visit) was a significant predictor of mortality.[22] Specifically, a 1.85-fold increase in mortality hazard (adjusted HR: 1.85 [95% CI: 1.22, 2.80]; P=0.004) was observed for every 1-level increase in NYHA class.[22] Additionally, in the placebo group in ATTR-ACT, lower rates of overall mortality and cardiovascular-related mortality were observed in patients in NYHA classes I and II compared to those in class III at baseline.[165]

Further, higher NYHA class (indicating more severe heart failure) is correlated with worse HRQoL in patients with ATTR-CM.[102] In this regard, a cross-sectional study of 169 patients with ATTR-CM from Sweden, Norway, Finland, and Denmark who were observed between January 2021 and January 2022 found that higher NYHA class was significantly correlated with decreased KCCQ scores (all domains), decreased EQ-5D-5L utility and VAS scores, and increased Major Depression Inventory (MDI) scores, all of which indicate decreased HRQoL or increased psychological burden.[102]

In addition, a study of UK patients with ATTR-CM identified that HCRU and associated costs to the healthcare system are higher in patients with ATTR-CM who are in more severe NYHA classes.[25]

Endpoint prioritisation in HELIOS-B

In HELIOS-B, the proportion of patients with improved or stable NYHA class over 30 months of treatment was assessed as a prespecified secondary endpoint (Section 2.3.5.2), whereas other potential disease staging measurements collected in HELIOS-B were only assessed as exploratory endpoints.[3]

Conclusion

The use of a NYHA class-based model ensures consistency and comparability with past appraisals, given the established precedent of using NYHA class-based models in prior economic evaluations in ATTR-CM.[114,156,158-164] In addition, NYHA class is widely used in clinical practice to assess the progression of ATTR-CM, and therefore, modelling of the benefits and costs of ATTR-CM treatment within the framework of the NYHA classification is directly relevant to real-world practice. In ATTR-CM, NYHA classes are representative of HRQoL and predictive of survival,[22,102,165] and are thus suitable for stratifying patients according to expected outcomes in a cost-effectiveness model for ATTR-CM. Finally, the pivotal HELIOS-B study of vutrisiran collected data on NYHA class changes as a prespecified secondary endpoint, allowing transitions across health states defined by NYHA class to be robustly modelled using these data. For these reasons, the use of NYHA classification to define disease progression in patients with ATTR-CM in this model is considered appropriate.

3.2.3 Cohort simulation

All patients begin treatment with either vutrisiran monotherapy or tafamidis monotherapy at model entry, with additional background treatment with therapies for heart failure

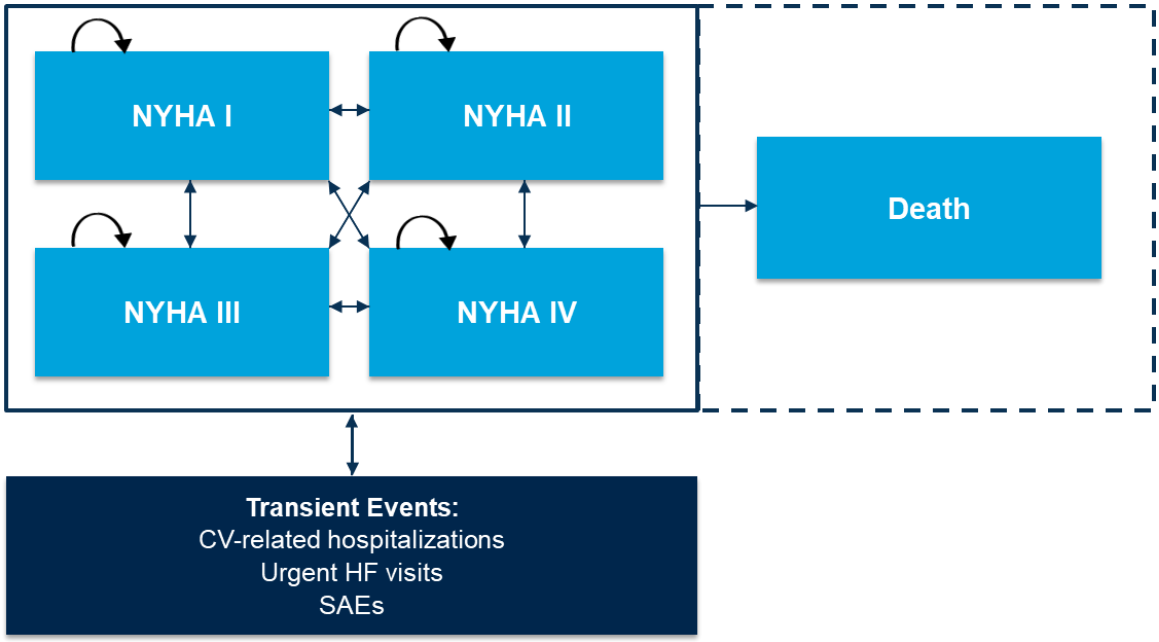
management. Patients remain on their treatment until discontinuation due to death (Section 3.3.4) or non-fatal causes (Section 3.3.5).

At model entry, the cohort is distributed across NYHA class-based health states based on the NYHA class distribution observed in HELIOS-B (Section 3.3.2) across both treatment arms (vutrisiran monotherapy and tafamidis monotherapy). In each subsequent cycle, patients can remain in the same health state or transition to a clinically more severe or less severe health state based on the transition probabilities estimated from HELIOS-B (Section 3.3.3). In each cycle, patients can also die (transition to the 'death' health state) from any of the 'alive' health states (Section 3.3.4).

Patients in any health state can also experience transient events related to ATTR-CM, namely, CV-related hospitalisations and urgent heart failure visits (Section 3.3.6), and SAEs (Section 3.3.7).

The structure of the model is presented in Figure 21.

Figure 21: NYHA class Markov model structure



SAE, serious adverse event; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association.

HRQoL in the model was based on utilities accrued over the time patients spend in each NYHA class-based health state (Section 3.4.1), with disutilities applied to account for the occurrence of CV-related hospitalisations and urgent heart failure visits when in a given health state (Section 3.4.5.1), and the occurrence of SAEs in each treatment arm (Section 3.4.5.2). Furthermore, due to the burdensome nature of providing care for patients with ATTR-CM, caregiver disutilities were also included in the base-case analysis (Section 3.4.5.3).

3.2.4 Time horizon and model cycles

A lifetime time horizon, corresponding to ~24 years, was modelled, ending at the age of 100 years, based on a baseline age of [redacted] at model entry. This modelled time horizon is accommodative of the assumed general maximum lifespan after the diagnosis of ATTR-CM. This approach is in keeping with HTA expectations on model duration for chronic diseases requiring chronic treatment. Shorter time horizons have been modelled in scenario analyses.

The model employs a 3-month cycle length with Simpson 1/3rd rule cycle correction, as described by Elbasha et al. (2016).[166] Expert consensus on the monitoring of ATTR-CM suggests monitoring patients (including clinical and functional assessments, assessment of cardiac biomarkers, and cardiac imaging) every 6 months.[105] Nonetheless, to allow for the possibility that meaningful changes in disease severity may occur over periods shorter than 6 months, a 3-month cycle length was chosen, ensuring that more rapid changes in patients' clinical status could be captured in the model in a manner that was not significantly delayed relative to their timing in the real-world setting.

3.2.5 Perspective

This analysis was conducted in line with the NICE reference case perspectives on outcomes and costs.[167] Specifically, costs were included from the NHS and personal social services (PSS) perspective, and outcomes were included from the patient and caregiver perspective. Since caring for patients with ATTR-CM is associated with a humanistic burden (Section 1.3.2.5), this submission has aligned with the NICE reference case by incorporating caregiver HRQoL in the base-case analysis.

3.2.6 Discounting

The discount factor applied to costs and effects occurring at some future time is given by $\frac{1}{(1+r)^t}$, where *r* is the annual discount rate and *t* represents time (in years) from model start. The model discounts costs and effects (LYs and QALYs) each at a rate of 3.5% per year.

3.2.7 Intervention technology and comparators

Vutrisiran is the intervention being assessed in this model, with tafamidis as the comparator treatment. Tafamidis is currently the only MHRA-approved[30] and NICE-recommended[163] treatment for ATTR-CM. All patients with ATTR-CM eligible for vutrisiran would otherwise be treated with tafamidis, the current standard of care; therefore, tafamidis is the only comparator considered in the company's CEA.

In this analysis, patients receiving vutrisiran or tafamidis also receive background medication for symptomatic heart failure management, consistent with real-world clinical practice. By incorporating symptomatic management as a concomitant treatment for both disease-specific therapies, the model accurately represents the comprehensive care typically provided to patients with ATTR-CM in the UK.

3.2.8 Comparison to other NICE appraisals in ATTR-CM

The only other NICE appraisal resulting in a positive recommendation in ATTR-CM was for tafamidis (TA984).[163] A comparison of model methodologies from the economic analysis submitted for tafamidis in TA984 and the current submission for vutrisiran is presented in Table 22.

Table 22: Comparison of previous NICE technology appraisals in ATTR-CM and the present submission

Parameter	TA984 (tafamidis)	Current submission for vutrisiran	Justification if different
Time horizon	Lifetime	Lifetime	–
Health states	NYHA classes	NYHA classes	–

Parameter	TA984 (tafamidis)	Current submission for vutrisiran	Justification if different
Cycle length	• 6-month cycles for health state transitions • Monthly cycles for all other events	3-month cycles	Described in Section 3.2.4
Source of utilities	Health state utilities based on EQ-5D-3L from ATTR-ACT	Health state utilities based on EQ-5D-5L from HELIOS-B mapped to EQ-5D-3L estimates	EQ-5D-5L utilities were collected in HELIOS-B
Survival	Parametric extrapolation of survival observed in ATTR-ACT tafamidis and placebo arms	Parametric extrapolation of survival observed in HELIOS-B vutrisiran and tafamidis monotherapy groups	–
Treatment waning after discontinuation	Treatment effectiveness with tafamidis was maintained after discontinuation in the submission, but the NICE committee preferred for them to be stopped at discontinuation	Treatment effectiveness ceases upon discontinuation of tafamidis and wanes in a graduated manner over time upon discontinuation of vutrisiran, until eventual complete cessation of effectiveness, based on TTR reversal data modelled using HELIOS-B pharmacodynamic data*	Described in 3.3.5.1
Source of costs	NHS and PSS	NHS and PSS	–

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; EQ-5D-3L, EuroQol 5-dimension 3-level; EQ-5D-5L, EuroQol 5-dimension 5-level; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PSS, personal social services. *Graduated treatment effect waning upon discontinuation of vutrisiran is only applied to NYHA class transition probabilities.

3.3 Clinical parameters and variables

3.3.1 Overview

Clinical inputs for the model—including transition probabilities, survival, and SAE incidence rates—were derived from three groups of patients from HELIOS-B:

- Vutrisiran monotherapy group: patients in the vutrisiran arm of the HELIOS-B monotherapy population (i.e., no background tafamidis at baseline; n=196).
- Tafamidis monotherapy group: patients in the placebo arm of the overall HELIOS-B population who were receiving background tafamidis at baseline (n=129).
- Placebo monotherapy group: patients in the placebo arm of the HELIOS-B monotherapy population (i.e., no background tafamidis at baseline; n=199).

To facilitate direct comparison of the vutrisiran and tafamidis monotherapy groups from HELIOS-B, baseline differences between the two groups were adjusted using IPTW (as discussed in Section 2.6.10). All clinical inputs related to HELIOS-B were derived from the individual patient-level data (IPD) of this adjusted population, based on the vutrisiran and tafamidis monotherapy groups, unless otherwise stated. Clinical parameters informed by

HELIOS-B include baseline characteristics, transition probabilities, overall survival, health-state utilities, treatment discontinuation rates, and rates of transient events, including SAEs, CV-related hospitalisations, and urgent heart failure visits.

Following discontinuation of vutrisiran or tafamidis, clinical and humanistic parameters are also informed by data from the placebo monotherapy group from HELIOS-B (herein referred to as best supportive care [BSC]).

Justification for the use of within-trial HELIOS-B outcomes for the model

Clinical outcomes for the tafamidis arm in the model were informed by the patients on background tafamidis therapy in the placebo arm in HELIOS-B (i.e., tafamidis monotherapy) instead of using data from the tafamidis arm in ATTR-ACT, the pivotal phase 3 trial of tafamidis in ATTR-CM. Due to differences in the time periods in which HELIOS-B and ATTR-ACT took place, patients in ATTR-ACT had worse levels disease at baseline and followed worse disease trajectories compared to patients in HELIOS-B.[38] As described in Section 2.10, this is related to the evolution of ATTR-CM clinical practice over time. In recent years, patients with ATTR-CM have increasingly been diagnosed earlier, and with less severe disease, due to increased disease awareness within the clinician community and improved diagnostic techniques,[104,109] while also benefiting from recent advances in supportive care that have improved baseline prognosis for all patients with ATTR-CM.[152] For this reason, using data from ATTR-ACT to inform model parameters for the tafamidis arm would not be an accurate representation of current outcomes of tafamidis treatment in a contemporary ATTR-CM patient population.

Limitations of using within-trial HELIOS-B outcomes for the model

A limitation of using data from the vutrisiran and tafamidis monotherapy groups in HELIOS-B is the difference in the timing of therapy initiation between these two groups in HELIOS-B. Patients in the vutrisiran monotherapy arm initiated vutrisiran at HELIOS-B baseline, whereas most of those in the tafamidis monotherapy arm had already been receiving tafamidis, for a median of 11.3 months (range: 1.1, 65.5) of pre-baseline tafamidis exposure, at HELIOS-B baseline. Given this difference, there is a potential for selection bias in favour of the tafamidis monotherapy subgroup. Specifically, in view of the observed pre-trial exposure to tafamidis in HELIOS-B, the tafamidis monotherapy subgroup may have selectively underrepresented patients who did not tolerate or had poor responses on tafamidis, and who thus may have discontinued (due to death or non-fatal reasons) tafamidis well before ~1 year on treatment in real-world practice. Additionally, there is a potential bias in survival favouring the tafamidis monotherapy arm due to the duration of time needed for the survival benefit to emerge after treatment initiation, for which tafamidis-treated patients in the model had an approximate 1-year lead time due to the pre-baseline exposure to tafamidis. For this reason, clinical parameters informed by the tafamidis and vutrisiran monotherapy groups in HELIOS-B—namely, transition probabilities, survival, and SAEs—are likely to be biased in favour of tafamidis, resulting in conservative estimates of cost-effectiveness for vutrisiran.

3.3.2 Baseline characteristics

The population of interest is patients diagnosed with ATTR-CM. Baseline characteristics of the model cohort are aligned with the baseline characteristics of the study population in HELIOS-B (Table 23). The proportion of patients in each NYHA class health state was derived from the combined (independent of treatment) proportion of patients in that state at baseline between the vutrisiran and tafamidis monotherapy groups in HELIOS-B.

Table 23: Baseline characteristics of the model population based on HELIOS-B baseline parameters

Characteristic	Model Input
Initial age (years)	[redacted]
Male (%)	[redacted]
NYHA class	
I (%)	[redacted]
II (%)	[redacted]
III (%)	[redacted]
IV (%)	[redacted]

NYHA, New York Heart Association. Note: Initial age and percentage male estimates were based on the vutrisiran monotherapy group at baseline in HELIOS-B. Source: Fontana et al. 2024[3]

3.3.3 Transition probabilities

Patients in each treatment arm enter the model distributed across NYHA class health states in the proportions outlined in Table 23. The model allows for potential improvement, maintenance, or worsening in NYHA class over time according to transition probabilities, reflecting the range of health state changes observed among patients in the vutrisiran and tafamidis monotherapy groups in HELIOS-B. There are two distinct periods representing distinct approaches for modelling patient transitions through NYHA class health states in this model:

1. Observed period (first 30 months [10 cycles], the duration over which NYHA class data were collected at 6-month intervals in the double-blind period of HELIOS-B). During this period, transition matrices in each 3-month cycle are derived from the corresponding 6-month transition matrix observed in HELIOS-B (i.e., the observed transition matrix for the 6-month interval in HELIOS-B within which the 3-month model cycle would fall [Section 3.3.3.1); and
2. Extrapolation period, where in all cycles thereafter (i.e., beyond 30 months), the average of the last two observed 6-month transition matrices (i.e., months 18–24 and 24–30) from the observed period was converted to a 3-month transition matrix, which was then carried forward for the remainder of the model time horizon for each treatment arm. The last two observed transition matrices (Months 18–30) were chosen instead of the last observed transition matrix (Month 24–30) since no transitions from to NYHA IV were observed in the last transition matrix in the vutrisiran monotherapy arm (whereas they were observed in the tafamidis monotherapy arm), and applying a zero probability of transition to NYHA IV in the extrapolated period for vutrisiran defies the expected clinical worsening of heart failure, especially as patients get older. Despite this approach being conservative towards vutrisiran, the company chose to employ this approach for extrapolating transition probabilities in the model's base-case analysis.

The following assumptions were included in the calculation of transition probabilities:

- *Unmeasured transition observations (i.e., instances in which patients could not have a transition ascertained at a given time point due to a missing NYHA class assessment) were censored*: While other options were considered, censoring all unmeasured transitions from the calculation of transition probabilities was concluded to be the most clinically relevant and unbiased approach.

    - One option to account for unmeasured transitions was to model an "unmeasured" NYHA class as a separate health state, but this lacked clinical relevance.
    - Another option for handling missing data regarding NYHA class changes is to use the last observation carried forward (LOCF) approach until the next non-missing NYHA class measurement (i.e., estimate transitions based on the assumption that the last observed NYHA class is maintained until another is measured); however, this approach was potentially biased, as patients with an unmeasured observation may be more likely to have missed the observation due to worsening disease.
- *Among patients who died, had a heart transplant, or received a ventricular assist device in HELIOS-B, transitions were censored thereafter*: In the calculation of transition matrices, patients who died in HELIOS-B were censored in the 6-month estimation interval in which they died. Further, clinical experts indicated that heart transplantation and ventricular assist device placement are not commonly used in patients with ATTR-CM in UK clinical practice. Therefore, these procedures were not included as separate health states in the model, and patients in HELIOS-B who underwent these clinical procedures were censored in the calculation of NYHA class health state transition probabilities, starting in the 6-month estimation interval in which the procedure occurred in the trial.

As described in Section 3.3.1, patients in the tafamidis monotherapy arm initiated treatment a median of 11.3 months (range: 1.1, 65.5) prior to HELIOS-B baseline. Given this difference compared to patients in the vutrisiran arm (who initiated vutrisiran at HELIOS-B baseline), there is a potential for selection bias in favour of the tafamidis monotherapy group, meaning that NYHA class transitions could be biased towards more favourable results in the tafamidis monotherapy arm.

3.3.3.1 Calculation of 3-month transition probabilities

In HELIOS-B, NYHA classification was recorded every 6 months during the double-blind period. To convert the observed 6-month transition probabilities into 3-month probabilities (to align with model cycle length), the following formula from Briggs et al. (2006) was used:[168]

$$p_{cycle} = 1 - \exp\left(\frac{\ln(1-p_{n\,month})}{n} * t\right),$$

where p_{cycle} is the probability per cycle of the event, $p_{n-month}$ is the observed probability of the event over a period of n months, and t is the cycle length in months.

Transition probabilities per cycle for the entire model time horizon are presented in Table 24 for vutrisiran and tafamidis. Transition probabilities for BSC (as used in estimating transition probabilities for patients who discontinue treatment in either arm) are presented in Appendix J.

Table 24: NYHA class transition probabilities per cycle for vutrisiran and tafamidis

From NYHA class	To NYHA class health state							
	Vutrisiran				Tafamidis			
	I	II	III	IV	I	II	III	IV
Months 0–3 and 3–6 (Cycles 1 and 2)								
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months 6–9 and 9–12 (Cycles 3 and 4)								
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months 12–15 and 15–18 (Cycles 5 and 6)								
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months 18–21 and 21–24 (Cycles 7 and 8)								
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months 24–27 and 27–30 (Cycles 9 and 10)								
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months 30+ (extrapolation phase, cycles 11+)								
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NYHA, New York Heart Association.

3.3.4 Survival

Survival in the vutrisiran and tafamidis arms was modelled in the following steps:

- Parametric functions were separately fitted to Kaplan–Meier (KM) survival curves from the HELIOS-B vutrisiran and tafamidis monotherapy arms, based on vital status data observed up to Month 42 from HELIOS-B baseline (Section 3.3.4.1).
- Long-term survival in both arms was estimated from these parametric functions, capped by survival in the age- and sex-matched UK general population (Section 3.3.4.2).
- The number of patients who died in each cycle according to this approach were allocated across NYHA class health states using NYHA class mortality HRs (Section 3.3.4.3). Mortality HRs were sourced from a retrospective study of patients with ATTR-CM (N=309) that demonstrated that NYHA class at baseline (first clinical visit) was a significant predictor of mortality, with a 1.85-fold increase in mortality hazard (adjusted HR: 1.85 [95% CI: 1.22, 2.80]; P=0.004) for every 1-level increase in NYHA class.[22]

3.3.4.1 Fitting parametric functions to observed KM curves from HELIOS-B

3.3.4.1.1 Observed KM curves in HELIOS-B

KM curves for vutrisiran and tafamidis monotherapy arms are presented in Figure 22.

Figure 22: KM survival curves for the vutrisiran and tafamidis monotherapy arms in HELIOS-B

KM, Kaplan–Meier.

[redacted] This is likely due to the differences in the timing of therapy initiation between the two groups in HELIOS-B, as patients in the vutrisiran monotherapy arm initiated vutrisiran at HELIOS-B baseline, whereas those in the tafamidis monotherapy arm had already been receiving tafamidis for a median of 11.3 months (range: 1.1, 65.5) at HELIOS-B baseline (Section 3.3.1). Therefore, the pattern of survival benefit observed from HELIOS-B is likely to be conservative for vutrisiran relative to tafamidis, as survival benefits with active treatments for ATTR-CM require some time to emerge after initiation of treatment, as has been demonstrated in phase 3 trials.[3,10,11] As a result, patients in the tafamidis monotherapy arm (having been on tafamidis for a median of 11.3 months) may already be deriving a survival benefit at baseline in HELIOS-B, whereas patients in the vutrisiran

monotherapy arm (having just started treatment) were not already deriving a survival benefit at baseline.

To address this issue of different time periods on treatment for the vutrisiran and tafamidis monotherapy arms prior to HELIOS-B baseline in relation to mortality estimates, two alternative approaches that used data from HELIOS-B were explored:

1. Basing survival in the tafamidis monotherapy arm on the survival of patients in the HELIOS-B placebo monotherapy group who initiated tafamidis treatment during the trial (i.e., tafamidis drop-in [Section 2.6.9]). In this approach, vital status could be monitored from the time of tafamidis initiation to inform survival estimates on tafamidis monotherapy. This approach was infeasible as only 41 patients in the HELIOS-B placebo monotherapy group initiated tafamidis, and they did so at a median of 17.0 months (range: 1.5, 33.8) after HELIOS-B baseline, such that follow-up after drop-in in these patients was limited.
2. Basing survival in the vutrisiran monotherapy arm on survival in the vutrisiran monotherapy group, with the KM survival curve “shifted left” by 11.3 months to align with the median duration of treatment with tafamidis at HELIOS-B baseline in the tafamidis monotherapy group, and estimating survival by considering vital status data only in the proportion of patients alive at 11.3 months from HELIOS-B baseline in the vutrisiran monotherapy arm. Therefore, the analysis in both model arms would incorporate a similar period of time on treatment prior to assessing mortality outcomes; however, this was also infeasible as it resulted in limited follow-up time for patients in the vutrisiran arm (i.e., as little as 22 months in some patients).

3.3.4.1.2 Rationale for fitting separate parametric functions for survival for the vutrisiran and tafamidis monotherapy arms

As a result of the survival trends in Figure 22, a plot of smoothed hazard rates showed that the hazard rate was initially greater in the vutrisiran monotherapy arm than in the tafamidis monotherapy arm; however, starting at Month 24 and until the end of the 42-month period used to inform the survival analysis, the hazard rate was greater in the tafamidis monotherapy arm. A complementary log-log plot revealed that the log-log curves for the vutrisiran and tafamidis monotherapy arms were not parallel, and a Schoenfeld residual plot showed deviation of the smoothed line from zero (Schoenfeld residuals P=0.0133), indicating that the proportional hazards assumption was not met. Therefore, independent fitting of survival models for the vutrisiran and tafamidis monotherapy arms (versus modelling based on the assumption of proportional hazards between arms) was the preferred method.

3.3.4.1.3 Overview of the parametric models explored and parametric model selection criteria

The parametric functions explored included exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma. Selection of the best-fitting function was based on goodness-of-fit criteria (via Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), inspection of hazard rates estimated by each function compared to observed hazard rates, visual fit to the observed KM plots, and clinical plausibility based on real-world evidence and expert clinical opinion obtained by structured expert elicitation (SEE; described in Section 3.3.4.4).

3.3.4.1.4 Selection of a parametric function for the vutrisiran arm

Parametric functions fit to survival in the vutrisiran monotherapy arm in HELIOS-B are displayed in Figure 23, and goodness-of-fit statistics are presented in Table 25.

Figure 23: Parametric functions fit to survival in the vutrisiran monotherapy arm in HELIOS-B

KM, Kaplan–Meier.

Table 25: AIC and BIC estimates for different parametric functions fit to vutrisiran monotherapy arm survival data in HELIOS-B

Fit statistic	Exp.	Weibull	Gomp.	Log-normal	Log-logistic	Gamma	Gen. gamma
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Exp., exponential; Gen. gamma, generalised gamma; Gomp., Gompertz.

Goodness-of-fit criteria show comparable AIC and BIC estimates across parametric functions, with the lowest estimates coming from the exponential function. Despite having the lowest AIC and BIC, the hazard rate from the exponential function did not align with the observed hazard from the vutrisiran monotherapy arm in HELIOS-B (Figure 24), and accordingly, the extrapolated curve using the exponential function was found to not follow the observed OS curve. After structured expert elicitation (SEE) (Section 3.3.4.4), the log-logistic function was selected to model survival in the vutrisiran arm in the base-case analysis.

Figure 24: Comparison of hazard rates for parametric functions fitted to survival in the vutrisiran monotherapy arm

3.3.4.1.5 Selection of a parametric function for the tafamidis arm

Parametric functions fit to survival in the tafamidis monotherapy arm in HELIOS-B are displayed in Figure 25, and goodness-of-fit statistics are presented in Table 26.

Figure 25: Parametric functions fit to survival in the tafamidis monotherapy arm in HELIOS-B

KM, Kaplan–Meier.

Table 26: AIC and BIC estimates for different parametric functions fit to tafamidis monotherapy arm survival data in HELIOS-B

Fit statistic	Exp	Weibull	Gomp.	Log-normal	Log-logistic	Gamma	Gen. gamma
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Exp., exponential; Gen. gamma, generalised gamma; Gomp., Gompertz.

Goodness-of-fit criteria show comparable AIC and BIC estimates across all functions assessed. The lowest AIC and BIC estimates were observed with the Gompertz function. However, visual inspection of hazard rates over 42 months showed that the log-normal function was best aligned with the observed hazard from HELIOS-B for the tafamidis monotherapy arm (Figure 26). Furthermore, SEE (Section 3.3.4.4) resulted in selection of the log-normal function as the most appropriate to model survival in the tafamidis arm in the base-case analysis.

Figure 26: Comparison of hazard rates for parametric functions fitted to survival in the tafamidis monotherapy arm

For BSC (used to inform the trajectory of patients after discontinuation of vutrisiran or tafamidis), the Weibull function was selected to model long-term survival, based on fit to KM survival data from the HELIOS-B placebo monotherapy (without background tafamidis at baseline) arm. Fit statistics and graphical depiction of observed survival and parametric survival functions for BSC are presented in Appendix J.

3.3.4.2 Capping mortality based on age-matched UK mortality

To avoid clinically implausible scenarios at the cohort level where the modelled survival in patients with ATTR-CM is higher than in the age-matched general population, modelling of survival was augmented using mortality data for the general population, sourced from Office for National Statistics 2020–2022 life tables. Life expectancy data from this source were used to generate per-cycle general population mortality hazard rates, which were adjusted for the age and sex of the modelled ATTR-CM population. In any cycle, if survival in the age- and sex-matched general population was lower than survival according to the fitted parametric survival curve for vutrisiran or tafamidis, then survival in that cycle for the treatment arm in question was modelled using the general population estimate rather than the fitted parametric survival curve.

A summary of overall survival in the vutrisiran and tafamidis arms in addition to UK age- and sex-matched general population survival, across the model time horizon, is presented in Figure 27.

Figure 27: Modelled survival in the vutrisiran and tafamidis arms

KM, Kaplan–Meier. Note: In the model, survival in the vutrisiran and tafamidis arms is capped by age- and sex-matched general population survival, such that the probability of death in the model treatment arms in any given cycle is never greater than the probability of death in the general population in that same cycle.

3.3.4.3 Disaggregating mortality by NYHA class health state

In each model cycle, to allocate patient deaths to individual NYHA class health states, a series of HRs were applied to the total proportion of patients who transitioned into the "death" health state in each treatment arm of the model.

Hazard ratios were sourced from a retrospective study by Cheng et al. (2020),[22] of 309 patients with ATTR-CM. The findings from this study showed that NYHA class at baseline (first clinical visit) was a significant predictor of mortality, with a 1.85-fold increase in mortality hazard (adjusted HR: 1.85 [95% CI: 1.22, 2.80]; P=0.004) for every 1-level increase in NYHA class. Assuming a hazard of 1 in NYHA I, relative mortality HRs for NYHA II, III, and IV versus NYHA I were calculated (Table 27). In each cycle, these NYHA mortality HRs were applied to calculate the probabilities of death for each NYHA class, which were then used to distribute the total number of deaths across NYHA class health states based on the number of survivors in each NYHA class from the previous cycle.

Table 27: Mortality HRs used to disaggregate mortality by NYHA class

Relative mortality comparison	HR	Source
NYHA II vs. NYHA I	1.85	Cheng et al. (2020),[22] calculated as the application of 1.85-fold increase in HR for every increase in NYHA class
NYHA III vs. NYHA I	3.42	
NYHA IV vs. NYHA I	6.33	

HR, hazard ratio; NYHA, New York Heart Association; PH, proportional hazards; SE, standard error.

3.3.4.4 Structured expert elicitation

In addition to aligning with NICE Decision Support Unit (DSU) Technical Support Documents 14 and 21 on approaches to survival analysis,[169,170] a robust SEE approach was used to validate the survival functions chosen to model survival in the vutrisiran and tafamidis arms in the base-case analysis.[171] The methodology for the SEE exercise was aligned with recent ISPOR task force recommendations on good practices for SEE protocols.[172]

The SEE exercise was performed by a vendor independent from Alnylam, and included the following clinical experts:[171]

[redacted]Individual elicitation on survival modelling was captured on 13 January 2025 and 21 January 2025, followed by group elicitation on 22 January 2025. To align modelled for vutrisiran and tafamidis with expected real-world survival, clinical experts were provided data from HELIOS-B (including results from the vutrisiran and tafamidis monotherapy groups) and data from ATTR-ACT and the ATTR-ACT long-term extension.[171] Experts then collaborated to provide estimates of the proportions of patients with ATTR-CM that would be alive after 8 years of treatment with either vutrisiran or tafamidis. Along with this estimate, the experts also provided an associated 95% CI for these proportions. These estimates were then used to determine which survival functions best represented survival in each treatment arm.[171]

In summary, it was determined that the use of the log-logistic function in the vutrisiran arm and the log-normal function in the tafamidis arm aligned most closely with feedback gathered from the SEE exercise.[171]

3.3.5 Treatment discontinuation

Treatment discontinuation in HELIOS-B over the double-blind period occurred for various reasons. In the vutrisiran monotherapy group, these reasons included death (n=[redacted]), withdrawal by participant (n=[redacted]), AEs (n=[redacted]), clinician decision (n=[redacted]), loss to follow-up (n=[redacted]), and non-compliance with the study drug (n=[redacted]). Survival modelling accounted for discontinuations due to death in the model. To account for treatment discontinuation from non-fatal causes (including all those described above), parametric functions were fitted to non-fatal treatment discontinuation data (i.e., excluding discontinuations due to death) from the double-blind period of HELIOS-B and extrapolated for the rest of the model time horizon. For the vutrisiran arm in the model, these parametric functions were informed by observed discontinuation rates (excluding death) in the vutrisiran monotherapy arm over the double-blind period in HELIOS-B. For tafamidis, it was assumed that non-fatal treatment discontinuation was equivalent to that modelled for vutrisiran. Considering the extended period of time that patients were exposed to tafamidis prior to HELIOS-B baseline (Section 3.3.1) in the tafamidis monotherapy group, it was deemed infeasible to use observed tafamidis monotherapy discontinuation rates to inform discontinuation in the tafamidis arm in the model, due to potential selection bias for patients who did not discontinue tafamidis prior to enrolling in HELIOS-B.

The methodologies used to select a parametric function to model non-fatal treatment discontinuation rates are in line with those described for overall survival in Section 3.3.4.1.3.

Parametric functions fit to observed non-fatal treatment discontinuation in the vutrisiran monotherapy arm in HELIOS-B are shown in Figure 28, and goodness-of-fit statistics are presented in Table 28.

Figure 28: Parametric functions fit to non-fatal treatment discontinuation in the vutrisiran monotherapy arm in HELIOS-B

Table 28: AIC and BIC estimates for different parametric functions fit to non-fatal treatment discontinuation in the vutrisiran monotherapy arm in HELIOS-B

Fit statistic	Exp.	Weibull	Gomp.	Log-normal	Log-logistic	Gamma	Gen. gamma
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Exp., exponential; Gen. gamma, generalised gamma; Gomp., Gompertz.

Based on goodness-of-fit statistics (AIC and BIC), visual inspection, and observation of alignment with the observed hazard rate for non-fatal treatment discontinuation in the vutrisiran monotherapy arm over 36 months (Figure 29), the Gamma function, which had the lowest AIC and BIC, was selected in the base case to model non-fatal treatment discontinuation.

Figure 29: Comparison of hazard rates for parametric functions fitted to non-fatal treatment discontinuation in the vutrisiran monotherapy arm

Patients who discontinued treatment in a given cycle were removed from the different NYHA classes in proportion to the distribution of patients by NYHA class at the end of the previous cycle.

3.3.5.1 Clinical outcomes and costs in patients who discontinue treatment

The proportion of patients who discontinue treatment (vutrisiran or tafamidis arm) stop incurring costs for these medications in the model cycle in which discontinuation occurs. The discontinuation can occur at any time point during a three-month cycle, which is accounted for by half-cycle correction.

NYHA class transition probabilities after discontinuing treatment

Tafamidis: Since steady-state, pharmacodynamically active levels of tafamidis in the body are not maintained without ongoing daily administration of the drug, patients in the tafamidis arm are assigned BSC-associated NYHA class transition matrices starting in the cycle in which they discontinue treatment, which continue for the rest of the model time horizon.

Vutrisiran: Each dose of vutrisiran (normally administered Q3M) can sustain knockdown of serum TTR (the driver of disease in ATTR-CM) for an extended period even in the absence of subsequent doses, as observed through pharmacokinetic modelling data.

Based on worldwide clinical expert opinion, an approximate 80% sustained reduction in serum TTR levels relative to pre-treatment baseline levels provides a signal of expected treatment benefit. This view has been supported by the following quote from the NICE appraisal of patisiran in hATTR-PN (HST10):[125]

> *"During consultation, clinical experts explained that the likelihood of halting or reversing amyloid deposition, and so reducing neuropathy and improving cardiac*

function, is dependent upon the extent of reduction in TTR. There is no threshold for an effect. The effect of a given reduction will vary from person to person because of differences in turnover and production of TTR. However, the clinical experts' view was that most patients would derive clinically meaningful benefit with a reduction of more than 80%."

Therefore, a graduated waning of the treatment effect on NYHA class transition probabilities for patients who discontinue vutrisiran was implemented in the model, based on observed data on the evolution of serum TTR levels after receiving a final dose of vutrisiran during the double-blind period of HELIOS-B (Figure 30).

Figure 30: Mean change in serum TTR from pretreatment baseline following final dose of vutrisiran during the double-blind period in HELIOS-B

TTR, transthyretin.

To account for the gradual reduction in serum TTR levels (and associated persistence of clinical benefits) that occur in patients who discontinue vutrisiran, a graduated waning of treatment efficacy was modelled over a 21-month period after discontinuation. In this approach, immediately after discontinuing vutrisiran, NYHA class transitions are solely based on those of the vutrisiran arm (for the first two cycles after discontinuation), but eventually become solely based on those of the BSC arm, from Month 21 onward. During the intervening time points, a time-dependent weighted-average transition matrix, driven by the level of continued reduction of serum TTR relative to pre-treatment baseline, was used to estimate NYHA class transition matrices for patients who discontinued vutrisiran.

To determine relative weights for the contributions of vutrisiran and BSC in this approach, in each cycle after discontinuation, it was assumed that if mean percent TTR reduction relative to pre-treatment baseline remained above the threshold of 80% during that cycle, there would be a 100% contribution from vutrisiran and 0% contribution from BSC (corresponding

to full efficacy of vutrisiran). If the mean percent TTR reduction relative to pre-treatment baseline during a post-discontinuation cycle was <80%, then that percent reduction was divided by 80% to obtain the proportional contribution of vutrisiran, and the proportional contribution of BSC in the same cycle was calculated as 100% minus the proportional contribution of vutrisiran. For example, in a given cycle post-discontinuation, if mean TTR reduction was 60% relative to pretreatment baseline, then 75% of the discontinued patients in that cycle (60% divided by 80%) were assigned to vutrisiran transitions, and 25% were assigned to BSC transitions (100% – 75%), creating a weighted average for NYHA class transitions. This calculation was based on the reductions in serum TTR depicted in Figure 30, and is summarised by cycle in Table 29.

Table 29: Application of treatment waning effects on transition matrices based on weighted contributions from vutrisiran and BSC following discontinuation of vutrisiran

Cycles after vutrisiran discontinuation (months)	Mean % TTR reduction*	Transition matrix weights for discontinued patients	
		Vutrisiran	BSC
1 (0–3)	[redacted]	[redacted]	[redacted]
2 (3–6)	[redacted]	[redacted]	[redacted]
3 (6–9)	[redacted]	[redacted]	[redacted]
4 (9–12)	[redacted]	[redacted]	[redacted]
5 (12–15)	[redacted]	[redacted]	[redacted]
6 (15–18)	[redacted]	[redacted]	[redacted]
7 (18–21)	[redacted]	[redacted]	[redacted]
8 (21+)	[redacted]‡	[redacted]	[redacted]

BSC, best supportive care; TTR, transthyretin. *Average TTR reduction was calculated by digitising the curve presented in Figure 30. †Serum TTR levels are assumed to be at pretreatment baseline level after 21 months from the last dose of vutrisiran.

Survival

In each treatment arm (vutrisiran and tafamidis) in the model, from the point at which patients discontinued treatment, their per-cycle probability of death was aligned with that of the BSC arm (Appendix J), whereas the per-cycle probability of death for the remaining patients on treatment in the same model treatment arm was adjusted accordingly, so that the total treatment arm (including both continuers and discontinuers) would follow the survival trajectory of the entire modelled treatment arm (i.e., vutrisiran: Section 3.3.4.1.4; tafamidis: Section 3.3.4.1.5).

As described above, due to the pharmacodynamic activity of vutrisiran and tafamidis, treatment effects are assumed to wane over a 21-month period following the discontinuation of vutrisiran, whereas they are assumed to cease immediately following the discontinuation of tafamidis. Therefore, considering that both tafamidis- and vutrisiran-treated patients who discontinue treatment immediately assume the same per-cycle probability of death as BSC-treated patients, the approach should be viewed as conservative for vutrisiran.

3.3.6 Transient events (CV-related hospitalisation and urgent heart failure visits)

Transient events (i.e., CV-related hospitalisations and urgent heart failure visits) that affect HRQoL (through the application of disutilities) and incur costs were modelled in the analysis. These events were assumed to be NHYA class health state-dependent, under the assumption that worsening heart failure severity would lead to increased rates of hospitalisations for CV or heart failure reasons. For each NYHA class at baseline of HELIOS-B, 6-month incidence rates of these events from the trial were averaged across all 6-month intervals from the double-blind period of the trial (and across treatment arms), and the resulting average NYHA class-specific incidence rate was converted to a 3-month incidence rate to align with model cycle length.

Although data for patients in NYHA class IV were not available from HELIOS-B, it was assumed that these patients are at a substantially higher risk of transient events compared to patients in other NYHA classes. Therefore, the relative risk of transient events in NYHA class IV was modelled to be [redacted] that in NYHA III, based on UK clinical expert feedback.

The per-cycle incidence of transient events (i.e., CV-related hospitalisations and urgent heart failure visits) by NYHA class is shown in Table 30.

Table 30: Per-cycle incidence of transient events in NYHA classes

NYHA class	CV-related hospitalisation	Urgent heart failure visit
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV*	[redacted]	[redacted]

CV, cardiovascular; NYHA, New York Heart Association. *Estimated to be [redacted] the probabilities in NYHA III, based on UK expert feedback.

3.3.7 Serious adverse events

Treatment-emergent SAEs that occurred in ≥3% of the patients in the vutrisiran monotherapy group or tafamidis monotherapy group during the double-blind period of HELIOS-B were included in the analysis. A 3% threshold was selected to capture treatment-emergent SAEs with sufficient frequency, while ensuring that rare SAEs from HELIOS-B did not disproportionately complicate the analysis.

SAEs were modelled as a one-time event at the start of the model time horizon, based on their overall incidence in HELIOS-B. Incidence rates for each SAE by treatment arm are presented in Table 31.

As described in Section 3.3.1, patients in the tafamidis monotherapy arm initiated tafamidis a median of 11.3 months (range: 1.1, 65.5) prior to HELIOS-B baseline. In view of the observed pre-trial exposure to tafamidis in HELIOS-B, the tafamidis monotherapy group may have selectively underrepresented patients who did not tolerate tafamidis, and who thus may have discontinued tafamidis (potentially due to AEs) well before ~1 year on treatment in real-world practice. For this reason, the use of SAE incidence rates in the model based on their occurrence in the vutrisiran and tafamidis monotherapy arms in HELIOS-B represents a conservative approach for vutrisiran.

Table 31: Incidence rate of SAEs in the vutrisiran and tafamidis arms (applied on one-time basis in model)

SAE	Vutrisiran (%)	Tafamidis (%)
Atrial fibrillation	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Atrial flutter	[redacted]	[redacted]
Ventricular tachycardia	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]

SAE, serious adverse event. Note: The incidence of SAEs did not incorporate weighting as described in Section 3.3.1.

3.4 Measurement and valuation of health effects

In the model, each NYHA class health state is assigned a specific utility value, reflecting the HRQoL associated with that health state. EQ-5D-5L data were prospectively collected in HELIOS-B, providing primary utility values directly relevant to this analysis. Utilities for individual NYHA class health states were estimated using data from the intention-to-treat (ITT) population instead of the vutrisiran monotherapy or tafamidis monotherapy groups and were modelled as treatment-independent estimates.

Further, disutilities were included to account for the occurrence of CV-related hospitalisations and urgent heart failure visits (Section 3.4.5.1) and SAEs (Section 3.4.5.2). Due to the burdensome nature of providing care for patients with ATTR-CM, caregiver disutilities were also included in the analysis (Section 3.4.5.3).

In line with submission requirements, a systematic literature review was conducted to identify alternate sources of utilities in ATTR-CM (Section 3.4.3).

3.4.1 Health-related quality-of-life data from clinical trials

In HELIOS-B, EQ-5D-5L data were collected at baseline, Month 12, Month 24, and Month 30. These data were used to inform NYHA class-specific utilities.

A linear mixed-effects model (LMEM) was fitted to EQ-5D-3L utilities (mapped from EQ-5D-5L data) from the HELIOS-B ITT population to enrich sample size for estimating utility values. The LMEM included covariates for baseline EQ-5D-3L, study visit, NYHA class, type of amyloidosis, age group, sex, and SAEs.

Utility estimates for each NYHA class were generated by considering all EQ-5D assessments performed on patients who were in that NYHA class at the time of the assessment, using the LMEM to predict patients' utility values at the time of each of those assessments, and then averaging the resulting LMEM-predicted values. Results from this approach are presented in Table 32. Utility scores reflect the expected declines in HRQoL with worsening NYHA class.

Table 32: EQ-5D-3L utilities by NYHA class from HELIOS-B LMEM analysis

Health state	Mean (SE)	95% CI
NYHA I	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]

CI, confidence interval; EQ-5D-3L, EuroQol 5-dimension 3-level; LMEM, linear mixed-effects model; NYHA, New York Heart Association; SE, standard error.

3.4.2 EQ-5D mapping: 5L to 3L

To inform the LMEM model, EQ-5D-5L data from HELIOS-B (described above) were mapped to EQ-5D-3L to obtain utility values in line with the NICE reference case methods, using the NICE Decision Support Unit Economic Methods of Evaluation in Health and Social Care Policy Research Unit (EEPRU) model.[173]

3.4.3 Health-related quality-of-life studies

Studies that reported EQ-5D data in patients with ATTR-CM were captured in the SLR described in Appendix F (as part of the burden of illness [BOI] SLR). In total, six records were identified, which are described in Table 33. Eldhagen et al. (2023) conducted a cross-sectional study of 169 Nordic patients with ATTR-CM,[102] which was the only identified study that reported EQ-5D-5L utilities by NYHA class in patients with ATTR-CM; however, the study included only three patients in NYHA IV, making these utility estimates unreliable for use in the model.

Table 33: Studies reporting EQ-5D utilities in ATTR-CM as identified in the SLR

Study	Study type	Population
Maurer et al. 2016[46]	THAOS: Global, multicentre, longitudinal, observational study	US patients with ATTR-CM. wtATTR: n=189 hATTR (all with V122I): n=91
Duca et al. 2019[174]	EXPRESS trial: Prospective cohort study of riociguat in patients with ATTR-CM over 4–6 months of follow-up from baseline (treatment initiation)	Austrian patients with ATTR-CM. Baseline assessment: n=13 Follow-up assessment: n=11
Gonzalez-Moreno et al. 2021[175]	THAOS: Global, multicentre, longitudinal, observational study	Spanish patients with ATTR-CM. Patients with cardiac-only phenotype: n=33 Patients with a mixed cardiac and neurologic phenotype: n=86

Study	Study type	Population
Damy et al. 2022[13]	French daily impact of amyloidosis study: Observational, cross-sectional study	French patients with ATTR-CM. wtATTR: n=109 hATTR: n=99
Eldhagen et al. 2023[102]	Nordic PROACT study: Observational, cross-sectional study	Nordic patients (Sweden, Norway, Finland, and Denmark) with ATTR-CM. hATTR: n=25 wtATTR: n=129 Disease type not determined: n=15
Poledniczek et al. 2024[176]	Cardiac amyloidosis registry at the Medical University of Vienna: Prospective registry study.	Austrian patients with ATTR-CM: hATTR: n=19 wtATTR: n=148

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; EQ-5D, EuroQol 5-dimensionl; hATTR, hereditary transthyretin amyloidosis; NYHA, New York Heart Association; PROACT, Patient-Reported Outcomes in Transthyretin Amyloid Cardiomyopathy; SLR, systematic literature review; THAOS, Transthyretin Amyloidosis Outcomes Survey; V122I, valine to isoleucine substitution at amino acid position 122; wtATTR, wild-type transthyretin amyloidosis.

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Treatment-independent NYHA class-specific utilities were used in the model, based on the LMEM-derived mean EQ-5D-3L utilities presented in Table 32. However, to avoid a situation where HRQoL of patients with ATTR-CM exceeded that of the general population, the LMEM-derived utilities were capped by those observed in the UK age-matched population, based on data from the 2014 Health Survey for England.[173]

Specifically, the mean EQ-5D-3L utility for NYHA I determined in the LMEM analysis ([redacted]) exceeded that of the UK age- and sex- matched general population corresponding to the model cohort at baseline ([redacted]). Therefore, as a result of the cap on utilities, the utility in NYHA class I was set equal to [redacted], and the difference between the capped and uncapped utility values ([redacted]) was then applied to all other LMEM-derived NYHA class utilities from Table 32 to generate the health-state utilities used in the analysis (Table 34).

Table 34: NYHA class-specific utilities

NYHA class	Utility	95% CI	Source
I	[redacted]	[redacted]	HELIOS-B LMEM analysis, with all values adjusted by a fixed amount ([redacted]) so that the utility in NYHA I at model baseline is equivalent to the age- and sex-matched UK general population utility.
II	[redacted]	[redacted]	
III	[redacted]	[redacted]	
IV	[redacted]	[redacted]	

CI, confidence interval; LMEM, linear mixed-effects model; NYHA, New York Heart Association.

Utility modification for ageing

The model accounts for the natural decline in HRQoL associated with ageing by adjusting earlier-stage NYHA class utilities via application of an age- and sex matched utility decrement. The decrement value was based on UK estimates from HSE 2014.[173] Every year of the model (in the first cycle of that year), a utility decrement associated with normal aging is applied to all patients in NYHA class I and II. For example, at age [redacted] (model baseline), the sex-adjusted general population utility estimate is 0.7914 (as described above), and when patients turn 77, the sex-adjusted general population utility estimate is 0.7874, corresponding to a difference of –0.004; thus, this decrement would be applied to all patients in NYHA class I and II in the first cycle of the year when patients turn 77 years old.

Disutilities for ageing were not applied to patients in NYHA class III or IV, since the effect of ageing is assumed to be negligible when compared to the detrimental effects of the disease on HRQoL.

3.4.5 Disutilities

3.4.5.1 Transient event disutilities (CV-related hospitalisation and urgent heart failure visits)

In each cycle, disutilities were applied to the proportion of patients who experienced a CV-related hospitalisation or urgent heart failure visit (per-cycle proportions listed in Table 30). These utility decrements could not be estimated from observed data in HELIOS-B because data from the EQ-5D-5L (administered at specified, fixed time points during the trial) were typically not available from patients at the time they were experiencing these events, which were generally of short duration and may have occurred at any time during the follow-up period.

Therefore, disutilities for CV-related hospitalisations were identified from a cost-effectiveness analysis by McEwan et al. (2021) of ferric carboxymaltose for iron deficiency in heart failure. McEwan et al. analysed EQ-5D-5L data from the Affirm-AHF trial of patients with heart failure in an LMEM model to account for repeat measures to determine a disutility for CV-related hospitalisations (–0.071; SD: 0.016)[177]. This disutility was calculated considering CV-related hospitalisations that occurred within 4 weeks prior to an EQ-5D-5L assessment and thus represents a utility decrement over a 4-week window.[177] Therefore, in the current analysis, the QALY loss per CV hospitalisation was determined by multiplying the disutility value by the proportion of 1 year represented by a 4-week period (7.67% of 1 year).

For urgent heart failure visits, the disutility value from the NICE submission for dapagliflozin for treating chronic heart failure with reduced ejection fraction (TA679) was used (–0.036; SE: 0.011),[178] and QALY loss per event was calculated using the same approach as used for CV-related hospitalisations (i.e., as the disutility was a 4-week disutility in TA679). Disutilities per transient event are summarised in Table 35.

Table 35: Disutilities for CV-related hospitalisations and urgent HF visits

	CV-related hospitalisation	Urgent HF visit
Disutility estimates sourced from the published literature	**–0.070**	**–0.036**
Duration	4 weeks	4 weeks
Source	McEwan et al. (2021)[177]	TA679[178]
QALY loss per event in the model	**–0.005**	**–0.003**

CV, cardiovascular; HF, heart failure; QALY, quality-adjusted life year.

3.4.5.2 SAE disutilities

To account for the effects of SAEs on HRQoL, for each SAE, a specific disutility is applied to the proportion of patients who experience that SAE in the vutrisiran and tafamidis monotherapy arms (Table 31).

Regarding the SAE incidence rates in Table 31, as described in Section 3.3.1, patients in the tafamidis monotherapy arm initiated tafamidis a median of 11.3 months (range: 1.1, 65.5) prior to HELIOS-B baseline. In view of the observed pre-trial exposure to tafamidis in HELIOS-B, the tafamidis monotherapy subgroup may have selectively underrepresented patients who did not tolerate tafamidis, and who thus may have discontinued tafamidis (potentially due to AEs) well before ~1 year on treatment in real-world practice. For this reason, the use of SAE incidence rates in the model based on their occurrence in the vutrisiran and tafamidis monotherapy arms in HELIOS-B represents a conservative approach for vutrisiran.

The LMEM analysis described in Section 3.4.1 informed a disutility value for each SAE; however, due to the rarity of some SAEs in HELIOS-B, and because the analysis estimated positive values for some SAEs (i.e., improvements in HRQoL), alternate disutility estimates were sought from the literature for certain SAEs. The duration of each SAE was based on data from HELIOS-B. The total disutility applied per SAE at cohort level is calculated by multiplying the proportion of patients who experience the SAE by the disutility estimate for the SAE and the proportion of one year represented by the duration of the SAE.

A summary of all SAE disutilities and their duration is provided in Table 36.

Table 36: SAE-related disutilities

SAE	Disutility	Source	Median duration, days (range)
Atrial fibrillation	[redacted]	HELIOS-B LMEM analysis, assumed to be the same as atrial flutter	[redacted]
Osteoarthritis	–0.149	McEwan et al. (2020),[179] assumed to be the same as fracture	[redacted]
Pneumonia	–0.100	McEwan et al. (2021),[177]	[redacted]
Acute kidney injury	[redacted]	HELIOS-B LMEM analysis	[redacted]
Atrial flutter	[redacted]	HELIOS-B LMEM analysis	[redacted]
Ventricular tachycardia	[redacted]	HELIOS-B LMEM analysis	[redacted]
Syncope	–0.048	Wehler et al. (2018)[180]	[redacted]
Chest pain	–0.050	Davies et al, (2015),[181] set equal to unstable angina.	[redacted]
Hyponatraemia	–0.121	TA797[182]	[redacted]
Urinary retention	[redacted]	HELIOS-B LMEM analysis	[redacted]

LMEM, linear mixed-effects model; SAE, Serious adverse event.

3.4.5.3 Caregiver disutilities

As described in Section 1.3.2.5, providing care for patients with ATTR-CM is burdensome and has detrimental effects on HRQoL for informal caregivers. Given the substantial HRQoL burden on informal caregivers, caregiver HRQoL was incorporated in the base-case analysis, with caregiver disutilities differing based on the NYHA class of the affected patient.

Caregiver disutilities were sourced from Acaster et al. (2023)[183] who reported EQ-5D-3L disutilities in 36 caregivers for patients with hATTR (among the patients cared for, 61% had

cardiomyopathy and 72% reported cardiac symptoms).[183] Caregiver EQ-5D-3L disutilities in Acaster et al. were specifically reported based on the ambulatory status of the patient that they were caring for (Table 37), based on familial amyloid polyneuropathy stage.

Table 37: Caregiver disutilities based on ambulatory status of the patient

FAP stage	Patient's ambulatory status	Caregiver EQ-5D-3L disutility (SE)
1	Requires no assistance walking	–0.031 (0.067)
2	Requires assistance with walking	–0.096 (0.055)
3	Requires a wheelchair/bedridden	–0.130 (0.121)

EQ-5D-3L, EuroQol 5-dimension 3-level; FAP, familial amyloid polyneuropathy; SE, standard error. Source: Acaster et al. 2023[183]

These disutility values were used as a proxy for caregiver disutilities based on the NYHA class of the patient that they provide care for. Specifically, values in the model were assigned as follows:

- NYHA I is proxied by FAP 1, disutility = –0.031
- NYHA II is proxied by FAP 2, disutility = –0.096
- NYHA IV is proxied by FAP 3, disutility = –0.130
- NYHA III: Assumed to be 80% of NYHA IV value, disutility = –0.104

Since NYHA classification is based on limitations in physical activity (due to heart failure), applying caregiver disutilities based on impairments in patients' ambulatory and functional status via FAP stages is an appropriate proxy for caregiver disutilities based on the NYHA class of the patient they provide care for. The need for physical assistance (and thus the burden to the caregiver) is expected to be driven by the severity of the patient's physical limitations, and is unlikely to differ depending on the cause of these limitations (i.e., whether heart failure of other ATTR-related symptoms).

Based on feedback from a UK expert (described in Section 3.7), 10%, 30%, 80%, and 100% of patients with ATTR-CM in NYHA class I, II, III, and IV require a caregiver, respectively. These proportions of patients requiring informal caregiving based on their NYHA class status are included in the calculation of health state-specific caregiver disutilities at cohort level (e.g., the caregiver disutility of –0.031 is applied to 10% of patients in NYHA I [the 10% estimated to require caregiver support] to calculate the total cohort-level caregiver disutility in NYHA I).

In addition, the calculation of health state-specific caregiver disutilities at cohort level incorporates expert feedback that patients in the most severe stages of ATTR-CM (NYHA class III and IV) require two caregivers, in those cases in which caregiver support is needed. However, the disutility burden was assumed to be equally shared by both caregivers in the NYHA III and NYHA IV health states.

3.5 Cost and healthcare resource use identification, measurement and valuation

The model incorporates costs from the NHS and PSS perspective. The health system resource-use components incorporated into the economic model as a basis for estimating costs are summarised in Table 38.

Table 38: Summary of costs incorporated in the model

Cost category	Description
Drug acquisition	Acquisition costs of vutrisiran or tafamidis were attributed to patients while they remained on treatment, by treatment arm.
Drug administration	A drug administration cost was applied only in the vutrisiran arm, and only for the first dose that is administered in-hospital and not for subsequent doses that are assumed to be self-administered or administered by a caregiver at home.
Background medication	Costs of symptomatic treatments used to manage the cardiac clinical presentation of ATTR-CM (heart failure and fluid imbalance), were applied based on treatment arm (separate for vutrisiran or tafamidis) for as long as patients remained in the model.
SAEs	Costs of treatment of SAEs were applied to patients based on treatment arm as one-off costs.
Transient events	Costs of CV-related hospitalisations and urgent heart failure visits were applied based on NYHA class.
Non-hospitalisation disease management	Costs for procedures, assessments, and other interventions that are performed in the course of ATTR-CM management but do not involve hospitalisation (e.g., specialist visits and routine tests) or background medications were applied based on NYHA class health state.
Terminal care	One-off costs are applied in the model to all patients who die to reflect the costs of terminal care shortly before death

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; NYHA, New York Heart Association; SAEs, serious adverse events.

Appendix G provides a description of search strategies for relevant cost and HCRU data for the CEA.

3.5.1 Intervention and comparator costs and resource use

3.5.1.1 Drug acquisition price

The posology, dosing frequency, and relative dose intensity of vutrisiran and tafamidis are presented in Table 39.

Table 39: Posology, dosing frequency, and RDI of vutrisiran and tafamidis

Product	Posology	Dosing frequency	RDI
Vutrisiran	25 mg SC injection	Q3M	1.0
Tafamidis	61 mg tablet taken orally	QD	1.0

RDI, relative dose intensity; Q3M, every 3 months; QD, every day; SC, subcutaneous.

A summary of the pack sizes, pack prices, and acquisition cost per year for vutrisiran and tafamidis is provided in Table 40. No drug wastage was modelled for vutrisiran or tafamidis. Pack prices for tafamidis was informed by the British National Formulary (BNF). The price for vutrisiran is the agreed on patient access scheme (PAS) price for vutrisiran.

Table 40: Pack size, pack price, and acquisition cost per year for vutrisiran and tafamidis

Product	Pack size	Pack price (£)	Packs required per year	Cost per year (£)
Vutrisiran	One prefilled syringe (25 mg vutrisiran)	[redacted]	4.00	[redacted]
Tafamidis	30 61 mg capsules	10,685.00	12.18	130,100.56

Appendix I summarises price details for vutrisiran and tafamidis.

3.5.1.2 Drug administration cost

Vutrisiran is administered via SC injection. The model assumes that the first SC injection is administered at the hospital (£108.90; NHS 2023/2024 National Schedule of Costs, based on the cost associated with specialist nursing, cancer-related, adult, face-to-face [HRG code: N10AF]).[184]

From April 2025 Alnylam anticipates an update to the SmPC allowing for self-administration of vutrisiran following an initial dose administered by healthcare personnel. Therefore, all subsequent administrations after the first dose administration are assumed to be done by the patient or a caregiver at home. Alnylam anticipates company-funded delivery of vutrisiran to patients' homes. Thus, self-administration or caregiver administration are assumed to not incur any cost.

Therefore, the cost for drug administration for vutrisiran is £108.90 in the first cycle and £0.00 in all subsequent cycles. No administration cost for tafamidis is modelled, which is a conservative assumption considering the potential delivery cost that may be required to deliver tafamidis to patients' homes.

3.5.2 Costs of background medication

In the model, all patients (including those who have discontinued vutrisiran or tafamidis) receive therapies that are not indicated for the treatment of ATTR-CM but are aimed at managing the associated cardiac symptoms of the disease. Per-cycle use rates were assigned to the vutrisiran arm and tafamidis arm based on use of these therapies in the vutrisiran and tafamidis monotherapy arms in HELIOS-B, respectively. Only medications that had both 1) the highest usage rate within their therapeutic class and 2) an absolute usage rate above 7% in either the vutrisiran or tafamidis monotherapy group were included. The threshold of 7% was selected as it was observed to capture at least one therapy from each relevant class of heart failure therapies. A summary of per-cycle use rates within each model arm is provided in Table 41. Per-cycle use rates for patients upon discontinuation of vutrisiran or tafamidis (as informed by data from the BSC arm of HELIOS-B) are summarised in Appendix J.

Table 41: Per-cycle use of background medication for symptomatic treatment of cardiac clinical presentation in the vutrisiran and tafamidis arms

Therapy	Proportion of patients receiving therapy	
	Vutrisiran (%)	Tafamidis (%)
Ramipril	[redacted]	[redacted]
Amiodarone	[redacted]	[redacted]
Allopurinol	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]

Therapy	Proportion of patients receiving therapy	
	Vutrisiran (%)	Tafamidis (%)
Bisoprolol	[redacted]	[redacted]
Omeprazole	[redacted]	[redacted]
Tamsulosin	[redacted]	[redacted]
Furosemide	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]
Spironolactone	[redacted]	[redacted]
Dapagliflozin	[redacted]	[redacted]
Empagliflozin	[redacted]	[redacted]

Note: Dapagliflozin and empagliflozin were suggested by a clinical expert to both be important background treatments in the management of symptoms of ATTR-CM and were therefore both included.

A summary of the posology and costs associated with background medications is provided in Table 42. All costs were informed from the BNF.

Table 42: Posology and cost of background medication for symptomatic treatment of cardiac clinical presentation in the model

Therapy	Unit dose per administration	Units administered per cycle	Units per pack	Pack cost (£)
Ramipril	5 mg	91.3 (QD)	28 pills	1.24
Amiodarone	200 mg	91.3 (QD)	28 pills	1.85
Allopurinol	100 mg	91.3 (QD)	28 pills	0.75
Apixaban	5 mg	182.6 (BID)	28 pills	4.75
Bisoprolol	10 mg	91.3 (QD)	28 pills	0.76
Omeprazole	20 mg	28.0* (QD)	28 pills	11.00
Tamsulosin	400 mcg	91.3 (QD)	30 pills	7.44
Furosemide	40 mg	91.3 (QD)	28 pills	0.67
Atorvastatin	20 mg	91.3 (QD)	28 pills	1.22
Spironolactone	50 mg	91.3 (QD)	28 pills	3.32
Dapagliflozin	10 mg	91.3 (QD)	28 pills	36.59
Empagliflozin	10 mg	91.3 (QD)	28 pills	36.59

BID, twice per day; QD, once per day. *Omeprazole is administered daily for 4 weeks. Note: All therapies are administered orally and have no cost assigned for administration.

Considering usage rates, the per-cycle cost of background medication for symptom treatment in the model was estimated to be £[redacted] in the vutrisiran arm and £[redacted] in the tafamidis arm.

3.5.3 Costs of transient events (CV-related hospitalisation and urgent heart failure visits)

As discussed in Section 3.3.6, patients on either treatment may be hospitalised for CV-related events or have urgent heart failure visits, the rates of which are NYHA class-specific. The unit costs for each of these two transient events were based on the NHS 2023/2024 National Schedule of Costs (Table 43).[184]

Table 43: Summary of transient event-related costs

Transient event	Unit Cost (£)	NHS 2023/2024 National Schedule of Costs
CV-related hospitalisation	3,959.24	**HRG codes**: • EB03A–EB03E (codes vary by critical care code) • EB07A–EB07E (codes vary by critical care code) **Calculation method:** • Weighted average of all ten relevant codes based on total completed clinician consultation sessions per code.
Urgent HF visit	652.62	**HRG codes**: • EB03A–EB03E, daycase department code (codes vary by critical care code) **Calculation method:** • Weighted average of all five relevant codes based on total completed clinician consultation episodes per code.

CV, cardiovascular; HF, heart failure; NHS, National Health Service.

Considering the frequency and cost of these transient events, Table 44 summarises costs per cycle, by NYHA class health state.

Table 44: Per-cycle transient event management costs by NYHA class health state

Health state	Per cycle cost (£)
NYHA I	[redacted]
NYHA II	[redacted]
NYHA III	[redacted]
NYHA IV	[redacted]

NYHA, New York Heart Association.

3.5.4 Non-hospitalisation disease management costs

Beyond hospitalisation, other healthcare services are incurred by patients with ATTR-CM, including clinician office visits and laboratory and imaging tests. Including these healthcare services in this model is in alignment with the recent NICE appraisal of tafamidis in ATTR-CM [TA696][157]), with inputs based on consultation with clinical experts who treat ATTR-CM (described in Section 3.7). It is anticipated that patients will require such services more frequently as disease worsens, and therefore the use of these services in the model differs based on NYHA class health state. Estimated per-cycle use within each health state was determined by consultation with clinical experts. A summary of per-cycle use based on NYHA class health state and unit costs for healthcare services is provided in Table 45.

Table 45: Unit costs and resource use for non-hospitalisation-related disease management

Resource item	Unit cost (£)	Source	Estimated units required per patient per-cycle by NYHA class			
			I	II	III	IV
Neurology outpatient follow-up visit	235.52	**NHS reference costs 2023/2024**: WF01A, neurology service, consultant led, non-admitted face-to-face attendance, follow-up, service code 400.	[redacted]	[redacted]	[redacted]	[redacted]
Community cardiology visit	138.93	**NHS reference costs 2023/2024:** WF01A, cardiology service, non-consultant led; non-admitted face-to-face attendance, follow-up, service code 320.	[redacted]	[redacted]	[redacted]	[redacted]
Specialist cardiology visit	180.15	**NHS reference costs 2023/2024:** WF01A cardiology consultant led; non-admitted face-to-face attendance, follow-up, service code 320.	[redacted]	[redacted]	[redacted]	[redacted]
General practitioner visit	34.00	**PSSRU report 2023:** Prescription cost per consultation.	[redacted]	[redacted]	[redacted]	[redacted]
Community nurse visit	19.00	**PSSRU report 2023:** Community nurse, band 6, without qualification costs), assuming a 20-minute appointment.	[redacted]	[redacted]	[redacted]	[redacted]
Renal function test	1.58	**NHS reference costs 2023/2024:** DAPS03, directly assessed pathology services, service code 999.	[redacted]	[redacted]	[redacted]	[redacted]
Liver function test	1.58	**NHS reference costs 2023/2024:** DAPS03, directly assessed pathology services, service code 999.	[redacted]	[redacted]	[redacted]	[redacted]
Haematocrit test	1.58	**NHS reference costs 2023/2024:** DAPS03, directly assessed pathology services, service code 999.	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP test	1.58	**NHS reference costs 2023/2024:** DAPS03, directly assessed pathology services, service code 999.	[redacted]	[redacted]	[redacted]	[redacted]
Echocardiogram	255.42	**NHS reference costs 2023/2024:** EY50Z, cardiology service, complex echocardiogram, outpatient procedure; service code 320.	[redacted]	[redacted]	[redacted]	[redacted]

NHS, National Health Service; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PSSRU, Personal Social Services Research Unit. Note: Estimated requirement of each item per cycle based on NYHA class was informed by consultation with clinical experts.

Considering the frequency and cost of these healthcare services, Table 46 summarises non-hospitalisation disease management costs per cycle, by NYHA class health state.

Table 46: Per-cycle non-hospitalisation disease management costs by NYHA class health state

Health state	Per cycle cost (£)
NYHA I	[redacted]
NYHA II	[redacted]
NYHA III	[redacted]
NYHA IV	[redacted]

NYHA, New York Heart Association.

3.5.5 Costs associated with SAEs

Per-event costs of managing SAEs are summarised in Table 47. Overall, SAE management costs are calculated based on these per-event costs and on the frequency of each SAE in the model arm of interest (Table 31).

Table 47: Costs associated with managing SAEs

SAE	Cost per event (£)	Reference
Atrial fibrillation	539.47	**NHS reference costs 2023/24:** EB07A–EB07E (non-elective short stay)
Osteoarthritis	549.11	**NHS reference costs 2023/2024:** currency code VC22Z
Pneumonia	673.14	**NHS reference costs 2023/2024:** DZ11R–DZ11V (non-elective short stay)
Acute kidney injury	675.34	**NHS reference costs 2023/2024:** currency code LA07H–LA07P (non-elective short stay)
Atrial flutter	539.47	**NHS reference costs 2023/2024:** currency code EB07A–EB07E (non-elective short stay)
Ventricular tachycardia	539.47	**NHS reference costs 2023/2024:** currency code EB07A–EB07E (non-elective short stay)
Syncope	551.78	**NHS reference costs 2023/2024:** currency code EB08A–EB08E (non-elective short stay)
Chest pain	486.90	**NHS reference costs 2023/2024:** currency code EB12A–EB12C (day case)
Hyponatraemia	34.00	Assumed same as GP visit (Table 45)
Urinary retention	34.00	Assumed same as GP visit (Table 45)

GP, general practitioner; NHS, National Health Service; SAE, serious adverse event.

Therefore, the per-cycle cost of treating SAEs in the model was estimated to be £[redacted] in the vutrisiran arm and £[redacted] in the tafamidis arm.

3.5.6 Terminal care costs

In each model cycle, the costs associated with terminal care are applied to the proportion of patients who die in that cycle, to reflect the costs of terminal care shortly before death. The unit cost of terminal care (£8,051) was identified from the PSSRU 2023 Unit Costs of Health and Social Care report.[185]

3.6 Severity

Analyses of absolute and proportional QALY shortfall resulted in shortfall estimates below thresholds applicable to severity modifiers (absolute: >12 QALYs; proportional: >0.85); therefore, these modifiers were not applied.

3.7 Uncertainty

ATTR-CM is a rare disease with awareness of the disease increasing only in recent years, and hence, the availability of related real-world evidence is limited. Thus, while the prevalence of ATTR-CM is increasing due to increasing clinician awareness and availability of less invasive diagnostic methods, identifying real-world evidence to supplement data from HELIOS-B in informing the economic analysis was in some cases challenging. In these situations, expert clinical feedback was sought, or real-world evidence related to general heart failure or other related cardiac conditions was used. In the latter case, two experts were consulted to validate or provide inputs to inform the model. The results of these expert consultation interviews are described herein. One clinical expert was consulted primarily to validate clinician inputs (Section 3.7.1), while the other validated the technical approaches employed in the model (Section 3.7.2).

3.7.1 Expert clinician interviews to determine and validate clinical inputs

In 2023 and 2024, Alnylam solicited expert opinion to validate the key modelling approaches, inputs, and assumptions from a clinical perspective for the economic analysis of vutrisiran for the treatment of ATTR-CM. The criteria for selecting the clinical expert consisted of ensuring the clinician was:

- A member of the amyloidosis highly specialised service at the NAC at the Royal Free Hospital, London.
- Responsible for treating patients with ATTR.

[redacted], met all criteria and agreed to participate in web-based interviews.

Two interviews (8 September 2023 and 14 November 2024) were conducted, each lasting 60–90 minutes.

Feedback on key clinical model inputs and assumptions is summarised in Table 48.

Table 48: Clinical validation on model assumptions and parameters

Model feature	Expert clinician feedback
8 September 2023	
Transient events and HCRU parameters included in the model	The clinician expert explained that for transient clinical events, capturing CV-related hospitalisations and urgent heart failure visits in the model was appropriate. For HCRU, the clinical expert suggested the following resources used along with their frequency of utilisation: • Neurologist visits ([redacted] times per year) • GP visits ([redacted] every 3 months) • Lab work/blood tests ([redacted] every 3 months) • Community nurse visits (heart failure specialist nurse) (once [redacted] • Outpatient procedures (e.g., echocardiogram) • Hospitalisations (including the number of hospitalisation days) Estimates were finalised in the 14 November 2024 interview, described below.
Cycle Length	The clinician expert confirmed that a 3-month cycle length was appropriate for the model, as meaningful changes in disease severity are not anticipated to occur over timeframes shorter than 3 months. This was taken into consideration in the company submission.
14 November 2024	
Disutility values for AEs	Due to a small sample size, the disutility values estimated for certain AEs from the LMEM analysis were not reliable, necessitating the use of a proxy value from the literature. The clinical expert suggested using “angina” as a proxy for “chest pain”. This was taken into consideration in the company submission.
Transient event incidence rates in NYHA IV	Based on the clinician expert’s experience with treating patients with ATTR-CM, the expert suggested that the relative risk of transient events in NYHA IV is [redacted] times that of NYHA III. This was taken into consideration in the company submission.
Caregiver support	The clinician expert suggested that in patients with ATTR-CM, need for a caregiver occurs in approximately [redacted]% in NYHA I, [redacted]% in NYHA II, [redacted]% in NYHA III, and [redacted]% in NYHA IV, including informal caregivers such as a family member. Further, the clinical expert noted that patients in NYHA III and IV require [redacted] caregivers. This was taken into consideration in the company submission.
Transient event costs	The clinician expert confirmed that the cost items currently used in company submission for CV-related hospitalisations and urgent heart failure visits were appropriate.
Treatment effect post discontinuation of vutrisiran	The clinician expert suggested that 3 or more months of continued full treatment effect post-discontinuation for vutrisiran was reasonable but also suggested that the maintenance of treatment effects could be longer, and the accurate duration would need to be calculated from data collected post-discontinuation. Considering this, in the company submission, treatment waning in the vutrisiran arm is based on pharmacodynamic data regarding the persistence of reductions in serum TTR levels relative to pre-treatment baseline following discontinuation of vutrisiran in HELIOS-B.

Model feature	Expert clinician feedback
HCRU for non-hospitalisation disease management	The following HCRU parameters and their frequency of use according to NYHA class were validated by the clinician expert: • **ECG**: [redacted] per year for [redacted], and [redacted] per year for [redacted]. • **Cardiology visit**: [redacted] per year for patients in [redacted], and [redacted] per year for patients in [redacted]. • **Specialist cardiologist visit**: [redacted] per year for patients in [redacted], and [redacted] per year for patients in [redacted]. • **GP visit**: [redacted] per year for patients in [redacted], and [redacted] for patients in [redacted]. • **Neurology visit**: [redacted] per year for all patients. • **Community nurse visit**: [redacted] for patients in [redacted]. [redacted] for patients in [redacted], with some patients in [redacted] requiring visits [redacted] per week. • **Blood tests**: Considered to occur whenever patients visited the [redacted], except for renal function tests for patients in [redacted], where it was assumed that the test would be required [redacted] per month. These parameters and their frequencies have been included in company submission.

AE, adverse event; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CEA, cost-effectiveness analysis; CV, cardiovascular; ECG, electrocardiogram; GP, general practitioner; HCRU, healthcare resource utilisation; LMEM, linear mixed effects model; NYHA, New York Heart Association; TTR, transthyretin.

3.7.2 Technical expert interviews to validate model features

In 2023 and 2024, Alnylam solicited expert opinion to validate key model features from a technical perspective.

One UK-based technical expert was approached and agreed to participate in web-based interviews ([redacted]). A total of two interviews (4 August 2023 and 20 December 2024) were conducted, each lasting 60–90 minutes.

Feedback from these interviews on key technical model features and assumptions is summarised in Table 49.

Table 49: Technical expert validation of the model assumptions and methodology

Model feature	Technical expert feedback
4 August 2023	
Source of data used to inform parameters in the tafamidis arm	Feedback was sought regarding the use of data from ATTR-ACT or HELIOS-B to inform the tafamidis arm in the model. The expert suggested that using the tafamidis monotherapy group within the HELIOS-B trial population would be an appropriate approach for direct comparison of vutrisiran vs. tafamidis. The company-submitted cost-effectiveness analysis uses this approach, comparing monotherapy groups within HELIOS-B for the treatments of interest.
Modelling survival	The expert confirmed using overall survival from HELIOS-B IPD was appropriate. Overall survival is modelled using this approach in the company submission.

Model feature	Technical expert feedback
Cycle length	The expert confirmed that use of a 3-month cycle length is appropriate, considering that it aligns with the dosing interval for the intervention, hence simplifying cost considerations. Cycle length is modelled accordingly in the company submission.
Transition probabilities	The expert confirmed the approach of estimating transition probabilities during the observed period (Months 0–30 from HELIOS-B) using count data. This approach has been included in the company submission.
20 December 2024	
Transition probabilities (extrapolation)	The expert confirmed that the approach of estimating transition probabilities during the extrapolated period (Months 30+) based on an average of the last two 6-month intervals in the observed period is reasonable, since using the data from only the last 6-month interval in the observed period would skew the results, given there are no transitions to NYHA IV during this period in the vutrisiran arm. This approach has been included in the company submission.
Treatment waning effect after discontinuation of vutrisiran	The expert confirmed that the proposed approach of modelling treatment waning in the vutrisiran arm using pharmacodynamic data on reversal of serum TTR reductions from pre-treatment baseline upon vutrisiran discontinuation is reasonable. This approach has been included in the company submission.

IPD, individual patient data; NYHA, New York Heart Association; TTR, Transthyretin.

3.8 Managed access proposal

Alnylam does not consider vutrisiran to be a candidate for managed access.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

Base-case analysis parameters are summarised in Table 50.

Table 50: Base-case analysis parameters

Parameter	Value/method used	Reference to section in submission
General parameters		
Mean age (SE)	[redacted]	3.3.2
Gender, % male	[redacted]	3.3.2
Time horizon	Lifetime (24 years)	3.2.4
Cycle length	3 months	
Discount rate (effect)	3.5%	3.2.6
Discount rate (costs)	3.5%	
Half-cycle correction	Yes	3.2.4

Parameter	Value/method used	Reference to section in submission
Transition probabilities		
Up to Month 30	Calculated from observed 6-month HELIOS-B vutrisiran and tafamidis monotherapy arm NYHA transitions (with conversion to per-cycle probabilities based on 3-month cycle length).	3.3.3
Extrapolation period (months 30+)	Extrapolated based on the average of the last two observed 6-month transition probability matrices from the period up to Month 30 in HELIOS-B (with conversion to per-cycle probabilities based on 3-month cycle length).	
Overall survival		
Vutrisiran arm	Derived from parametric functions fit to observed 42-month survival in the vutrisiran monotherapy group in HELIOS-B using the log-logistic function in the base-case analysis.	3.3.4.1
Tafamidis arm	Derived from parametric functions fit to observed 42-month survival in the tafamidis monotherapy group in HELIOS-B using the log-normal function in the base-case analysis.	
Survival cap	Modelled survival in each treatment arm was capped by age-matched general UK population survival.	3.3.4.2
NYHA class allocation of deaths	Deaths in each cycle are allocated across NYHA classes based on NYHA class-specific mortality HRs from Cheng et al. (2020).[22]	3.3.4.3
Treatment discontinuation		
Treatment discontinuation	Derived from parametric functions fitted to observed non-fatal treatment discontinuation data from the vutrisiran monotherapy arm in HELIOS-B (non-fatal discontinuation rates conservatively assumed to be the same in the tafamidis arm as in the vutrisiran arm).	3.3.5
Treatment waning effect	In the vutrisiran arm, treatment effects on transition probabilities decline in a graduated manner from the full effect of vutrisiran over seven cycles post-discontinuation, before fully transitioning to BSC trajectory. For tafamidis, transition to BSC trajectory for transition probabilities occurs in same cycle as discontinuation.	3.3.5.1
Transient events		
CV-related hospitalisations and urgent heart failure visits	Modelled to occur based on occurrence in HELIOS-B according to NYHA class health state.	3.3.6
SAEs	Modelled to occur based on occurrence in the vutrisiran and tafamidis monotherapy arms in HELIOS-B.	3.3.7

Parameter	Value/method used	Reference to section in submission
Utilities		
NYHA class health-state utilities	Treatment-independent NYHA class-specific utilities determined via LMEM analysis of EQ-5D-3L utility values mapped from EQ-5D-5L data collected prospectively in the HELIOS-B trial. Utilities were capped to not exceed sex- and age-matched general population utilities. Utility decrements for ageing for patients in NYHA I and II were applied.	3.4.4
Transient event disutilities	Sourced from published literature.	3.4.5.1
SAE-related disutilities	Estimated from previously mentioned HELIOS-B LMEM analysis or sourced from published literature.	3.4.5.2
Caregiver disutilities	Sourced from published literature.	3.4.5.3
Costs		
Drug administration	Sourced from the NHS 2023/2024 National Schedule of Costs	3.5.1.2
Treatment for symptoms management	Sourced from the BNF.	3.5.2
Transient events	Sourced from NHS 2023/2024 National Schedule of Costs	3.5.3
Non-hospitalisation disease management	Sourced from NHS 2023/2024 National Schedule of Costs and PSSRU Unit Costs of Health and Social Care 2023 Manual	3.5.4
SAE-related treatment	Sourced from NHS 2023/2024 National Schedule of Costs	3.5.5
Terminal care	Sourced from PSSRU Unit Costs of Health and Social Care 2023 Manual	3.5.6

BNF, British National Formulary; BSC, best supportive care; EQ-5D-3L, EuroQol 5-dimension 3-level; EQ-5D-5L, EuroQol 5-dimension 5-level; HR, hazard ratio; LMEM, linear mixed-effects model; NHS, National Health Service; NYHA, New York Heart Association; PH, proportional hazards; PSSRU, Personal Social Services Research Unit; SAE, serious adverse event; SE, standard error.

3.9.2 Assumptions

Model assumptions are listed in Table 51.

Table 51: Model assumptions

Assumption	Rationale
Data from the tafamidis monotherapy group from HELIOS-B were used to inform clinical outcomes in the tafamidis model arm, despite pre-baseline exposure to tafamidis (median 11.3 months) in this group.	Due to differences in the time periods in which HELIOS-B and ATTR-ACT were run, patients in ATTR-ACT had worse levels disease at baseline and followed worse disease trajectories compared to patients in HELIOS-B.[38] These differences are related to the evolution of ATTR-CM clinical practice: over time. In recent years, patients with ATTR-CM have increasingly been diagnosed earlier in the disease course, with less severe disease, due to increased disease awareness within the clinician community and improved diagnostic techniques,[104,109] while also benefiting from recent advances in supportive care that have improved baseline prognosis for all patients with ATTR-CM.[152] For this reason, using data from ATTR-ACT to inform model parameters for the tafamidis arm would not be an accurate representation of current outcomes of tafamidis treatment in a contemporary ATTR-CM patient population. Therefore, the more appropriate source to inform parameters in the tafamidis arm was the contemporary tafamidis monotherapy group within the placebo arm in HELIOS-B. However, patients in the tafamidis monotherapy group in HELIOS-B were exposed to tafamidis prior to HELIOS-B baseline, which likely biased health outcomes in favour of tafamidis, as it may have led to selective underrepresentation of patients who did not tolerate or had poor responses on tafamidis well before ~1 year on treatment in real-world practice (and therefore discontinued tafamidis). Additionally, there is a potential bias in survival favouring the tafamidis monotherapy arm due to the duration of time needed for the survival benefit to emerge after treatment initiation, for which tafamidis-treated patients in the model had an approximate 1-year lead time due to the pre-baseline exposure to tafamidis. Therefore, this assumption can be considered as conservative for vutrisiran.
Following discontinuation of vutrisiran, treatment effects of vutrisiran on transition probabilities wane in a graduated manner over 7 cycles.	A dose of vutrisiran (normally administered Q3M) has been shown to knockdown serum TTR (the driver of disease in ATTR-CM) for an extended period even in the absence of subsequent doses. Based on worldwide clinical expert opinion, an approximate 80% sustained reduction in serum TTR levels relative to pre-treatment baseline levels provides a signal of expected treatment benefit. Therefore, a graduated treatment waning effect on NYHA class transition probabilities for patients who discontinue vutrisiran was implemented in the model, based on observed data on the evolution of serum TTR levels after patients received a final dose of vutrisiran during the double-blind period of HELIOS-B (see Section 3.3.5.1).

Assumption	Rationale
Rate of treatment discontinuation in the tafamidis arm is assumed to be the same as the vutrisiran arm.	Discontinuation in the vutrisiran arm is modelled with parametric extrapolation based on observed non-fatal treatment discontinuation in the vutrisiran monotherapy arm of HELIOS-B. Non-fatal discontinuation data from patients in the tafamidis monotherapy group in HELIOS-B could not be used to inform discontinuations in the tafamidis model arm in the same manner, since patients in the tafamidis monotherapy group within the placebo arm in HELIOS-B had been on tafamidis for a median of 11.3 months at trial baseline. In view of the observed pre-trial exposure to tafamidis in HELIOS-B, the tafamidis monotherapy group may have underrepresented patients who did not tolerate tafamidis, and who thus may have discontinued tafamidis well before ~1 year on treatment in real-world practice, This could create bias towards increased treatment persistence in the tafamidis arm of the model, which does not reflect expected real-world practice.
Age-based utility decrements are only applied to patients in NYHA I and II.	Since patients with ATTR-CM in more advanced NYHA classes (NYHA III and IV) exhibit severely reduced HRQoL (via utilities derived in the HELIOS-B LMEM analysis), there was less need to further incorporate HRQoL impairment associated with normal ageing for these patients, as the magnitude of age-related impairment would be minimal relative to the magnitude of disease-related impairment.
Caregiver disutilities were based on disutilities for caring for patients in different FAP stages, as a proxy for NYHA classes.	The burden of caregiving in ATTR is strongly related to the level of disability of the patient being cared for. FAP stages and NYHA classes both assess patients' level of physical disability, with stages/classes that range from no physical limitation, to extreme limitation of physical activity. Only the extent of physical limitations, and not the cause (i.e., heart failure or other ATTR-related symptoms), is expected to affect the level of burden in providing care (see Section 3.4.5.3). Therefore, FAP stages are considered an appropriate proxy for NYHA classes in estimating caregiver disutility by NYHA class.

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HRQoL, health-related quality of life; LMEM, linear mixed-effects model; NYHA, New York Heart Association; FAP, familial amyloid polyneuropathy; TTR, transthyretin.

3.10 Base-case results

Vutrisiran use resulted in a gain of 1.19 QALYs and [redacted] LYs versus tafamidis use, driven by patients on vutrisiran living longer and relatively healthier (occupying less severe NYHA class health states) versus those on tafamidis. The incremental cost-effectiveness ratio (ICER) for vutrisiran versus tafamidis was £[redacted]/QALY.

Table 52 presents a summary of results of the base-case CEA for vutrisiran versus tafamidis, from the NHS public payer perspective in the UK. Considering the incremental gain with vutrisiran of 1.19 discounted QALYs at a discounted incremental cost of £[redacted], the CEA yielded a discounted ICER of £[redacted]/QALY for vutrisiran versus tafamidis. At the willingness-to-pay (WTP) threshold of £30,000/QALY, the discounted net monetary benefit (NMB) for vutrisiran versus tafamidis was –£[redacted].

Table 52: Results of the deterministic base-case CEA for vutrisiran vs. tafamidis

	LYs	QALYs	Costs (£)	ICER (£/QALY)	NMB at £30,000/QALY (£)	NMB at £20,000/QALY (£)
Discounted						
Vutrisiran	[redacted]	4.91	[redacted]	–	–	–
Tafamidis	[redacted]	3.72	[redacted]	–	–	–
Vutrisiran vs. tafamidis	[redacted]	**1.19**	[redacted]	[redacted]	[redacted]	[redacted]
Undiscounted						
Vutrisiran	[redacted]	[redacted]	[redacted]	–	–	–
Tafamidis	[redacted]	[redacted]	[redacted]	–	–	–
Vutrisiran vs. tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CEA, cost effectiveness analysis; ICER, incremental cost-effectiveness ratio; LY, life-year; NMB, net monetary benefit; QALY, quality-adjusted life-year.

A summary of clinical outcomes, including overall survival and health-state distributions over the model time horizon is provided in Appendix H, along with a summary of disaggregated results.

3.11 Exploring uncertainty

Robustness of the deterministic base-case analysis was confirmed by the probabilistic sensitivity analysis (PSA), which showed similarity between the deterministic base-case ICER (£[redacted]/QALY) and the PSA mean base-case ICER (£[redacted]/QALY).

A deterministic one-way sensitivity analysis (OWSA) revealed that modifying the transition probability for NYHA II to NYHA II (i.e., the proportion of patients who remain in NYHA II) in Months 24–27 and 27–30 in the tafamidis arm had the greatest impact on the ICER.

3.11.1 Probabilistic sensitivity analysis

The degree to which model results were impacted by uncertainty around model parameters was assessed through a PSA. The distributions from which parameter values could be sampled for the PSA included beta, Dirichlet, gamma, normal, and log-normal distributions, depending on the parameter type. The model also included Cholesky decomposition matrix calculation fields for modelling uncertainty in pairs of input parameters for which the covariance structure between the two variables was known. For example, for each survival curve, the two survival function parameters were varied using this method to account for the correlation between the two parameters. The variance and covariance matrices of the survival function parameters were derived from the curve-fitting procedures.

The PSA was run for 2,000 simulations. Results of the PSA are presented in Table 53.

Table 53: Mean results of the PSA for vutrisiran vs. tafamidis

	LYs	QALYs	Costs (£)	ICER (£/QALY)	NMB at £30,000/QALY (£)	NMB at £20,000/QALY (£)
Vutrisiran	[redacted]	4.85	[redacted]	–	–	–
Tafamidis	[redacted]	3.72	[redacted]	–	–	–
Vutrisiran vs. tafamidis	[redacted]	**1.13**	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LY, life-year; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year. Note: Discounted results are presented.

In addition, Figure 31 shows that [redacted]% of all iterations resulted in increased QALYs in the vutrisiran arm, and [redacted]% of iterations resulted in increased costs in the vutrisiran arm. The base-case deterministic ICER and the PSA mean ICER were similar (deterministic base case: [redacted]/QALY; PSA: [redacted]/QALY), confirming the overall robustness of the model results.

Figure 31: Distribution of results of the PSA iterations in the CE plane for vutrisiran vs tafamidis

CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; PSA, probabalistic sensitivity analysis; QALY, quality-adjusted life year.

The cost-effectiveness acceptability curve (CEAC) for vutrisiran versus tafamidis is presented in Figure 32.

Figure 32: Cost-effectiveness acceptability curve for vutrisiran vs tafamidis

WTP, willingness-to-pay.

3.11.2 Deterministic sensitivity analysis

A deterministic OWSA was conducted by varying the base-case values of key input parameters one at a time. The range of values over which each parameter was varied was one of the following:

- The 95% CI of the parameter based on observed data or published reports
- ±10% of the mean base-case value

In the OWSA, the greatest change in the ICER occurred when the transition probability for NYHA II to NYHA II (i.e., the proportion of patients who remain in NYHA II) in Months 24–27 and 27–30 in the tafamidis arm was varied (Figure 33), resulting in variation of £ in the ICER (Table 54). Other parameters, namely, the uncertainty associated with the point estimate of the utility in the NYHA II health state and the probability of remaining in the NYHA II health state for patients treated with vutrisiran during Months 24–30 of HELIOS-B, had the second and third highest impact on the ICER, respectively.

Figure 33: Tornado diagram of the 10 variables for which OWSA resulted in the greatest variation in ICER for vutrisiran vs. tafamidis

ICER, incremental cost-effectiveness ratio; Mx, month X; NYHA, New York Heart Association; OWSA, one-way sensitivity analysis; TP, transition probability.

Table 54: OWSA parameters with the greatest impact on the ICER for vutrisiran vs. tafamidis

Parameter	Base-case value	OWSA lower value	OWSA upper value	Lower value ICER (£/QALY)	Upper value ICER (£/QALY)	ICER variation* (£)
Tafamidis, TP, NYHA II to II, M24–M27 and M27–M30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vutrisiran, NYHA II utility†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vutrisiran, TP, NYHA II to II, M24–M27 and M27–M30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate, effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis, TP, NYHA II to II, M18–M21 and M21–M24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate, costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vutrisiran, treatment discontinuation, gamma distribution, rate parameter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis, survival, log-normal distribution, meanlog parameter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis, NYHA II utility†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; Mx, month X; NYHA, New York Heart Association; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year; TP, transition probability. *Represents the sum of absolute variation around the base-case ICER (absolute variation with lower parameter value + absolute variation with upper parameter value). †Variations in NYHA class utilities were tested separately in each treatment arm.

3.11.3 Scenario analysis

The largest reduction in ICER from the base-case analysis was seen when alternate annual treatment costs were included for vutrisiran and tafamidis, which resulted in a [redacted]% decrease in the ICER.

Scenario analyses were performed to assess the cost-effectiveness of vutrisiran under various scenarios involving assumptions and inputs that differ from the base case but may still reflect plausible real-world circumstances or other specific situations of interest for decision-making.

3.11.3.1 Scenarios explored

3.11.3.1.1 Altered discounting for costs and effects

In this scenario, different sets of discount rates for costs and effects were tested, including at 0% and 5%.

3.11.3.1.2 Altered time horizons

In this scenario analysis, time horizons were varied to, including 5, 10, 15, and 25 years.

3.11.3.1.3 Extrapolated transition probabilities based on the last observed transition matrix

In this scenario analysis, the transition probabilities in the extrapolation period (M30+) were informed only by observed transitions from Months 24–30 (per-cycle transition probability matrices for Months 24–27 and 27–30) from HELIOS-B, translated to 3-month transition rates (Table 24).

3.11.3.1.4 Full societal perspective

In this scenario analysis, the full societal perspective was considered by including costs associated with productivity losses for caregivers (in addition to HRQoL impacts from the base-case analysis). Further, productivity losses in patients with ATTR-CM were also included in the full societal perspective scenario analysis. A separate scenario analysis was also conducted where only caregiver productivity losses were included (in addition to HRQoL impacts from the base-case analysis).

Caregiver productivity losses

As described in Section 3.7, UK expert clinicians provided feedback that informed the following model inputs regarding patients' need for caregiver support:

- 10%, 30%, 80%, and 100% of patients with ATTR-CM in NYHA class I, II, III, and IV require a caregiver, respectively.
- Patients in NYHA class III and IV require two caregivers, in cases in which caregiver support is needed.

Further, an analysis by Lahoz et al. (2021)[186] of 361 caregivers for patients with heart failure from France, Germany, Italy, Spain, and the UK determined average hourly time spent providing care per week based on NYHA class of the patient (NYHA I: 11.8 hours; NYHA II: 18.1 hours; NYHA III and IV: 25.9 hours). These hourly estimates were used to determine caregiver-associated labour productivity loss (cost of missed employment) in the full societal perspective scenario in the model.

The cost for one hour of lost productivity associated with missing employment due to caregiving (£18.64) was sourced from the 2024 median hourly earnings from the ONS.

These parameters regarding the intensity and hourly cost of caregiver support were used to estimate caregiver costs in the model, as summarised in Table 55. Conservatively, it was assumed that the total weekly time required to care for a patient in NYHA III was 80% of the total weekly time required to care for a patient in NYHA IV.

Table 55: Summary of inputs used to calculate caregiver costs

NYHA class	Proportion of patients requiring a caregiver	Hours spent on caregiving per week per caregiver	Number of caregivers required per patient	Cost of one hour of lost productivity (£)	Caregiver productivity loss per cycle (£)
NYHA I	10%	11.8	1	18.64	[redacted]
NYHA II	30%	18.1	1		[redacted]
NYHA III	80%	20.72*	2		[redacted]
NYHA IV	100%	25.9	2		[redacted]

NYHA, New York Heart Association. *The total weekly time required to care for a patient in NYHA III was assumed to be 80% of the total weekly time required to care for a patient in NYHA IV.

Patient productivity loss

The inability to work and be productive in ATTR-CM is driven by debilitation from worsening heart failure. A Delphi panel of 11 experts in heart failure by Çavuşoğlu et al. (2022)[187] determined work impairment levels in patients with heart failure based on NYHA class, revealing that more severe heart failure led to greater percentages of overall work impairment (i.e., the proportion of normal work time that is missed due to heart failure; Table 56).

Table 56: Proportion of work missed due to heart failure severity in patients with heart failure

NYHA Class	I	II	III	IV
Proportion of patients who miss work based on their disease severity	21%	36%	66%	92%

NYHA, New York Heart Association. Source: Çavuşoğlu et al. (2022)[187]

Therefore, in the full societal scenario, the proportions from Table 56 are used to estimate the proportion of work missed by patients with ATTR-CM, assuming a 40-hour work week, and assuming that 12.1% of the overall model cohort is employed. The latter assumption is based on data from the ONS that showed a 12.1% employment rate in people ≥65 years of age as of September 2024.[188]

Lost productivity costs in patients were calculated by determining the total number of work hours missed per cycle and multiplying by 2023 median hourly earnings ($18.64), sourced from the ONS.[189]

3.11.3.1.5 Altered rates of transient events in patients in NYHA IV

In this scenario analysis, the per-cycle incidence for transient events (CV-related hospitalisations and urgent heart failure visits) in NYHA class IV was assumed to be 4 to 5 times higher than in NYHA III (as opposed to 3 times higher in the base-case analysis).

3.11.3.1.6 Altered baseline age

In recent years, patients with ATTR-CM have increasingly been diagnosed earlier, with less severe disease, due to increased disease awareness within the clinician community and improved diagnostic techniques.[104,109] In clinical practice in the UK, patients are likely to start vutrisiran at an age that is younger than the mean baseline age employed in the model ([redacted]). Therefore, in this scenario analysis, baseline age was assumed to be 72 years.

3.11.3.1.7 Similar survival in the vutrisiran and tafamidis arms

In this scenario analysis, the rates of survival in the vutrisiran and tafamidis arms are set to be very similar. To generate comparable survival rates in both treatment arms, the exponential function was used to model survival in the tafamidis arm, while the log-logistic function was maintained in the vutrisiran arm.

3.11.3.1.8 Altered annual treatment acquisition costs for vutrisiran and tafamidis

[redacted].

3.11.3.2 Scenario analysis results

Results of the scenario analyses are shown in Table 57. The largest reduction in ICER from the base-case analysis was observed when alternate annual treatment acquisition costs were included for vutrisiran and tafamidis, which resulted in a [redacted]% decrease in the ICER (Table 57).

Further, reductions in ICER were also demonstrated in the full societal perspectives, where lost productivity for caregivers ([redacted]% reduction in ICER) and lost productivity for patients and caregivers ([redacted]% reduction in ICER) were included, highlighting the benefits of vutrisiran relative to tafamidis in keeping patients in less severe stages of disease, allowing them and their caregivers to be more productive in society.

Other scenarios that reduced the ICER included when the discount for effects was set at 0%, when transition probabilities in the extrapolation period were based on transition probabilities from HELIOS-B from Months 24–30 (per-cycle transition probability matrices for Months 24–27 and 27–30), when incidence rates for transient events in NYHA IV were assumed to be four or five times the rates in NYHA III, when baseline age was 72 years old, and when survival was assumed to be similar between vutrisiran and tafamidis.

The ICER was increased when the discount for effects was set at 5%, and in scenarios with altered time horizons.

Table 57: Scenario analysis results

Scenario	Incremental discounted costs (£)	Incremental discounted QALYs	Discounted ICER (£/QALY)	% of discounted base case ICER
Base Case	[redacted]	1.19	[redacted]	–
Discounting				
Costs=0%, effects=0%	[redacted]	[redacted]	[redacted]	[redacted]
Costs=0%, effects=5%	[redacted]	[redacted]	[redacted]	[redacted]
Costs=5%, effects=0%	[redacted]	[redacted]	[redacted]	[redacted]
Costs=5%, effects=5%	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon				
5 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]
Transition matrix				
Extrapolated TPs based on TPs in M24–27 and 27–30	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of full societal perspective				
Include caregiver lost productivity	[redacted]	[redacted]	[redacted]	[redacted]
Include caregiver and patient lost productivity (full societal perspective)	[redacted]	[redacted]	[redacted]	[redacted]
Per-cycle transient event incidence rates in NYHA class IV				
Rate in NYHA IV is four times rate in NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
Rate in NYHA IV is five times rate in NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
Baseline age				
72 years old	[redacted]	[redacted]	[redacted]	[redacted]
Survival				
Similar survival in vutrisiran and tafamidis arms	[redacted]	[redacted]	[redacted]	[redacted]
Annual acquisition costs for vutrisiran and tafamidis				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life year; TP, transition probability.

3.12 Subgroup analysis

Subgroup analyses were not performed. Alnylam regards it reasonable that subgroups defined by level of heart failure severity (via NYHA classification) and disease type (hATTR-CM vs wtATTR-CM) may be of potential interest to assess clinical effectiveness and cost effectiveness. Nevertheless, vutrisiran demonstrated consistent efficacy across all predefined subgroups in HELIOS-B, which included patients in NYHA I/II versus NYHA III, and patients with wtATTR-CM versus hATTR-CM.

3.13 Benefits not captured in the QALY calculation

The NYHA class-based health states used in the cost-effectiveness model of vutrisiran for ATTR-CM are focused on the status of cardiac manifestations of ATTR, namely, heart failure and its associated clinical presentation. As a result, these health states do not fully capture the burden of neuropathy-related clinical manifestations that are present as a consequence of systemic TTR amyloid deposition in the peripheral and autonomic nerves in some patients with ATTR-CM. QALY calculations from the current analysis therefore likely do not capture the proven neuropathy-related clinical benefits of vutrisiran in addressing this burden. Vutrisiran has also shown superior benefits in treating neuropathy in patients with hATTR-PN compared to tafamidis.[190]

Vutrisiran received a positive recommendation from NICE for the treatment of hATTR-PN,[7] and is the current standard-of-care therapy for the treatment of patients with hATTR-PN in the UK. This recommendation was based on results from HELIOS-A, a phase 3 trial investigating the efficacy and safety of vutrisiran as a treatment for hATTR-PN, in which vutrisiran demonstrated statistically and clinically significant benefits in patients with hATTR-PN in terms of neuropathy disability, HRQoL, ambulatory speed, nutritional status, and the ability to perform everyday activities.[153]

Conversely, in the pivotal Fx-005 trial of tafamidis in hATTR-PN, tafamidis failed to meet either of the co-primary endpoints of treatment response (binary outcome) on Neuropathy Impairment Score in the lower limbs (NIS-LL) and LS mean change from baseline in Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN) total scores, in patients with hATTR-PN with early-stage polyneuropathy (i.e., FAP 1).[191] Tafamidis is not recommended by NICE for the treatment of hATTR-PN.

Aside from its benefits in terms of polyneuropathy, by virtue of its less frequent administration (i.e., Q3M), vutrisiran provides a convenient, patient-centric treatment profile expected to limit the risk of non-adherence when compared to tafamidis, which requires more frequent (daily) oral administration. These administration-associated benefits of vutrisiran are not captured in QALY calculations.

In addition, a change to the SmPC will allow for self-administration of vutrisiran (anticipated April 2025), which will further strengthen these administration-associated benefits.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

An independent quality assessment was conducted to ensure the model is error-free and correctly programmed. This involved validating the logical structure, input parameters, and series of calculations. Any model implementation errors, computational errors, or inconsistencies were addressed during this process. Model accuracy was assessed by an internal peer reviewer who was not involved in the original programming of the model.

This included a series of tests and checks on the computational framework of the model, including:

- Verification of all model inputs and their correct linkage with the computational framework.
- Verification of all formulae used in the model, specifically ensuring that cells with conditional equations based on different selectable parameters provide the correct values for each condition.

- Tracing of all links across Microsoft Excel® sheets to ensure that all outputs are displayed in the right location.
- Reviewing and debugging all Visual Basic for Applications code.
- Searching and resolving common Microsoft Excel® errors (e.g., #REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors).
- Verification of text and formatting to remove any typographical errors or formatting irregularities.
- An extreme-value sensitivity analysis was also conducted on all relevant model inputs. To conduct this analysis, the validator assessed the direction and magnitude of change in results for each extreme parameter value tested and confirmed that the change aligned with the expected result (e.g., if all drug cost inputs are set to £0, the model should output total drug costs of £0). The model validation process uncovered minimal discrepancies and no substantive calculation errors. Any discrepancies found were corrected.
- External validation was conducted in line with good modelling practice guidelines.[192] Model outputs, including survival parameters, estimated life years, QALYs, and costs, were externally validated against clinical data, real-world evidence, and previous economic studies to ensure face validity.
    - Survival outputs from the model were compared with the observed data in ATTR-CM from clinical trials including HELIOS-B and from real-world UK clinical practice as reported by Gillmore et al (2018).[14]
    - Other outputs from the model, including LYs, QALYs, and costs, were compared with results from tafamidis HTA submissions (listed in Table 20).
    - SEE was performed to validate modelled survival (Section 3.3.4.4).

3.15 Interpretation and conclusions of economic evidence

Vutrisiran use resulted in a gain of 1.19 QALYs and [redacted] LYs versus tafamidis use, driven by patients on vutrisiran living longer and relatively healthier (occupying less severe NYHA class health states) versus those on tafamidis. Scenario analysis results highlight that the ICER is sensitive to the acquisition cost of vutrisiran and tafamidis.

[redacted]

Vutrisiran is an innovative synthetic RNAi therapeutic developed as a disease-modifying treatment for ATTR-CM. Vutrisiran suppresses the production of wild-type and variant TTR, which drive the disease process leading to the symptoms, morbidity, and mortality observed in affected patients. In HELIOS-B, vutrisiran led to statistically significant and clinically meaningful benefits versus placebo in patients with ATTR-CM across all primary and secondary endpoints in both the overall population and the monotherapy group (i.e., patients not on background tafamidis at study entry).

The present cost-effectiveness model compares health outcomes and associated costs between vutrisiran and tafamidis for the treatment of patients with ATTR-CM in the UK. The model incorporated key clinical data from HELIOS-B and was customised to the UK healthcare setting.

Over the full time horizon (lifetime), there was a gain of 1.19 QALYs for patients who received vutrisiran compared with those who received tafamidis. This was attributable to

improved overall survival and more time in less severe health states for patients treated with vutrisiran versus those treated with tafamidis. Further, although improved survival in the vutrisiran arm would result in patients requiring caregiver support for a longer period of time, caregiver HRQoL was improved in the vutrisiran arm compared to that in the tafamidis arm in the base-case analysis (Appendix H), since patients treated with vutrisiran spent less time in more severe health states that are associated with greater caregiver burden.

The total lifetime cost for a patient treated with vutrisiran was £[redacted] more than the lifetime costs incurred by a patient treated with tafamidis. The resulting ICER for vutrisiran compared with tafamidis was £[redacted]/QALY.

The PSA confirmed the robustness of the base-case results, and the OWSA showed that the CEA results are most sensitive to variation in the transition probability from NYHA II to NYHA II in Months 24–27 and 27–30 in the tafamidis arm.

Based on the results of this CEA, vutrisiran should be viewed as an effective treatment option for patients with ATTR-CM, as relative to tafamidis, it led to improved survival and HRQoL in patients with ATTR-CM, and also improved caregiver HRQoL. Scenario analyses showed that the ICER was sensitive to the acquisition cost of vutrisiran and tafamidis.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Summary of Information for Patients (SIP)

February 2025

File name	Version	Contains confidential information	Date
ID6470_Vutrisiran_SIP_[noCON]	1.0	No	10 February 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

The medicine being evaluated is vutrisiran, which is the generic name of the active ingredient. The brand name for vutrisiran is AMVUTTRA™.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Vutrisiran will be used to treat adults who have transthyretin amyloidosis with cardiomyopathy. This condition is explained in more detail in Section 2a of this document.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

A marketing authorisation grants the right to prescribe or sell a medicine. In the United Kingdom, marketing authorisation is granted by the Medicines & Healthcare products Regulatory Agency. The agency is anticipated to approve vutrisiran in July 2025 for treating patients with transthyretin amyloidosis with cardiomyopathy. Vutrisiran already has marketing authorisation for the treatment of hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provide

Alnylam has participated in the following collaborations: • Provided an educational grant for Amyloidosis UK's rebrand and communications development project to develop infrastructure to facilitate and educate an engaged transthyretin amyloidosis community. Alnylam contributed £15,000 towards this project. • Collaborated with Amyloidosis UK to develop and fund the "One Step Further" disease awareness campaign and materials currently accessible on Amyloidosis UK's website, to provide advice and support for those caring for someone with transthyretin amyloidosis. As part of the collaboration agreement, Alnylam funded Amyloidosis UK with £3,500 at the outset of the campaign in 2021.

- Provided an educational grant for Cardiomyopathy UK's 2025 Healthcare Professional Education programme, which provides online learning and meeting opportunities, with the aim of improving the ability of healthcare professionals to diagnose and treat all forms of cardiomyopathy. Alnylam contributed £15,000 towards this programme.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact:

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Transthyretin amyloidosis with cardiomyopathy is a rare and fatal condition that primarily affects the heart.

Transthyretin amyloidosis is caused by abnormalities with a protein called transthyretin,[2,3] which is produced in the liver and carries vitamin A and a thyroid hormone called thyroxine to different parts of your body.[4-6] In patients with transthyretin amyloidosis, certain abnormalities cause this protein to clump together and form amyloid deposits.[5,7] Over time, these amyloid deposits can build up in various parts of the body, including the heart, nerves, and digestive system, causing damage in the organs where it is deposited.[5,8-11] Transthyretin amyloidosis can be caused by a genetic variation in the transthyretin gene (this is known as "hereditary transthyretin amyloidosis") or by non-genetic factors related to ageing (this is known as "wild-type transthyretin amyloidosis").

In some patients with transthyretin amyloidosis, the condition can lead to issues with the functioning of the heart (called transthyretin amyloidosis with cardiomyopathy). In transthyretin amyloidosis with cardiomyopathy, amyloid deposits build up in the heart, making the heart muscle rigid. As the condition progresses, the heart becomes unable to properly pump blood to the body, resulting in heart failure.[12] In heart failure, the heart is unable to pump blood to different organs of the body, depriving them of the oxygen supply that is needed for normal functioning, which is very detrimental for patients' overall health.[6,13] Transthyretin amyloidosis with cardiomyopathy can also cause the heart to beat irregularly (known as heart arrhythmias) in cases where transthyretin amyloid damages tissues that control the heart's rhythm,[14-16] and this can lead to even further worsening of health.

Transthyretin amyloidosis with cardiomyopathy can cause premature death. In patients living with the condition, heart failure and arrhythmias prevent patients from functioning normally.

Without effective treatment, patients with transthyretin amyloidosis with cardiomyopathy die approximately 2.1–5.8 years after they are diagnosed with this condition, on average.[6,17-26] While living with the condition, patients with transthyretin amyloidosis with cardiomyopathy tend to experience symptoms (such as fatigue, fluid buildup in the body, being out of breath, and dizziness) that rapidly worsen over time due to transthyretin amyloid buildup in the heart.[6,27,28] Related to this, patients' physical capacity gets worse over time; eventually, patients become unable to walk without extreme discomfort and experience breathlessness even while at rest.[21,29,30]

Patients with transthyretin amyloidosis with cardiomyopathy and their caregivers experience poor quality of life.

Patients with transthyretin amyloidosis have a poor quality of life, as the condition causes burdensome symptoms and ongoing worsening of physical capacity.[21] As patients become physically exhausted more easily, their independence in engaging in everyday activities is severely limited, negatively affecting their quality of life. The condition also causes patients to worry about their future and disrupts their personal relationships.[31] Additionally, many patients require caregivers, who are usually a close family member or friend of the patient. These caregivers experience reduced quality of life as well, as providing informal care for patients with transthyretin amyloidosis can lead to increased fatigue, anxiety, and depression.[32,33] Some caregivers also report that caring for patients with transthyretin amyloidosis can reduce their ability to be productive, including at their job, and have a negative impact on their career and their social life.[32-34]

Transthyretin amyloidosis with cardiomyopathy is a rare condition.

Transthyretin amyloidosis with cardiomyopathy is a rare condition. Clinical experts at the National Amyloidosis Centre in the UK believe that in 2024, there were around 1,300 patients who were living with a diagnosis of transthyretin amyloidosis with cardiomyopathy and being treated in the UK.

2b) Diagnosis of the condition (in relation to the medicine being evaluated):

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Transthyretin amyloidosis with cardiomyopathy is difficult to diagnose and many patients wait a long time to receive a confirmed diagnosis of the condition. Patients who are suspected of having transthyretin amyloidosis with cardiomyopathy based on their symptoms and/or other assessments are referred to the National Amyloidosis Centre. The National Amyloidosis Centre is a part of University College London Centre for Amyloidosis, and is the only centre in the UK that specialises in amyloidosis.

At the National Amyloidosis Centre, for patients suspected of having transthyretin amyloidosis with cardiomyopathy, diagnosis is confirmed using specialised blood tests and scans or tissue biopsy to see if transthyretin amyloid deposits are present in the heart. In addition, if a diagnosis is confirmed, genetic testing is performed to determine whether the patient has hereditary or wild-type transthyretin amyloidosis.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

To date, only one drug has been available in the UK for patients with transthyretin amyloidosis with cardiomyopathy. This drug, called tafamidis, works by stabilising transthyretin proteins in the

bloodstream after they leave the liver, thereby making these proteins less likely to clump together and form amyloid deposits in the heart. Tafamidis is available as a capsule that is taken orally once daily.

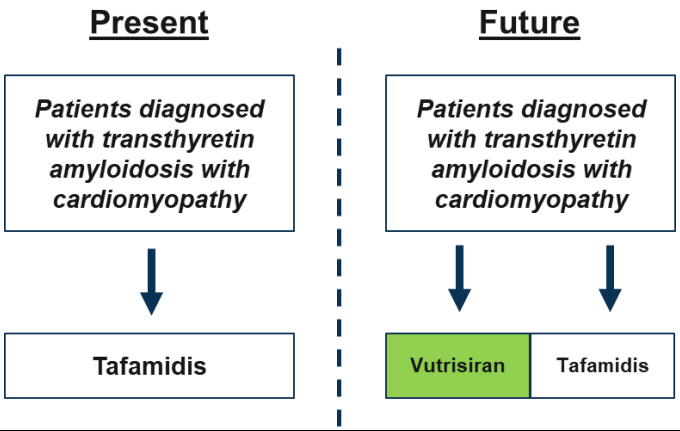
Tafamidis had its clinical efficacy and safety evaluated in patients with transthyretin amyloidosis with cardiomyopathy in a clinical trial called ATTR-ACT.[35] In this trial, patients who received tafamidis were less likely to die and less likely to be hospitalised for heart problems compared to patients who received placebo (treatment without a medical ingredient). Additionally, over the 30-month period of the study, declines in physical capacity and worsening of quality of life happened more slowly in patients who received tafamidis compared to patients who received placebo.[35]

However, during the ATTR-ACT trial, almost one third (30%) of patients who received tafamidis died, and patients' physical capacity and quality of life worsened over time even while receiving tafamidis [35] The trial also showed that tafamidis may be less effective in patients who have more severe heart failure—specifically, patients in whom heart failure symptoms, like fatigue and shortness of breath, are triggered by less-than-ordinary levels of physical exertion (this is known as "New York Heart Association Class III" heart failure)—at the time they start tafamidis treatment.[35]

For these reasons, patients with transthyretin amyloidosis with cardiomyopathy urgently need new treatment options, which potentially achieve the following:

- Address the underlying cause of the condition by quickly and effectively limiting the production of transthyretin, the protein that forms amyloid deposits in patients' organs in transthyretin amyloidosis
- Prolong survival of patients
- Halt or substantially slow down worsening in physical capacity and quality of life
- Work effectively in all patients, including those with more severe heart failure
- Offer a method of administration that is easy for older patients who may also be taking multiple other oral medicines

Vutrisiran is expected to address these needs and become a new standard-of-care treatment option for all patients with transthyretin amyloidosis with cardiomyopathy in the UK, including those patients who are currently treated with tafamidis but do not achieve an adequate response.



2d) Patient-based evidence (PBE) about living with the condition:

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

As shown in a focus group of patients with transthyretin amyloidosis with cardiomyopathy, the condition has a significant impact on the day-to-day lives of patients, due to intolerance to physical exertion, inability to exercise, insomnia, and fatigue.[29] These physical limitations drastically impair patients' daily life and social functioning.[29]

A survey of French patients with transthyretin amyloidosis with cardiomyopathy (*the French daily impact of amyloidosis study*[31]) identified more specific issues related to patients' social function. In that study, more than half of patients surveyed experienced anger or anxiousness, about two thirds were worried about their future, more than half experienced a problem in their relationship with their partner, and more than half reported fear of being a burden on their family and friends as a result of their condition.[31]

An assessment tool used to measure quality of life in patients with heart failure is called the Kansas City Cardiomyopathy Questionnaire.[36,37] It captures important aspects of patients' well-being, including how burdensome their symptoms are, how much patients are physically and socially limited by their heart failure, how well patients understand how to manage their heart failure, and their quality of life.[36,37] This questionnaire has been used in many clinical trials of patients with transthyretin amyloidosis with cardiomyopathy, and it has shown that in patients without treatment, quality of life declines rapidly over time.[35,38,39] In one trial (ATTR-ACT), this questionnaire revealed that out of all the aspects measured, declines in physical and social function had the biggest impact on the patients' well-being.[40]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How vutrisiran works:

Vutrisiran belongs to a family of drugs called ribonucleic acid interference therapies. Vutrisiran works in an innovative and novel way to treat transthyretin amyloidosis with cardiomyopathy. It targets the first step in the disease process by rapidly decreasing the production of transthyretin protein in the liver. This rapidly reduces the amount of transthyretin protein in the bloodstream, thereby making it less likely for transthyretin proteins to clump together as amyloid deposits in the heart. Vutrisiran works in all patients with transthyretin amyloidosis with cardiomyopathy, whether caused by genetics or by non-genetic, age-related factors.

Benefits associated with how vutrisiran works:

The mechanism of action of vutrisiran, which rapidly decreases the production of transthyretin protein in the liver, differs from that of the only other existing treatment, tafamidis, which does not interfere with transthyretin production in the liver and only acts on unstable transthyretin in the bloodstream that has already been formed and released from the liver.[41] Based on differences in the way the two drugs work, there are potential benefits to acting at earlier stages in the disease process, as vutrisiran does.

3b) Combinations with other medicines:

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Vutrisiran is not anticipated to be administered with any other medicines that are approved to treat transthyretin amyloidosis with cardiomyopathy, namely, tafamidis.

3c) Administration and dosing:

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of vutrisiran is 25 mg to be given by injection under the skin (subcutaneously) once every 3 months. This equals four injections every year. In contrast, the existing treatment, tafamidis, is an oral capsule taken once daily.

After starting treatment with vutrisiran, patients are to continue to receive vutrisiran for the rest of their life. Stopping treatment with vutrisiran can occur in some circumstances based on the opinion of the doctor that prescribes vutrisiran for the patient.

It is anticipated that patients themselves or their caregivers will administer vutrisiran at home after the first administration. The first dose is anticipated to be administered by a health care professional in the hospital outpatient setting.

3d) Current clinical trials:

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Vutrisiran has been investigated in two clinical trials, one in patients with transthyretin amyloidosis with cardiomyopathy (HELIOS-B) and one in patients hereditary transthyretin amyloidosis with polyneuropathy (HELIOS-A). Results from HELIOS-A led to it receiving a positive recommendation from NICE for use in patients with hereditary transthyretin amyloidosis with polyneuropathy.[42] The trials are described below.

HELIOS-B[38]	
Location	HELIOS-B was conducted at 79 sites in 26 countries, including the UK.
Population	Patients with transthyretin amyloidosis with cardiomyopathy.
Eligibility criteria	To be enrolled in HELIOS-B, participants had to have transthyretin amyloidosis with cardiomyopathy, which could be caused by genetic or non-genetic, age-related factors. Participants also had to have been to the hospital for heart problems at least once in the past, or to have had other specific signs or symptoms of heart failure. Participants who were most severely ill (for example, patients who had heart failure symptoms like breathlessness even when resting) were excluded from the trial.[38]
Patient group size and intervention and comparator	There were 654 patients in HELIOS-B, including 326 patients who received vutrisiran and 328 patients who received placebo. Since tafamidis was available for treatment of transthyretin amyloidosis with cardiomyopathy in some countries at the time HELIOS-B started, some patients (approximately 40%) were taking tafamidis when the trial started. These patients, who continued to take tafamidis along with their study treatment (vutrisiran or placebo) during HELIOS-B, were split equally between the vutrisiran and placebo groups at the start of HELIOS-B.
Trial design	Patients received vutrisiran or placebo every 3 months for approximately 3 years, and the health of these participants was measured over this period. Treatment outcomes were compared between vutrisiran and placebo in two groups of patients: 1) All patients in HELIOS-B ("overall population"; vutrisiran: 326 patients; placebo: 328 patients). This included patients who were also taking tafamidis when the trial started. 2) Patients in the overall population who were not taking tafamidis when HELIOS-B started ("monotherapy population"; vutrisiran: 196 patients; placebo: 199 patients).
Outcomes	Within the overall and monotherapy populations, the following health outcomes were compared between patients treated with vutrisiran and patients treated with placebo over a period of approximately 3 years:

	• The chances of dying due to any cause or having to go to the hospital for a heart problem. This outcome was designated as the most important outcome of the study (primary endpoint). It was measured over a period of 33 to 36 months from the start of patients' treatment in the study. • The chances of dying due to any cause. This was measured over a maximum of 42 months from the start of patients' treatment in the study. • The change in patients' physical capacity, which was tested by measuring how far patients could walk in 6 minutes (6-minute walk test). This test was done once every 6 months, beginning at the start of HELIOS-B and ending 30 months later, near the end of HELIOS-B. • The change in patients' quality of life, which was measured using a questionnaire called the Kansas City Cardiomyopathy Questionnaire. This questionnaire is designed specifically to measure quality of life in patients with heart problems. Patients filled out the questionnaire every 6 months, beginning at the start of HELIOS-B and ending 30 months later, near the end of HELIOS-B. • The change in patients' heart failure severity, which was assessed using the New York Heart Association classification system. New York Heart Association classes range from I (least severe) to IV (most severe). In class I, heart failure does not cause any limitations in physical activity, whereas in class IV, patients have symptoms of heart failure (e.g., breathlessness) even when they are resting. Heart failure severity was measured every 6 months, beginning at the start of HELIOS-B and ending 30 months later.
Completion date	Primary completion date: May 2024
ClinicalTrials.gov	https://clinicaltrials.gov/study/NCT04153149
Publication	https://www.nejm.org/doi/full/10.1056/NEJMoa2409134
HELIOS-A[43]	
Location	The trial was conducted at 79 sites in 26 countries, including the UK.
Population	Patients with a diagnosis of hereditary transthyretin amyloidosis with polyneuropathy, which causes damage to peripheral nerves (i.e., nerves other than those of the brain and spinal cord)
Eligibility criteria	Patients in the trial had to meet the following criteria: • Male and female patients aged 18 to 85 years • Diagnosis of hereditary transthyretin amyloidosis with a transthyretin gene mutation • Mild to moderate neurological impairment/polyneuropathy Patients who had received previous therapies that altered transthyretin protein production were excluded. Other exclusion criteria included: • Previous liver transplantation • Severe heart disease
Patient group size, intervention, and comparator	A total of 164 patients were included in the trial. Of these 164 patients, 122 were treated with vutrisiran and 42 patients were treated with patisiran (another approved treatment for hereditary transthyretin amyloidosis with polyneuropathy). Vutrisiran (25 mg given every 3 months) was compared to: • the 42 patients treated with patisiran (0.3 mg/kg given every 3 weeks) in HELIOS-A

	• 77 patients treated with placebo (an inactive substance). The results for this placebo group were taken from a previous trial in patients with hereditary transthyretin amyloidosis with polyneuropathy called APOLLO[44]
Outcomes	The study examined the effect of the interventions on: • Nerve damage and function • Walking speed • Health-related quality of life • Nutritional status • Ability to perform activities of daily living For certain outcomes, the aim of the study was to assess whether vutrisiran produced results comparable to those seen with patisiran. For other outcomes, the aim was to assess whether vutrisiran produced results superior to those seen in the absence of treatment (as represented by placebo).
Completion date	Primary completion date: November 2020
ClinicalTrials.gov	https://clinicaltrials.gov/study/NCT03759379
Publication	https://www.tandfonline.com/doi/full/10.1080/13506129.2022.2091985

3e) Efficacy:

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In HELIOS-B, patients who were treated with vutrisiran over approximately 3 years had a lower risk of dying or having to go to the hospital for a heart problem than patients who received placebo. These benefits of vutrisiran were observed regardless of whether patients were also receiving tafamidis treatment, that is, both in the overall population and in the monotherapy population. Patients who received vutrisiran also maintained their levels of physical capacity and quality of life over the course of the study; in contrast, patients treated with placebo steadily worsened over that time period. Importantly, vutrisiran treatment was beneficial for all types of patients, regardless of their heart failure severity or other characteristics at the start of treatment.[38]

A full summary of the benefits experienced by patients who received vutrisiran compared to patients who received placebo is as follows:

- Patients treated with vutrisiran were ~28%–33% less likely to die or need hospitalisation for a heart problem, over a period of 33 to 36 months.
- Patients treated with vutrisiran were ~35% less likely to die from any cause over a period of up to 42 months.
- Patients treated with vutrisiran had significantly better physical capacity outcomes over 30 months, as measured by the distance they were able to walk in 6 minutes.
  - On average, over 30 months of treatment with vutrisiran, physical capacity was preserved near its original level at the start of HELIOS-B.
  - This result is important, since patients with transthyretin amyloidosis with cardiomyopathy experience a substantial decline in physical capacity over this time period without treatment.[35,38,39,45]

- This is also important because patients with transthyretin amyloidosis with cardiomyopathy have noted that intolerance to physical exertion and an inability to exercise have a significant impact on their day-to-day lives.[29]

- Patients who were treated with vutrisiran showed a significant benefit in their quality of life over 30 months, as measured by the Kansas City Cardiomyopathy Questionnaire.
  - On average, over 30 months of treatment with vutrisiran, quality of life was preserved near its original level at the start of HELIOS-B.
  - This result is important, since patients with transthyretin amyloidosis with cardiomyopathy without treatment would normally have had their quality of life substantially decline over this time period.[35,38,39]
- Patients treated with vutrisiran showed a significant benefit in terms of their heart failure status, as more patients who were treated with vutrisiran than with placebo had their heart failure remain stable or become less severe (New York Heart Association class) over 30 months from the start of HELIOS-B.
- Vutrisiran provided benefits over placebo in all patient types, regardless of patients' age, whether their condition was caused by genetic or non-genetic, age-related factors, their heart failure stage (including patients with more severe heart failure [i.e., patients in New York Heart Association Class III]), and the degree of heart injury present at the start of HELIOS-B.

3f) Quality of life impact of the medicine and patient preference information:

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other condition specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In HELIOS-B, vutrisiran resulted in a quality of life benefit versus placebo that was statistically significant and meaningful to patients.[38]

Quality of life was measured as described in Section 3e, by the Kansas City Cardiomyopathy Questionnaire. The questionnaire was designed to measure well-being specifically in patients with heart failure.[36,37] It captures important aspects of patients' well-being, including how burdensome their symptoms are, how much patients are physically and socially limited by their heart failure, how well patients understand how to manage their heart failure, and their quality of life.[36,37] The maximum score on the questionnaire is 100 points, and a change in score of more than 5 points is considered meaningful to patients. Notably, when assessing the change in Kansas City Cardiomyopathy Questionnaire overall scores over 30 months from the start of HELIOS-B, the benefit provided by vutrisiran over placebo exceeded 5 points. These results show that vutrisiran provides benefit in quality of life in comparison to placebo, and that this improvement is meaningful for patients. Further, on average, treatment with vutrisiran led to questionnaire response scores remaining near their original level at the start of HELIOS-B, indicating that patients' well-being was preserved over the duration of the trial.

3g) Safety of the medicine and side effects:

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Vutrisiran was well tolerated and had an acceptable safety profile in HELIOS-B.[38]

In the HELIOS-B study, the incidence of side effects with vutrisiran was similar to or lower than that with placebo.[38] During the trial, 78 out of 326 patients stopped treatment with vutrisiran, including 37 patients who died and 10 patients who stopped due to a side effect, although none of these side effects were considered to be related to vutrisiran. Side effects that occurred the most frequently (i.e., in at least 15% of patients) in either the vutrisiran or placebo group are summarised in the table below.[38] None of the side effects shown occurred more frequently in patients who were treated with vutrisiran.[38]

Side effect, n (%)	Vutrisiran (N=326)	Placebo (N=328)
Cardiac failure	101 (31)	128 (39)
Covid-19	87 (27)	99 (30)
Atrial fibrillation	69 (21)	68 (21)
Gout	48 (15)	51 (16)
Dyspnoea	43 (13)	51 (16)
Fall	42 (13)	69 (21)

3h) Summary of key benefits of treatment for patients:

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Vutrisiran acts earlier in the disease process compared to tafamidis.

The mechanism of action of vutrisiran represents a potential benefit compared to that of tafamidis, a transthyretin stabiliser. Vutrisiran decreases the production of transthyretin, whereas tafamidis does not interfere with transthyretin production and only acts on unstable transthyretin that has already been formed and released from the liver into the bloodstream.[41] By acting earlier in the disease process, vutrisiran may offer some potential clinical benefits.

Vutrisiran prolongs survival.

When considering patient health, vutrisiran provides important clinical benefits for patients with transthyretin amyloidosis with cardiomyopathy, including a reduced risk of death, leading to prolonged survival.[38] Importantly, vutrisiran appears to enable patients to survive as long as healthy patients of the same age in the general population who do not have transthyretin amyloidosis with cardiomyopathy.[46] This is important considering that patients receiving tafamidis, the only treatment available currently, continue to experience some degree of premature death (despite having improved survival compared to placebo-treated patients).[35]

Vutrisiran preserves patients' physical capacity and quality of life.

Vutrisiran also provides benefits in patients' physical capacity and quality of life. Results of the HELIOS-B trial show that vutrisiran either preserves or significantly reduces the decline in physical capacity and quality of life.[38] This is important, considering that the clinical trial for tafamidis showed that patients continued to decline in physical capacity and quality of life from the start of the trial onward even when treated with tafamidis.[35]

Vutrisiran provides benefits in all patient types.

Importantly, vutrisiran provided benefits over placebo in all patient types that were included in HELIOS-B (i.e., patients with transthyretin amyloidosis with cardiomyopathy who have had heart

problems in the past but were not severely ill), regardless of patients' age, whether their condition was caused by genetic or non-genetic, age-related factors, their heart failure stage (including patients in New York Heart Association Class III), and the degree of heart injury present at the start of HELIOS-B.[38] This is important considering tafamidis may be less effective in patients who are in New York Heart Association Class III.[35]

Vutrisiran has a convenient dosing schedule.

Vutrisiran only needs to be administered once every 3 months.

3i) Summary of key disadvantages of treatment for patients:

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Transthyretin primarily transports vitamin A in the body.[4-6] Since vutrisiran decreases transthyretin production, it is anticipated that patients with transthyretin amyloidosis with cardiomyopathy who are treated with vutrisiran will be advised to supplement with vitamin A.

3i) Value and economic considerations:

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition:

- A model was developed that measures health outcomes in patients and costs to the National Health Service for the treatment of transthyretin amyloidosis with cardiomyopathy.
- The model compares these outcomes between patients who receive vutrisiran and those who receive tafamidis.
- The model uses results from HELIOS-B (approximately 3 years long) and projects health and cost outcomes for the remainder of patients' lifespan.
- Results from HELIOS-B used in the model were sourced from two groups of patients:

    - Patients who only received vutrisiran in HELIOS-B, called the vutrisiran monotherapy group (patients who received vutrisiran in HELIOS-B and were not taking tafamidis when the trial started [196 patients])
    - Patients who were only receiving tafamidis in HELIOS-B, called the tafamidis monotherapy group (patients who received placebo in HELIOS-B and were taking tafamidis when the trial started [129 patients]).
- The model projects how the severity of patients' condition will change over time, as measured by heart failure severity using New York Heart Association classes. New York Heart Association classes range from I to IV (least to most severe). In class I, patients have no physical activity limitations due to heart failure, whereas in class IV, patients have symptoms of heart failure (e.g., breathlessness) even when they are resting. As time passes in the model, patients' New York Heart Association class can improve, stay the same, or worsen. Data regarding changes in New York Heart Association class in the vutrisiran and tafamidis monotherapy groups over 30 months in HELIOS-B were used to project how patients moved between these classes in the model over their lifetime following the start of treatment with vutrisiran or tafamidis.
- The model also projects the occurrence of deaths, hospitalisations due to heart problems, and side effects of treatment in patients receiving vutrisiran and patients receiving tafamidis, based primarily on results from HELIOS-B

Modelling how much a treatment extends life:

- To project patient survival following the start of treatment with vutrisiran or tafamidis, the model used results collected on the survival of patients over 42 months in the vutrisiran and tafamidis monotherapy groups from the HELIOS-B trial.
- The model found that patients treated with vutrisiran would have a longer lifespan than would patients treated with tafamidis.

Modelling how much a treatment improves quality of life:

- Quality of life in the model was reflected by the time patients in each treatment arm spent in different New York Heart Association classes, with higher (more severe) classes leading to worse quality of life.
- Quality of life was also negatively affected by specific events, including how often patients had to go to the hospital for a heart problem and for when side effects from treatment happened.
- Since caring for a patient with transthyretin amyloidosis with cardiomyopathy can negatively affect quality of life of caregivers, caregiver quality of life was also included in the economic model, with caring for patients with worse heart failure (i.e., those in higher New York Heart Association classes) causing worse quality of life for caregivers.
- The impacts on quality of life of being in a given New York Heart Association class and experiencing side effects were determined using a quality-of-life questionnaire called the EQ-5D, which was completed by patients at planned time-point intervals during the course of HELIOS-B. To assess the impact of having to go to the hospital for a heart problem on quality of life, EQ-5D data from published sources were used, since this information was not available from HELIOS-B. Similarly, since HELIOS-B did not collect data to assess the impact of the condition on caregivers' quality of life, EQ-5D data for caregivers were used from published sources.
- The model showed that patients treated with vutrisiran were more likely to remain in less severe stages of heart failure compared to patients who were treated with tafamidis, and as a result, had a better quality of life. Patients treated with vutrisiran also had small benefits in quality of life as a result of having fewer hospital visits for heart problems and fewer side effects compared to patients who received tafamidis. Caregiver quality of life was also improved when patients were treated with vutrisiran as opposed to tafamidis.

Modelling how the costs of treatment differ with the new treatment:

- The model included costs for:
  - Treatment with vutrisiran or tafamidis.
  - Treatment with therapies that are not specific for transthyretin amyloidosis but help with managing heart failure symptoms that may accompany transthyretin amyloidosis. The frequency with which patients used these therapies was modelled based on their use in the vutrisiran and tafamidis monotherapy groups of the HELIOS-B trial.
  - Hospitalisation for heart problems. The frequency with which patients were hospitalised for heart problems in the model was based on data from the HELIOS-B trial and increased as heart failure became more severe (measured by New York Heart Association class).
  - Routine management of the condition (such as seeing the doctor or having a blood test for monitoring of the condition). The frequency of routine management procedures in the model was based on input from a clinical expert and varied depending on heart failure severity (measured by New York Heart Association class).
  - Managing side effects. The frequency of side effects in the model was based on results from the vutrisiran and tafamidis monotherapy groups in the HELIOS-B trial.
  - Terminal care. The model included additional costs associated with end-of-life care at the time of patients' death.
- The model showed that vutrisiran was associated with savings in costs for hospitalisation for heart problems, routine monitoring and management procedures, management of side effects associated with the condition and treatments, and terminal care, in comparison to tafamidis.

Uncertainty:

- If clinical results required for the model were not available from the HELIOS-B trial, then published literature was searched to identify other sources of results. However, since transthyretin amyloidosis with cardiomyopathy is a rare condition, there was limited information available from other published research. In situations where further information was needed for the model but could not be identified from published studies of patients with transthyretin amyloidosis with cardiomyopathy, results from research in patients with heart failure from other causes was used, or clinical experts were asked for their opinions to inform the model.

Additional factors:

- Vutrisiran has already been recommended by NICE for use in patients with hereditary transthyretin amyloidosis with polyneuropathy (damage to peripheral nerves—i.e., nerves other than those of the brain and spinal cord).[42] Like transthyretin amyloidosis with cardiomyopathy, this condition is caused by the buildup of transthyretin amyloid deposits, but it is only caused by a patients' genetics, specifically in the transthyretin gene. This condition affects the nerves, causing a range of burdensome symptoms like nerve pain, numbness, muscle weakness, loss of the ability to walk, and gastrointestinal issues such as nausea, vomiting, diarrhoea, and weight loss.[5]
- Transthyretin amyloidosis with cardiomyopathy often occurs together with polyneuropathy, because amyloid buildup from transthyretin protein in the bloodstream may affect both the heart and the nerves, respectively, in a given patient.[47]
- Thus, because transthyretin protein in the bloodstream may also lead to polyneuropathy by accumulating as amyloid in the nerves, vutrisiran—which decreases the production of transthyretin in the liver before the protein enters the bloodstream—is anticipated to provide benefits in addressing nerve-related symptoms in patients with hereditary transthyretin amyloidosis with cardiomyopathy who also have polyneuropathy.

- Tafamidis is not recommended for treating hereditary transthyretin amyloidosis with polyneuropathy by NICE and, in general, has shown limited benefits in treating patients with hereditary transthyretin amyloidosis with polyneuropathy.[48]
- The economic model for vutrisiran did not account for the effects of treatment on polyneuropathy manifestations. Therefore, in terms of treating polyneuropathy manifestations that may be present in those patients with transthyretin amyloidosis who primarily have cardiomyopathy, vutrisiran likely provides additional clinical benefits over tafamidis that were not captured in the model.

3j) Innovation:

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Vutrisiran is an innovative and novel therapy for the treatment of transthyretin amyloidosis with cardiomyopathy, as it rapidly decreases the production of transthyretin, the protein which drives the disease process in transthyretin amyloidosis with cardiomyopathy.[6,13]

The way that vutrisiran works may provide a potential benefit compared to tafamidis. Vutrisiran decreases the production of transthyretin, which is the first step in the disease-forming process. In contrast, tafamidis does not interfere with transthyretin production and only acts at a later stage of the disease-forming process, by stabilising unstable transthyretin that has already been released from the liver into the bloodstream.[41] Importantly, there may be potential benefits associated with acting earlier in the disease process, as vutrisiran does.

As noted (Section 3h), vutrisiran provides important health benefits for patients with transthyretin amyloidosis with cardiomyopathy, including lowering the risk of premature death.[38] Importantly, vutrisiran appears to enable patients to live as long as healthy people of the same age in the general population who do not have transthyretin amyloidosis with cardiomyopathy.[46] Further, vutrisiran provided health benefits in all patient types who participated in HELIOS-B, regardless of patients' age, whether their condition was caused by genetic or non-genetic, age-related factors, their heart failure stage, and their degree of heart injury.[38]

Vutrisiran also preserves patients' physical capacity and quality of life, or significantly slows their decline,[38] and has a convenient administration schedule of once every 3 months.

As described in Section 3i, vutrisiran provides benefits for both patients with transthyretin amyloidosis with cardiomyopathy and those with hereditary transthyretin amyloidosis with polyneuropathy.[38,43] Because some patients with hereditary transthyretin amyloidosis with cardiomyopathy also experience symptoms of polyneuropathy, vutrisiran can potentially provide benefits for symptoms related to both conditions in such patients. Unlike vutrisiran, tafamidis has shown limited efficacy in treating polyneuropathy caused by hereditary transthyretin amyloidosis.[48]

3k) Equalities:

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here
Health inequalities exist among patients with transthyretin amyloidosis with cardiomyopathy, as patients with the hereditary form of the condition who have a specific transthyretin gene variant are disproportionately of African descent.[49-51] This form of the condition is also associated with a higher death rate than other forms of transthyretin amyloidosis with cardiomyopathy.[21,23] Alnylam is therefore aware that the burden of transthyretin amyloidosis with cardiomyopathy is notable in populations of African descent.

SECTION 4: Further information, glossary and references

4a) Further information:

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
HELIOS-B primary publication, including the plain language summary: https://www.nejm.org/doi/full/10.1056/NEJMoa2409134 Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms:

General terms about the condition:

Transthyretin: The protein that is responsible for transthyretin amyloidosis when it takes on abnormal or misfolded forms that can form amyloid deposits in tissues and organs.

Amyloid deposits: Build-ups/clumps of abnormal or misfolded transthyretin protein that accumulate in organs in the body, including the heart, which causes cardiomyopathy.

Clinical trial names:

HELIOS-B: Clinical trial that tested vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy.

HELIOS-A: Clinical trial that tested vutrisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy.

ATTR-ACT: Clinical trial that tested tafamidis in patients with transthyretin amyloidosis with cardiomyopathy.

HELIOS-B health outcome measurements:

6-minute walk test: A test that measures the distance a patient can walk in 6 minutes. It is often used in clinical trials to measure patients' physical capacity.

Kansas City Cardiomyopathy Questionnaire: A questionnaire often used in clinical trials that is completed by patients and measures quality of life in patients with heart failure.

New York Heart Association classes: A series of 4 classes that quantify the severity or stages of heart failure based on limitations in physical activity.

HELIOS-B patient populations:

Monotherapy population: Patients in HELIOS-B who were not receiving tafamidis treatment when the trial started.

Overall population: All patients in HELIOS-B, including patients who were receiving tafamidis at the start of HELIOS-B, and those who were not.

Tafamidis monotherapy group: Patients who were only receiving tafamidis in HELIOS-B, meaning patients who received placebo in HELIOS-B and were receiving tafamidis when the trial started.

Vutrisiran monotherapy group: Patients who only received vutrisiran in HELIOS-B, meaning patients who received vutrisiran in HELIOS-B but were not receiving tafamidis when the trial started.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6470_Vutrisiran_Clarification Questions_[CON_DPD]	1	Yes	17 March 2025

Section A: Clarification on effectiveness data

HELIOS-B

A1. PRIORITY: The EAG is concerned that the interpretation of the NYHA data presented in the clinical section (Table 16) of the CS (which is aggregated and focused on stable/improvement presented over the entire 30 months follow-up) seems disconnected from the per-cycle NYHA class transition probabilities for vutrisiran monotherapy and tafamidis monotherapy (Table 24 in the CS) applied in the economic model.

Please supply for all four treatment groups (vutrisiran+tafamidis, vutrisiran monotherapy, tafamidis monotherapy, placebo monotherapy) a more detailed of NYHA progression, for example:

Proportions in each NYHA class at end of each year of follow-up

Proportions declining by 1 or more classes in each year

If feasible, a proportional odds model for impact of vutrisiran (and tafamidis) vs placebo on NYHA class

Please provide a single NYHA class transition matrix estimated over the full double-blind period of HELIOS-B (i.e., not split by specific time intervals) for the:

population included in the economic model (adjusted vutrisiran monotherapy and tafamidis monotherapy) and;

the comparison vutrisiran monotherapy vs. placebo.

A summary of patient transitions through New York Heart Association Classes (NYHA) for all four requested treatment groups (vutrisiran + tafamidis, vutrisiran monotherapy, placebo + tafamidis [tafamidis monotherapy], and placebo monotherapy) in HELIOS-B is presented in Table 1. Since NYHA class data were collected as a secondary endpoint in HELIOS-B from baseline to Month 30, data are available at baseline and Months 12, 24, and 30. It should be noted that the HELIOS-B trial was not designed or powered to assess the relative efficacy of vutrisiran versus tafamidis or the relative efficacy of tafamidis versus placebo, and that similarly, the trial was not intended and also not adequately powered to assess the relative efficacy of vutrisiran plus tafamidis versus tafamidis.

In addition, any effort to compare results between the tafamidis monotherapy group and the vutrisiran monotherapy group is likely to be biased in favour of tafamidis, as patients in the tafamidis monotherapy group started tafamidis treatment before baseline, such that they may have already been benefiting from tafamidis at the time they entered HELIOS-B. In contrast, patients in the vutrisiran monotherapy group could not have benefited from vutrisiran treatment prior to baseline, as they did not start treatment with vutrisiran until HELIOS-B baseline.

Table 1: NYHA class proportions at baseline, Month 12, Month 24, and Month 30 in the placebo monotherapy group, vutrisiran monotherapy group, tafamidis monotherapy group, and the vutrisiran plus tafamidis group in HELIOS-B

NYHA class	Placebo monotherapy (N=199)	Vutrisiran monotherapy (N=196)	Tafamidis monotherapy (N=129)	Vutrisiran + tafamidis (N=130)
Baseline				
NYHA I, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12				
NYHA I, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved or no change, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Worsened, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
NYHA I, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved or no change, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Worsened, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

NYHA class	Placebo monotherapy (N=199)	Vutrisiran monotherapy (N=196)	Tafamidis monotherapy (N=129)	Vutrisiran + tafamidis (N=130)
Month 30				
NYHA I**, n(%)**	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II**, n(%)**	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III**, n(%)**	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV**, n(%)**	[redacted]	[redacted]	[redacted]	[redacted]
Missing**, n(%)**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved or no change, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Worsened, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

NYHA, New York Heart Association. Source: Alnylam data on file
Data are reported as n (%) unless stated otherwise

A comparison of the odds of a stable or improved NYHA class from baseline to 30 for vutrisiran versus placebo and tafamidis versus placebo in HELIOS-B is presented in Table 2.

[redacted]

Table 2: Relative odds of having stable or improved NYHA class from baseline for vutrisiran versus placebo and tafamidis versus placebo

Timepoint	Overall population, vutrisiran (n=326) vs. placebo (n=328)	Monotherapy population, vutrisiran (n=196) vs. placebo (n=199)	Background tafamidis population, vutrisiran (n=130) vs. placebo (n=129)	Monotherapy population, tafamidis (n=129) vs placebo (n=199)
Month 30, OR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Note: Analysis using the Cochran-Mantel-Haenszel method with multiple imputation for missing data.
CI, confidence interval; NYHA, New York Heart Association; OR, odds ratio. Source: Alnylam data on file

The results of this odds ratio (OR) model for NYHA improvement or stabilisation are in line with the statistically significant adjusted difference in the percentage of patients with stable or improved NYHA class from baseline to Month 30 for vutrisiran versus placebo, favouring vutrisiran, in the overall population and monotherapy population (secondary endpoint analysis), as reported in Section 2.6.6 of the Company Submission.

A NYHA transition matrix estimated from Baseline to Month 30 is provided in Table 3 for vutrisiran monotherapy versus tafamidis monotherapy, and in Table 4 for vutrisiran monotherapy versus placebo monotherapy (pure placebo). In contrast to the secondary endpoint analysis of NYHA class, for the calculation of NYHA transition probabilities in the economic model, unmeasured observations were censored to avoid introducing a separate, clinically invalid health state; and transitions to death, heart transplantation, or left ventricular assist device (LVAD) placement were also censored, as overall survival was modelled

separately and mortality was allocated across NYHA classes rather than directly modelling NYHA-specific survival.

Table 3: NYHA transition matrix from Baseline to Month 30 for the vutrisiran monotherapy and tafamidis monotherapy groups

From NYHA class	To NYHA class health state							
	Vutrisiran monotherapy (IPTW adjusted)				Tafamidis monotherapy (IPTW adjusted)			
	I	II	III	IV	I	II	III	IV
I	[redacted]							
II	[redacted]							
III	[redacted]							
IV	[redacted]							

DB, double-blind; IPTW, inverse probability of treatment weighting; NYHA, New York Heart Association.

Table 4: NYHA transition matrix from Baseline to Month 30 for the vutrisiran monotherapy and placebo monotherapy groups

From NYHA class	To NYHA class health state							
	Vutrisiran monotherapy (IPTW adjusted)				Placebo monotherapy (IPTW adjusted)			
	I	II	III	IV	I	II	III	IV
I	[redacted]							
II	[redacted]							
III	[redacted]							
IV	[redacted]							

DB, double-blind; IPTW, inverse probability of treatment weighting; NYHA, New York Heart Association.

A2. Please provide an overview of baseline characteristics for the following patient characteristics:

a. Co-existing ATTR-PN (polyneuropathy) per study arm.

b. SGLT-2 inhibitor concomitant use and mineral corticoid receptor antagonist use per study arm.

Table 5 summarises the following data as specified during the clarification meeting:

- The percentage of patients in HELIOS-B with a baseline history of polyneuropathy (any cause),
- Patients' polyneuropathy disability (PND) score (a measure of sensory and motor impairment, with a score of zero indicating no functional impairment and higher scores indicating increasing levels of functional impairment) at baseline, and
- Concomitant use rates for sodium-glucose cotransporter 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists (spironolactone and eplerenone) .

Table 5: Patients with a history of polyneuropathy at baseline, baseline PND score distribution, and patients with concomitant use of SGLT2 inhibitors and mineralocorticoid receptor antagonists in HELIOS-B

Parameter	Overall population		Monotherapy population		Background tafamidis population	
	Placebo (N=328)	Vutrisiran (N=326)	Placebo (N=199)	Vutrisiran (N=196)	Placebo (N=129)	Vutrisiran (N=130)
History of polyneuropathy at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PND score at HELIOS-B baseline, n (%)						
0	211 (64.3)	225 (69.0)	142 (71.4)	132 (67.3)	[redacted]	[redacted]
1	91 (27.7)	87 (26.7)	44 (22.1)	57 (29.1)	[redacted]	[redacted]
2	25 (7.6)	14 (4.3)	12 (6.0)	7 (3.6)	[redacted]	[redacted]
Missing	1 (0.3)	0	1 (0.5)	0	[redacted]	[redacted]
SGLT2 inhibitor concomitant use at baseline or initiated post-baseline (drop-in), n (%)						
Baseline	11 (3.4)	10 (3.1)	[redacted]	[redacted]	[redacted]	[redacted]
Drop-in	114 (34.8)	102 (31.3)	[redacted]	[redacted]	[redacted]	[redacted]
Mineralocorticoid receptor antagonist concomitant use during the DB period, n (%)						
Spironolactone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eplerenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DB, double-blind; PND, polyneuropathy disability; SGLT2, Sodium-glucose cotransporter 2. Note: SGLT2 inhibitor use was assessed by baseline use and drop-in use, but these data were not available for spironolactone and eplerenone. Source: Fontana et al. 2024[1]; Alnylam data on file

A3. HELIOS-B appears to have comparable arms for most baseline characteristics. However, there appear to be clinically significant between-arm differences in NYHA class and NT-proBNP troponin. Please comment on how these differences might affect internal validity of the trial.

As summarised in Table 6, there were imbalances in several parameters between patients randomised to vutrisiran and those randomised to placebo. The proportions of patients in NYHA class III at baseline were slightly higher in the placebo group compared to those in the vutrisiran group in both the overall population and monotherapy population. However, the proportions of patients in NYHA I/II are largely similar between treatment arms, a robust finding given the large sample sizes for these NYHA classes at baseline. In contrast, any differences in the proportion of patients in NYHA III are likely a function of small sample size in that class.

In the monotherapy population of HELIOS-B, there was a statistically significant (P<0.05) imbalance in baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin I levels between the vutrisiran and placebo groups. Specifically, median NTproBNP (2402.00 versus 1865.00 ng/L) and percentage of patients with NT-proBNP >2000 ng/L (58.7% versus 46.2%) were both considerably higher in the vutrisiran group than in the placebo group. Median troponin I was also higher in the vutrisiran group than in the placebo group (76.25 versus 62.20 ng/L) within the monotherapy population. In addition, there were more patients with NAC disease Stage 2 (34.7% versus 27.6%) or Stage 3 (7.7% versus 3.0%) in the vutrisiran group than in the placebo group within the monotherapy population (Table 6).[2]

Higher NYHA class, National Amyloidosis Centre (NAC) stage, and NT-proBNP levels have all independently been shown to significantly increase mortality risk when measured cross-sectionally in patients with ATTR-CM, while higher NYHA class and NT-proBNP levels are also well-known risk factors for cardiovascular (CV) hospitalisation. The baseline NYHA class distribution was modestly shifted toward more severe classes in the placebo arm of HELIOS-B; in contrast, however, differences between treatment arms in terms of NT-proBNP levels and the distribution of NAC stages (which consider NT-proBNP together with estimated glomerular filtration rate [eGFR]) at HELIOS-B baseline indicated more severe disease in the vutrisiran arm than in the placebo arm, and thus suggest a bias disfavouring vutrisiran relative to placebo, in the HELIOS-B monotherapy population.

Given their prognostic significance and the potential for imbalances to impact trial results, baseline NYHA class and NT-proBNP were prespecified in the HELIOS-B statistical analysis plan (SAP) as key factors for adjustment in the analysis models for all outcome-based endpoints.[2] In addition, the inverse probability of treatment weighting (IPTW) method, commonly used to adjust for key covariate imbalances between treatment groups, was employed to generate adjusted Kaplan-Meier (KM) curves for all-cause mortality (ACM) and time to first CV event or mortality; NYHA class, NT-proBNP, troponin I, and eGFR (which, together with NT-proBNP, determines a patient's NAC stage) were all included as covariates in the model used to generate IPTW weights. Therefore, the baseline differences observed between the vutrisiran and placebo arms do not impact the internal validity of the trial, as appropriate statistical measures were used to account and adjust for these differences.

Table 6: NYHA class and NAC stage proportions and NT-proBNP levels at baseline of HELIOS-B (taken from Table 12 of the Company Submission)

	Overall population (N=654)		**Monotherapy population (N=395)**	
Parameter at baseline	**Vutrisiran (n=326)**	**Placebo (n=328)**	**Vutrisiran (n=196)**	**Placebo (n=199)**
NYHA class				
I, n (%)	49 (15.0)	35 (10.7)	15 (7.7)	12 (6.0)
II, n (%)	250 (76.7)	258 (78.7)	172 (87.8)	169 (84.9)
III, n (%)	27 (8.3)	35 (10.7)	9 (4.6)	18 (9.0)
NT-proBNP, median, ng/L (IQR)	2021 (1138, 3312)	1801 (1042, 3081)	2402 (1321, 3867)	1865 (1067, 3099)
Troponin I, median, ng/L (IQR)	71.9 (44.9, 115.9)	65.2 (41.0, 105.5)	76.3 (48.4, 138.8)	62.2 (39.2, 105.6)
NAC stage				
1, n (%)	208 (63.8)	229 (69.8)	113 (57.7)	138 (69.3)
2, n (%)	100 (30.7)	87 (26.5)	68 (34.7)	55 (27.6)
3, n (%)	18 (5.5)	12 (3.7)	15 (7.7)	6 (3.0)

IQR, interquartile range; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association. Source: Fontana et al. 2024[1]

A4. The assessment of HELIOS-B quality in Appendix B concludes there were no risks of bias. However, to confirm this, there are two areas of ambiguity that require clarification:

a. For the primary outcome, there does not appear to have been imputation for early dropouts.

i. Why was there no imputation for early dropouts for the primary outcome?

ii. Please explain how many early dropouts there were in each group for the primary outcome.

iii. How was attrition bias avoided for the primary outcome?

b. It is not completely clear in section 9.4.6 of the CSR that outcome assessors were blinded to group. Please clarify.

Patients who discontinued the study no longer reported CV events but were followed up for vital status. In the semiparametric proportional rates model by Lin, Wei, Yang, and Ying (LWYY model), the follow-up duration needs to be the same for CV events and deaths; therefore, deaths recorded after study discontinuation were excluded from the LWYY model, to ensure the same duration of follow-up for CV events and deaths, but were still included in the component analysis of ACM.

There were 30 patients randomised to placebo and 20 patients randomised to vutrisiran who withdrew from the study for reasons other than death. Of these patients, 12 in the placebo group and 6 in the vutrisiran group died after withdrawal from the study.

In a prespecified sensitivity analysis, CV events were imputed after study discontinuation to assess the impact of missing CV events due to early study discontinuation. The imputation was up to the last survival follow-up date in the double-blind period for patients who discontinued study earlier but were still alive at the last survival follow-up date in the double-blind period (Month 30). For patients who discontinued study early but subsequently died during the double-blind period, the missing CV events between the study discontinuation date and death date were imputed.

This imputation resulted in an additional 13 CV events imputed in the placebo arm and 7 CV events imputed in the vutrisiran arm. The results of this sensitivity analysis were consistent with the primary analysis of the primary outcome. In the sensitivity analysis, the hazard ratio (HR) was 0.723 (95% CI 0.562, 0.930) in the overall population and 0.681 (95% CI 0.499, 0.930) in the vutrisiran monotherapy subgroup. Based on these results, it can be concluded that the results of the primary endpoint analysis in HELIOS-B were not sensitive to attrition bias.

A5. Please specify whether the measure of eGFR slope in the results sections of the company submission is expressed as the change in eGFR per year, or another time period.

As discussed in the clarification meeting, this request was not intended for this appraisal.

A6. Please supply results of tests for differences between subgroups for the subgroup analyses in Appendix C Table 2.

These analyses were not planned or included in the HELIOS-B SAP and would require de novo development of post hoc statistical models that enable testing for differences between subgroups, as the SAP-prespecified analysis for each subgroup of interest involved a statistical model informed by data only from that subgroup (and not from other subgroups for the same variable). The company does not plan on conducting these additional analyses, as creating an additional set of models for this purpose could result in effect estimates that differ from those obtained in the SAP-prespecified subgroup analyses, rendering any outputs from such models unsuitable as the basis for Committee decision-making.

Nonetheless, estimates of the magnitude and direction of treatment effect on the primary composite endpoint of all-cause mortality and recurrent CV events, and on all secondary endpoints, were consistent across all prespecified subgroups (see Appendix C in the Company Submission). Collectively, these results show that in patients with ATTR-CM, treatment with vutrisiran (relative to placebo) results in a lower risk of death from any cause, a lower risk of recurrent CV events, preserves functional capacity and quality of life, and prevents worsening of heart failure symptoms, with consistent effects across all prespecified subgroups.[1]

Tafamidis in HELIOS-B

A7. PRIORITY: The submission and economic model relies on data on patients in HELIOS-B who were receiving tafamidis at time of randomisation. Therefore, please supply data for the patients receiving both vutrisiran and tafamidis and tafamidis plus placebo, specifically:

a. **Expand Table 12 to include baseline data for patients receiving tafamidis at randomization (both with and without vutrisiran).**

A summary of baseline characteristics of patients in the background tafamidis group in HELIOS-B is provided in Table 7.

Table 7: Baseline characteristics of patients in the HELIOS-B background tafamidis population

Parameter at baseline	Background tafamidis population (N=259)	
	Placebo (n=129)	Vutrisiran (n=130)
Age at randomisation, median, years (range)	75.0 (46.0, 85.0)	77.0 (45.0, 85.0)
Male, n (%)	123 (95.3)	121 (93.1)
Race, n (%)		
White	106 (82.2)	108 (83.1)
Asian	4 (3.1)	6 (4.6)
Black/African American	13 (10.1)	13 (10.0)
Other/not reported	6 (4.7)	3 (2.3)
Disease type, n (%)		
hATTR	14 (10.9)	14 (10.8)
V122I	[redacted]	[redacted]
wtATTR, n (%)	115 (89.1)	116 (89.2)
Time since diagnosis, median, years (range)	1.53 (0.1, 10.8)	1.26 (0.0, 11.1)
Time on tafamidis prior to start of study, median, months (range)	11.30 (1.1, 65.5)	9.18 (1.1, 65.3)
NYHA class, n (%)		
I	23 (17.8)	34 (26.2)
II	89 (69.0)	78 (60.0)
III	17 (13.2)	18 (13.8)
NAC stage, n (%)		
1	91 (70.5)	95 (73.1)
2	32 (24.8)	32 (24.6)
3	6 (4.7)	3 (2.3)
6-MWT, mean, metres (SD)*	[redacted]	[redacted]
KCCQ-OS score, mean, points (SD)*	[redacted]	[redacted]
NT-proBNP, median, ng/L (IQR)	1746.0 (968.0, 2906.0)	1759.5 (1085.0, 2685.0)
Troponin I, median, ng/L (IQR)	68.3 (44.8, 104.6)	64.9 (42.9, 93.2)

Parameter at baseline	Background tafamidis population (N=259)	
	Placebo (n=129)	Vutrisiran (n=130)
eGFR, median, mL/min/1.73m^2 (IQR)	64.0 (50.0, 81.0)	64.5 (51.0, 80.0)

6-MWT, 6-minute walk test; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP; N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; V122I, valine to isoleucine substitution at amino acid position 122; wtATTR, wild-type transthyretin amyloidosis. Alnylam data on file

b. Expand Table 15 to report outcomes for patients receiving tafamidis at randomization, and hazard ratios and mean differences for the vutrisiran+tafamidis vs tafamidis monotherapy comparisons.

Again, the company notes that HELIOS-B was not designed or powered to assess the relative efficacy of vutrisiran versus tafamidis, and similarly, it was not intended and also not adequately powered to assess the relative efficacy of vutrisiran plus tafamidis versus tafamidis. A summary of efficacy outcomes (aligned with Table 15 of the Company Submission) is provided in Table 8

Table 8: Summary of efficacy results for patients in the HELIOS-B background tafamidis population

Measure	Background tafamidis population (N=259)	
	Placebo (n=129)	Vutrisiran (n=130)
Composite of ACM and recurrent CV events over up to 36 months		
Patients with at least one event, n (%)	[redacted]	[redacted]
HR (vutrisiran/placebo) (95% CI)	0.79 (0.51, 1.21) [redacted]	
Change in 6-MWT over 30 months*		
LS mean change over 30 months, metres (95% CI)	[redacted]	[redacted]
LS mean difference (vutrisiran – placebo), metres (95% CI)	18.4 (0.4, 36.5) [redacted]	
Change in KCCQ-OS score over 30 months†		
LS mean change over 30 months, points (95% CI)	[redacted]	[redacted]
LS mean difference (vutrisiran – placebo), points (95% CI)	1.8 (–2.9, 6.4) [redacted]	
ACM over up to 42 months		
Deaths, n (%)	[redacted]	[redacted]
HR (vutrisiran/placebo) (95% CI)	0.59 (0.32, 1.08) [redacted]	

Measure	Background tafamidis population (N=259)	
	Placebo (n=129)	Vutrisiran (n=130)
Change in NYHA class over 30 months‡		
Stable/improved over 30 months, %	[redacted]	[redacted]
Adjusted difference (vutrisiran – placebo), % (95% CI)	3.0 (–8.4, 14.4) [redacted]	

6-MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire; LS, least square; NYHA, New York Heart Association. *Missing change values at a given visit due to death or inability to walk because of disease progression were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit from the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline value for the patient with the missing data]. †Missing change values at a given visit due to death were derived from imputed domain change scores; domain change scores were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline domain score for the patient with the missing data]. ‡Missing change values at Month 30 due to death, heart transplantation, or left ventricular assist device placement were imputed as NYHA class IV; all other missing values were imputed via a probabilistic approach (Markov Chain Monte Carlo method) that predicts NYHA class at Month 30 from patients' baseline characteristics and pre-Month 30 NYHA class assessments. Source: Alnylam data on file

c. Supply versions of all figures 13 to 20 for patients receiving tafamidis at randomization.

Time to ACM or first CV event over up to 36 months from baseline in HELIOS-B is presented in Figure 1 for patients in the background tafamidis population.

Figure 1: Time to ACM or first CV event (whichever occurred first) in the background tafamidis population in HELIOS-B

ACM, all-cause mortality; CV, cardiovascular; HR, hazard ratio. Note: The reported HR is a comparison of vutrisiran versus placebo within the background tafamidis population. Source: Alnylam, data on file

Change from baseline to Month 30 in 6-minute walk test (6-MWT) distance for patients in the background tafamidis population in HELIOS-B is presented in Figure 2 (least squares [LS] mean change) and Figure 3 (median change with observed values).

Figure 2: LS mean change from baseline to Month 30 in 6-MWT distance in the background tafamidis population in HELIOS-B

6-MWT, 6-minute walk test; LS, least square; SEM, standard error of the mean. Note: For patients with missing data at a given time point due to death or inability to walk because of disease progression, data at that time point were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline value for the patient with the missing data]. Source: Alnylam, data on file

Figure 3: Median change from baseline to Month 30 in 6-MWT distance in the background tafamidis population, observed values

6-MWT, 6-minute walk test; CI, confidence interval. Note: Median changes reflect the observed results from surviving patients with available data. Source: Alnylam, data on file

Change from baseline to Month 30 in Kansas City Cardiomyopathy Questionnaire – Overall Summary (KCCQ-OS) score for patients in the background tafamidis population in HELIOS-B is presented in Figure 4 (LS mean change) and Figure 5 (median change with observed values).

Figure 4: LS mean change from baseline to Month 30 in KCCQ-OS score in the background tafamidis population in HELIOS-B

CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least square; SEM, standard error of the mean. Note: For patients with missing data at a given time point due to death, data at that time point were derived from imputed domain change scores; domain change scores were imputed via random sampling from the worst 10% of outcomes for all patients at the same visit in the same treatment group and baseline tafamidis use group, with imputed values capped by [0 – baseline domain score for the patient with the missing data]. Source: Alnylam, data on file

Figure 5: Median change from baseline to Month 30 in KCCQ-OS score in the background tafamidis population, observed values

CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary. Note: Median changes reflect the observed results from surviving patients with available data. Source: Alnylam, data on file

A plot of adjusted cumulative mortality rates over time for patients in the background tafamidis population in HELIOS-B is presented in Figure 4.

Figure 6: ACM over up to 42 months in the background tafamidis population in HELIOS-B

ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio. Note: The HR is reported as a comparison of the vutrisiran group versus the placebo group within the background tafamidis population. This analysis included vital status data collection through up to Month 6 of the OLE. Source: Alnylam, data on file

Adjusted geometric mean fold change from baseline to Month 30 in serum NT-proBNP level for patients in the background tafamidis population in HELIOS-B is presented in Figure 7.

Figure 7: Adjusted geometric mean fold change from baseline to Month 30 in serum NT-proBNP in the background tafamidis population in HELIOS-B

6-MWT, 6-minute walk test; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; MMRM, mixed models for repeated measures; NT-proBNP, N-terminal pro-brain natriuretic peptide. Note: Analyses were carried out using the same MMRM model used for 6-MWT and KCCQ-OS score, but with baseline log-transformed NT-proBNP value as a covariate instead of baseline 6-MWT/KCCQ-OS score. Source: Alnylam, data on file

Time to first oral loop diuretic intensification (including new initiation of oral loop diuretics), first CV event, or ACM over up to 36 months from baseline in HELIOS-B is presented in Figure 8 for patients in the background tafamidis population.

Figure 8: Time to first oral loop diuretic intensification, first CV event, or ACM (whichever occurred first) in the background tafamidis population in HELIOS-B

ACM, all-cause mortality; CV, cardiovascular; HR, hazard ratio; ODI, oral loop diuretic intensification; PH, proportional hazards. Note: HRs are reported as a comparison of the vutrisiran group versus the placebo group within the background tafamidis population. This endpoint was assessed over the double-blind period (up to 36 months from baseline) via log-rank test and Cox PH model, including the same stratification factors and covariates as those used in the ACM secondary endpoint analysis. Source: Alnylam, data on file

d. Expand Table 16 to include outcomes for vutrisiran+tafamidis and placebo-only (no tafamidis) groups

e. For all outcomes in Table 16 supply hazard ratios or mean differences for all six possible between-group comparisons (e.g. also supply HRs for ACM for:

- **tafamidis monotherapy vs placebo,**
- **vutrisiran+tafamidis vs placebo only,**
- **vutrisiran+tafamidis vs vutrisiran monotherapy**
- **vutrisiran+tafamidis vs tafamidis monotherapy**

f. **Expand the subgroup analyses (Appendix C) to report outcomes for patients receiving tafamidis at randomization**

HELIOS-B was designed to compare vutrisiran versus placebo in two populations: the overall population, which included patients who were receiving background tafamidis at baseline and those who were not, and the monotherapy population, which included only those patients in the overall population who were not receiving background tafamidis at baseline. HELIOS-B was not intended and not powered to address other comparisons, including the comparison of vutrisiran versus tafamidis and other comparisons described in Clarification question A7, parts d and e.

Noting, the company submission decision problem considers:

- Vutrisiran will be positioned as a monotherapy at launch, based on anticipated lack of cost-effectiveness of combination use of two branded medicines (i.e., vutrisiran and tafamidis) given current NICE STA cost-effectiveness thresholds and clinician intentions for the use of vutrisiran once it is available
- Tafamidis as the sole comparator

A post hoc within-trial comparison of vutrisiran monotherapy (vutrisiran plus no background tafamidis) and tafamidis monotherapy (placebo plus background tafamidis) in HELIOS-B was provided in the Company Submission (Table 16). This comparison was determined to be the best available source of comparative data on vutrisiran and tafamidis monotherapy, given the limitations identified on feasibility assessment of an indirect treatment comparison (ITC) between vutrisiran in HELIOS-B and tafamidis in ATTR-ACT (described fully in Section 2.10 of the Company Submission). Since the allocation of patients in HELIOS-B to the vutrisiran monotherapy and tafamidis monotherapy groups was not random, the IPTW method was used to balance baseline differences between the two groups and thus reduce bias (summarised in response to Clarification question A14).

The company conducted a post hoc comparison of tafamidis monotherapy versus placebo monotherapy (i.e., patients in the placebo group who were not receiving tafamidis at baseline), focusing on key event-based outcomes (primary composite endpoint and secondary endpoint of ACM) and (as requested in Clarification question A1) on NYHA class change from baseline. Results of these analyses are provided in Table 9.

Table 9: Summary of results from HELIOS-B for the tafamidis monotherapy versus placebo monotherapy groups

v	Placebo monotherapy (N=199)	Tafamidis monotherapy (n=129)
Composite of ACM and CV events over up to 36 months (primary endpoint)		
Patients with at least one event, n (%)	[redacted]	[redacted]
HR (95% CI), tafamidis vs. placebo*	[redacted]	
ACM over up to 42 months†		
Deaths, n (%)	[redacted]	[redacted]
HR (95% CI), tafamidis vs placebo*	[redacted]	
Change in NYHA class over 30 months‡		
Stable/improved over 30 months, %	[redacted]	[redacted]
Adjusted % difference (tafamidis – placebo)	[redacted]	
OR (95% CI) at Month 30, tafamidis vs placebo	[redacted]	

6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LVAD, left ventricular assist device; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PND, polyneuropathy disability.
These comparisons used stabilised inverse probability of treatment weighting based on propensity scores, calculated through a logistic regression model of the odds of being in the tafamidis monotherapy vs. placebo monotherapy group, conditional on patients' baseline characteristics. The following parameters were included as covariates: age category, ATTR disease type, NYHA class, log-transformed troponin I, log-transformed NT-proBNP, KCCQ-OS score, average peak longitudinal strain, eGFR, sex, race category, history of antithrombotic agents, PND score, and 6-MWT. *Hazard ratios are based on the modified Andersen-Gill model and include treatment, log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT as covariates. †Analysed using a Cox proportional hazards model with treatment group, log-transformed NT-proBNP, log-transformed troponin I,

and 6-MWT as covariates. ‡Adjusted difference and 95% CI were derived from multiple imputation procedure by combining estimates per Rubin's rules based on 100 datasets where missing NYHA class values due to death, heart transplantation, and left ventricular assist device placement are imputed as class IV, and the other missing NYHA class values are imputed using a Markov chain Monte Carlo procedure including selected baseline variables and postbaseline NYHA class assessments. For each imputed dataset, adjusted proportions, odds ratios, and 95% CI are based on a logistic regression model including treatment group, log-transformed NT-proBNP, log-transformed troponin I, 6-MWT, and baseline NYHA as covariates. Source: Alnylam data on file

The analyses comparing vutrisiran + tafamidis versus placebo, vutrisiran, and tafamidis, respectively, as requested in Clarification question A7, parts d and e, were not generated and are not available post hoc. The company notes the decision problem in the Company Submission does not consider combination usage for the afore stated reasons.

A8. PRIORITY: The KM curves presented in Figure 27 of the CS comparing vutrisiran monotherapy vs. tafamidis monotherapy (inverse probability of treatment weighting [IPTW] adjusted population) suggest that [redacted]. This is inconsistent with the HR on ACM over up to 42 months reported for this comparison in Table 16 of the CS (HR=[redacted]. Furthermore, the labelling of the treatment comparisons reported in Table 16 of the CS is inconsistent with the columns suggesting a comparison between vutrisiran monotherapy and tafamidis monotherapy, while the comparison for the relative effects on the outcomes is labelled as "vutrisiran vs. placebo".

a) **Please confirm that the unadjusted by IPTW ACM KM curves for the vutrisiran monotherapy and tafamidis monotherapy correspond to Figure 8 (page 18) in the pre-read evidence dossier supplied jointly with the Structured Elicitation (SEE) Report and, if not, please provide these KM curves.**

b) **Please provide the HR for vutrisiran monotherapy vs. tafamidis monotherapy the unadjusted by IPTW ACM KM curves for the vutrisiran monotherapy and tafamidis monotherapy.**

The company acknowledges that all results in Table 16 are for the comparison of vutrisiran versus tafamidis. In certain cells in this table, the designation "*(vutrisiran/placebo)*" was inadvertently used in place of "*(vutrisiran/tafamidis)"* to label treatment effect estimates.

The company also confirms that in Figure 8 (page 18) in the pre-read evidence dossier supplied jointly with the Structured Elicitation (SEE) Report, the curves provided are unadjusted ACM KM curves for the vutrisiran monotherapy and tafamidis monotherapy

groups. Unadjusted and adjusted HRs for ACM in HELIOS-B for vutrisiran monotherapy versus tafamidis monotherapy are provided in Table 10

Table 10: HRs for ACM for vutrisiran monotherapy versus tafamidis monotherapy in HELIOS-B

Model	HR (95% CI)
Model 1: treatment group only, no other covariates	[redacted]
Model 2: treatment group, age group, ATTR disease type, baseline NYHA class, log-transformed NT-proBNP and Troponin, baseline 6-MWT, baseline KCCQ-OS, and baseline eGFR as covariates.	[redacted]

ATTR, transthyretin amyloidosis; 6-MWT, 6-minute walk test; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

c) Please provide the interpretation of the relative treatment effects reported in Table 16 of the CS, in terms of the treatments that are being compared for each outcome and whether these estimates are IPTW adjusted.

In Table 16 of the Company Submission, the following can be concluded from the relative treatment effects of vutrisiran monotherapy versus tafamidis monotherapy in the IPTW analysis:

- Vutrisiran was associated with a numerical reduction in the composite risk of ACM and recurrent CV events over up to 36 months from baseline compared to tafamidis.
- Vutrisiran was associated with a numerical reduction in the risk of ACM over up to 42 months from baseline compared to tafamidis.

d) [redacted] If the HR on all-cause mortality over up to 42 months reported in Table 16 of the CS (HR=[redacted] represents the relative treatment effect on this outcome for vutrisiran monotherapy vs. tafamidis monotherapy, please clarify how this is consistent with the visual comparison of the KM curves (which suggest [redacted]).

The value of 0.81 reported in Table 16 of the Company Submission represents the HR *not adjusted for baseline differences between treatment groups*, whereas the KM curves show the vutrisiran and tafamidis survival, weighted using IPTW. Therefore, Table 16 and KM curves do not reflect the same data. The weighted HR for vutrisiran monotherapy versus tafamidis monotherapy is [redacted] ([redacted]), which is more in line with the weighted KM curves presented in Figure 22 of the Company Submission.

The HR metric is interpreted as the ratio of the instantaneous hazard of an event for one exposure group to the instantaneous hazard of that event in another exposure group. HRs are estimated based on event data observed over a specified time interval, and thus provide

a single summary measure that reflects the totality of data observed over that interval. In this context, the underlying assumption (proportional hazards assumption) is that the HR remains constant over the interval in which it is estimated and thus represents the ratio (between the two exposure groups) of instantaneous event hazards at any given point during that interval.

In the analysis provided by the company, [redacted] In particular, the HR is intended to be a single summary measure representing a ratio of event hazards that is constant and uniformly applicable over the follow-up period in which it is estimated, but violation of the proportional hazards assumption (as observed here) suggests that the ratio of event hazards is not constant and thus not uniformly applicable over the follow-up period.

These considerations notwithstanding, the numerically lower mortality rate in the tafamidis monotherapy group than in the vutrisiran monotherapy group during the initial portion of the follow-up interval is likely due to the differences in the timing of therapy initiation between the two groups in HELIOS-B, as patients in the vutrisiran monotherapy group initiated vutrisiran at HELIOS-B baseline, whereas those in the tafamidis monotherapy group had already been receiving tafamidis for a median of 11.3 months (range: 1.1, 65.5) at HELIOS-B baseline. Therefore, the pattern of survival benefit observed in HELIOS-B is likely to be conservative for vutrisiran relative to tafamidis, as survival benefits with active treatments for ATTR-CM require some time to emerge after initiation of treatment, as has been demonstrated in multiple phase 3 trials.[1,3,4] As a result, patients in the tafamidis monotherapy group (having been on tafamidis for a median of 11.3 months) may have already been deriving a survival benefit at baseline in HELIOS-B, whereas patients in the vutrisiran monotherapy group (having just started treatment) were not already deriving a survival benefit at baseline. For similar reasons, comparison of ACM between the vutrisiran monotherapy and tafamidis monotherapy groups is also likely to be impacted by survivor bias favouring the tafamidis monotherapy group.

A9. It is unclear how much tafamidis the 'placebo patients on background tafamidis' received during the trial.

a. Please provide data on the total doses of tafamidis given throughout the trial to the 'placebo patients on background tafamidis'

Please provide the numbers of 'placebo patients on background tafamidis' who were still receiving a) full doses of tafamidis at 30 months, b) reduced doses of tafamidis at 30 months.

Patients in the background tafamidis population were receiving tafamidis at baseline of HELIOS-B; however, detailed data regarding tafamidis dose administrations in this group of patients was not collected post-baseline in HELIOS-B, as the study was not intended to assess the efficacy or safety of tafamidis. Therefore, the data requested in A9a and A9b cannot be provided. Nonetheless, the tafamidis label does not have any allowance for dose

reduction, so patients who were receiving tafamidis were likely receiving the full indicated dose.

Adverse Events

A10. The CSR data on adverse events provides evidence that adverse events for vutrisiran were similar to placebo.

a. Constipation was the only gastrointestinal complaint reported (included in the list of adverse events affecting > 10% of participants). Please provide specific reporting on gastrointestinal events

b. Please report adverse events related to impaired thyroxin and vitamin A transport should also be reported.

In the overall population, a total of [redacted] ([redacted]%) patients in the placebo group and [redacted] ([redacted]%) patients in the vutrisiran group had a gastrointestinal adverse event (AE) during the double-blind treatment period. A summary of all gastrointestinal AEs by preferred term is provided in Table 11. Gastrointestinal AEs with the largest differences between vutrisiran and placebo (>2% difference) were [redacted].

Table 11: Summary of all AEs by preferred term in the gastrointestinal system organ class, during the double-blind period of HELIOS-B

Adverse event, n (%)	Overall population	
	Placebo (N=328)	Vutrisiran (N=326)
Abdominal discomfort	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Abdominal hernia	[redacted]	[redacted]
Abdominal mass	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain lower	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Abdominal tenderness	[redacted]	[redacted]
Abnormal faeces	[redacted]	[redacted]
Anal haemorrhage	[redacted]	[redacted]
Anal incontinence	[redacted]	[redacted]
Anal stenosis	[redacted]	[redacted]
Angular cheilitis	[redacted]	[redacted]
Anorectal discomfort	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Barrett's oesophagus	[redacted]	[redacted]
Change of bowel habit	[redacted]	[redacted]

Adverse event, n (%)	Overall population	
	Placebo (N=328)	Vutrisiran (N=326)
Chronic gastritis	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dental alveolar anomaly	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]
Dental discomfort	[redacted]	[redacted]
Dental necrosis	[redacted]	[redacted]
Diaphragmatic hernia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Diverticulum	[redacted]	[redacted]
Diverticulum intestinal	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Duodenogastric reflux	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]
Epigastric discomfort	[redacted]	[redacted]
Erosive duodenitis	[redacted]	[redacted]
Eructation	[redacted]	[redacted]
Faecaloma	[redacted]	[redacted]
Faeces discoloured	[redacted]	[redacted]
Faeces hard	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]
Frequent bowel movements	[redacted]	[redacted]
Gastric mucosa erythema	[redacted]	[redacted]
Gastric polyps	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]
Gastric ulcer haemorrhage	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
Gastritis erosive	[redacted]	[redacted]
Gastrointestinal disorder	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Gastrointestinal motility disorder	[redacted]	[redacted]
Gastrointestinal mucosa hyperaemia	[redacted]	[redacted]
Gastrointestinal pain	[redacted]	[redacted]
Gastrointestinal vascular malformation haemorrhagic	[redacted]	[redacted]
Gastro-oesophageal reflux disease	[redacted]	[redacted]
Gingival bleeding	[redacted]	[redacted]
Gingival hypertrophy	[redacted]	[redacted]
Glossitis	[redacted]	[redacted]
Haematemesis	[redacted]	[redacted]
Haematochezia	[redacted]	[redacted]

Adverse event, n (%)	Overall population	
	Placebo (N=328)	Vutrisiran (N=326)
Haemorrhoidal haemorrhage	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]
Hiatus hernia	[redacted]	[redacted]
Hyperaesthesia teeth	[redacted]	[redacted]
Ileus	[redacted]	[redacted]
Incarcerated inguinal hernia	[redacted]	[redacted]
Inguinal hernia	[redacted]	[redacted]
Intestinal atony	[redacted]	[redacted]
Intestinal polyp	[redacted]	[redacted]
Intra-abdominal fluid collection	[redacted]	[redacted]
Irritable bowel syndrome	[redacted]	[redacted]
Large intestine polyp	[redacted]	[redacted]
Lower gastrointestinal haemorrhage	[redacted]	[redacted]
Melaena	[redacted]	[redacted]
Mesenteric panniculitis	[redacted]	[redacted]
Mouth haemorrhage	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Noninfective gingivitis	[redacted]	[redacted]
Obstructive pancreatitis	[redacted]	[redacted]
Oesophageal food impaction	[redacted]	[redacted]
Oesophageal obstruction	[redacted]	[redacted]
Oesophagitis	[redacted]	[redacted]
Pancreatic cyst	[redacted]	[redacted]
Pancreatic failure	[redacted]	[redacted]
Pancreatic mass	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pancreatitis acute	[redacted]	[redacted]
Proctalgia	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
Rectal polyp	[redacted]	[redacted]
Rectal ulcer	[redacted]	[redacted]
Salivary hypersecretion	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]
Small intestinal perforation	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Tongue disorder	[redacted]	[redacted]
Tooth loss	[redacted]	[redacted]
Toothache	[redacted]	[redacted]
Ulcerative gastritis	[redacted]	[redacted]

Adverse event, n (%)	Overall population	
	Placebo (N=328)	Vutrisiran (N=326)
Umbilical hernia	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]
Varices oesophageal	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

AE, adverse event. Source: Alnylam, data on file

b. Please report adverse events related to impaired thyroxin and vitamin A transport should also be reported.

Vitamin A circulates through the plasma primarily bound to retinol binding protein (RBP). The clearance of RBP from the circulation is greatly reduced through its binding to TTR.[5,6] The safety of lowering vitamin A through TTR reduction has been confirmed in clinical studies with RNAi therapeutics targeting TTR (e.g., patisiran and vutrisiran), where no AEs considered attributable to vitamin A deficiency have been observed in either healthy subjects or patients with ATTR amyloidosis, despite >80% lowering of both TTR and vitamin A for over 18 months. In addition, physiological consequences of this reduction in vitamin A levels have not been observed in the post-marketing setting.

During the double-blind period of HELIOS-B, AEs in the eye disorders system organ class were reported in 47 (14.4%) patients in the vutrisiran group and 66 (20.1%) patients in the placebo (Table 12). No AEs of night blindness, vitamin A decreased, or vitamin A deficiency were observed. The types of ocular AEs reported were not suggestive of vitamin A deficiency, and the medical history was consistent with ocular symptoms and eye disorders that are frequently reported in patients with ATTR amyloidosis and are similar to eye disorders reported in the general population of this age (i.e., median age of 76 years at baseline).

Table 12: AEs in the eye disorders system organ class in ≥1% of patients in either group (placebo or vutrisiran) during the double-blind period (Safety analysis set)

Preferred term	Placebo (N=328; PY=822.4)			Vutrisiran (N=326; PY-833.9)		
	Patients, n (%)	Events		Patients, n (%)	Events	
		n	ER		n	ER
At least 1 eye disorder AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diplopia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; ER, exposure adjusted event rate per 100 years; PY, patient years
Source: Study 003 CSR1, Table 14.3.1.2[7]

While TTR is a known carrier protein for thyroxine (T4), it is only one of several carrier proteins and plays a relatively minor role in thyroxine transport. In completed clinical studies with patisiran and vutrisiran, there were no thyroid AEs considered related to study drug. During the double-blind period of HELIOS-B, thyroid AEs (e.g., preferred terms [PTs] Hyperthyroidism, Hypothyroidism, Thyroiditis, Blood thyroid stimulating hormone decreased, and Blood thyroid stimulating hormone increased) were reported at a similar or lower frequency in the vutrisiran group compared to the placebo group.[7]

A11. Please provide data comparing adverse events between vutrisiran monotherapy and tafamidis monotherapy subgroups.

A summary of AEs in the vutrisiran monotherapy and tafamidis monotherapy groups in HELIOS-B is provided in Table 13. A numerically larger proportion of patients in the vutrisiran monotherapy group experienced cardiac failure compared to patients in the placebo plus tafamidis group. It should be noted that the AE rates presented in Table 13 are unadjusted and therefore confounded by differences in baseline characteristics/baseline disease severity between the two groups, which were not randomly allocated.

Table 13: Adverse events in patients receiving vutrisiran plus no background tafamidis and in patients receiving placebo plus background tafamidis in HELIOS-B

Event, n (%)	Vutrisiran plus no background tafamidis (n=199)	Placebo plus background tafamidis (N=196)
At least 1 AE	[redacted]	[redacted]
AEs occurring in ≥15% of patients in either arm		
Cardiac failure	[redacted]	[redacted]
Fall	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Gout	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]
SAEs occurring in ≥5% of patients in either arm		
Cardiac failure	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Cardiac failure acute	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Any severe AE	[redacted]	[redacted]
Cardiac AEs	[redacted]	[redacted]
Cardiac SAEs	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]
AEs leading to death	[redacted]	[redacted]

AE, adverse event; SAE, serious adverse event. Source: Alnylam, data on file

Indirect treatment comparisons

A12. PRIORITY The company has not provided sufficient evidence to ascertain the extent to which alternative approaches to produce estimates of relative treatment effect for vutrisiran monotherapy vs. placebo and for vutrisiran monotherapy vs. tafamidis conduce mitigate (or not) the uncertainty and risk of bias compared to the company's preferred approaches.

We note that, as both trials include a placebo arm, anchored MAIC and network meta-analysis can, in principle, be performed which may reduce the imbalance concerns. Therefore, please provide the full MAIC analysis report comparing HELIOS-B and ATTR-ACT, to enable the EAG to fully assess the methodology and results. This should be an anchored MAIC, for preference.

The feasibility assessment of an ITC of vutrisiran monotherapy in HELIOS-B versus tafamidis (80 mg) in ATTR-ACT was summarised in Section 2.10 of the Company Submission. Based on this assessment, it was determined that a methodologically robust ITC of vutrisiran in HELIOS-B versus tafamidis in ATTR-ACT was not feasible. Consequently, as detailed in the company response to Clarification question A14, part b, a within-trial comparison of vutrisiran monotherapy and tafamidis monotherapy in HELIOS-B using a stabilised IPTW approach for propensity score weighting was considered to be the most appropriate source of data on the comparative efficacy of vutrisiran and tafamidis in patients with ATTR-CM.

The infeasibility of a methodologically robust ITC of vutrisiran in HELIOS-B versus tafamidis in ATTR-ACT, is also supported by the following statement by [redacted], clinical experts at the National Amyloidosis Centre (NAC):{Alnylam, 2024 #902}

> "HELIOS—B and ATTR-ACT have differing patient populations meaning that outcomes from these studies are not comparable. The patients enrolled in ATTR-ACT were much more advanced in terms of disease progression, vs. those enrolled in HELIOS-B, in which patients had milder disease. This was primarily driven by the advances in cardiovascular health in recent years, meaning HELIOS-B was much more reflective of current clinical practice with more intensive use of cardiovascular medications, vs. ATTR-ACT, in which there was under utility of cardiovascular medications vs. current clinical practice."

While noting the considerations that limit the feasibility of a methodologically robust ITC between vutrisiran in HELIOS-B and tafamidis in ATTR-ACT, the company acknowledges the reviewers' interest in considering the results of such an ITC and has thus generated MAIC results on an exploratory basis in response to the reviewers' request in Clarification question A13.

A13. PRIORITY Please conduct network meta-analyses comparing HELIOS-B to ATTR-ACT for the primary outcome, ACM and NHYA data, where this is feasible.

As previously mentioned, the company has generated MAIC results on an exploratory basis in response to the reviewers' request, while noting the considerations that are expected to introduce bias in these results.

The exploratory analysis that has been conducted employs an unanchored MAIC approach. An anchored approach would rely on the existence of a common comparator between HELIOS-B and ATTR-ACT, to allow "bridging" of results between the two trials. Nominally, placebo serves as this common comparator, but in practice (as discussed in section 2.10 of the Company Evidence Submission),

[redacted]

This unanchored MAIC approach was used to generate relative treatment effect estimates for the endpoints of ACM and NYHA class change from baseline. Results for the composite endpoint of ACM and CV events were not obtained; although this composite endpoint was assessed in both HELIOS-B and ATTR-ACT, the reported summary measure in ATTR-ACT was the Finkelstein-Schoenfeld win ratio, and established methods of generating indirect treatment effect estimates based on this relatively novel metric do not exist.

Baseline characteristics of the relevant patient populations from HELIOS-B and ATTR-ACT before and after MAIC weighting are presented in Table 14.

Table 14: Baseline characteristics of patients from HELIOS-B and ATTR-ACT before and after unanchored MAIC weighting

Characteristic	Before weighting			After unanchored MAIC weighting		
	Vutrisiran (HELIOS-B) N=195	Tafamidis 80mg (ATTR-ACT) N=176	P Value (Vutrisiran vs. Tafamidis)	Vutrisiran (HELIOS-B) N=195	Tafamidis 80mg (ATTR-ACT) N=176	P Value (Vutrisiran vs. Tafamidis)
Age (years)	[redacted]					
Sex: Male						
Sex: Female						
Race: White						
Race: Black						
Race: Asian						
Race: Other race						
NYHA class I/II						
NYHA class III						
ATTR type: hereditary						
ATTR type: wild-type						

Characteristic	Before weighting			After unanchored MAIC weighting		
	Vutrisiran (HELIOS-B) N=195	Tafamidis 80mg (ATTR-ACT) N=176	P Value (Vutrisiran vs. Tafamidis)	Vutrisiran (HELIOS-B) N=195	Tafamidis 80mg (ATTR-ACT) N=176	P Value (Vutrisiran vs. Tafamidis)
Region: USA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region: Ex-USA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6MWT distance (m)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-OS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-PL score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP level (pg/mL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP level greater than median in ATTR-ACT trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Troponin I level (ng/mL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Troponin I level greater than median in ATTR-ACT trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global longitudinal strain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Left ventricular ejection fraction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since ATTR-CM diagnosis (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Implanted cardiac defibrillator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Permanent pacemaker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Modified BMI (kg/m^2 x g/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAC stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAC stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAC stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--

Means and standard deviations are shown for continuous variables and percentages are shown for categorical variables.
P values for continuous variables are calculated using the Wald test. P-values for categorical variables are calculated using the chi-square test or (for categorical variables with low frequency [n<5]) the Fisher exact test.

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - Overall Summary; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; USA, United States of America; wtATTR, wild-type transthyretin amyloidosis;.

[redacted]**Table 15: Outcomes from MAIC of vutrisiran monotherapy in HELIOS-B and tafamidis (80 mg) in ATTR-ACT**

Parameter	Unanchored MAIC
ACM HR, (vutrisiran vs. tafamidis; 95% CI)	[redacted]
Difference in proportion with stable/improved NYHA class from baseline to 30 months (vutrisiran – tafamidis; 95% CI)	[redacted]

ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NYHA, New York Heart Association.

It should be noted that the two trials assessed ACM at different time points. In HELIOS-B, ACM was assessed over up to 42 months, whereas in ATTR-ACT, it was assessed up to Month 30. This additional limitation further reinforces the appropriateness of using within-trial IPTW analysis of HELIOS-B to estimate the relative efficacy of vutrisiran and tafamidis for the purpose of economic modelling, particularly considering that the HELIOS-B population represents contemporary patients with ATTR-CM, in contrast to ATTR-ACT, which enrolled patients more than a decade ago (from 2013 to 2015).[8]

A14. PRIORITY The stabilized IPTW approach, where the HELIOS-B vutrisiran monotherapy arm is compared to the HELIOS-B 'placebo patients on background tafamidis', is used instead of a MAIC.

a. For the IPTW approach please report:

i. why was IPTW selected over other statistical methods?

ii. full details of the methodology used, particularly the matching procedures; the rationale for variable selection for baseline characteristics IPTW adjustment;

iii. Assessment of patient baseline characteristics balance across treatment groups before and after IPTW adjustment;

iv. Standard mean difference comparisons before and after IPTW adjustment for each variable;

v. If any sensitivity analyses were conducted (e.g., alternative variables selected for adjustment), list them and report how robust were the transition probability estimates applied in the model to the results of these analyses.

Unlike the pre-specified comparisons across the randomised vutrisiran and placebo arms of HELIOS-B designed for regulatory submission, the analyses referred to in Clarification question A14 were post hoc comparisons of non-randomised patient groups (vutrisiran and tafamidis monotherapy groups) within HELIOS-B. As such, these analyses need to be appropriately statistically adjusted and interpreted, as described further below.

Adjustment for baseline differences between the vutrisiran and tafamidis monotherapy groups was done using the IPTW approach. Specifically, a logistic regression model was fitted for the odds of being in the vutrisiran monotherapy group versus the prevalent tafamidis monotherapy group (i.e. patients in the placebo group who are on tafamidis at baseline).

Based on consideration of prognostic factors for outcomes of interest, the following baseline characteristics were initially proposed for adjustment in this analysis via inclusion in the propensity score models described below.

- High priority adjustment factors:
  - Age group
  - Type of ATTR amyloidosis (wtATTR vs hATTR)
  - NYHA class
  - Troponin I

    - NT-proBNP
    - KCCQ-OS
- Other candidate adjustment factors, including (but not limited to) the following:
    - Echocardiography parameters (e.g., left ventricular ejection fraction, global longitudinal strain)
    - KCCQ subdomain scores
    - eGFR
    - Time since ATTR-CM diagnosis

Selection of the final adjustment factors (listed in Table 16) prioritised factors with greater observed imbalances between the vutrisiran and tafamidis monotherapy groups and factors without substantial missing data. To assess balance of baseline characteristics between groups, standardised mean differences (SMD) between groups before and after weighting were calculated for all adjusted patient characteristics. An absolute SMD of <10% for high-priority baseline parameters (indicated with an asterisk in Table 16) and <25% for other baseline parameters is considered to indicate good balance between the groups.[9-11]

Outcomes were compared between the vutrisiran monotherapy and the tafamidis monotherapy groups accounting for differences in baseline characteristics between the two groups using weighted regression models. The weights applied in the models for both groups were the stabilised IPTW weights as described above. As such, in order to allow the use of all available data, there was no matching procedure implemented.

A summary of baseline characteristics before and after application of stabilised IPTW weights is provided in Table 16 along with the SMD between groups for each parameter. None of the high priority baseline parameters had an SMD of >10% between the vutrisiran monotherapy and tafamidis monotherapy groups after stabilised IPTW. Among all other baseline parameters (i.e., those that were not high priority), only serum TTR concentration, region, and heart rate had a standardised difference of >25% between the vutrisiran monotherapy and tafamidis monotherapy groups after stabilised IPTW. Differences in these baseline parameters are not anticipated to have a substantial impact on the results of the analysis. Since tafamidis is understood to increase patients' serum TTR levels,[12] and since patients who were receiving background tafamidis in HELIOS-B had been receiving treatment for a median of 11.3 months prior to baseline, a notable difference in serum TTR levels was expected between the tafamidis monotherapy group and the vutrisiran monotherapy group.;Data on other baseline clinical characteristics suggest that the stabilised IPTW approach used in this analysis adequately addressed any relevant differences in baseline clinical status that may have resulted from the observed difference in baseline serum TTR levels.[1] With regard to differences in geography, due to the earlier regulatory approval of tafamidis for ATTR-CM in the US than in other geographies, a larger proportion of patients in the tafamidis monotherapy group were located in the US. Despite this, the two main outcomes used from the IPTW analysis to inform the cost-effectiveness model were ACM and NYHA class transitions, neither of which are anticipated to be affected by geography, as geography is not known to be a predictor of mortality or NYHA class progression in ATTR-CM. Similarly, the difference in baseline mean heart rate between the vutrisiran monotherapy group and the tafamidis monotherapy group in the IPTW-adjusted population is not expected to have a meaningful impact on clinical outcomes.

Table 16 Baseline characteristics in the vutrisiran monotherapy and tafamidis monotherapy groups before and after stabilised IPTW

Parameter	Before stabilised IPTW		After stabilised IPTW	
	Vutrisiran Monotherapy (N=196)	Tafamidis Monotherapy (N=129)	Vutrisiran Monotherapy	Tafamidis Monotherapy
***Age category in years, n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
<75	[redacted]		[redacted]	
≥75				
Standardised difference (%)				
Sex, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Male				
Female	[redacted]		[redacted]	
Standardised difference (%)				
Race, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
White				
Black				
All other races	[redacted]		[redacted]	
Standardised difference (%)				
Region, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
US				
Europe				
Rest of World	[redacted]		[redacted]	
Standardised difference (%)				
BMI, kg/m^2	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
***ATTR type, n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
hATTR				
wtATTR	[redacted]		[redacted]	
Standardised difference (%)				
***NYHA class, n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
I				
II				
III	[redacted]		[redacted]	
Standardised difference (%)				
Prior heart failure hospitalisation, n (%)				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes				
Standardised difference (%)	[redacted]		[redacted]	
6-MWT, m	[redacted]	[redacted]	[redacted]	[redacted]
n				
Mean (SD)	[redacted]		[redacted]	
Standardised difference (%)				

Parameter	Before stabilised IPTW		After stabilised IPTW	
	Vutrisiran Monotherapy (N=196)	Tafamidis Monotherapy (N=129)	Vutrisiran Monotherapy	Tafamidis Monotherapy
***KCCQ-OS score**	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
KCCQ-FTT score	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
KCCQ-PFS score	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
Average peal longitudinal strain, %				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]		[redacted]	
Standardised difference (%)				
Mean LV wall thickness, cm	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
LV ejection fraction, %	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
Interventricular wall thickness, cm				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)				
Standardised difference (%)	[redacted]		[redacted]	
***Log-transformed Troponin I**	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
***Log-transformed NT-proBNP**	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]	
Mean (SD)				
Standardised difference (%)				
PND score, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
0				
1				
2	[redacted]		[redacted]	
Standardised difference (%)				
mBMI, kg/m^2 x g/L	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Before stabilised IPTW		After stabilised IPTW	
	Vutrisiran Monotherapy (N=196)	Tafamidis Monotherapy (N=129)	Vutrisiran Monotherapy	Tafamidis Monotherapy
n Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
eGFR, mL/min/1.73m^2	[redacted]		[redacted]	
n Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
Time from diagnosis to treatment initiation, years				
n	[redacted]		[redacted]	
Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
Serum TTR levels, mg/L	[redacted]		[redacted]	
n Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
Implanted cardiac defibrillator, n (%)				
No Yes	[redacted]		[redacted]	
Standardised difference (%)	[redacted]		[redacted]	
Permanent pacemaker, n (%)	[redacted]		[redacted]	
No Yes	[redacted]		[redacted]	
Standardised difference (%)				
Diastolic blood pressure, mmHg				
n	[redacted]		[redacted]	
Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
Systolic blood pressure, mmHg				
n	[redacted]		[redacted]	
Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
Heart rate, beats/min	[redacted]		[redacted]	
n Mean (SD) Standardised difference (%)	[redacted]		[redacted]	
History of agents acting on renin-angiotensin system, n (%)				
No Yes	[redacted]		[redacted]	
Standardised difference (%)	[redacted]		[redacted]	

Parameter	Before stabilised IPTW		After stabilised IPTW	
	Vutrisiran Monotherapy (N=196)	Tafamidis Monotherapy (N=129)	Vutrisiran Monotherapy	Tafamidis Monotherapy
History of beta-blockers, n (%)				
No				
Yes				
Standardised difference (%)				
History of diuretics, n (%)				
No				
Yes				
Standardised difference (%)				
History of antithrombotic agents, n (%)				
No				
Yes				
Standardised difference (%)				

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; IPTW, inverse probability of treatment weighting; KCCQ-FTT, Kansas City Cardiomyopathy Questionnaire – Functional Status Subscale; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; KCCQ-PFS, Kansas City Cardiomyopathy Questionnaire – Physical Functioning Subscale; LV, left ventricular; mBMI, modified body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin; US, United States; wtATTR, wild-type transthyretin amyloidosis. *Indicates a high priority adjustment factor. Source: Alnylam, data on file

To further account for remaining differences in key baseline patient characteristics after propensity score adjustment, the statistical models used to estimate differences between treatment groups all included log-transformed NT-proBNP and log-transformed troponin I concentrations and baseline 6-MWT distance as covariates; the statistical model for estimating differences in NYHA class change also included baseline NYHA class as a covariate, while the statistical model for estimating differences in EQ-5D-5L index score change included baseline EQ-5D-5L index score and a treatment-by-visit interaction term. Patients were not censored at tafamidis drop-in. Sensitivity analyses were conducted without inclusion of log-transformed NT-proBNP and log-transformed troponin I concentrations and baseline 6-MWT distance as covariates in the statistical models, and additional sensitivity analyses were conducted with censoring at tafamidis drop-in. The results of these sensitivity analyses were largely consistent with those of the main analyses as reported in Section 2.6.10 of the Company Submission.

b. Please explain how the IPTW approach (section 2.6.10 in company submission) used by the company when comparing vutrisiran and tafamidis is expected to produce more valid results for decision making than a MAIC, given that the differences between the HELIOS-B vutrisiran monotherapy arm and the HELIOS-B 'placebo patients on background tafamidis' at baseline appear no more comparable than the unmatched arms from HELIOS-B and ATTR-ACT.

As described in Section 2.10 of the Company Submission and alluded to above in the response to A13, during the period between the ATTR-ACT and HELIOS-B trials, the management of ATTR-CM has evolved substantially, in such a way that an unbiased MAIC between vutrisiran monotherapy in HELIOS-B and tafamidis in ATTR-ACT is infeasible.

Additionally, as noted in the response to A12, the infeasibility of an unbiased MAIC is supported by a statement by clinical experts at the NAC.[13]

Key changes in the management of ATTR-CM in the time since the ATTR-ACT trial include:

- *Earlier diagnosis, resulting in improved health at the time of ATTR-CM diagnosis*
    - In recent years, patients with ATTR-CM have tended to be diagnosed earlier, with less severe disease, due to increased disease awareness within the clinician community and improved diagnostic techniques (e.g., more widespread availability of technetium scintigraphy as a non-invasive alternative to cardiac biopsy).[14,15] Accordingly, patients in the ATTR-ACT trial had more severe disease at baseline compared to patients in HELIOS-B, and these differences could not fully be resolved in a MAIC (discussed further below).
- *Advances in background supportive care, potentially modifying the effects of ATTR-CM treatments*
    - Advances in general management of heart failure have improved the baseline prognosis of patients with ATTR-CM in a way that may modify the magnitude of effect of an active disease-modifying treatment
    - This potential effect modification cannot be accounted for in a MAIC, due to the unavailability of full information on concomitant medication use in ATTR-ACT (to inform propensity score adjustment). Moreover, even if detailed data on concomitant medication use were available from ATTR-ACT, certain background therapies used in HELIOS-B may not have even been considered for use in patients in ATTR-ACT trial, and this would have presented an additional barrier to propensity score adjustment in a MAIC. For example, a substantial proportion of patients in HELIOS-B used SGLT2 inhibitors concomitantly (described in response to Clarification question A2); however, concomitant use of these agents in ATTR-ACT is unlikely, as SGLT2 inhibitors received European Medicines Association (EMA) and US Food and Drug Administration (FDA) approval for treating heart failure in 2020 (after ATTR-ACT concluded).[16,17]

As a result of these changes in the management of ATTR-CM, two key issues arise that limit the potential for an unbiased MAIC. First, as demonstrated in Section 2.10 of the Company Submission, even after propensity score adjustment, there are still key differences between patients in the vutrisiran monotherapy group in HELIOS-B and the ATTR-ACT population – namely, differences in race, geographic region, troponin I levels, global longitudinal strain, left ventricular ejection fraction (LVEF), modified body mass index (mBMI), and percentage of patients with diabetes. Among these factors, troponin I, global longitudinal strain, LVEF, and mBMI have all been shown to have statistically significant associations with mortality risk in patients with ATTR-CM,[18-20] and similarly, the presence of diabetes is understood to increase the risk of morbidity and mortality in patients with heart disease.[21] In contrast, while baseline differences exist between the vutrisiran monotherapy and tafamidis monotherapy groups within HELIOS-B, these differences were largely resolvable via propensity score adjustment. As a result, after stabilised IPTW, these two groups within HELIOS-B were well-balanced for all high-priority adjustment factors, as discussed in the company's response to question A14, part a.

Beyond differences in variables for which data are available, another limitation of the MAIC approach relates to a key variable for which full data are not available – use of concomitant supportive care therapies. As discussed, the expected substantial differences between the HELIOS-B and ATTR-ACT populations in terms of supportive care medication use cannot be adjusted for due to the lack of complete data on concomitant medication use (and the potentially negligible use of certain concomitant medications, such as SGLT2 inhibitors) in

ATTR-ACT. On the other hand, rates of SGLT2 inhibitor use at baseline (vutrisiran monotherapy: [redacted]%; tafamidis monotherapy: [redacted]%) and SGLT2 inhibitor drop-in (vutrisiran monotherapy: [redacted]%; tafamidis monotherapy: [redacted]%) are known to be nearly identical between the vutrisiran monotherapy and tafamidis monotherapy groups within HELIOS- B, ensuring that differences in the use of these therapies do not confound results from the within-trial comparison of vutrisiran monotherapy and tafamidis monotherapy.

Table 18 in the Company Submission empirically illustrates the potential bias that would impact a MAIC of vutrisiran in HELIOS-B versus tafamidis in ATTR-ACT. The findings presented in this table indicate that even after propensity score adjustment, patients in the placebo group in ATTR-ACT had higher mortality risk, increased occurrence of CV events, and greater declines in functional exercise capacity (measured by 6-MWT) and HRQoL (measured by KCCQ-OS score) over the course of clinical trial follow-up, when compared with patients in the placebo group in HELIOS-B. This observation of substantially different outcomes between the propensity score-adjusted placebo arm of HELIOS-B and the placebo arm of ATTR-ACT is likely due to baseline parameters that remained significantly different after propensity score matching, and due to differences (which could not be adjusted for due to data availability) in supportive care practices between the time periods in which HELIOS-B and ATTR-ACT were conducted. These results further support the conclusion that an unbiased ITC is infeasible, and that a within-trial comparison between the vutrisiran monotherapy and tafamidis monotherapy groups in HELIOS-B is preferable for assessing the relative efficacy of these two treatments.

c. In Table 16 in the CS, it is stated that the IPTW arm level results are unadjusted. Can you confirm that the between-arm results in the same table are IPTW-adjusted?

We confirm that all between-arm (vutrisiran vs. tafamidis) results in Table 16 of the Company Submission are adjusted. The only unadjusted results included in Table 16 of the Company Submission were the following results provided separately for the vutrisiran monotherapy arm and tafamidis monotherapy arm:

- The number and percentage of patients with at least one event in the primary composite endpoint of ACM or recurrent CV events over up to 36 months.
- The number and percentage of patients with an ACM event over up to 42 months.
- The number of total recurrent CV events over up to 36 months.

Section B: Clarification on cost-effectiveness data

Comparators

B1. PRIORITY: While the EAG acknowledges that tafamidis monotherapy is the main comparator in this appraisal, the EAG considers that a comparison with best supportive care (BSC) should also be included in the model to inform NICE committee decision making. The comparison between vutrisiran monotherapy and BSC is particularly relevant to inform recommendations for the treatment of patients for whom tafamidis is contra-indicated or who do not achieve sufficient response with tafamidis.

Please provide an updated version of the electronic model with the flexibility to evaluate the cost-effectiveness of vutrisiran compared to BSC (i.e., the model should have the flexibility to select either tafamidis monotherapy or BSC), using clinical effectiveness evidence from the HELIOS-B monotherapy population (i.e., not on treatment with tafamidis at baseline), and please:

a) **Present base-case cost-effectiveness results for the comparison between vutrisiran monotherapy and BSC.**

b) **Report information for the per-cycle NYHA class transition probabilities for vutrisiran monotherapy and BSC (i.e., the equivalent to Table 24 in the CS for the evidence used in the comparison against BSC).**

c) **If the model is updated to more formally link the overall survival (OS) extrapolation and NYHA class progression (as per Question B2), please ensure that this functionality is also incorporated for the BSC comparison.**

d) **Include details of the assessment of alternative parametric extrapolation models for the BSC treatment group and rationale for preferred model selection.**

The following statement from [redacted] supports the Company Submission decision problem where the sole appropriate comparator is tafamidis and that BSC would not be an appropriate comparator for vutrisiran in this appraisal or supportive of committee decision-making.[13]

"*In the UK in 2024, there were approximately 1,500 patients living with ATTR-CM. Of these, all patients eligible for treatment (i.e. those patients in which the disease is not so advanced that they are not suitable for disease-modifying therapy) have been initiated with tafamidis since it became available in August 2024. Therefore, for any new disease-modifying treatment, tafamidis is the appropriate comparator treatment as the only disease-modifying therapy currently available.*

Amyloid deposit in ATTR-CM can manifest as heart failure as well as conduction system diseases; the use of supportive medications to manage any such manifestations is independent to the use of disease-modifying therapy to reduce the amyloid deposit formation.

As a chronic, progressive condition, patients who are currently treated with tafamidis do not have their therapy discontinued if disease progression occurs. There are no stopping criteria in place.

Tafamidis only has one contra-indication (hypersensitivity), which has a very low level of occurrence in our patient population, so in reality there are no patients for which we would consider 'best supportive care' as an alternative choice to disease modifying therapy currently.

Therefore, in our expert view, best supportive care is not an appropriate comparator to vutrisiran in the treatment of ATTR-CM."

Tafamidis only has one contra-indication (hypersensitivity), which has a very low level of occurrence in our patient population, and in real-world practice.[22] Thus, there are no patients for whom BSC would be considered as an alternative choice to tafamidis currently or to vutrisiran in the future.

Survival modelling approach

B2. PRIORITY: The company's models OS independently from the changes in NYHA class over the time horizon, thus omitting an important structural link between NHYA progression and mortality. The EAG is concerned that the lack of formal structural link creates potential inconsistencies in the assumptions used for NHYA transitions and mortality estimates, leading to potentially implausible and optimistic survival extrapolations requiring logical constraints to be imposed over a relatively short time period (e.g., mortality hazard capped

by general population hazards).This is also in contrast with previous NICE technology appraisals (TAs) of tafamidis in ATTR-CM (TA696 andTA984), where OS was modelled using a relative survival approach which combines general population lifetable risks with an additional excess risk of disease-specific mortality associated with ATTR-CM. The economic model then combined all-cause HRs for each NYHA class with the overall NYHA-independent excess mortality risks to estimate the distribution of excess mortality deaths across the NYHA states in each cycle.

a) Please contrast the survival modelling approach taken by the company in the current appraisal with the approach taken in TA696/TA984.

In the NICE technology appraisal of tafamidis in ATTR-CM (TA696 and TA984), overall survival in the economic model was estimated based on parametric survival models fitted to survival data from the ATTR-ACT trial using an excess hazard modelling approach, which directly incorporated general background mortality into the modelling process. A survival model derived from all patients regardless of NYHA class was preferred over a NYHA-specific survival model, as it required estimation of fewer direct parameters (for the NYHA-specific risk of mortality) and indirect parameters (for NYHA state transitions) that would affect the precision of the overall survival estimate. Within the economic model, this NYHA class-independent survival model was used to compute the overall probability of death within each model cycle, conditional upon being alive at the start of the model cycle, and this probability was converted to a total number of deaths expected. The contribution of each NYHA class to this total number of deaths was then estimated, on the basis that this contribution would be proportional to the number of patients in the NYHA class at the start of the cycle and the relative hazard of mortality in that class.

In the current submission for vutrisiran in ATTR-CM, the company adopted the standard survival modelling approach by modelling ACM hazard directly and incorporating general background mortality (ONS life tables) to cap survival in the economic model. For the relative risk of death by NYHA class, an approach similar to the one used in the appraisal of tafamidis was used. That is, a survival model derived from all patients regardless of NYHA class was preferred over a NYHA-specific survival model. Within the economic model, the probability of death within each model cycle, conditional upon being alive at the start of that cycle, was computed using this NYHA class-independent survival model and converted to a total number of deaths expected. The contribution of each NYHA class to this total number of deaths is then proportional to the number of patients in the NYHA class at the start of the cycle and the relative hazard of mortality in that class.

b) Please comment on the rationale and implications of deviating from the approach taken in TA696/TA984.

Both TA696/TA984 and the current submission incorporate UK-specific ACM in survival modelling, but the two approaches differ slightly due to data maturity constraints.

The excess hazard modelling approach considered in TA696/TA984 prevents all-cause hazard rates from dropping below the general background mortality rate, thus anchoring the long-term survival extrapolation. Nonetheless, regarding this type of approach, NICE DSU TSD 21 notes that "*a cause-specific approach rather than an all-cause approach will*

decrease the number of events, impacting on uncertainty. Given that in most trials the disease of interest will likely dominate the short-term (duration of trial follow-up) all-cause background mortality, this is unlikely to have a large impact for the short-term fit." Thus, although suitable for modelling survival data from ATTR-ACT, excess hazard modelling presents severe feasibility limitations that complicate use of this approach to model the IPTW weighted HELIOS-B OS data. The following challenges exist in applying excess hazard modelling to the weighted HELIOS-B data:

- The overall survival data from HELIOS-B involve a smaller number of mortality events, due to the less severely affected, contemporary patient population recruited in this trial, unlike in ATTR-ACT (TA984), where the larger number of mortality events in the more severely affected historical ATTR-CM population allowed for a better exploration of survival models.
- Relatedly, not all standard parametric models recommended by NICE DSU TSD 14 could be reliably fitted using excess hazard modelling due to convergence issues. Only two models (Weibull and Log-normal) converged for the vutrisiran monotherapy arm, and four models (Weibull, Gamma, Log-logistic, and Log-normal) converged for tafamidis monotherapy, reinforcing the instability of excess hazard modelling with this dataset.
- The failure of most models to converge conflicts with the recommendation in TSD 14 to fit multiple parametric models to identify the best extrapolation.

Additionally, there were difficulties in selecting the best excess hazard model from among those parametric models that did converge, as the fitted excess hazard models failed to provide reliable hazard estimates. The modelled all-cause and excess hazards for the vutrisiran monotherapy and tafamidis monotherapy arms are presented in Figure 9 and Figure 10. For the vutrisiran monotherapy arm, both fitted models estimated a lower mortality rate due to the condition compared to the general background mortality from time 0, which is deemed clinically implausible. Additionally, fitted models did not estimate the shape of the observed hazard (i.e., they failed to reflect the trend of hazard increasing initially and then decreasing). For the tafamidis monotherapy arm, none of the fitted distributions estimated a convergence to the background mortality rate at 8 years, which is contradicted by clinical expert feedback in the Structured Expert Elicitation (SEE) exercise.

Figure 9 Modelled all-cause (solid line) and excess mortality hazard (dashed line) for the vutrisiran monotherapy arm.

Note: The black dashed line represents the age- and gender-matched background mortality.

Figure 10 Modelled all-cause (solid line) and excess mortality hazard (dashed line) for the tafamidis monotherapy arm.

Note: The black dashed line represents the age- and gender-matched background mortality.

The fitted survival distributions for both arms based on the excess hazard modelling approach are shown in Figure 11.

Figure 11 Modelled survival using excess hazard approach

As excess hazard modelling based on the HELIOS-B dataset has important limitations, the approach used in the company's submission ensures robust survival extrapolation without the use of excess hazard modelling. Instead of using an excess hazard model with significant reliability concerns, the company applied standard all-cause survival modelling as per NICE TSD 14 while incorporating UK general population mortality estimates to cap survival and thus ensure clinically plausible survival projections. This approach prevents unrealistic overestimation of long-term survival (via capping) while avoiding the instability introduced by forcing an excess hazard model onto a dataset involving a smaller number of mortality events. To further strengthen the credibility of the approach used in the current submission, the company conducted a SEE exercise, ensuring that the chosen method is aligned with expert expectations and clinical plausibility in ATTR-CM as modelled. The SEE process mitigates concerns raised in TA984, where the EAG highlighted the importance of formal expert validation for long-term survival projections.

In summary, given the convergence issues, the estimated hazard rates lacking clinical plausibility, and additional challenges in applying excess hazard modelling robustly, the company used standard parametric survival models with UK general population mortality applied to cap survival. Additionally, to address concerns raised in TA984, the company conducted a SEE exercise to validate the survival extrapolation approach in a formal and robust manner. This approach ensures that the selected extrapolation is clinically appropriate and aligned with expert expectations.

c) Please consider providing additional analyses where you more formally link the OS extrapolation to the NYHA states.

Competing risks or multi-state survival analysis and modelling could formally link overall survival extrapolation to NYHA class transitions; however, this approach is not advisable for the following reasons:

- Trial data are limited, with the relevant subset of the trial dataset including only 325 patients across both arms chosen for the cost-effectiveness analysis, with a highly skewed distribution of NYHA class at baseline (80.3% in NYHA class II, 11.7% in

NYHA class I, 8% in NYHA class III, and no patients in NYHA class IV). The sparsity of data in NYHA classes I and III and the absence of class IV overall survival data at baseline, together with the relatively small number of mortality events in HELIOS-B, means that there were insufficient data to reliably derive NYHA-specific survival estimates with competing risks for NYHA transitions.

- TA696/TA984 did not adopt a competing risk or multi-state survival analysis approach.[23] Instead, a "survival model derived from all patients unconditional upon NYHA class was preferred over a NYHA-specific survival model, as it requires estimation of fewer direct parameters (for the NYHA-specific risk of mortality) and indirect parameters (for NYHA state transition) that would affect the precision of the overall survival estimate".

B3. PRIORITY: The use of tafamidis "drop-in" in the vutrisiran monotherapy may have potentially biased health outcomes for the comparison with tafamidis monotherapy considered in the economic model. Please justify why the vutrisiran monotherapy treatment effectiveness estimates used in the model were not formally adjusted for the potential confounding introduced by tafamidis "drop-in" use, and consider presenting additional analyses exploring alternative adjustment approaches (e.g., treatment switching adjustments).

Tafamidis drop-in has only a small impact on patients in the vutrisiran monotherapy group, considering the limited number of patients in whom drop-in occurred and the amount of time spent on study after drop-in by those patients. Of 196 patients, 45 (23%) had tafamidis drop-in during the study period, with a median time to drop-in from baseline of 17.7 months (range: 6.4, 39.1 months; mean 20.8 months). As noted in Section 2.3.1 of the Company Submission,

[redacted] In cases in which the reason for drop-in was categorised as "potential clinical benefit", patients were not progressing in disease, but rather, the decision to initiate treatment with tafamidis was based on a lack of expectation of potential negative repercussions from doing so, with potential for clinical benefit. Note that during HELIOS-B, tafamidis received regulatory approval in multiple countries and regions such as Canada,131 Australia,132 and the EU.33,133 Within these regions, which contained many HELIOS-B trial sites,130 the regulatory approval of tafamidis, resulting in the availability of a new, potentially beneficial treatment option, likely contributed to the occurrence of tafamidis drop-in for "potential clinical benefit" during the trial.

Of note, tafamidis drop-in rates were similar in the vutrisiran and placebo groups within the monotherapy population; however, drop-in use for "potential clinical benefit" (i.e., not in situations where patients were progressing in disease) was more common in vutrisiran-treated patients, while drop-in use for disease progression was more common in placebo-administered patients

Accordingly, for the vutrisiran monotherapy group, negligible differences in survival curves with and without censoring for tafamidis drop-in were noted (Figure 12). Given that drop-in did not substantially impact patient outcomes, the vutrisiran monotherapy treatment effectiveness estimates used in the model were not formally adjusted for tafamidis drop-in.

Figure 12 Impact of tafamidis drop-in on survival in the vutrisiran monotherapy group

Moreover, alternative adjustment approaches to account for tafamidis drop-in (e.g., treatment switching adjustments) were not feasible because limited data were available for tafamidis drop-ins (only 45 cases).

B4. In Section 3.3.4.1.1 of the CS (page 94), the company describes two alternative approaches to quantitatively explore the potential impact of differential timing of treatment initiation with tafamidis and vutrisiran monotherapy on the survival estimates.

a) Please provide for the analysis whereby survival in the vutrisiran monotherapy arm is based on survival in the vutrisiran monotherapy group, with the KM survival curve “shifted left” by 11.3 months to align with the median duration of treatment with tafamidis at HELIOS-B baseline in the tafamidis monotherapy group, and estimating survival by considering vital status data only in the

proportion of patients alive at 11.3 months from HELIOS-B baseline in the vutrisiran monotherapy arm:

i. The KM curves for the vutrisiran and tafamidis monotherapy treatment groups (including numbers at risk) and the;

ii. Corresponding HR for vutrisiran vs. tafamidis (with 95% CIs).

b) Please consider providing further evidence to support the claim in Table 51 of the CS that the comparison between vutrisiran and tafamidis in HELIOS-B may be biased by tafamidis having been received before the start of the trial. We suggest supplying the following, where feasible:

i. Plots of 6-MWT results with a similar 11.3-month shift.

ii. Hazard ratios (or odds ratios) and mean differences comparing vutrisiran monotherapy and tafamidis monotherapy for the primary outcome, ACM, change in NYHA class (stable/improved), and 6-MWT, accounting for this time shift

To address the issue of different treatment initiation times for the vutrisiran and tafamidis monotherapy arms and the potential impact of this difference on mortality estimates, two alternative approaches that used data from HELIOS-B were explored. The first approach explored involved basing survival in the tafamidis monotherapy arm on the survival of patients in the HELIOS-B placebo monotherapy group who initiated tafamidis treatment during the trial (i.e., tafamidis drop-in). In this approach, the vital status of these patients could be monitored from the time of tafamidis initiation to inform survival estimates on tafamidis monotherapy. This approach was determined to be infeasible, as only 41 patients in the HELIOS-B placebo monotherapy group initiated tafamidis, and they did so at a median of 17.0 months (range: 1.5, 33.8) after HELIOS-B baseline, such that follow-up after drop-in in these patients was limited.

The second approach that was explored involved basing survival in the vutrisiran monotherapy arm of the model on survival data from the vutrisiran monotherapy group of HELIOS-B, with the KM survival curve “shifted left” by 11.3 months. This approach was determined to be infeasible because it resulted in limited follow-up time for patients in the vutrisiran arm (i.e., as little as 22 months in some patients). Furthermore, the company believes this approach has additional, important methodological limitations that make its use inappropriate, as follows:

- Uniformly shifting outcome data leftward by 11.3 months for the HELIOS-B vutrisiran monotherapy group would only address the bias introduced by the difference in treatment initiation times if all patients in the tafamidis monotherapy group had exactly 11.3 months of pre-baseline tafamidis exposure. This is the case because the underlying assumption in this approach is that the health status of patients on tafamidis at HELIOS-B baseline reflects the effects of a uniform 11.3 months of pre-baseline exposure across all patients (such that this pre-baseline exposure can be replicated in the vutrisiran monotherapy arm by considering outcome data only after

all patients have had 11.3 months of exposure to vutrisiran). However, the 11.3 months of pre-baseline tafamidis exposure among patients in the tafamidis monotherapy group in HELIOS-B is a median duration of pre-baseline exposure (i.e., exposure ranged from 1.1 to 65.5 months). Thus, the underlying assumption that patients' baseline health status in the tafamidis monotherapy group reflected exactly 11.3 months of pre-baseline tafamidis exposure for all patients would underestimate/overestimate the effect of tafamidis for each patient, depending on whether that patient's true exposure to tafamidis in the pre-baseline period was less than or more than 11.3 months. In this way, the approach of shifting outcome data leftward for the HELIOS-B vutrisiran monotherapy arm would not resolve the bias it was intended to resolve and would introduce new biases into the estimation of relative treatment effects for vutrisiran versus tafamidis.

- If treatment effects for patients in the vutrisiran monotherapy arm were to be considered only starting at 11.3 months after HELIOS-B baseline, propensity score weights based on patient characteristics at month 11.3 would have to be reconstructed for patients in this group to allow propensity score-adjusted comparison with the tafamidis monotherapy group. Because there were no scheduled study visits for 11.3 months, data from the last available visit before that timepoint (either month 6 or 9, depending on the patient characteristic of interest) would have to be used. This is a major limitation given that the data on baseline characteristics for the patients in the tafamidis monotherapy arm are more precise (most measurements were made the same day as randomisation), whereas the corresponding data for patients in the vutrisiran monotherapy arm would have to be taken from an assortment of different visits and assumed to be applicable to the 11.3-month time point.

Transition probabilities between NYHA health states

B5. PRIORITY: Please clarify whether the transition probabilities between NYHA health states applied in the economic model were adjusted using IPTW (similarly to what was done for all-cause mortality). If an adjustment was performed but is different from what was done for all-cause mortality, please describe the approach taken to perform this adjustment, reporting:

a) **Statistical method selected to perform the adjustment and how was this selected;**

b) **Rationale for variable selection for baseline characteristics IPTW adjustment;**

c) **Assessment of patient baseline characteristics balance across treatment groups before and after IPTW adjustment;**

d) **Standard mean difference comparisons before and after IPTW adjustment for each variable;**

The company confirms that transition probabilities between NYHA health states applied in the economic model were adjusted using the same IPTW model that was used for ACM. The approach taken for IPTW and sensitivity analyses are detailed in the company's response to question A14.

Transient cardiovascular events

B6. Please clarify which subpopulation of HELIOS-B was used to inform the per-cycle incidence of transient events in NYHA classes (i.e., is this the same IPTW adjusted population that was used to inform the all-cause mortality inputs and justify its selection.

Treatment-independent estimates were used to inform the per-cycle incidence of transient events by NYHA class. Incidence estimates were obtained based on data from the pooled, IPTW-weighted population of vutrisiran monotherapy arm and patients in the tafamidis monotherapy arm. In aggregate, this was the same IPTW-adjusted population that was used to inform ACM estimates. A pooled approach was chosen over using treatment-specific estimates because stratifying by both treatment and NYHA class resulted in very low event counts for some subgroups, leading to unreliable estimates with limited face validity.

Treatment discontinuation from non-fatal causes

B7. PRIORITY: The EAG is concerned that the company's approach to modelling treatment discontinuation from non-fatal causes for tafamidis monotherapy (i.e., assuming the same treatment discontinuation from non-fatal causes as for vutrisiran monotherapy) is not consistent with assuming treatment specific differences in health outcomes (e.g., all cause mortality and NYHA class transitions). Please update the electronic model with functionality to perform a scenario analysis whereby the non-fatal treatment discontinuation curve for tafamidis is informed evidence from the double-blind period of HELIOS-B for patients on treatment with tafamidis only at baseline, and present the results of this analysis.

Tafamidis discontinuation was not systematically evaluated as an outcome in HELIOS-B, as the study was not intended to assess the efficacy or safety of tafamidis. Thus, in the absence of the required data, it is not feasible to model the requested scenario in which the non-fatal treatment discontinuation curve for tafamidis is informed by evidence on tafamidis discontinuation in the tafamidis monotherapy group during the double-blind period of HELIOS-B. For this same reason, non-fatal discontinuation rates for tafamidis monotherapy are assumed to be the same as for vutrisiran monotherapy in the economic model.

Adverse events

B8. Please justify why adverse events were modelled as one-off impacts on costs and health-related quality of life, given the chronic nature of the treatments under comparison.

AEs were modelled as one-off impacts on costs and HRQoL in the first cycle rather than being applied per cycle to reflect observed treatment-emergent serious AEs in HELIOS-B. Clinical data indicate that AEs tend to cluster early in the course of treatment and become less frequent as patients continue therapy, rather than occurring consistently in each cycle. Applying a constant per-cycle rate could lead to over-representation of AEs and an overestimation of their impact on costs and quality of life, particularly when their long-term effects remain uncertain. Additionally, this approach aligns with previous NICE appraisals, including tafamidis (TA696/TA984), ensuring consistency in evaluating treatments for ATTR-CM. Given the lack of evidence supporting the persistence of AEs over time, modelling them as one-time events provides a more accurate representation of their clinical and economic impact and ensures that the methodology remains aligned with standard health economic analysis methods, as well as with past appraisals in ATTR-CM.

Health-related Quality of Life

B9. PRIORITY: The company capped health state utility values to account for the fact that mean EQ-5D-3L utility for NYHA I estimated from HELIOS-B data exceeded that of the UK age- and sex- matched general population corresponding to the model cohort at baseline. Furthermore, the company applied to all patients in NYHA class I and II age- and sex matched utility decrements (i.e., an additive utility age and sex adjustment) in the first cycle of every year in the model. The company does not provide a justification to support i) the use of an additive, rather than a multiplicative approach which is generally preferred [24], and ii) not applying utility adjustments at every cycle in the model.

a. Please justify the approach taken to adjust for general population utility, particularly in terms of the use of an additive adjustment method and intermittent cycle adjustment.

The company acknowledges EAG's preference for a multiplicative approach to age-related utility adjustments, as outlined in NICE TSD 12, but maintains that an additive approach is more appropriate in this model. To satisfy the request, scenario analyses using the multiplicative approach have been provided in the response to clarification question B9b.

b. Update the cost-effectiveness model with the functionality to perform a scenario analysis using a multiplicative approach to adjust for age-related

utility in the general population, with adjustments applied every cycle and without capping utility health state values by the UK age- and sex- matched general population. Please present results for this scenario analysis.

As per the request by EAG, the following scenario analyses were conducted:

- Additive approach (per-cycle)
    - Utility decrements for age- and sex-matched general population are applied via subtraction at every model cycle (e.g., every 3 months), rather than annually.
    - No capping of health state utilities at the UK general population norm.
- Multiplicative approach (per-cycle)
    - Age-related utility adjustments are applied multiplicatively in each cycle, allowing baseline utilities to reduce proportionally.
    - No capping of health state utilities at the UK general population norm.

Results of these scenario analyses are presented in Table 17.

Table 17: Results of EAG-requested scenario analyses

Utility Adjustment Approach	Capping NYHA I Utility	Incremental Costs	Incremental QALYs	ICER
Additive (base case)	**Yes (base case)**	[redacted]	**1.19**	[redacted]
Additive	No	[redacted]	[redacted]	[redacted]
Multiplicative	Yes	[redacted]	[redacted]	[redacted]
Multiplicative	No	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life years.

B10. In Section B.3.4.1 of the CS, the company briefly describes the linear mixed-effects model (LMEM) that was fitted to EQ-5D-3L utilities (mapped from EQ-5D-5L data) from the HELIOS-B ITT population to derive health state and serious adverse events utility estimates. The company does not, however, provide sufficient detail for the EAG to critique the appropriateness of the statistical model used to derive the utility estimates described above.

a. Please justify the preferred utility regression model specification, particularly the selection of regression covariates and how was model fit assessed, and state how missing data was handled

A base LMEM for estimating health state and SAE utility estimates was assumed to include the following covariates:

- EQ5D-3L at baseline
- Study visit
- Disease staging (NYHA) at each study visit

- ATTR diagnosis at baseline
- Age (<75 years, ≥75 years) at baseline
- Sex

The following additional covariates were then investigated for inclusion:

- Disease staging (NYHA) at baseline

Separately, the potential to estimate treatment-dependent utilities was also investigated by including the following covariates along with those in the base LMEM:

- Treatment
- Treatment by baseline NYHA stage interaction
- Treatment by study visit interaction

The potential to estimate AE disutilities was also investigated. Each AE was first coded as a binary variable that indicated whether or not the event had occurred during the interval leading up to a given study visit (i.e., before that visit but after the preceding study visit). Coefficients for all of the following AEs could then be estimated, along with the covariates specified in the base LMEM:

- Atrial fibrillation
- Osteoarthritis
- Pneumonia
- Acute kidney injury
- Atrial flutter
- Ventricular tachycardia
- Syncope
- Chest pain
- Hyponatraemia
- Urinary retention

Model selection (based on AIC) indicated that the base LMEM (treatment-independent, excluding AEs) had the best model fit (Table 18). However, given the importance of estimating AE disutilities for the economic model, results for the LMEM including AEs (both treatment-dependent and treatment-independent) are presented.

In the intention-to-treat (ITT) dataset, the proportion of patients with available EQ-5D data was 99.2% at baseline, 89.9% at 12 months, 78.6% at 24 months, and 76.3% at 30 months. LMEMs were fitted to available measurements, assuming missing at random.

In the ITT dataset, data on NHYA class were missing in 0.04% of follow-up observations. Given the low proportion of missing data, as a post hoc imputation, we assumed that staging at any missing follow-up measurement was the same as at the most recent prior non-missing follow-up measurement (Last Observation Carried Forward). No data-missingness was seen for NYHA class or NAC stage at baseline.

Table 18 shows model fit statistics for LMEMs fitted to the ITT population of HELIOS-B. Fitted models include the base model and models of increasing complexity that add covariates for AEs, baseline NYHA, treatment, study visit, and/or interaction terms involving treatment and baseline NYHA class / study visit.

Table 18: Fit statistics for candidate LMEM models for generating utility estimates

Model	DF	AIC
Base	[redacted]	[redacted]
Base+ AEs	[redacted]	[redacted]
Base+ AEs + baseline NYHA	[redacted]	[redacted]
Base+ AEs + treatment	[redacted]	[redacted]
Base+ AEs + treatment + baseline NYHA	[redacted]	[redacted]
Base+ AEs + treatment + (treatment × study visit)	[redacted]	[redacted]
Base+ AEs + treatment + (treatment × baseline NYHA)	[redacted]	[redacted]

AE, adverse event; AIC, Akaike Information Criterion; DF, degrees of freedom, NYHA, New York Heart Association.

b. Please report the regression output (coefficients and corresponding 95% confidence intervals) for the LMEM used to derive utility values

The regression output (coefficients, standard error and corresponding 95% confidence intervals) for the LMEM used to derive utility values is presented in Table 19 Please note that the estimates presented in Table 13 of the Company Submission are marginal estimates, obtained by averaging over LMEM fitted values for each of the individuals within HELIOS-B, within each NYHA stage.

Table 19: LMEM model coefficients for the selected model (Base model + AEs, treatment-independent) fitted to the ITT population of HELIOS-B.

Covariate	Estimate	SE	t value	95% CI lower limit	95% CI upper limit
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study visit (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study visit (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study visit (Month 30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnosis (wtATTR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group (>=75 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial flutter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Estimates represent the change in EQ5D-3L for a unit change in the covariate

AE, adverse events; CI, confidence interval; EQ-5D-3L, EuroQol-5 Dimension-3-Level; ITT, intention to treat; LMEM, linear mixed-effects model; NYHA, New York Heart Association; SE, standard error; wtATTR-wild type transthyretin amyloidosis.

c. Please report if alternative model specifications were explored and comment on the robustness of the preferred utility regression model to any sensitivity analyses performed.

A variety of alternative model specifications were explored (see response to Clarification question B10, part a) A sensitivity analysis that excluded patients in the vutrisiran monotherapy arm with tafamidis drop-in was also performed; however, it had only a minimal impact on the utilities for each NYHA stage (Figure 13).

Figure 13 Marginal EQ-5D-3L values for the base-case LMEM and the sensitivity analysis excluding patients in the vutrisiran monotherapy arm who initiated tafamidis post-randomisation.

Values represent mean (95% CI) EQ5D-3L values. Results are presented by NYHA stage within the ITT population of HELIOS-B from the selected treatment-independent model.
EQ-5D-3L, EuroQol-5 Dimension-3-Level; NYHA, New York Heart Association.

d. Please comment on the appropriateness of using the HELIOS-B data to derive disutilities associated with specific serious adverse events (e.g., ventricular tachycardia), given the transient nature of these events

The company considered using AE disutilities from HELIOS-B whenever possible to be the most appropriate approach, given that patients from HELIOS-B represent the population of interest (i.e., contemporary patients with ATTR-CM). To reflect the potentially transient nature of AEs, the company assumed that disutilities due to AEs would impact utility assessments only at the next follow-up after the AE occurred. This was the only possible approach whilst using the HELIOS-B data, since utilities were only measured at discrete follow-up times. Depending on the duration of the AE and when it occurred in relation to the EQ-5D measurement, this approach may underestimate the disutility of the AE. However, the company believes that this limitation is outweighed by the value of using data from the population of interest. Additionally, this is likely a conservative assumption, given the higher rate of AEs in the tafamidis arm. Moreover, as an additional measure to ensure the appropriateness of AE disutility inputs, in cases where the HELIOS-B-derived utility for a

given AE lacked face validity, we sourced alternative disutilities from the literature (Table 36 of the Company Submission).

Severity modifier

B11. Please provide a brief description of the calculations performed to estimate proportional and absolute QALY shortfall, including the definition of standard of care and evidence sources used to inform the calculations.

QALY shortfall was calculated using mortality data from UK life tables and UK age- and sex-matched utility data from HSE 2014. To estimate QALYs in a general population cohort, assuming the entire cohort to be alive at the starting age (76 years) of patients that entered the model, the proportion of the cohort alive at the beginning of each year was calculated using mortality data obtained from the UK life table. The results were used to calculate the total LYs and (using age specific utilities based on HSE 2014) QALYs for the general population cohort, with half cycle correction and discounting applied.

For the ATTR-CM cohort, the standard of care was assumed to be tafamidis since it has been approved by NICE for reimbursement in the UK, and thus the QALYs for this cohort were estimated from the tafamidis monotherapy arm of the model. The resulting QALY estimate was subtracted from the QALYs calculated for the general UK population as described above to derive the absolute QALY shortfall. The proportional QALY shortfall was calculated by taking the ratio of the absolute QALY shortfall to the QALYs calculated for the general UK population. This method is consistent with the approach described in TSD 23 and University of York RShiny application for calculating QALY shortfall.

Uncertainty

B12. Please clarify how uncertainty was captured in the estimates of health state utility values used in the economic model. If not already included, please incorporate uncertainty in the regression outputs through the variance-covariance matrix in the economic model, and update the probabilistic analysis accordingly.

Uncertainty has been captured using one-way sensitivity analysis and probabilistic sensitivity analysis for the utility estimates. To account for deterministic uncertainty, a one-way sensitivity analysis was implemented in the model utilising the 95% confidence intervals (CIs) for the NYHA class-specific utilities, as calculated from the observed data in the HELIOS-B study. These CIs were used to set the upper and lower bounds of the parameters.

In the probabilistic sensitivity analysis, the Beta distribution was employed based on the mean and standard errors from the marginal estimates, with percentile matching applied (i.e., same random number used to generate probabilistic values of all four health state utilities), thus maintaining a clinically appropriate decreasing order from NYHA I to NYHA IV. The calculation of the marginal estimates is described in response to question B10b.

Section C: Textual clarification and additional points

Search strategies for the clinical effectiveness SLR

C1. Line 47 is missing from the update search of MEDLINE (table 20, page 39, Appendix B) for the clinical effectiveness SLR. Please provide this line showing how results were limited by date.

The requested information for Line 47 is provided below.

Search syntax and results	Search narrative
47 (2022* or 2023* or 2024* or 2025*).dt,dp,ed,ep,yr.	The search is limited to studies published in 2022, 2023, 2024, or 2025

Search strategies for the cost-effectiveness SLR

C2. Please confirm if the following databases (mentioned on page 10, Appendix E) were searched:

a) Database of Abstracts of Reviews of Effects (DARE) https://www.crd.york.ac.uk/CRDWeb/

b) HTA database https://www.crd.york.ac.uk/CRDWeb/

c) If these databases were searched, please provide the search strategies for both the original and the update searches.

We can confirm that the DARE and HTA databases were not searched. However, our search had no restrictions, making it comprehensive enough to capture relevant reviews. In addition, the company obtained up-to-date, comprehensive information on past HTAs to inform this HTA submission by directly searching individual HTA agency websites, as follows:

- National Institute for Health and Care Excellence (NICE)
- Canadian Agency for Drugs and Technologies in Health (CADTH) – now Canada's Drug Agency (CDA)
- Australian Pharmaceutical Benefits Advisory Committee (PBAC)
- Scottish Medicines Consortium (SMC)
- Haute Autorité de Santé (HAS)
- Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV)

C3. Please provide the full search strategy for the database NHS EED for the original and update searches. Currently a list of terms only has been provided (Table 6, page 26 and Table 13, page 31, Appendix E).

Thank you for highlighting this. The full search strategies for NHS EED for the original and updated searches are provided in Table 20 and Table 21.

Table 20: Original SLR Search Strategy: NHS EED (13 September 2023)

CRD (University of York) Platform: NHS EED (13 Sept 2023)		
Number	**Search Terms**	**Hits**
1	("Transthyretin amyloidosis with cardiomyopathy" OR "ATTR-CM" OR "cardiac amyloidosis") AND ("tafamidis" OR "patisiran" OR "vutrisiran" OR "eplontersen" OR "acoramidis")	0

Table 21: SLR Update Search Strategy: NHS EED (5 November 2024)

CRD (University of York) Platform: NHS EED (5 Nov 2024)		
Number	**Search Terms**	**Hits**
1	("Transthyretin amyloidosis with cardiomyopathy" OR "ATTR-CM" OR "cardiac amyloidosis") AND ("tafamidis" OR "patisiran" OR "vutrisiran" OR "eplontersen" OR "acoramidis")	0

C4. Please clarify the source (with a reference where available) of the study design search terms used to limit to economic evaluations in the following tables in Appendix E:

a) Table 3, line 10, page 24-25

b) Table 4, line 10, page 25-26

c) Table 10, line 10, page 29

d) Table 11, line 10, page 30

For **Table 4 and Table 11 - line 10** (search strategy for Medline in Process through PubMed platform), we referred to the CDA/CADTH search filters: **Economic Evaluations & Models – MEDLINE.** [25]

For Table 3 and Table 10 - line 10 (search strategy for Embase platform), we referred to the CDA/CADTH and SIGN search filters to develop a comprehensive search strategy.[25,26]

C5. Please confirm if the following Emtree terms were searched in the strategies presented in Table 3, page 24, and Table 10, page 29, Appendix E:

a) hereditary transthyretin amyloidosis/

b) senile systemic amyloidosis/

c) familial amyloid cardiomyopathy/

d) familial amyloidosis/5

We confirm that the following Emtree terms were used in the search strategy, though not exactly as written; they were applied in a modified manner:

a) **Hereditary transthyretin amyloidosis/** – The term "hereditary amyloid*" was combined with the Boolean operator "OR" with the term "transthyretin amyloidosis."
b) **Senile systemic amyloidosis/** – The term "senile amyloid*" was combined with the Boolean operator "OR" with the term "systemic amyloidosis."
c) **Familial amyloid cardiomyopathy/** – The term "familial amyloid*" was combined with the Boolean operator "OR" with the term "cardiomyopathy."
d) **Familial amyloidosis/5** – The term "familial amyloid*" was used (line 4 in table 3 and table 10).

C6. Please clarify if MeSH headings were searched in the strategies presented in Table 3, page 24, and Table 10, page 29, Appendix E.

We confirm the use of terms appropriate for the Embase database, as the search was conducted through that platform, where the alternatives to MeSH headings are '/syn' for focusing on synonyms and '/exp' for expanding to related concepts, similar to MeSH terms. These operators were used in the strategies presented in Table 3 (page 24) and Table 10 (page 29) of Appendix E.

Missing material

C7. Please provide appendices of the CSR.

CSR appendices have been provided.

Confidentiality

C8. Some statistical methods and some data for HELIOS-B are marked as confidential (e.g. Table 10, 13, 14 and Section 2.4.2). As HELIOS-B has been published we do not understand the reasons for keeping this material confidential. Please either:

a. Provide a rationale for retaining confidentiality in line with current NICE guidance.

b. Or confirm which material can have confidentiality marking removed

With reference to the confidentiality request in the clarification questions and communication from NICE dated March 3rd, 2025, please see below the changes implemented by Alnylam.

Redactions to the following have been removed:

- Statistical analysis methods for primary and secondary endpoints in HELIOS-B (pages 50-54, Section 2.4 of company evidence submission), as well as any other data on methods used to conduct a study or to analyse data from a study.
- Data derived from clinical opinion and assumptions (e.g. feedback from experts on caregiver requirements, as was used to inform the model, pages 111,130 and 131)
- Baseline and patient characteristics of whole trial population informing the company's decision problem (e.g. patient disposition in HELIOS-B, p47-48 of company evidence submission)
- QALY output from the company's economic model

The following data have been kept redacted as they are commercial-in-confidence – the company is not intending to publish these data, and disclosure could impact the company commercially given the competitive nature of the data. The company requests dialogue with the NICE team supporting the appraisal to discuss potential options to support transparency during the committee meeting as needed:

- Summary of results from the IPTW-adjusted comparison of vutrisiran and tafamidis monotherapy arms in HELIOS-B (p70 of company evidence submission)
- KM survival curves and associated hazard rates from the IPTW-adjusted vutrisiran and tafamidis monotherapy arms in HELIOS-B (p 93, 95, 96, 97, 98, and 99 of company evidence submission)
- KM curves for treatment discontinuation and associated hazard rates in the vutrisiran monotherapy arm in HELIOS-B (p101-102 of company evidence submission)
- Changes in serum TTR levels following discontinuation of vutrisiran in HELIOS-B (p103-104 of company evidence submission)
- Usage frequencies of background therapies in the vutrisiran and tafamidis monotherapy arms in HELIOS-B (p113-114 of company evidence submission)
- Utility data (p107-108 of company evidence submission)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Amyloidosis UK (formerly UK ATTR Amyloidosis Patients Association or UKATPA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a small national charity who aim to improve the lives of anyone affected by amyloidosis in the UK by providing information, support and access to a community of other living with the disease. To the best of our knowledge, we are the only charity in the UK dedicated solely to supporting patients living with amyloidosis. Our board of trustees consists entirely of individuals living with amyloidosis, ensuring patient-led insight in all our work. We are funded through a combination of donations and industry grants. While we are not a membership organisation, we currently maintain a mailing list of approximately 330 individuals.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Alnylam £15000.00 Provide Educational grant to support Amyloidosis UK with their “Rebrand & Communications Development Project".

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information about the experiences of patients and caregivers in the following ways: • Our board of trustees comprises only amyloidosis patients, including two ATTR-CM patients, therefor the patient experience is always at the heart of our work. • Speaking directly to patients about their lived experience of cardiac ATTR amyloidosis. • Observing the common problems & questions people seek our support with. • Engaging with healthcare professionals who have a wealth of experience in caring for patients with ATTR amyloidosis including staff from the National Amyloidosis Centre, and members of our advisory group.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Cardiac ATTR amyloidosis (ATTR-CM) progressive, debilitating and ultimately fatal disease that affects every aspect of a patient's life. It causes loss of mobility and independence, leading to a poor quality of life for both sufferers and their carers. Patients with ATTR-CM can experience a wide range of multisystemic symptoms and severely delayed or misdiagnoses are common, meaning patients often live with these symptoms for years without appropriate treatment. Below is a description of some of the impacts of living with ATTR-CM **as expressed by patients:** **Severely reduced exercise/exertion tolerance** Many patients struggle to walk up the stairs in their homes. One patient said he needs to rest after climbing every 2 to 3 steps, so it can take a long time, sometimes resorting to using his hands and knees to 'crawl' up the stairs. Many patients have to simply avoid walking up even small inclines. This can affect every aspect of life from work, shopping, visiting family and friends, to holidays. Another patient described the feeling of not being able to join in with the dancing at a family party, saying how this made him feel frustrated and upset. *[Patients with ATTR-CM] reported low energy, malaise, and "heaviness" in their limbs, 'twitching, clumsiness, buckling knees, and trouble maintaining their balance*.[1] 1. Rintell, D., Heath, D., Braga Mendendez, F., Cross, E., Cross, T., Knobel, V., Gagnon, B., Turtle, C., Cohen, A., Kalmykov, E. and Fox, J. (2021). Patient and family experience with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) amyloidosis: results of two focus groups. *Orphanet Journal of Rare Diseases*, 16(1). doi:https://doi.org/10.1186/s13023-021-01706-7. **Fatigue** Fatigue is very common among ATTR-CM patients. One patient described how he struggles to walk 300 to 400 yards from his car to his desk at work and is fatigued by the time he gets to his desk. Fatigue has a substantial impact on every aspect of life, including work, social and family life. It frequently interferes with the patient's ability to take part in everyday tasks or activities that previously brought enjoyment. Many ATTR-CM patients are forced to retire early due to fatigue. **Breathlessness** Breathlessness is another symptom common symptom that contributes to reduced mobility and can be very distressing. Almost all patients with cardiac ATTR amyloidosis, even those at earlier stages of the disease, find that the breathlessness is extremely limiting in their usual daily activities, and for some can be the cause of anxiety or panic.

	'I used to walk the dog all the time, every day, morning and at night. Now, when I physically start to walk, I get really tired, my legs ache, get out of breath, that is the thing that really bugs me, is getting out of breath.' – Patient **Dizziness, falling and fainting.** Many patients have unstable blood pressure so if they stand up too quickly it can cause them to feel very dizzy such that they have to sit down again, or they fall over or faint. This can happen anywhere, is dangerous, and can result in serious injury and hospitalisation. The fear of fainting or falling is very common among patients with some restricting their activities for fear of fainting when out in public or alone. 'I*f I get up too quick, I might faint or when I am walking and out of breath or if I bend over try to do my shoelaces or whatever and I find I get a little bit lightheaded'.* - Patient **Abnormal heart rhythms** One of the effects of ATTR-CM is that the heart develops abnormal rhythms- beating too slow, too fast or skipping beats. These can be distressing when they happen and can also be dangerous, causing people to faint or the heart can even stop beating which can result in death. To manage these arrhythmias patients often need to have pacemakers and/or other medical devices fitted. Sometimes, even that does not work, patients, therefore, must live with the constant spectre of a potential heart attack. **Pain** People with cardiac amyloidosis can experience severe chest pain, as well as pain in the limbs. Water retention in the legs can make them swell and become uncomfortable or painful further restricting mobility. ATTR-CM can cause gastric symptoms, so stomach pain and cramps are also common among patients. **Loss of independence** Being less mobile and breathless after even minor tasks means that patients must depend on their caregivers more and more as the disease advances. Male and female patients alike find this difficult as they are less and less able to care for themselves independently or to carry out household tasks. Frequently patients' partners and sometimes their children become carers. Patients often struggle with the loss of independence coupled with feeling like a burden on their loved ones. **Financial burden** Having to retire earlier than expected can place a financial strain on patients and their families. **Caregivers** often also retire or reduce working hours due to the burden of care. Traveling (sometimes very long distances) to hospital appointments can cost significant amounts of time and money. Purchasing mobility aids (e.g., wheelchair, mobility

	scooter) and modifying the home to aid mobility can lead to further expense. With NHS social care services under strain, many families must foot the bill for care themselves. This coupled with family members' reduced ability to work further compounds the financial burden carried by ATTR-CM patients and their loved ones. **Psychological burden** Living with ATTR cardiomyopathy (ATTR-CM) can place a significant psychological burden on patients, affecting their mental health, emotional well-being, and quality of life. It is not uncommon for patients to experience low mood or depression as a result. Some key aspects of this burden: *Emotional Distress & Anxiety* • Uncertainty about the future: ATTR-CM is a progressive disease, and the unpredictability of symptoms (such as worsening heart function and mobility issues) can cause anxiety and stress. • Fear of complications: Patients often worry about heart failure, arrhythmias, and other serious complications, leading to constant worry about their health. *Depression & Low Mood* • Loss of independence: As physical limitations increase, patients may struggle with activities they once found easy, leading to feelings of helplessness and frustration. • Social withdrawal: Fatigue and mobility issues can lead to reduced participation in social activities, which may result in isolation and loneliness. • Guilt & burden on family: Many patients feel guilty about depending on caregivers and family members for support, adding to their emotional distress. *Cognitive & Mental Fatigue* • Brain fog & concentration issues: Some patients report difficulty with memory and focus, which can make daily tasks and decision-making more challenging. • Medication side effects: Treatments like Tafamidis can help slow disease progression, but managing medications and medical appointments can feel overwhelming. *Coping with Diagnosis & Adjustment* • Shock & denial: Many patients have trouble accepting their diagnosis, particularly if they were previously active and healthy.

	• Adjustment challenges: Adapting to lifestyle changes, dietary restrictions, and new routines can be mentally exhausting. *Impact on Relationships* • Strained relationships: Partners, family, and friends may struggle to understand the emotional toll of the disease, sometimes leading to misunderstandings or frustration. • Fear of being a burden: Patients may hesitate to express their struggles, further increasing their sense of loneliness. *Impact on Family* • Some forms of ATTR-CM are hereditary, meaning that multiple members of the same family may be affected. This brings a huge psychological burden to the patient and their family members. Many have watched their grandparents, parents or even siblings succumb painfully to the disease; they therefore worry for themselves and for their children and grandchildren who may inherit the disease. **Caregivers** The burden on caregivers is significant. Most caregivers are partners or spouses, sometimes children. Watching the health of someone you love deteriorate is inherently stressful. In addition to the financial burden mentioned above caregivers often experience chronic fatigue; apart from caring for their spouse they also gradually assume more and more of the household duties as their spouse/parent becomes less and less able to help. Caregivers also experience isolation as they are either afraid or unable to leave their spouses alone or simply spend so much of their time caring that they have limited opportunity to get out of the house and socialise. Caregivers often suffer from low mood, depression, or anxiety because of the impact of the disease on them and their families.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Tafamidis is only one other disease altering treatment available in the UK at present, it has only been available in the UK for a few months but has been widely available internationally for over a decade. Tafamidis is seen by patients and carers as a lifeline. It slows the progression of the disease, giving patients a better quality of life, for longer. It is generally well tolerated and as an oral medication patients find it simple to administer.
8. Is there an unmet need for patients with this condition?	While the approval of tafamidis has been welcomed by both patients and caregivers, it only slows the progression of ATTR-CM. This condition remains progressive and ultimately fatal, and not all patients will respond to or tolerate tafamidis. Beyond the need for more effective treatments, there is a significant gap in holistic care that addresses the wide range of challenges faced by ATTR-CM patients. For most patients, this need for comprehensive support remains unmet.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	If Vutrisiran were to be approved, it would become the second disease-modifying treatment available for ATTR-CM patients in the UK. Since not all treatments are suitable for every patient, having an additional option is seen as a significant advantage by the patient community. Patients also feel that the availability of Vutrisiran could open the door to potential combination therapies, which may further slow disease progression and improve outcomes.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Some patients see the injection administration route as a minor disadvantage, requiring an appointment with a health care provider once every three months.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	ATTR-CM disproportionately affects two protected characteristic groups due to the nature of the disease. First, wild-type ATTR-CM primarily impacts older individuals, with most patients presenting at age 60 or older. Second, the most common hereditary ATTR mutation, V122I, is found almost exclusively in individuals of West African ancestry. Therefor both these groups will be disproportionately impacted by the approval or rejection of this treatment.

Other issues

13. Are there any other issues that you would like the committee to consider?	Diagnosis is a major challenge for amyloidosis patients. Most clinicians remain unaware of amyloidosis resulting in many ATTR-CM patients going undiagnosed or misdiagnosed for years. **Accurate** diagnosis down to the exact type of amyloidosis is crucial for patients to get the appropriate treatment. As awareness and treatment options increase there is a corresponding increase in the risk that patients will be misdiagnosed and started on an inappropriate treatment. This needs to be managed carefully to ensure the best outcomes for patients.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• ATTR-CM is a progressive, debilitating and ultimately fatal condition that impacts every aspect (physical, financial, social, emotional, psychological) of a patient's life. • ATTR-CM has a major impact on patients' family and friends, with partners or other loved ones often adjusting their own life so they can take on caring responsibilities as the patient deteriorates. • Not all treatments are suitable for all patients. The approval of Vutrisiran would give patients a second option and open up the possibility of combined treatments. • People over 60 years old and those of West African decent are disproportionately affected by ATTR-CM as compared with the general population. • Delayed/inaccurate diagnosis and a lack of access to care close to home are both major challenges for patients living with ATTR-CM.

Thank you for your time.

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Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Cardiomyopathy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cardiomyopathy UK is the national charity for people affected by all forms of cardiomyopathy. The charity provides a range of support and information services, provides clinical education opportunities, raises awareness of the condition among the general public, supports research and advocates for improved access to quality treatment. The charity's database contains 18,000 individuals and there are around 150 active volunteers who facilitate support groups, provide peers support, advocate for improvements in health services, undertake fundraising activities and take on a range of other roles. The charity's trustees, the majority of whom have personal experience of the condition are ultimately responsible for the charity and are supported by a professional staff team. The charity is funded by community fundraising, donations and legacies (72%) charitable trusts and foundations (13%) the pharmaceutical industry (15%) Total income from the year January - December 2023 was £1,053,351
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment	Total income received from the pharmaceutical industry in 2023 (the most recent audited accounts) was £161,700. This comprises: Bristol Myers Squibb £35,000: Towards national survey project Cytokinetics £35,000: Towards national survey project

companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Cytokinetics £15,000: Towards case study content creation AstraZeneca £10,000: Towards online medical education work Pfizer £26,700: Towards regional advocacy work Tenaya £40,000: Towards national conference and helpline costs Accounts for 2024 are currently under audit and are expected to be finalised in May 2025. During the year the charity received a total of £159,800 from the pharmaceutical industry which is expected to be 14% of total income. This comprised: Alnylam £10,000: Towards online medical education AstraZeneca £15,000: Towards online medical education Tenaya £38,500: Towards national conference and helpline Cytokinetics £16,000: Towards case study content creation Cytokinetics £35,000: Towards national survey Pfizer £30,000: Towards regional advocacy work In addition to this £6,500 was raised as commercial income from the pharmaceutical industry for the provision of exhibition stand space at medical education events. Of this amount £2,000 was from Alnylam and £1,500 was from Pfizer who are listed as stakeholders for this technology appraisal. A further £8,800 was raised through services on advisory boards and steering groups. Of this amount £3,000 was from Pfizer who are listed as a stakeholder for this technology appraisal.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients	Cardiomyopathy UK conducted a national survey of the cardiomyopathy community, called the MyInsight survey, in summer 2024. Cardiomyopathy UK commissioned the Picker Institute to provide expertise on the

and carers to include in your submission?	survey development and design. Picker is a leading international health and social care charity, which carries out research to understand individuals' needs and their experiences of care. A total of 1323 people responded to the survey. Of those respondents, 22 reported having amyloidosis cardiomyopathy. Cardiomyopathy UK also ran a focus group with 5 people who reported having amyloidosis cardiomyopathy in December 2024. Cardiomyopathy UK ran a follow up focus group in January 2025 with 4 people who reported having amyloidosis cardiomyopathy, in which participants provided feedback on this Cardiomyopathy UK submission to ensure it reflects their views and experiences.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The MyInsight survey of the cardiomyopathy community in 2024 found the following: • 62% of all people with cardiomyopathy reported that their exercise had been negatively impacted in the last two years. • This is in comparison to 80% of people with amyloidosis cardiomyopathy stated that exercise had been negatively impacted by amyloidosis cardiomyopathy. • 34% of all people with cardiomyopathy reported that their mobility had been negatively impacted in the last wo years. • By contrast, 55% of people with amyloidosis cardiomyopathy stated that their mobility had been negatively impacted by amyloidosis cardiomyopathy. • 51% of all people with cardiomyopathy reported that their self-confidence had been negatively impacted in the last two years. • 50% of people with amyloidosis cardiomyopathy stated that their self-confidence had been negatively impacted by amyloidosis cardiomyopathy. • 49% of all people with cardiomyopathy reported that their mental health had been negatively impacted in the last two years. • 40% of people with amyloidosis cardiomyopathy stated that their mental health had been negatively impacted by amyloidosis cardiomyopathy. Participants in the focus group described a feeling that their body was wearing away, or losing a little bit of life every day. Most reported that they cannot do as much as they used to. This was often due to an enforced reduction in physical activity: Several of the participants had previously been very active, but now this was not possible due to breathlessness and neuropathy, which are symptoms of amyloidosis cardiomyopathy. As one person explained, even as a 70-year-old, he used to play golf and walk, run and go to the gym four times a week, until he experienced severe breathlessness – as well as a decrease in physical activity, he has also stopped doing a hobby that he really enjoyed. Participants in the focus group also reported a negative impact on their mobility and self-confidence. As one person described, he experiences neuropathy in his feet (a symptom of amyloidosis) and recently fell as he couldn't feel his feet. He now is feeling less confident to go outside or walk too far in case he falls again.

	One participant in the focus group explained that the amyloidosis has affected his mobility, the ability to swallow, his bowels and circulation. Participants did also report that, given their age (amyloidosis cardiomyopathy is more prevalent in older people), they are living with comorbidities. This means that the symptoms of amyloidosis cardiomyopathy can worsen other conditions and vice versa. It is important to note that all the focus group participants had been referred to the National Amyloidosis Centre (NAC). A lack of awareness of amyloidosis was a barrier in getting a diagnosis and accessing treatment, as reported by the participants, but the NAC has been a much more positive experience. As a result of being under the NAC, all participants had been offered the opportunity to take part in clinical trials. Nevertheless, the focus group participants all reported feeling isolated, given that amyloidosis is a rare condition. The psychological impact of amyloidosis cannot be ignored.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The focus group participants reported mixed views of current drug treatment for amyloidosis. Most had a positive experience with no side effects from tafamadis. One person reported that he had diarrhoea and needed to take pro-biotics now alongside tafamadis.
8. Is there an unmet need for patients with this condition?	In the MyInsight survey (2024), people with cardiomyopathy overall reported the following: • 76% do not have a care or treatment plan which details their care and support. • 32% do not have mood or emotional support, but wanted or needed this. • 32% do not have support from a dietician of nutritionist, but wanted or needed this. • 39% have had no support around physical activity, but wanted or needed this. Among people with amyloidosis cardiomyopathy, these data are as follows: • 62% have no care plan. • 39% do not have but wanted emotional support. • 38% do not have but would like support from a dietician or nutritionist. • 37% do not have but wanted support around physical activity. A lack of care plan was also reflected in feedback from the focus group participants. As a result, they reported feeling in the dark about their care a disease management. The participants also described the challenges of presenting at the Emergency Department without a care plan as emergency doctors are not familiar with amyloidosis cardiomyopathy to understand what are 'normal' test results for the individual. One participant explained he now has a personal information sheet which requests the emergency doctors contact his consultant for more information on amyloidosis cardiomyopathy. Several of the participants reported a lack of cardiac rehabilitation and were unsure how much exercise they could do to build muscle mass and improve their fitness without causing a shortness of breath or aggravating other symptoms of amyloidosis cardiomyopathy.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	One participant in the focus group had been on the clinical trial for Vutrisiran. Now he knows that he is actively taking the drug, he reported feeling much better after a few months of taking it. He was able to walk 7 thousand to 8 thousand steps a day and experienced no breathlessness over the summer of 2024. He did report, however, that the breathlessness had returned later in 2024, although his heart function has improved. Another participant in the second focus group is taking Vutrisiran as he has hATTR. He has no problems or side effects from taking the drug, he no longer gets as breathless and feels much better. He has a nurse visit him at home every 12 weeks to administer the injection.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	One participant commented that, as he lives in a remote part of the UK, it would be preferable if the injection could be self-administered every 3 months, rather than travelling a long distance to the National Amyloidosis Centre. Other participants agreed that travelling to a hospital every 3 months for an injection could be a disadvantage and suggested that self-administration would be preferable. The injections are not painful and the participant involved in the clinical trial reported no side effects at the injection site. The participant in the clinical trials reported that it is necessary to take vitamin supplements while taking Vutrisiran. While he did not report this as an issue, it is worth noting that it does increase the amount of tablets to take, which could be a disadvantage to some people.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	The participants in the focus groups expressed that, as amyloidosis cardiomyopathy is a rare condition, it can be harder to diagnose or take a long time to diagnose. Several of the participants had been misdiagnosed initially. As a result, there can be delays in receiving drug treatments.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Amyloidosis cardiomyopathy has an impact on the whole person, including self-confidence, mental wellbeing and physical activity. • It is important that people with amyloidosis cardiomyopathy are given a choice in drug treatments, which are most suitable for their personal circumstances and their medical condition. • Some people with amyloidosis cardiomyopathy could benefit from taking a combination of drug treatments and these should be offered where suitable and appropriate. • The establishment of referral pathways and the provision of ongoing support close to home are important factors that impact on a persons ability to live with the condition. •

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Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	Dr William Moody
2. Name of organisation	British Cardiovascular Society (BCS)
3. Job title or position	Consultant Cardiologist, Queen Elizabeth Hospital Birmingham; Hon Senior Lecturer, University of Birmingham; Member of the BCS Guidelines and Practice Committee.
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify): N/A
5a. Brief description of the organisation (including who funds it).	Founded in 1922, the BCS has evolved into a complex organisation that plays a pivotal role in the delivery of cardiovascular health across the UK. We currently have over 3,000 members including the majority of UK consultant cardiologists. Specialist registrars, GPs with a special interest, nurses and other professionals with an interest in cardiovascular medicine are also members. The Society became a UK Registered Charity in 2002.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	BCS has not received funding from the following companies in 2024: Alnylam, Ionis and BridgeBio - £0 Pfizer, Bayer and AstraZeneca are Principal Partners of BCS. BCS has received sponsorship for courses, the BCS conference, and the partnership agreement from the following companies in 2024: Pfizer, £ 131,130+VAT Bayer, £ 37,000+VAT Astra Zeneca, £ 127,574+VAT
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve the health outcomes of patients with transthyretin amyloid cardiomyopathy (ATTR-CM). This includes patients with the hereditary (ATTRv-CM) and non-hereditary forms (ATTRwt-CM) of the condition.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	If you ask most patients this question, an improvement in their quality of life and functional status, and the avoidance of hospitalisation for this ageing population of ATTRwt-CM (in whom the median age at diagnosis is 80 in our institution) are usually felt to be the most important outcome measures. For most cardiologists harder endpoints such as a reduction in all-cause mortality and the avoidance of CV hospitalisation represent a clinically meaningful treatment response but there is increasing recognition that delivering what patients want is more important. How one defines disease progression in ATTR-CM is hotly debated. Prof Fontana's group has demonstrated the importance of assessing 6-minute walk distance, outpatient diuretic intensification and worsening renal function (reduction in eGFR >20% from baseline at 1 year). Please see https://doi.org/10.1016/j.jacc.2023.12.036; https://doi.org/10.1001/jamacardio.2024.4578; https://doi.org/10.1016/j.jacc.2024.04.011 While practical and easy to assess in routine clinical practice, these are all relatively late and reactive measures of disease progression. The earliest markers of disease progression may well in fact be PROMs such as KCCQ-QS scores, based being the earliest outcome measures to differ between treated and placebo patients in the TTR disease modifying therapy trials performed to-date.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is a large unmet need still in this disease. In the ATTR-ACT trial of tafamidis, there was a 33% reduction in overall mortality with an NNT of 8 at 30 months and NNT of 5 to prevent one CV admission at 30 months follow up. Despite this efficacy, there was still a very high residual burden of morbidity with continued worsening functional status among the tafamidis arm as determined by a decline in 6 minute walk distance and KCCQ-QS quality of life scores. Furthermore, there was still a 50% residual mortality at 5 years in the patients treated with tafamidis.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Conservative medical management consists of anticoagulation for atrial fibrillation (present in roughly 50% of patients with ATTRwt-CM at baseline), pacemakers for bradycardia (conventional indications), SGLT2 inhibitors and MRAs and potential suspension of ACEi and beta-blockers (based on limited quality retrospective observational data and expert consensus guidance). The only licensed disease modifying therapy targeted at TTR available for the treatment of patients with ATTR-CM on the NHS is tafamidis. Only those patients with ATTRv-CM and evidence of polyneuropathy are currently eligible for RNA based therapies (vutrisiran and eplontersen), acknowledging that many patients in the UK with the T60A *TTR* variant will have evidence of a concomitant cardiomyopathy.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are 2021 ESC guidelines (European Heart Journal, Volume 42, Issue 16, 21 April 2021, Pages 1554–1568, https://doi.org/10.1093/eurheartj/ehab072) and 2023 ACC guidelines (J Am Coll Cardiol doi: 10.1016/j.jacc.2022.11.022). Thus far other than the NICE guidance, for ATTR the only UK specific guidelines relate either to the diagnostic imaging (BSE: Moody et al, Echo Res Pract 2023 and BNMS: Wechelekar et al, Nuc Med Bull 2023) or the specific management of UK and Ireland hereditary ATTR patients (Gillmore et al Adv Ther. 2022 doi: 10.1007/s12325-022-02139-9.)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care in England is in a transitional period. The diagnosis of ATTR cardiac amyloidosis is based on the validated non-biopsy Gillmore algorithm published in Circulation, 2016 following a multi-centre international study which has enabled the diagnosis of ATTRwt-CM in the majority (4 out of 5 patients) without the need for tissue biopsy. This diagnostic pathway has been accepted across all international guidelines (ESC and AHA/ACC). At present the only commissioned centre for amyloidosis care is the National Amyloidosis Centre (NAC) based at the Royal Free Hospital, London. A NHS England amyloidosis network has been proposed and there was a tendering process with submissions completed in November, which are currently being evaluated by NHSE. It is anticipated that there will initially be 4 centres outside of London that will work closely with the National Amyloidosis Centre, Royal Free London that will be commissioned and tasked with delivering equitable care across all of England from May 2025 onwards.
9c. What impact would the technology have on the current pathway of care?	If vutrisiran was to be approved for use in ATTR-CM as well as ATTRv patients with polyneuropathy, this treatment would potentially be prescribed by clinicians within the NHSE amyloidosis network centres and not just at the discretion of the NAC.
10. Will the technology be used (or is it already used)	Currently vutrisiran is only licensed and available for use in NHS patients with ATTRv-CM with neuropathy. The pricing of the product for ATTRwt-CM will need to reflect the prevalence of this disease which is far higher. The

in the same way as current care in NHS clinical practice?	key factor will be whether the drug offers additional or synergistic effect to TTR stabiliser therapy with tafamidis which is current standard of care. The fact that tafamidis comes off patent in 2026 will also influence this decision.
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	If approved, specialist units within the NHSE network should prescribe vutrisiran with the ability to track patients in sufficient numbers to be able to learn from the real-world practice clinical data. This is critical as there are still so many unknowns even among amyloid "experts" about a number of issues surrounding novel amyloid therapies including: How and when to treat pre-symptomatic ATTRv carriers? Which class of TTR directed treatment to initiate initially? The level of organ dependency? How to assess for response to therapy? The role for combination therapy?
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is still lacking. The proposed funding from NHSE to network centres is likely to be inadequate (210k per year per centre outside of the NAC, for the next 5 years for all amyloidosis healthcare including both ATTR *and* AL amyloidosis) to truly address the imbalance of equity of access to expert healthcare across England.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, based on the HELIOS-B data it is likely that this treatment would work synergistically with TTR stabilisers. Extrapolating from the the data on AL amyloidosis we know that treatments aimed at reducing the precursor protein provide meaningful benefits to patients. Quantifying the degree of added benefit in QALYs/monetary terms beyond tafamidis will be based on a number of assumptions and will be challenging particularly as there were a lot of differences between the 2 trial populations at baseline (ATTR-ACT patients had more advanced ATTR-CM relative to HELIOS-B patients)
11a. Do you expect the technology to increase length of life more than current care?	As discussed above. This is very challenging to answer with the current available data. If only monotherapy was available to clinicians they would have to choose between a TTR stabiliser and a RNA based therapy. In scientific terms it would make sense to reduce the substrate (TTR knockdown by 80% on average), which leads

	to amyloid formation. I think measurement of TTR levels could inform this decision. If TTR knockdown was inadequate within 8 weeks of therapy then a stabiliser might be preferred.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, based on HELIOS-B there was very early separation in terms of KCCS-QS scores.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with life expectancy of <12 months because of other co-morbidities would be much less likely to gain benefit; these patients were not enrolled in the trial. The availability of frailty scores from the original HELIOS-B trial would add value in helping clinicians decide which patients would and would not benefit from treatment. There was a lack of heterogeneity in the sub-group analyses which is encouraging but there is still a signal to support the fact that the patients that benefit most from vutrisiran are those at earlier NYHA stages. I would not, for example, prescribe any high cost disease modifying therapy to patients bedbound with NYHA IV symptoms.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	If a 'package of care' was included with the availability of a nurse to help administer the drug subcutaneously at 3 monthly intervals in the community then that would be a very useful addition to the NHS, would be welcome for patients and avoid unnecessary travel which is often challenging in this ageing cohort. This along with serum TTR measurements would also help ensure compliance for a high cost treatment. Talking to patients, most find subcutaneous injection as attractive if not more so than tablet forms of therapy.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I feel progression to NYHA Class IV would be an indication to stop high cost treatments. Inadequate response in terms of TTR knockdown could also be considered for RNA based therapies such as vutrisiran.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	In my experience many of these patients are the main carers for their spouses. Do not therefore underestimate the importance of drug therapy which would prevent hospital admissions in an elderly co-morbid population. Admissions to hospital for the patient with ATTR-CM can frequently result in their spouse also being admitted to social care or hospital. It is also noteworthy that many patients with ATTR-CM rely on the their son/daughter to attend outpatients. Any treatment that minimises the need for frequent outpatient reviews would minimise the number of work days lost for patient's main carers which would have an important wider economic impact.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This drug is safe based on the events seen in the trial but we also have much longer-term safety data in the ATTRv with polyneuropathy population that is very encouraging. Other than mild injection site related pain there appears to be no worrisome adverse effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, many patients that were enrolled in the multicentre international HELIOS-B phase 3 trial of vutrisiran came from the UK. There will always be differences between trial patients and real-world patients. This is why a further analysis of the trial outcomes in relation to patient's baseline frailty status would be informative.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	See answer to Q7.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	N/A.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA984?	There is longer-term open label extension data for both ATTR-ACT and the Acoramidis trial worthy of review.
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Despite tafamidis demonstrating efficacy on the basis of trial and now real-world clinical data, there remains a huge unmet need in terms of addressing residual mortality and morbidity • In an ageing cohort of patients with ATTRwt-CM, traditional hard outcome measures such as all-cause mortality are less important to patients than QoL measures and functional status. While functional outcomes may not traditionally carry as much importance for heart failure clinicians in terms of defining a clinically meaningful response to therapy, perhaps this mind-set now needs to change (as has been highlighted by the collaborative work from the James Lind Alliance / Cardiomyopathy UK / Amyloidosis UK) • Both TTR stabilisers and siRNA therapies have now been proven to be effective in ATTR-CM. There appears to be no significant difference in terms of safety between the existing available NHS treatment (tafamidis) and vutrisiran. The factors which would influence first line choice of therapy (if combination therapy was not deemed to be cost-effective) would depend on patient choice / preference of administration (oral versus subcut), the ability to check compliance (through blood serum TTR levels) and what package of care if any, is available alongside the basic administration of the drug (heart failure nurse input which is often lacking in the community in patients with “HFpEF”). • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for NHS England in general? Yes Commissioning services for NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England purpose is to lead the NHS in England to deliver high-quality services. We work with the wider NHS, national partner organisations and other key stakeholders to optimise the use of digital technology, research and innovation, and to deliver value for money and increased productivity and efficiency for all. We directly commission retained Prescribed Specialised Services, including amyloidosis services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The National Amyloidosis Centre (NAC) leads the guidelines and prescribing for patients with amyloidosis in England, for both cardiac and other variants of the disease.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined. The NAC are currently the only centre that can initiate patients onto treatment for cardiac variants of amyloidosis and they prescribe for the majority of patients. A network of providers is currently being commissioned, phase one of a two phase process. There are some overall system challenges in completing the diagnostic pathway due to access and there is limited clinical expertise.
8. What impact would the technology have on the current pathway of care?	This technology would not change the current pathway.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	The technology is currently used for hereditary transthyretin-related amyloidosis in adults with stage 1 or stage 2 polyneuropathy, in line with NICE TA868, which is approximately 200 people.
10. Will the technology be used (or is it already used) in the same way	This appraisal would enable the technology to be considered for the wider cohort of people with ATTR-CM, approximately 1200, all of whom are currently receiving treatment with tafamidis.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The use of the technology is impacted by the license and NICE recommendation which have up to now been limited to patients with stage 1 or stage 2 polyneuropathy
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This drug would only be used in secondary care, in specialist MDTs
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Home care for drug delivery is a system pressure. Staff in the network centres would need some training from the drug company about the drug. Patients would also need access to information about the drug
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The clinicians would need to advise on where this drug would sit in the pathway, I do not think it is inferior to tafamidis but there are also other therapies for this cohort going through the approvals process and in the pipeline.
11. What is the outcome of any evaluations or audits of the use of the technology?	The clinicians and the company would need to advise on this.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are no potential equality issues to be taken into account when considering this treatment.
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Clinical expert statement

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send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 22 August 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating transthyretin amyloidosis with cardiomyopathy (ATTR-CM) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Julian Gillmore
2. Name of organisation	National Amyloidosis Centre
3. Job title or position	Head, UCL Centre for Amyloidosis & Research Lead, National Amyloidosis Centre
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ATTR-CM? ☒ A specialist in the clinical evidence base for ATTR-CM or vutrisiran? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for ATTR-CM?	To prolong life by stopping progression and improve or stabilise quality of life

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A halting of the inexorable clinical decline and increasing disease burden associated with ATTR-CM
10. In your view, is there an unmet need for patients and healthcare professionals in ATTR-CM?	Yes, many patients progress despite existing therapies
11. How is ATTR-CM currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Supportive care (of heart failure and other clinical manifestations of this multisystem disease) + tafamidis Yes, all disease-modifying therapy (tafamidis) is prescribed by the UK National Amyloidosis Centre team and the pathway of care is very well defined The technology will provide an alternative therapy to tafamidis for the same group of patients
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will be used as an alternative to tafamidis, either because of patient preference, adverse effects from tafamidis or in some scenarios, because it may be a preferable option. It will be used only in a specialist care setting Homecare for delivery of the technology for patients and in some cases, for sub-cutaneous administration (I believe this will be funded by the manufacturing company?)

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, it is likely to increase length of life in some patients with ATTR-CM (such as those with particular pathogenic TTR mutations, those that do not tolerate tafamidis and those who respond poorly to tafamidis) Yes, among patients who have evidence of neuropathy as well as CM, vutrisiran is likely to increase health-related QoL to a greater degree than existing therapies. This is also likely to be the case in some patients with pure CM
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not particularly. Possibly patients with hereditary ATTR-CM but this is not proven. It will be more appropriate for patients who may not wish to take additional tablets.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This technology will be easier for some patients and more difficult for others (one is a daily oral treatment and the other is a sub-cutaneous injection which can potentially be self-administered every 3 months)
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Disease progression on an alternative therapy may be used as a starting rule (however, there are no firm guidelines on how to measure disease progression). Intolerance of an alternative therapy is another starting rule. Progression to end-stage heart failure could potentially be an informal stopping rule
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, will enable ongoing full functioning (and potentially employment) of patients who are treated at a relatively early stage of the disease natural history The self administration is definitely an advantage for some patients

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, this is the first RNA interference therapy for ATTR-CM and indeed for any cardiomyopathy and constitutes a huge step change in the treatment of ATTR amyloid cardiomyopathy Yes, it is the first treatment for ATTR amyloidosis in which there is unequivocal evidence of benefit in both cardiomyopathy and polyneuropathy and which can lead to disease improvement (in some patients)
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	It is generally very well tolerated. A very small proportion of patients may develop joint pain which may or may not be related to the drug
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the UK was the greatest global contributor to the seminal HELIOS-B trial
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA984]?	No
23. How do data on real-world experience compare with the trial data?	Our real world experience is absolutely consistent with the clinical trial data
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	None that I am aware of. Black people are disproportionately affected by ATTR-CM (there is a particular pathogenic TTR mutation which is present in 4% of Afro-Carribean and those of West African descent). Availability of this treatment will undoubtedly benefit this particular community although all other ethnicities also stand to gain from it.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is a life preserving and quality of life preserving technology

The technology offers significant advantages for some patients over existing therapy of ATTR-CM

The technology offers and alternative to patients who do not tolerate or respond poorly to the single existing disease-modifying therapy for ATTR-CM

The technology is extremely well tolerated according to the results of the seminal clinical trial (HELIOS0-B) and our own real world experience of patients with ATTR amyloidosis

The potential for self administration will enable some patients to feel that they have more control of their condition and will directly benefit those for whom this is an important aspect of their holistic care

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating transthyretin amyloidosis with cardiomyopathy (ATTR-CM) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr William Moody
2. Name of organisation	Midlands Amyloidosis Service, University Hospitals Birmingham NHS Foundation Trust; British Cardiovascular Society
3. Job title or position	Consultant Cardiologist; Chair of British Cardiovascular Society Guidelines and Practice Committee.
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ATTR-CM? ☒ A specialist in the clinical evidence base for ATTR-CM or vutrisiran? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for ATTR-CM?	

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in ATTR-CM?	
11. How is ATTR-CM currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA984]?	

23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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External Assessment Group Report
Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

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None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Eleonora Uphoff wrote Section 3.1 and 3.2 of this report and contributed generally to the report as a whole.

Anqian Zhou performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 5 of the report.

Mark Perry wrote Section 2 and Section 3.3 of the report.

Melissa Harden provided information services and database support for the project and critically appraised the search strategies for the literature reviews.

Vijay Gc performed the critical review of the economic analyses, conducted the EAG additional analyses, contributed to writing Section 4 of the report, adapted the economic model and provided leadership support throughout the project.

Mark Simmonds oversaw the clinical components of the report, wrote parts of Section 3, and takes joint responsibility for the report as a whole.

Ana Duarte performed the critical review of the economic analyses, conducted the EAG additional analyses, contributed to writing Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Note on the text

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List of abbreviations

6-MWT	Six-minute walk test
ACM	All-cause mortality
AFFIRM-AHF	A randomized, placebo-controlled trial of intravenous ferric carboxymaltose in hospitalized acute heart-failure patients with iron deficiency
AIC	Akaike Information Criterion
ATTR	Transthyretin Amyloidosis
ATTR-ACT	A randomised double-blind placebo-controlled, phase 3 trial of tafamidis
ATTR-CM	Transthyretin Amyloidosis with Cardiomyopathy
BIC	Bayesian Information Criterion
BID	Twice per day
BNF	British National Formulary
BSC	Best Supportive Care
CI	Confidence Intervals
CS	Company Submission
CSR	Clinical Study Report
CV	Cardiovascular
EAG	External Assessment Group
eGFR	Estimated Glomerular filtration rate
EMA	European Medicines Agency
EQ5D	Standardised instrument for use as a measure of health outcome
EQ-5D-3L	EuroQoL 5-level health questionnaire
EQ-5D-5L	EuroQoL 3-level health questionnaire
FAP	familial amyloid polyneuropathy
FDA	Food and Drug Administration
GI	Gastrointestinal
hATTR-CM	hereditary ATTR-CM
HELIOS-B	A randomized, double-blind placebo-controlled phase 3 trial of vutrisiran
HF	Heart failure
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Appraisal
ICER	Incremental Cost-Effectiveness Ratio
IPTW	Inverse Probability of Treatment Weighting
IQR	Interquartile range
ITT	Intention to Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan Meier
LMEM	Linear mixed effects model
LS	Least Squares
LVEF	Left ventricular ejection fraction
LY	Life Year
LYG	Life Years Gained
MAIC	Matching-Adjusted Indirect Comparison
MD	Mean Difference
MHRA	Medicines and Healthcare products Regulatory Agency
N	Number
NAC	National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network Meta-Analysis
NYHA	New York Heart Association
NY-proBNP	N-terminal pro B-type natriuretic peptide

ODI	Oral loop diuretic intensification
OR	Odds Ratio
OS	Overall Survival
OWSA	One Way Sensitivity Analysis
PAS	Patient Access scheme
PfC	Points for Clarification
Pro-BNP	pro B-type natriuretic peptide
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QD	Once per day
RCT	Randomised Controlled Trial
RIO	Rational Impartial Observer
RNA	Ribonucleic acid
SAEs	Serious adverse events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEE	Structured Expert Elicitation
SLR	Systematic Literature Review
SmPC	Summary of product characteristics
SOC	Standard of Care
STA	Single Technology Appraisal
TA	Technology Appraisal
THAOS	Transthyretin Amyloidosis Outcomes Survey
TP	Transition probability
TTD	Time to Treatment Discontinuation
TTR	Transthyretin
UK	United Kingdom
USA	United States of America
VBA	Visual Basic for Applications
wtATTR-CM	Wild-type ATTR-CM

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of Key Issues

ID	Summary of issue	Report sections
1	Best supportive care is not included as a comparator.	2.3.3, 4.2.4
2	Limited evidence on key patient subgroups.	2.3.5, 3.2.8, 4.2.3.1
3	Comparison of vutrisiran with tafamidis is based on non-randomised data.	3.2.4, 3.7.1
4	Clinical evidence comparing vutrisiran to tafamidis shows no evidence of difference in effectiveness.	3.2.6, 4.2.6.1
5	Modelled treatment effectiveness implies greater difference between treatments than the clinical data suggests.	4.2.6.1, 4.2.6.2, 4.2.6.3
6	All-cause mortality (ACM) is modelled independently from New York Hearth Association (NYHA) classification and transient cardiovascular events.	4.1, 4.2.2, 4.2.6.3
7	Treatment effect waning with vutrisiran is uncertain	4.2.6.4
8	General population utility adjustments are additive rather multiplicative	4.2.9.2
9	The appropriateness of considering caregiver disutilities in the cost-effectiveness analysis is uncertain.	4.2.9.5
10	The vutrisiran acquisition and administration costs may have been underestimated.	4.2.2, 4.2.10.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Include an additional pairwise comparison between vutrisiran monotherapy and BSC.
- Vutrisiran monotherapy curve extrapolated with exponential distribution.
- No treatment effect waning for vutrisiran monotherapy.
- No difference in survival between vutrisiran and tafamidis monotherapy.
- No difference in transition probabilities between NYHA health states between vutrisiran and tafamidis monotherapy.
- Use of a multiplicative approach to reflect decreases in HRQoL in the age and sex-matched general population.
- Removal of the within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy.
- Vutrisiran monotherapy administration costs in line with Summary of Product Characteristics (SmPC)[1], which only allowed for administration to be undertaken by a healthcare professional.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs compared to tafamidis monotherapy by:

- delaying progression across NYHA class health states (with improved health related quality of life [HRQoL] for patients and carers) due to higher utility and fewer cardiovascular events (with associated disutility) in less severe health states compared to more severe ones.
- improving survival.
- reducing the incidence of adverse events.

Overall, the technology is modelled to affect costs compared to tafamidis monotherapy by:

- [redacted] drug acquisition (including background medication) and administration costs
- delaying progression across NYHA class health states (with lower costs associated with cardiovascular events and disease management).
- reduces the costs associated with managing adverse events compared to tafamidis monotherapy.

The modelling assumptions that have the greatest effect on the ICER are:

- Inclusion of BSC as a comparator in a separate pair wise comparison with vutrisiran monotherapy;
- No difference in treatment effect for vutrisiran vs. tafamidis monotherapy on transition probabilities between NYHA class health states;
- Use of a multiplicative approach to reflect decreases in HRQoL in the age and sex-matched general population;
- Removal of the within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Best supportive care is not included as a comparator

Report section	2.3.3, 4.2.4
Description of issue and why the EAG has identified it as important	Comparison with best supportive care (BSC) is not included in the clinical or cost-effectiveness analyses, despite the comparison against BSC being one for which there is randomised controlled data (unlike for the comparison against tafamidis, see issue 3). Furthermore, the NICE scope defines established clinical practice without vutrisiran as one of the comparators (the other being tafamidis); the EAG interprets this as corresponding to BSC. The EAG considers the comparison to BSC to also be of relevance for patients for whom tafamidis cannot be used (e.g., due to intolerance or lack of treatment response).
What alternative approach has the EAG suggested?	The EAG suggests that the placebo arm in HELIOS-B is a reasonable representation of outcomes for patients receiving best supportive care. Since the company has not updated the economic model to include the comparison against BSC, the EAG used inputs from the placebo arm of the HELIOS-B monotherapy population (available within the economic model for the purpose of modelling the outcomes of patients who discontinue active treatment) to inform this comparison in the cost-effectiveness analysis. This approach has limitations, given that the vutrisiran monotherapy group data from HELIOS-B in the model was adjusted for comparison with tafamidis, and it is unclear whether the placebo arm (informing BSC) was also similarly adjusted. The EAG would have preferred for unadjusted vutrisiran and placebo arms data from HELIOS-B monotherapy population to have been used to inform the comparison between vutrisiran and BSC. The EAG suggests that the placebo arm in HELIOS-B is a reasonable representation of outcomes for patients receiving BSC.
What is the expected effect on the cost-effectiveness estimates?	The deterministic incremental cost-effectiveness ratio (ICER) for vutrisiran monotherapy vs. BSC ranges between [redacted] per additional quality-adjusted life-year (QALY) under the company's base-case assumptions and [redacted]per additional QALY under the EAG's base-case assumptions, when including caregiver disutility. If caregiver disutilities are excluded from the analysis the ICER ranges between [redacted]per additional QALY under the company's base-case assumptions and [redacted]per additional QALY under the EAG's base-case assumptions.

What additional evidence or analyses might help to resolve this key issue?	The company should formally model the comparison of vutrisiran monotherapy vs. BSC, as informed by randomised evidence from the HELIOS-B trial.

Issue 2 Limited evidence on key patient subgroups

Report section	2.3.5, 3.2.8, 4.2.3.1
Description of issue and why the EAG has identified it as important	The company submission did not present detailed data on key patient subgroups as listed in the scope.
What alternative approach has the EAG suggested?	The EAG notes that evidence on key subgroups (NYHA class, ATTR type) was reported in part in the appendices to the company submission, and in the publications of the HELIOS-B trial and the ATTR-ACT trial. The EAG notes that evidence is limited due to small sample sizes, but considering these subgroups may be clinically important.
What is the expected effect on the cost-effectiveness estimates?	Although the evidence is uncertain, variation in effectiveness across NYHA class and ATTR type might affect the choice of treatment for some patients. This has not been assessed formally by the company and the impact on the ICER is therefore unknown.
What additional evidence or analyses might help to resolve this key issue?	Formal modelling and testing for subgroup differences in both HELIOS-B and ATTR-ACT would be desirable. Further trial data on small subgroups would be helpful.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 3 Comparison of vutrisiran with tafamidis is based on non-randomised data

Report section	3.2.4, 3.7.1
Description of issue and why the EAG has identified it as important	The company's preferred comparison for vutrisiran against tafamidis is based on two patient groups that HELIOS-B trial was not designed to directly compare, namely (i) patients receiving tafamidis prior to randomisation and who were randomised to the placebo arm, versus (ii) patients not receiving tafamidis prior to randomisation and who were randomised to the vutrisiran arm; this comparison is the only one considered by the company in the cost-effectiveness analysis. While the company performed a post-hoc adjustment (inverse probability of treatment weighting [IPTW] of baseline characteristics) to try to address possible biases, the results for this comparison remain at risk of confounding. Other possible confounding factors could not be corrected for, such as the patients in the tafamidis group having received this treatment

	prior to randomisation, and use of tafamidis drop-in in the vutrisiran group after the double-blind period.
What alternative approach has the EAG suggested?	The EAG would have preferred to see a fuller investigation of tafamidis use in HELIOS-B, and indirect comparison (using anchored MAIC and NMA) of HELIOS-B with the ATTR-ACT trial of tafamidis. The EAG has performed limited NMAs comparing HELIOS-B with ATTR-ACT.
What is the expected effect on the cost-effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	More in-depth modelling of the HELIOS-B trial, such as regression modelling adjusting for confounding factors and use of tafamidis treatment both before and after randomisation would be useful. A full indirect comparison of HELIOS-B with ATTR-ACT using both anchored MAIC and NMA methods, would also be useful. However, as the HELIOS-B trial was not designed or powered to compare vutrisiran to tafamidis, it may be that a head-to-head RCT comparing the two treatments is needed.

Issue 4 Clinical evidence comparing vutrisiran to tafamidis shows no evidence of difference in effectiveness.

Report section	3.2.6, 4.2.6.1
Description of issue and why the EAG has identified it as important	The clinical evidence presented comparing vutrisiran to tafamidis, both within HELIOS-B and when compared to ATTR-ACT, showed no conclusive evidence of any difference between the treatments. This conflicts with the company's economic model, where differences between vutrisiran and tafamidis are included for both mortality and NYHA class transitions.
What alternative approach has the EAG suggested?	The EAG thinks that, in the absence of any conclusive evidence of superiority of vutrisiran over tafamidis, the treatments should be considered equivalent in effectiveness for this assessment.
What is the expected effect on the cost-effectiveness estimates?	Assuming the same effect on all-cause mortality and NYHA class transitions probabilities (and only accounting for differences in safety outcomes) increases the ICER for the vutrisiran vs. tafamidis monotherapy to [redacted] per additional QALY.
What additional evidence or analyses might help to resolve this key issue?	A head-to-head RCT comparing vutrisiran to tafamidis would probably be needed to demonstrate any difference between them, should it exist, but the EAG acknowledges that may not be feasible.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Modelled treatment effectiveness implies greater difference between treatments than the clinical data suggests

Report section	4.2.6.1, 4.2.6.2, 4.2.6.3
Description of issue and why the EAG has identified it as important	Whilst the company's clinical effectiveness evidence from HELIOS-B for the comparison between vutrisiran and tafamidis monotherapy (and broader evidence identified by the EAG) showed no conclusive evidence of any difference between the treatments, the modelled outcomes suggest incremental health gains with vutrisiran ([redacted] LYs and [redacted] QALYs in the company's probabilistic base case analysis). The EAG considers that this is partly driven by the extrapolation of treatment effects over a time horizon considerably greater than the observed data follow-up. Another contributing factor is that the data observed in the trial follow-up may not accurately reflect the outcomes of ATTR-CM across the full spectrum of disease severity, as the population in HELIOS-B had relatively low proportion of patients with more severe disease. This contributes to the uncertainties of the transition probabilities between NYHA health states and the survival outcomes, and is potentially exacerbated by the survival outcomes being independently modelled from NYHA classification (see Issue 6). Finally, the company's preferred ACM extrapolation curves for both vutrisiran and tafamidis monotherapy is driven in part by observed hazards, which are likely to be heterogeneous and display trends (decreasing hazards in the long-term) that are implausible to persist over the modelled time horizon for a progressive and fatal disease. The EAG thinks this is likely to result in overestimation of survival outcomes, particularly for the vutrisiran group.
What alternative approach has the EAG suggested?	The EAG could not address the majority of the contributing factors to this issue. Only the impact of using a less optimistic ACM extrapolation model for vutrisiran could be formally explored in the model, by applying an exponential distribution; this favoured the cost-effectiveness of vutrisiran as the lower survival also reduced costs. The EAG reiterates that in the absence of any conclusive evidence of superiority of vutrisiran over tafamidis, the treatments should be considered equivalent in effectiveness for this assessment.
What is the expected effect on the cost-effectiveness estimates?	Unknown, but potentially large.

What additional evidence or analyses might help to resolve this key issue?	The EAG considers that this issue cannot be handled without jointly addressing the contributing factors, and that is not possible with the evidence currently available.

Issue 6 All-cause mortality is modelled independently from NYHA classification and transient cardiovascular events.

Report section	4.1, 4.2.2, 4.2.6.3
Description of issue and why the EAG has identified it as important	The company's modelling approach omits a structural link between disease progression across NYHA classes and mortality, due to survival being modelled independently from NYHA class changes over the time horizon. This omission may introduce inconsistencies in the assumptions used for NYHA transitions and mortality estimates, leading to potentially implausible and optimistic survival extrapolations, requiring logical constraints (i.e., general population mortality cap) to be imposed at relatively early time points of the model horizon. This feature of the model may also lead to inconsistent and potentially clinically implausible impacts on other outcomes. One such inconsistency is the implied higher proportion of patients treated with tafamidis spending time in NYHA class IV health state over the model time horizon compared to the less severe and lower mortality health state NYHA III in the company's base analysis.
What alternative approach has the EAG suggested?	The use of a state transition modelling approach with competing risks, could allow overcoming this limitation. However, the HELIOS-B evidence is not sufficient to appropriately parameterise such model and external evidence in a contemporaneous ATTR-CM population is not available.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Long-term robust evidence on the impact on mortality by NYHA health states for vutrisiran vs. tafamidis monotherapy.

Issue 7 Treatment effect waning with vutrisiran is uncertain.

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The company's approach to model a gradual treatment waning effect over 21 months post-treatment discontinuation on NYHA class transition probabilities for vutrisiran monotherapy relies on a number of assumptions on how treatment effect persistence relates to levels of TTR, which are not supported by empirical data and are highly uncertain
What alternative approach has the EAG suggested?	The EAG explored the impact of the treatment effect of vutrisiran monotherapy persisting for only [redacted] after vutrisiran monotherapy discontinuation, as by that time point patients the average TTR level reduction compared to baseline values would have gone below the 80% threshold (proposed by the company). The EAG also assessed the impact of assuming no waning of treatment effect for vutrisiran monotherapy.
What is the expected effect on the cost-effectiveness estimates?	The impact of these scenarios over the company's base case assumption appears to be marginal, but when combined with the EAG assumptions of no treatment effectiveness of vutrisiran vs. tafamidis monotherapy on transition probabilities between NYHA classes and survival, the impacts are substantial. For the analyses including caregiver disutilities, the ICER becomes £[redacted] per additional QALY for the scenarios assuming treatment waning and no treatment waning, respectively. For the analyses including caregiver disutilities, the ICER becomes [redacted] per additional QALY for the scenarios assuming treatment waning and no treatment waning, respectively.
What additional evidence or analyses might help to resolve this key issue?	Long-term robust evidence on the impact on mortality across NYHA health states for vutrisiran vs. tafamidis monotherapy.

Issue 8 General population utility adjustments are additive rather multiplicative

Report section	4.2.9.2
Description of issue and why the EAG has identified it as important	The company has taken an additive approach to reflect the decrease in HRQoL in the general population in the health state utilities rather than a multiplicative approach, as applied in previous NICE technology appraisals in ATTR-CM and recommended by current NICE guidance. This was not justified by the company.
What alternative approach has the EAG suggested?	The use of the multiplicative approach was explored by the EAG in scenario analysis.

What is the expected effect on the cost-effectiveness estimates?	For the comparison with tafamidis, the ICER increases to [redacted] per additional QALY for analyses with and without caregiver disutilities, respectively. For the comparison with BSC, the ICER changes to [redacted] per additional QALY for analyses with and without caregiver disutilities, respectively.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 9 The appropriateness of considering caregiver disutilities in the cost-effectiveness analysis is uncertain.

Report section	4.2.9.5
Description of issue and why the EAG has identified it as important	The company included NYHA class specific caregiver disutilities, but it is unclear whether these should be considered for the modelled population. This is because these were not included in previous NICE technology appraisals in ATTR-CM and the evidence provided by the company does allow ascertaining whether this impact is greater than would be expected in other disease areas where carer burden is not routinely accounted for in the QALY estimates (e.g., in oncology in adult patients). Furthermore, the disutility estimates were not specific to ATTR-CM and required mapping to NYHA classification, which increases the uncertainty of the estimates.
What alternative approach has the EAG suggested?	The EAG analyses are presented with and without including caregiver disutilities.
What is the expected effect on the cost-effectiveness estimates?	For the vutrisiran vs. tafamidis monotherapy; ICERs increase substantially in all scenarios where vutrisiran and tafamidis monotherapy are assumed to have differences in clinical effectiveness. For the comparison against BSC the exclusion of caregivers disutilities consistently decreases the ICERs compared to the corresponding analysis with caregiver disutilities.
What additional evidence or analyses might help to resolve this key issue?	EQ-5D data collected from carers of a contemporaneous (predominantly wtATTR) ATTR-CM population across NYHA health classification. The company could also present evidence to allow ascertaining whether the caregiver burden in ATTR-CM is greater than would be expected in other disease areas where carer burden is not routinely accounted for in the QALY estimates.

Issue 10 The vutrisiran acquisition and administration costs may have been underestimated.

Report section	4.2.2, 4.2.10.3
Description of issue and why the EAG has identified it as important	The vutrisiran acquisition and administration costs in the company's cost-effectiveness analysis may have been underestimated. The EAG thinks that, given that the periodicity of drug administration completely aligns with the modelled cycle length. these costs should not have been subject to any within-cycle correction. The administration costs for vutrisiran are also not in line with the summary of product characteristics (SmPC),[1] which does not allow for self-administration.
What alternative approach has the EAG suggested?	The EAG explores this in two separate scenario analyses: • Scenario 6 removes the within-cycle correction from vutrisiran administration ad acquisition costs. • Scenario 7 assumes that administration costs for vutrisiran are in line with the SmPC[1]
What is the expected effect on the cost-effectiveness estimates?	When including caregiver disutilities, removal of the within-cycle correction for vutrisiran monotherapy acquisition and administration costs increases the ICER to £[redacted] per QALY for the comparison against tafamidis monotherapy and against BSC, respectively. When excluding caregiver disutilities, the ICER increases to [redacted] per QALY for the comparison against tafamidis monotherapy and against BSC, respectively. The inclusion of vutrisiran administration costs commensurate with administration at the hospital until treatment discontinuation has a modest impact across all EAG analyses.
What additional evidence or analyses might help to resolve this key issue?	None, but the EAG acknowledges that the administration costs for vutrisiran monotherapy may change if the SmPC[1] allows for [redacted] in the future. In recognition of this, the EAG also presents the EAG base-cases assuming self-administration of vutrisiran is possible for all patients.

1.6 Other key issues: summary of the EAG's view

None

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 Summary of EAG's preferred assumptions and ICER for vutrisiran vs. tafamidis

Deterministic scenario	Incremental cost	Including caregiver disutilities		Excluding caregiver disutilities	
		Incremental QALYs	ICER** (/QALY)	Incremental QALYs	ICER ** (/QALY)
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment effect waning for vutrisiran monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM extrapolation for vutrisiran monotherapy with exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No effect on transition probabilities between NYHA class or survival*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age and sex adjusted utilities using multiplicative approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vutrisiran monotherapy administration costs in line with SmPC[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*assuming vutrisiran extrapolation with exponential distribution; **change from company base case

Table 3 Summary of EAG's preferred assumptions and ICER for vutrisiran vs. BSC

Deterministic scenario	Incremental cost	Including caregiver disutilities		Excluding caregiver disutilities	
		Incremental QALYs	ICER** (/QALY)	Incremental QALYs	ICER** (/QALY)
Company's base case assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment effect waning for vutrisiran monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM extrapolation for vutrisiran monotherapy with exponential distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age and sex adjusted utilities using multiplicative approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vutrisiran monotherapy administration costs in line with SmPC[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*assuming vutrisiran extrapolation with exponential distribution; **change from company base case)

For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 6.1.1, 6.2, 6.3 and 9.

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of the company's submission to NICE on the clinical and cost-effectiveness of Vutrisiran (Amvuttra®) for treating transthyretin amyloidosis with cardiomyopathy (ATTR-CM).

Vutrisiran is currently awaiting EMA approval for the treatment of ATTR-CM. FDA approval was granted in March 2025.

2.2 Background

2.2.1 Transthyretin amyloidosis with cardiomyopathy (ATTR-CM)

Transthyretin (TTR) is a protein predominantly produced in the liver, that is used for transport of thyroxine and vitamin A.[2] Aging-related and/or genetic factors may cause TTR proteins to break up into smaller units, which may misfold and eventually form amyloid fibrils. [2] These amyloid fibrils may deposit in cardiac tissue and cause the pathological changes of transthyretin amyloidosis with cardiomyopathy (ATTR-CM). Such changes include an increase in the thickness and stiffness of cardiac walls, as well as conduction disturbances, which lead to progressive heart failure.[2] Symptoms include shortness of breath, palpitations, fatigue, reduction in exercise tolerance, fainting, ascites, nausea, chest pain, and ankle swelling. Untreated, ATTR-CM causes death within about 2-5 years from diagnosis.[2]

There are two main types of ATTR-CM: hereditary (or variant) and wild-type. Wild-type ATTR-CM is the more common of the two types. It mostly affects older individuals (aged 60 or above) and is more common in men than women.[3] Hereditary ATTR-CM affects people born with inherited mutations in the TTR gene. The most prevalent TTR variants in the UK are Val112Ile and Thr60Ala. People with African or Caribbean and Hispanic family backgrounds are more likely to have hereditary ATTR-CM.[3, 4] It often presents before 60 years of age, and occasionally in people as young as their twenties. The company estimates that about 12.5% to 16.7% of patients have the hereditary type, although higher figures of 28.6% [5] and 30.5% [6] have been suggested. This discrepancy is potentially important, given the differing age-groups affected.

The number of diagnosed and treated people in the UK is estimated by the company to be around 1,300, and an NHS publication estimated 1,500 diagnosed patients in the UK. [7] The EAG's clinical

advisor estimates that, as more patients are diagnosed early in recent years, there may be 1,500-2,000 diagnosed UK patients. [2, 7]

2.2.2 Burden of disease

The CS provides a comprehensive summary of the burden of disease (CS, section 1.3.2.3 to 1.3.2.5). A brief summary is provided here.

The symptoms of ATTR-CM can impair physical capacity to the point where many activities of daily living become difficult or impossible. For this reason, and because of other disease effects, quality of life is reduced, with scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) being lower in people with ATTR-CM than in those with other cardiac conditions. Both quality of life and function deteriorate over time, which progressively adds to the disease burden.

Emotional and social impairments may also occur, resulting from anger, anxiety, relationship problems and fear of being a burden to family and friends. A loss of mobility and function, as well as pain and discomfort, may also contribute.

An economic burden may result from a loss of work productivity and the need for caregivers. There is also a large burden on the healthcare system, with larger numbers of outpatient visits, larger numbers and duration of hospitalisations, and greater numbers of surgical procedures. The company estimates that, after diagnosis the mean costs per patient per month may vary from £92 for a patient with New York Heart Association (NYHA) class I to £621 for a patient with NYHA IV (CS Table 6). The NYHA classification categorises functional status based on heart failure related limitations in physical activity, ranging from I (no limitation of physical activity) to IV (symptoms of heart failure at rest).

2.2.3 Vutrisiran

The company's description of Vutrisiran is summarised here.

Vutrisiran is a 'small interfering RNA' that causes the catalytic breakdown of TTR RNA, thus reducing the amount of TTR protein produced in the liver. The reduction in serum TTR will then reduce the amount of amyloid fibrils resulting from TTR degradation, and thus lead to a reduced build-up of amyloid deposits in tissues such as the heart. Vutrisiran is given by 25mg subcutaneous injections every 3 months. MHRA approval for the use of vutrisiran for ATTR-CM is expected in August 2025.

2.2.4 Clinical pathway of care and intended positioning of vutrisiran

2.2.4.1 Diagnosis and staging

The company's description of the diagnostic process is summarised here.

Suspicious signs and symptoms (such as those of heart failure) first prompt monoclonal testing. If monoclonal testing excludes light chain amyloidosis, bone scintigraphy is performed if available. If scintigraphy reveals amyloid deposits in the heart this confirms the diagnosis of ATTR-CM. If monoclonal testing does not exclude light chain amyloidosis, or if scintigraphy is not available, or if scintigraphy is negative in the presence of continued clinical suspicion, an endomyocardial biopsy is performed. The presence of TTR on Congo Red staining provides a confirmation of the diagnosis of ATTR-CM. Genetic sequencing may then be carried out to determine the type of ATTR-CM.

According to the company, staging of disease may be carried out by National Amyloidosis Centre (NAC) staging, as shown in Table 2. This is in addition to the NYHA functional classification (section 2.2.2).

Table 2 NAC staging of ATTR-CM (CS Table 8)

Stage	Criteria	
I	NT-proBNP ≤3,000 ng/L AND eGFR ≥45 ml/min	**Worsening disease** 
II	Remainder of patients not in stage I or III	
III	NT-proBNP >3,000 ng/L AND eGFR <45 ml/min	
Note: Both specified criteria (i.e., for NT-proBNP and eGFR) need to be met for a patient to be categorised in stage I or III.		

2.2.4.2 Current treatment pathway

The only currently MHRA-approved disease-modifying treatment for ATTR-CM is tafamidis. Supportive treatments for heart failure-related symptoms include diuretics, anticoagulants and lifestyle changes.

The EAG notes that other possible treatments for ATTR-CM exist, such as inotersen, diflunisal, doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid. However, discussion with the EAG clinical advisor suggests that these are not relevant to clinical practice in the UK, though some may occasionally be prescribed off-label.

2.2.4.3 Intended positioning of vutrisiran

The company sets out its expectation on the positioning of vutrisiran in CS Section 1.3.3.4. This states that the anticipated position of vutrisiran is as a new standard-of-care treatment for all patients with ATTR-CM in the UK, including those patients currently treated with tafamidis with inadequate response. The company stated that treatment with tafamidis leads to continued worsening in physical capacity, quality of life, and cardiac injury, with limited treatment benefit in some patient types (CS Section 1.3.3.2). The company assumes that this will make vutrisiran preferred over tafamidis. Vutrisiran is anticipated to be positioned as a monotherapy at launch, based on the anticipated lack of cost-effectiveness of tafamidis-vutrisiran combination therapy.

Clinical advice to the EAG, and stakeholder submissions for this appraisal, suggest there is no clear desire for tafamidis to be replaced entirely. Tafamidis appears to be widely used to treat ATTR-CM, and is believed to be effective and well-tolerated. Vutrisiran may be an alternative to tafamidis, for example, in patients for whom tafamidis is unsuitable. There is also interest in the possible use of tafamidis-vutrisiran combination therapy, to potentially take advantage of their different modes of action to maximise treatment benefit. However, the EAG's clinical advisor notes there is no evidence to support combination therapy currently, and the EAG acknowledges that combination therapy is outside the scope of this assessment.

2.2.5 Equality considerations

The company submission states that the V122I gene variant for ATTR-CM is associated with higher mortality and is far more prevalent in people of African descent.

2.2.6 Other relevant appraisals in progress

NICE technology appraisals currently in progress for ATTR-CM include eplontersen (TSID12015) and acoramidis (ID6354).

2.3 Critique of company's definition of decision problem

2.3.1 Population

The company's identified population – people with ATTR-CM - is identical to the final scope issued by NICE.

2.3.2 Intervention

The decision problem defines the intervention as vutrisiran monotherapy, whereas the NICE scope defines the intervention as vutrisiran, thereby allowing some leeway for combination therapy. Vutrisiran has been restricted to monotherapy in the decision-problem on the basis that combination therapy with vutrisiran and tafamidis was not anticipated to be cost effective by the company.

The EAG judges the company's positioning of vutrisiran as monotherapy acceptable. We note that tafamidis will be coming off-patent in 2026, or sometime thereafter. This will likely result in a reduction of acquisition cost for tafamidis over time in both monotherapy and in combination with vutrisiran.

2.3.3 Comparators

The decision problem is restricted to tafamidis, but the NICE scope also included established clinical management without vutrisiran. The company justifies this restriction by stating that tafamidis is the only current standard of care treatment.

Based on discussion with the EAG clinical advisor, the EAG agrees that focussing on the comparison with tafamidis is reasonable. However, there will be some people for whom tafamidis is unsuitable, although the proportion of patients affected is unclear and likely to be small. Absolute contraindications include conception/contraception, pregnancy and breast feeding and relative contraindications include hepatic impairment.[8] In addition, hypersensitivity or allergy to tafamidis appear to be rare but may occur.[9]

There are a significant proportion of patients who may withdraw from tafamidis treatment due to adverse effects, disease progression, or lack of treatment effectiveness. For example, Maurer et al. (2018)[10] showed that 21.2% of patients withdrew from tafamidis treatment in an RCT. This rate of discontinuation was equivalent to that in the placebo group, suggesting that most discontinuation was unlikely to be drug-related. Nevertheless, in clinical practice a similar proportion of people would be expected to withdraw from treatment and might be looking for alternative treatments. Therefore, the discontinuation rate of over a fifth of tafamidis patients might still be relevant clinically.

The EAG considers that comparing vutrisiran to established clinical management is important to determine if vutrisiran will be cost effective in such people. Therefore, the EAG requested that the company supplied a comparison with established clinical management (or best supportive care) as per the NICE scope. The EAG also notes that there is no randomised or controlled evidence to compare vutrisiran to tafamidis: the only randomised and controlled comparison is between vutrisiran and placebo.

2.3.4 Outcomes

The decision problem outcome list contains all those in the NICE scope, but also introduces an additional outcome: time to first oral loop diuretic intensification (ODI). The company justifies the addition of ODI to the NICE outcomes on the basis that it is a predictor of mortality. The EAG accepts the addition, but is unclear why ODI needs to be added, given that mortality is already an outcome and ODI is not included in the economic model.

2.3.5 Subgroups

The decision problem did not consider any subgroups, although the NICE scope specified two subgrouping strategies, relating to severity of heart failure and type of ATTR-CM. The company justified their decision on the basis that the subgroups in the HELIOS-B trial were too small. The EAG notes that, despite this claim, subgroup data were reported for the HELIOS-B trial, so these subgroups are evaluated in this report (Section 3.2.8).

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Population	People with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)	People with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)	NA	None
Intervention	Vutrisiran	Vutrisiran monotherapy	The company submission considers that vutrisiran will be positioned as a monotherapy at launch. This is based on anticipated lack of cost-effectiveness of combination use of two branded medicines (i.e., vutrisiran and tafamidis) given current NICE STA cost-effectiveness thresholds and clinician intentions for the use of vutrisiran once it is available.	Stakeholders expressed an interest in combination therapy, but the company does not make a case for vutrisiran-tafamidis combination therapy due to anticipated lack of cost-effectiveness.
Comparator(s)	• Tafamidis Established clinical management without vutrisiran	Tafamidis	Alnylam understands that all treatment-eligible patients for vutrisiran would otherwise be treated with tafamidis, the current standard of care (SOC). Therefore, it is the only comparator considered in the company cost-effectiveness analysis.	The EAG regards it as reasonable to focus on the comparison with tafamidis. However, a comparison with established clinical management is needed to evaluate the cost-effectivness of vurtrisiran where tafamidis in unsuitable.
Outcomes	The outcome measures to be considered include: • overall survival	The outcome measures to be considered include: • overall survival	Alnylam regards the outcomes to be appropriate; however, given the role of loop diuretics for	The EAG is unclear why ODI was added, given that mortality is already an outcome.

	• cardiovascular-related mortality • cardiac function (such as global longitudinal strain BNP level) • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients and carers).	• cardiovascular-related mortality • cardiac function (such as global longitudinal strain or BNP level) • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients and carers) • ODI	symptomatic management of worsening heart failure, loop diuretic dose has also emerged as a useful indicator of disease severity in ATTR-CM.[11] Specifically, longitudinal changes in daily loop diuretic dose have shown prognostic value in patients with ATTR-CM, as patients seen at the NAC (n=1,598) experiencing ODI (defined as initiation of oral loop diuretics or any increase in loop diuretic dose [furosemide equivalent]) from diagnosis to 1 year post-diagnosis, had a 1.9-fold increase (vs. patients without ODI) in mortality risk from 1 year post-diagnosis onward.[6] Therefore, Alnylam has included results from outcomes that incorporate ODI in patients with ATTR-CM in the submission.	
Economic analysis	As per NICE reference case	As per the NICE scope.		As per NICE scope, except for the intervention and comparators, as noted above.
Subgroups to be considered	• Severity of heart failure (such as by NYHA classification class) Wild-type ATTR-CM (wtATTR-CM) or hereditary ATTR-CM (hATTR-CM)	No subgroup analyses were performed.	Subgroup analyses were not performed. Alnylam regards it reasonable that subgroups defined by level of heart failure severity (via NYHA classification) and disease	While some subgroups may be small the EAG disagrees that this is justification for not evaluating them. As outcome data by subgroup was reported for the

			type (hATTR-CM vs wtATTR-CM) may be of potential interest to assess clinical effectiveness and cost effectiveness. However, there were very few patients within these subgroups in the vutrisiran and tafamidis monotherapy groups in HELIOS-B, meaning that reliable estimates of cost-effectiveness could not be generated. Further, vutrisiran demonstrated consistent efficacy across all predefined subgroups in HELIOS-B,[12] which included patients in NYHA I/II versus NYHA III, and in patients with wtATTR-CM versus hATTR-CM.	HELIOS-B trial, it is evalauted by the EAG.

Source: Table 1, CS

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company presents a systematic literature review (SLR) for clinical evidence, and one to identify evidence relating to the burden of illness.

3.1.1 Searches

The company searches to identify studies for their clinical effectiveness SLR were included in a report by Stratenym embedded within Appendix B of the submission. The original searches took place in December 2023 with a further update search in October 2024.

The search strategies matched the eligibility criteria for the review, were of high quality, and clearly reported. The full appraisal of the searches, including minor weaknesses identified by the EAG, are detailed in Table 4.

Table 4 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	A search line was missing from the update search of MEDLINE in table 20 but was provided in the company response to the PfCs.
Were appropriate sources searched?	PARTLY	No searches of databases containing non-Cochrane systematic reviews (e.g. Epistemonikos, KSR Evidence, DARE, PROSPERO). Limited searching of HTA websites (NICE, CADTH and SMC only).
Was the timespan of the searches appropriate?	YES	Databases and grey literature sources were searched from inception to October 2024. Conference proceedings were searched from 2022-2024.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population: ATTR-CM AND Interventions: (acoramidis OR patisiran OR tafemidis OR vutrisiran) AND Study design: RCTs. An additional search of vutrisian only may have been helpful to identify any publications containing adverse effects data.
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	YES	A search filter to limit retrieval to RCTs and controlled clinical trials designed by CADTH was used in the searches of MEDLINE and Embase. Additional search terms were added to the filter to ensure comprehensive retrieval of trials.

3.1.2 Inclusion criteria

The SLR aimed to identify clinical evidence for acoramidis, patisiran, tafamidis, and vutrisiran. Acoramidis for the treatment of ATTR-CM is anticipated to be reviewed by NICE through a Single

Technology Appraisal (STA) in 2025. Patisiran was approved in 2019 for the treatment of hATTR in adults with stage 1 and 2 polyneuropathy. The EAG considers the selection criteria to be appropriate.

3.1.3 Critique of data extraction

Screening of records was performed in accordance with standards and guidance for the conduct of SLRs. Data extraction was not completed in duplicate, which increases opportunities for error. This is unlikely to impact on findings reported in the CS, as the company only report on data from the HELIOS-B trial.

3.1.4 Quality assessment

Quality assessments were conducted appropriately and reported in full. See section 3.2 for the EAG's assessment of the HELIOS-B trial of vutrisiran.

3.1.5 Evidence synthesis

No synthesis of the evidence was provided, as only data relating to the HELIOS-B trial was included in the CS.

3.2 Critique of HELIOS-B trial

The only Phase III trial of vutrisiran eligible for this assessment was HELIOS-B.[13] Between November 2019 and August 2021, participants of HELIOS-B were recruited in 26 countries, and randomly allocated to vutrisiran (326 participants) or placebo (329 participants). The trial included 151 UK patients (23.1%). The double-blind period of the trial was planned to last between 30 and 36 months for each participant. The statistical analysis plan (SAP) was changed in February 2024 to increase minimum follow-up in the double-blind period from 30 to 33 months for the primary analysis. The last patient finished the randomised, double-blind period in June 2024. An open-label extension period of two years, in which all patients are allocated vutrisiran, is ongoing.

The company provides outcome data on the HELIOS-B study arms, and various subgroups (Table 5). The term 'monotherapy' is used in the CS to refer to participants who did not receive tafamidis at baseline, although a proportion did receive tafamidis during the double-blind trial period. The term 'background tafamidis' is used to refer to participants who were receiving tafamidis at baseline. In the CS, the subgroup on background tafamidis randomised to placebo is also called 'Tafamidis monotherapy' (CS Table 16, p. 70).

Table 5 Description of HELIOS-B study arms and subgroups

Population company definition	Study arm/ subset company definition	Description	Participants (N)
Overall study population	Vutrisiran study arm	Participants randomised to vutrisiran	326
	Placebo study arm	Participants randomised to placebo	328
Monotherapy	Vutrisiran monotherapy	Subset of participants randomised to vutrisiran, who were not on tafamidis at baseline.	196
	Placebo monotherapy	Subset of participants randomised to placebo, who were not on tafamidis at baseline.	199
Background tafamidis	Vutrisiran	Subset of participants randomised to vutrisiran, who were receiving tafamidis at baseline.	130
	Placebo/ Tafamidis monotherapy	Subset of participants randomised to placebo, who were receiving tafamidis at baseline.	129

3.2.1 Selection criteria

The EAGs clinical advisor deemed the selection criteria of HELIOS-B appropriate and relevant for UK clinical practice. Patients with NYHA class IV, or class III in combination with NAC stage III (NT-proBNP > 3000 ng/L and eGFR < 45 ml/min) were excluded. The clinical advisor indicated this is largely consistent with clinical practice. Clinicians in the UK would not currently treat NYHA Class IV patients with tafamidis, which suggests these patients would not receive vutrisiran either. However, patients in NYHA class III and NAC stage III are currently offered tafamidis and the clinical advisor therefore indicated these patients could be considered a relevant group for treatment with vutrisiran. The trial also excluded concomitant non-dihydropyridine calcium channel blockers, which were used by 11% of patients in a UK retrospective cohort study.[13]

Tafamidis naïve patients were not enrolled if the investigator anticipated starting treatment with tafamidis within 12 months of baseline. However, a proportion of participants did start tafamidis during the double-blind period (N=85; 21.5%). These participants started on tafamidis 1.5 to 39.1 months from baseline, with a median 17.7 months in the vutrisiran study arm and 17.0 months in the placebo arm (p. 170 CSR).

3.2.2 Baseline characteristics of HELIOS-B participants

In table 12 (pp. 46-47) of the CS, the company reports baseline characteristics of HELIOS-B participants for the vutrisiran and placebo study arms, and for the vutrisiran monotherapy and placebo monotherapy subsets. Monotherapy in this context refers to patients who were not receiving tafamidis at the time of randomisation. In response to our clarification questions (Question A9, Table 7), the company also provided baseline characteristics on the 'background tafamidis' population.

Table 6 provides an overview of baseline characteristics for the two randomised groups and the four subgroups. Information on world regions and history of polyneuropathy and concomitant medications was shared by the company in the clarification response.

3.2.2.1 *Overall population*

Randomisation was stratified by baseline tafamidis use, ATTR type (hATTR versus wtATTR) and NYHA class combined with age (class I/II and < 75 years old versus other). The EAG agrees with the company that characteristics were generally comparable between vutrisiran and placebo study arms.

3.2.2.2 *Vutrisiran monotherapy and placebo*

Participants in the vutrisiran and placebo monotherapy subgroups were not receiving tafamidis at randomisation. A proportion of participants received tafamidis (referred to as tafamidis drop-in in the CS) during the trial (22.4 vutrisiran versus 20.6% placebo). The company draws attention to the lower proportion of participants with NAC stage 1 and higher level of NT-proBNP in the vutrisiran monotherapy subset, compared to the placebo monotherapy subset. However, a higher proportion of participants in the vutrisiran monotherapy subset were in NYHA class III compared to the placebo monotherapy subset (9.0% vs 4.6%). Patients in the monotherapy population were more recently diagnosed compared to the overall population.

3.2.2.3 *Vutrisiran and placebo subgroups on background tafamidis treatment*

Most participants in the background tafamidis population were from the US [redacted]. Characteristics of participants in the vutrisiran and placebo study arms who were receiving tafamidis at randomisation were generally comparable. [redacted]

Table 6 Baseline characteristics for randomised study arms and subgroups

Parameter at baseline	Overall population (N=654)		Monotherapy population (N=395)		Background tafamidis population (N=259)	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=130)	Placebo (n=129)
World region, n (%)[#]						
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at randomisation, median, years (range)	77.0 (45.0–85.0)	76.0 (46.0–85.0)	76.0 (53.0–85.0)	77.5 (46.0–85.0)	[redacted]	[redacted]
Male, n (%)	299 (91.7)	306 (93.3)	183 (92.0)	178 (90.8)	[redacted]	[redacted]
Race						
White	277 (85.0)	275 (83.8)	169 (84.9)	169 (86.2)	[redacted]	[redacted]
Asian	18 (5.5)	19 (5.8)	15 (7.5)	12 (6.1)	[redacted]	[redacted]
Black/African American	23 (7.1)	24 (7.3)	11 (5.5)	10 (5.1)	[redacted]	[redacted]
Other/not reported	8 (2.5)	10 (3.0)	4 (2.0)	5 (2.6)	[redacted]	[redacted]
Disease type						
hATTR, n (%)	37 (11.3)	39 (11.9)	25 (12.6)	23 (11.7)	[redacted]	[redacted]
V122I, n (%)	24 (7.4)	25 (7.6)	16 (8.0)	13 (6.7)	[redacted]	[redacted]
wtATTR, n (%)	289 (88.7)	289 (88.1)	174 (87.4)	173 (88.3)	[redacted]	[redacted]
Time since diagnosis, median, years (range)	0.9 (0–11.1)	1.0 (0–10.8)	0.6 (0–6.2)	0.5 (0–8.3)	[redacted]	[redacted]
Tafamidis baseline use, n (%)	130 (39.9)	129 (39.3)	–	–	130 (100)	129 (100)
Time on tafamidis prior to start of study, median, months (range)	9.2 (1.1–65.3)	11.3 (1.1–65.5)	–	–	[redacted]	[redacted]
Tafamidis drop-in use, n (%)	44 (13.5)	41 (12.5)	44 (22.4)	41 (20.6)	-	-

Parameter at baseline	Overall population (N=654)		Monotherapy population (N=395)		Background tafamidis population (N=259)	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=130)	Placebo (n=129)
Timing of tafamidis initiation, median, months (range)	17.7 (6.4-39.1)	17.0 (1.5-33.8)	17.7 (6.4-39.1)	17.0 (1.5-33.8)		
NYHA class						
I, n (%)	49 (15.0)	35 (10.7)	12 (6.0)	15 (7.7)	[redacted]	[redacted]
II, n (%)	250 (76.7)	258 (78.7)	169 (84.9)	172 (87.8)	[redacted]	[redacted]
III, n (%)	27 (8.3)	35 (10.7)	18 (9.0)	9 (4.6)	[redacted]	[redacted]
NAC stage						
1, n (%)	208 (63.8)	229 (69.8)	138 (69.3)	113 (57.7)	[redacted]	[redacted]
2, n (%)	100 (30.7)	87 (26.5)	55 (27.6)	68 (34.7)	[redacted]	[redacted]
3, n (%)	18 (5.5)	12 (3.7)	6 (3.0)	15 (7.7)	[redacted]	[redacted]
6-MWT, mean, metres (SD)*	372.0 (103.7)	377.1 (96.3)	372.8 (98.1)	362.7 (102.7)	[redacted]	[redacted]
KCCQ-OS score, mean, points (SD)*	73.0 (19.4)	72.3 (19.9)	69.9 (20.8)	70.3 (20.2)	[redacted]	[redacted]
NT-proBNP, median, ng/L (IQR)	2021 (1138, 3312)	1801 (1042, 3081)	1865 (1067, 3099)	2402 (1321, 3867)	[redacted]	[redacted]

Source = Table 14.1.2.1 CSR Section 14. * Source = PfC response Table 5. ** Source = PfC response table 5, 7.

3.2.2.4 *Comparison with UK clinical practice*

The EAG's clinical advisor recommended a retrospective cohort study of 1967 ATTR-CM patients from the National Amyloidosis Centre (NAC) as the best source of contemporary data on patient characteristics in UK clinical practice.[13] Table 7 compares baseline participant characteristics of HELIOS-B with the cohort study data from 2017 to 2021. Of patients in the cohort, 29% were involved in clinical trials for treatment of ATTR-CM, and 16.4% received disease-modifying therapies. This comparison shows a general alignment between the trial and clinical practice population. Patients with the most severe disease symptoms were not included in HELIOS-B, and patients with hereditary ATTR-CM subtype V122I appear under-represented.

Table 7 Comparison of HELIOS-B baseline characteristics and UK patients with ATTR-CM

	HELIOS-B study arms		**UK clinical practice 2017-2021 (n=968)**
	Vutrisiran (n=326)	Placebo (n=328)	
Age, median	77.0	76.0	76.0[#]
Male	91.7%	93.3%	86.2%
Disease subtype hATTR T80A (T60A) hATTR V122I hATTR other wtATTR	 5% 7.4% 4.0% 88.7%	 15% 7.6% 4.3% 88.1%	 8.6% 20.0% 5.1% 66.3%
NYHA class[*] I II III IV	 15% 76.7% 8.3% NA	 10.7% 78.7% 10.7% NA	 14.0% 67.9% 13.8% 0.5%
NAC stage[**] 1 2 3	 63.8% 30.7% 5.5%	 69.8% 26.5% 3.7%	 53.3% 31.2% 11.0%
6-MWT meters, mean	372.0	377.1	368
NT-proBNP, median, ng/L	2021	1801	2505
eGFR median, mL/min/1.73m^2	64	65	61[#]

mean. * 2.3% missing cohort data. ** 4.9% missing cohort data.

3.2.3 Critical appraisal of HELIOS-B

The critical appraisal of the HELIOS-B trial is reported in appendix B of the CS. The EAG agrees with the assessment of low risk of bias for all domains but notes the following caveats.

Randomisation was carried out appropriately. Randomisation was stratified by baseline tafamidis use, ATTR type, and NYHA class combined with age. Analyses of the comparison between vutrisiran

monotherapy and tafamidis monotherapy rely on non-randomised treatment allocations which were not randomised nor blinded to treatment with tafamidis.

Missing data were imputed appropriately. For the outcome 'change in NYHA class', data were imputed using baseline characteristics and results of previous assessments. In the PfC response (QA4), the company provide additional information regarding measures taken to avoid attrition bias.

In February 2024, before the primary data cut, several secondary and exploratory outcomes were changed. Change in NYHA class (% stable/ improved) was added as a secondary outcome and subsequently reported on in the CS (CS pp. 64-65). Time to first oral diuretic intensification, first CV event, or ACM was added as an exploratory outcome and reported as such in the CS (pp. 67-68).

3.2.4 Clinical evidence in HELIOS-B

The company shared evidence on the five comparisons summarised here.

1. The **overall population**, with randomised study arms vutrisiran (n=326) and placebo (n=328).

The primary outcome is a composite measure of all-cause mortality (ACM) and recurrent cardiovascular (CV) events over a maximum of 36 months. CV events include CV hospitalisations and urgent heart failure visits. Secondary outcomes include change in 6-minute walk test (6-MWT) over 30 months, change in Kansas City Cardiomyopathy Questionnaire (KCCQ-OS) score over 30 months, ACM up to 42 months, and change in NYHA class over 30 months.

In the study sample, 52.6% of participants were receiving tafamidis, either at baseline (39.6%) or through drop-in use during the trial period (13.0%). Whether participants were receiving tafamidis at baseline likely depends on the timing of the introduction of tafamidis in the study country, and clinical decision-making. In the response to clarification question A14, the company explain that tafamidis was approved in the US before it was approved in other countries, and patients from the tafamidis monotherapy group were therefore predominantly from the US (see Table 6).

2. The pre-specified **monotherapy population**, comparing vutrisiran and placebo for participants who did not receive tafamidis prior to and at baseline/ randomisation. The analyses conducted are for the same outcomes as those reported for the overall population.

3. The **background tafamidis population**, comparing vutrisiran and placebo in post-hoc analyses for participants who were receiving tafamidis prior to and at baseline/ randomisation, with the same outcomes reported as listed above.

4. The **vutrisiran monotherapy versus tafamidis monotherapy** comparison, for which the primary outcome is reported along with ACM over 42 months and change in NYHA class over 30 months.

These post-hoc analyses compare participants receiving vutrisiran without tafamidis at randomisation with participants in the placebo group who were prescribed tafamidis at the time of randomisation. To adjust for imbalances in key covariates, IPTW was used alongside further adjustment by including a selection of covariates in the model.

Data from these analyses are the main source of clinical evidence used in the economic model.

5. The **tafamidis monotherapy versus placebo comparison**, for which post-hoc analyses of the primary outcome are reported along with ACM over 42 months and change in NYHA class over 30 months. To adjust for imbalances in key covariates, IPTW was used alongside further adjustment by including a selection of covariates in the model.

Results are summarised below for vutrisiran versus placebo (comparisons 1, 2, 3) vutrisiran versus tafamidis monotherapy (comparison 4), and tafamidis versus placebo (comparison 5).

3.2.5 HELIOS-B vutrisiran versus placebo

3.2.5.1 Comparison 1: study arms vutrisiran (n=326) versus placebo (n=328).

Comparing the randomised vutrisiran and placebo study arms, vutrisiran was associated with a reduced risk of mortality and CV events combined, less decline over time on the 6-MWT, less decline over time on the KCCQ-OS, and a higher proportion of patients classed as stable or improved on the NYHA classification (Table 8). ACM over 42 months was lower in the vutrisiran arm (18.4%) compared to the placebo arm (25.9%).

Table 8 Results of primary and secondary endpoints comparison 1

Population/ comparison	**1. Overall population (N=654)**	
Measure	**Vutrisiran (n=326)**	**Placebo (n=328)**
Primary endpoint: composite of ACM and recurrent CV events over up to 36 months		
ACM, n (%)	51 (15.6)	69 (21.0)
Patients with at least one CV event, n (%)	112 (34.4)	133 (40.5)
Patients with at least one event total, n (%)	125 (38.3)	159 (48.5)
HR total events (vutrisiran/placebo) (95% CI)	0.72 (0.56, 0.93) P=0.01	
Secondary endpoint: change in 6-MWT over 30 months		
LS mean change over 30 months, metres (95% CI)	–45.4 (–54.5, –36.3)	−71.9 (−81.3, −62.4)
LS mean difference (vutrisiran – placebo), metres (95% CI)	26.5 (13.4, 39.6) P<0.001	

Population/ comparison	1. Overall population (N=654)	
Measure	**Vutrisiran (n=326)**	**Placebo (n=328)**
Secondary endpoint: change in KCCQ-OS score over 30 months		
LS mean change over 30 months, points (95% CI)	−9.7 (−12.0, −7.4)	−15.5 (−18.0, −13.0)
LS mean difference (vutrisiran – placebo), points (95% CI)	5.8 (2.4, 9.2) P<0.001	
Secondary endpoint: ACM over up to 42 months		
Deaths, n (%)	60 (18.4)	85 (25.9)
HR (vutrisiran/placebo) (95% CI)	0.65 (0.46, 0.90) P=0.01	
Secondary endpoint: change in NYHA class over 30 months		
Stable/improved over 30 months, %	67.8	60.5
Adjusted difference (vutrisiran – placebo), % (95% CI)	8.7 (1.3, 16.1) P=0.02	
Odds ratio of stability/improvement (vutrisiran/placebo) (95% CI)	[redacted]	

Source: Table 15 CS, CSR p.77, response to clarifications Table 2.

3.2.5.2 *Comparison 2: vutrisiran monotherapy (n=196) versus placebo (n=199), no tafamidis at baseline.*

All reported outcomes favoured vutrisiran monotherapy over placebo (Table 9). Cardiovascular events, mortality over 36 months, and mortality over 42 months were slightly higher in both subgroups when compared with the overall population (including patients receiving tafamidis). Similarly, there was more deterioration in 6-MWT, KCCQ-OS score, and NYHA class in the subgroups compared to the overall population.

For this comparison, the company also performed a sensitivity analysis to account for the possible influence of tafamidis drop-in use (22.4% in vutrisiran subgroup, 20.6% in placebo subgroup). The sensitivity analysis [redacted] (Table 14.2.2.1.7 CSR Section 14). [redacted]

Table 9 Results of primary and secondary endpoints comparison 2

Population/ comparison	**2. Monotherapy (N=395)** (no tafamidis at baseline)	
Measure	**Vutrisiran (n=196)**	**Placebo (n=199)**
Primary endpoint: composite of ACM and recurrent CV events over up to 36 months		
ACM, n (%)	36 (18.4)	46 (23.1)
Patients with at least one CV event, n (%)	66 (33.7)	87 (43.7)
Patients with at least one event total, n (%)	76 (38.8)	105 (52.8)
HR total events (vutrisiran/placebo) (95% CI)	0.67 (0.49, 0.93) P=0.02	
Secondary endpoint: change in 6-MWT over 30 months		
LS mean change over 30 months, metres (95% CI)	−59.7 (−72.7, −46.7)	−91.8 (−104.4, −79.2)
LS mean difference (vutrisiran – placebo), metres (95% CI)	32.1 (14.0, 50.2) P<0.001	
Secondary endpoint: change in KCCQ-OS score over 30 months		
LS mean change over 30 months, points (95% CI)	−10.8 (−14.1, −7.5)	−19.5 (−22.9, −16.1)
LS mean difference (vutrisiran – placebo), points (95% CI)	8.7 (4.0, 13.4) P<0.001	
Secondary endpoint: ACM over up to 42 months		
Deaths, n (%)	43 (21.9)	58 (29.1)
HR (vutrisiran/placebo) (95% CI)	0.66 (0.44, 0.97) P=0.045	
Secondary endpoint: change in NYHA class over 30 months		
Stable/improved over 30 months, %	66.3	56.4
Adjusted difference (vutrisiran – placebo), % (95% CI)	12.5 (2.7, 22.2) P=0.01	
Odds ratio of stability/improvement (vutrisiran/placebo) (95% CI)	[redacted]	

Source: Table 15, CS.

3.2.5.3 Comparison 3: vutrisiran with background tafamidis (n=130) versus placebo with background tafamidis (n=129).

[redacted]

(Table 10).[redacted]

The interpretation of these results is complicated by the comparison of a subgroup with definite exposure to vutrisiran, to a subgroup with uncertain background exposure to tafamidis. The company explained in the PfC response they do not hold data on background tafamidis use during the trial

period, and it is therefore unclear what proportion of participants in the 'background tafamidis' placebo subgroup was receiving tafamidis at any one time during the double-blind period and beyond.

Table 10 Results of primary and secondary endpoints comparison 3

Population/ comparison	3. Background tafamidis (N=259)	
Measure	**Vutrisiran (n=130)**	**Placebo/ Tafamidis (n=129)**
Primary endpoint: composite of ACM and recurrent CV events over up to 36 months		
ACM, n (%)	[redacted]	[redacted]
Patients with at least one CV event, n (%)	[redacted]	[redacted]
Patients with at least one event total, n (%)	[redacted]	[redacted]
HR total events (vutrisiran/placebo) (95% CI)	[redacted]	
Secondary endpoint: change in 6-MWT over 30 months		
LS mean change over 30 months, metres (95% CI)	[redacted]	[redacted]
LS mean difference (vutrisiran – placebo), metres (95% CI)	[redacted]	
Secondary endpoint: change in KCCQ-OS score over 30 months		
LS mean change over 30 months, points (95% CI)	[redacted]	[redacted]
LS mean difference (vutrisiran – placebo), points (95% CI)	[redacted]	
Secondary endpoint: ACM over up to 42 months		
Deaths, n (%)	[redacted]	[redacted]
HR (vutrisiran/placebo) (95% CI)	[redacted]	
Secondary endpoint: change in NYHA class over 30 months		
Stable/improved over 30 months, %	[redacted]	[redacted]
Adjusted difference (vutrisiran – placebo), % (95% CI)	[redacted]	
Odds ratio of stability/improvement (vutrisiran/placebo) (95% CI)	[redacted]	

Source: PfC response Table 8, CSR Table 14.2.1.1.

3.2.6 Vutrisiran monotherapy versus tafamidis monotherapy

Table 11 provides an overview of results for the comparison of vutrisiran to tafamidis within HELIOS-B.

It should be noted that the comparison between vutrisiran monotherapy and tafamidis monotherapy was not randomised, and the decision to give tafamidis, both before randomisation and as "drop-in" after randomisation, was based on clinical judgment. Among participants in the placebo subgroup, those on background tafamidis (at baseline/ randomisation) were relatively healthy when comparing baseline characteristics (see Table 6). There was evidence that treatment with tafamidis was more

common in [redacted] (response to clarification question A14, Table 16).

In order to address the possible biases that these differences might produce the company used Inverse Probability of Treatment Weighting (IPTW) to adjust the data. The EAG accepts that this is a reasonable approach to take to balance the two treatment arms. The EAG accepts that appropriate patient factors were adjusted for, and that the IPTW approach seems to have generated balanced treatment arms (except for [redacted] clarification question A14, Table 16). However, it should be noted that this does not guarantee a fair comparison between vutrisiran and tafamidis, as some key patient factors may not have been identified and adjusted for.

The company confirmed that all comparisons between vutrisiran and tafamidis were adjusted for imbalances in key covariates between the subgroups, using IPTW and further adjustment adding log-transformed NT-proBNP, troponin I, and baseline 6-MWT as covariates. For NYHA class change, baseline NYHA was added as a covariate.

There is [redacted] between participants who received vutrisiran (n=196) and those on background tafamidis/ placebo (n=129) in the primary outcome of composite ACM and recurrent CV events, ACM over up to 42 months, recurrent CV events over up to 36 months, change in NYHA class over 30 months, and change in EQ-5D-5L over 30 months. It should be noted that although the results for ACM were in the direction of [redacted] when adjusting using IPTW, unadjusted results were in the direction of [redacted] from clarification response to Question A8 Table 10).

Seeking to explain the [redacted] for vutrisiran compared to tafamidis, the company argue the tafamidis monotherapy group is at an advantage, as participants have been exposed to tafamidis prior to trial enrolment (median 11.3 months, range 1.1; 65.6), benefiting long-term outcomes. Vutrisiran-treated patients meanwhile do not benefit from vutrisiran until treatment starts at baseline. This argument however does not explain the [redacted] between subgroups in change in NYHA class, which reflects changes from baseline. No data was provided on change in secondary endpoints 6-MWT and KCCQ-OS score.

As for comparison 3 discussed above, the comparison is complicated by unclear tafamidis exposure during the trial. A proportion of participants previously prescribed tafamidis may have stopped tafamidis during the trial period. The EAG's clinical advisor suggests 5-10% may stop tafamidis due to side effects, and 5-10% may have their prescription terminated at end stage heart failure or in the palliative phase.

Table 11 Results of primary and secondary endpoints comparison 4

Population/ comparison	4. Vutrisiran monotherapy vs tafamidis monotherapy (placebo background tafamidis)	
Measure	**Vutrisiran (n=196)**	**Placebo/ Tafamidis (n=129)**
Primary endpoint: composite of ACM and recurrent CV events over up to 36 months		
ACM, n (%)	36 (18.4)	[redacted]
Patients with at least one CV event, n (%)	66 (33.7)	[redacted]
Patients with at least one event total, n (%)	76 (38.8)	[redacted]
HR total events (vutrisiran/tafamidis) (95% CI)	0.83 (0.54, 1.29)	
Secondary endpoint: ACM over up to 42 months		
Deaths, n (%)	[redacted]	[redacted]
HR (vutrisiran/tafamidis) (95% CI)	0.81 (0.50, 1.34)	
Secondary endpoint: change in NYHA class over 30 months		
Stable/improved over 30 months, %	[redacted]	[redacted]
Adjusted difference (vutrisiran – tafamidis), % (95% CI)	[redacted]	
Odds ratio of stability/improvement (vutrisiran/tafamidis) (95% CI)	[redacted]	

Source: CS Table 16.

3.2.7 Tafamidis monotherapy versus placebo without tafamidis

At the request of the EAG the company provided a comparison of patients receiving background tafamidis ("tafamidis monotherapy") to those receiving only placebo without tafamidis or vutrisiran ("placebo monotherapy") in HELIOS-B, to investigate the effectiveness of tafamidis. This is presented in Table 12.

Results for tafamidis vs placebo [redacted] with those for vutrisiran monotherapy vs placebo. As in Table 11, there is [redacted] between vutrisiran and tafamidis. Results for all-cause mortality are [redacted] with the evidence from the ATTR-ACT trial of tafamidis [10].

Table 12 Results of primary and secondary endpoints comparison for tafamidis vs placebo

Population/ comparison	5. Tafamidis monotherapy (placebo background tafamidis) vs placebo monotherapy (placebo without background tafamidis or vutrisiran)	
Measure	**Placebo monotherapy (n=199)**	**Tafamidis monotherapy (n=129)**
Primary endpoint: composite of ACM and recurrent CV events over up to 36 months		
ACM, n (%)	[redacted]	[redacted]
Patients with at least one CV event, n (%)	[redacted]	[redacted]
HR total events (tafamidis/ placebo) (95% CI)	[redacted]	
Secondary endpoint: ACM over up to 42 months		
Deaths, n (%)	[redacted]	[redacted]
HR (tafamidis/ placebo) (95% CI)	[redacted]	
Secondary endpoint: change in NYHA class over 30 months		
Stable/improved over 30 months, %	[redacted]	[redacted]
Adjusted difference (tafamidis - placebo), % (95% CI)	[redacted]	
Odds ratio of stability/improvement (tafamidis/ placebo) (95% CI)	[redacted]	

Source: response to clarification questions, Table 9

3.2.8 Subgroup analyses (Comparison 1: overall population)

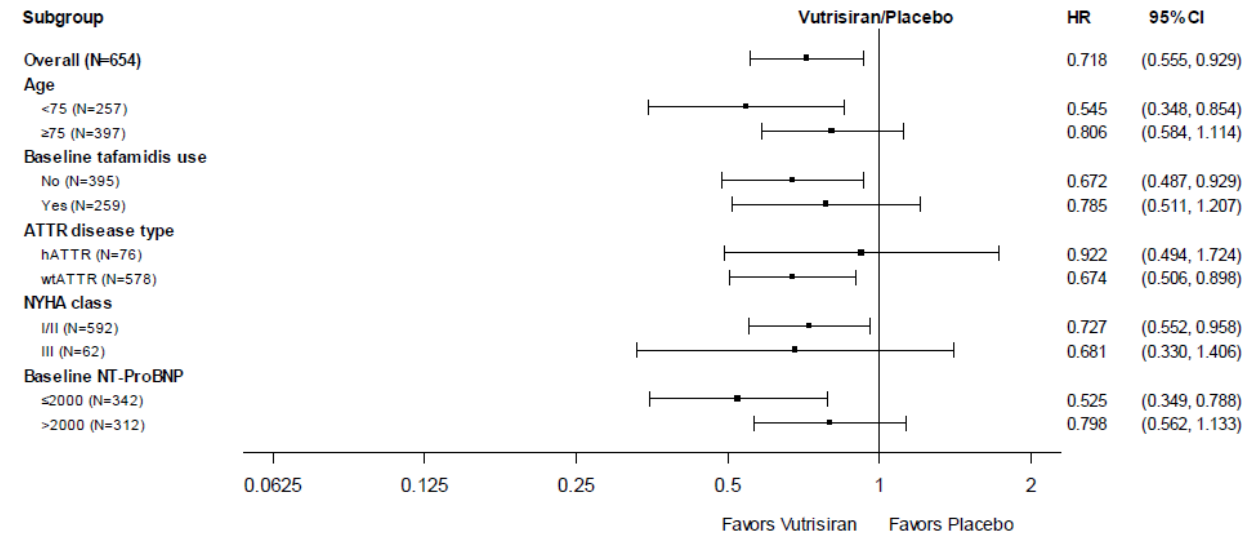
As part of the CS, the company provided results of pre-specified subgroup analyses for the primary composite outcome and for ACM up to 42 months (CS Appendix C). The company declined to provide the tests for differences requested by the EAG as part of the clarification response (PfC QA6). The forest plots below, including those for additional outcomes change in 6-MWT, change in KCCQ-OS, and change in NYHA class, were copied from the CSR, Section 14 (received after the PfC response).

Despite uncertainty in the results due to these subgroups not being adequately powered, we note three results of interest. For the change-from-baseline outcomes, particularly KCCQ-OS and NYHA class, there appears to be less benefit of vutrisiran for participants receiving tafamidis at baseline. Vutrisiran also appears to show less efficacy for participants with higher levels of baseline NT-proBNP. Thirdly, there is no evidence of a benefit of vutrisiran in the small subgroup of participants with hATTR.

3.2.8.1 Subgroup analyses composite ACM/ CV events

Figure 1 shows that in the full analysis set, the estimated efficacy of vutrisiran compared to placebo was lower for older participants, hATTR versus wtATTR, and participants with a higher baseline NT-proBNP.

Figure 1 Forest plot of subgroup analyses: composite ACM/ recurrent CV events

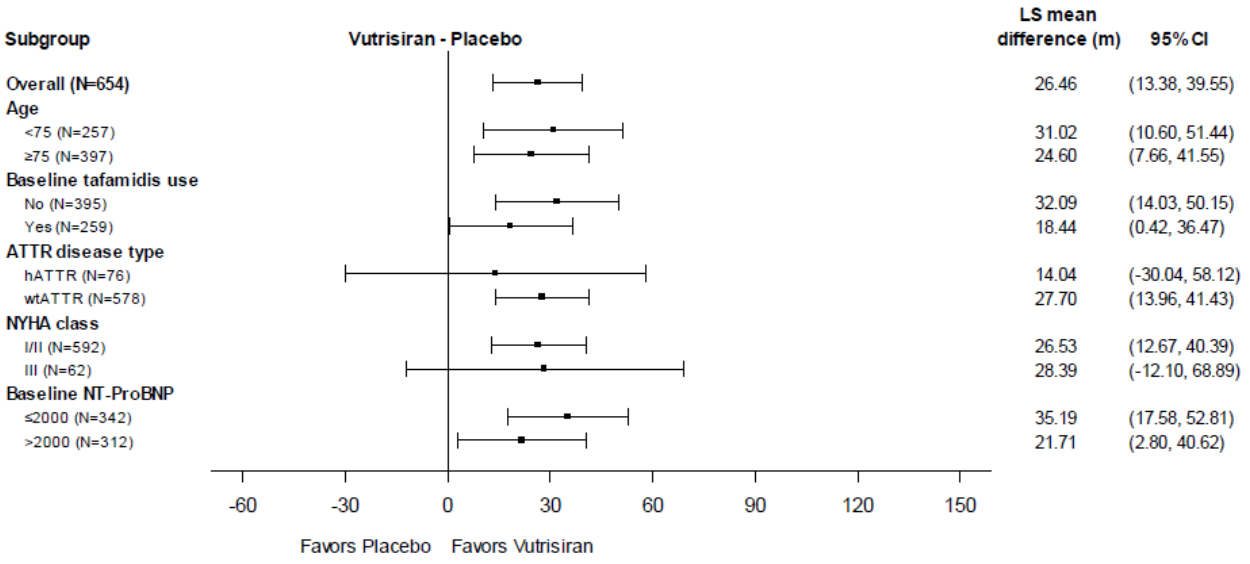


Source: CSR Figure 14.2.3.

3.2.8.2 Subgroup analyses change from baseline in 6-MWT

Figure 2 shows comparable results between subgroups for change in 6-MWT, with high uncertainty in smaller subgroups (hATTR and NYHA class III).

Figure 2 Forest plot of subgroup analyses change: from baseline in 6-MWT

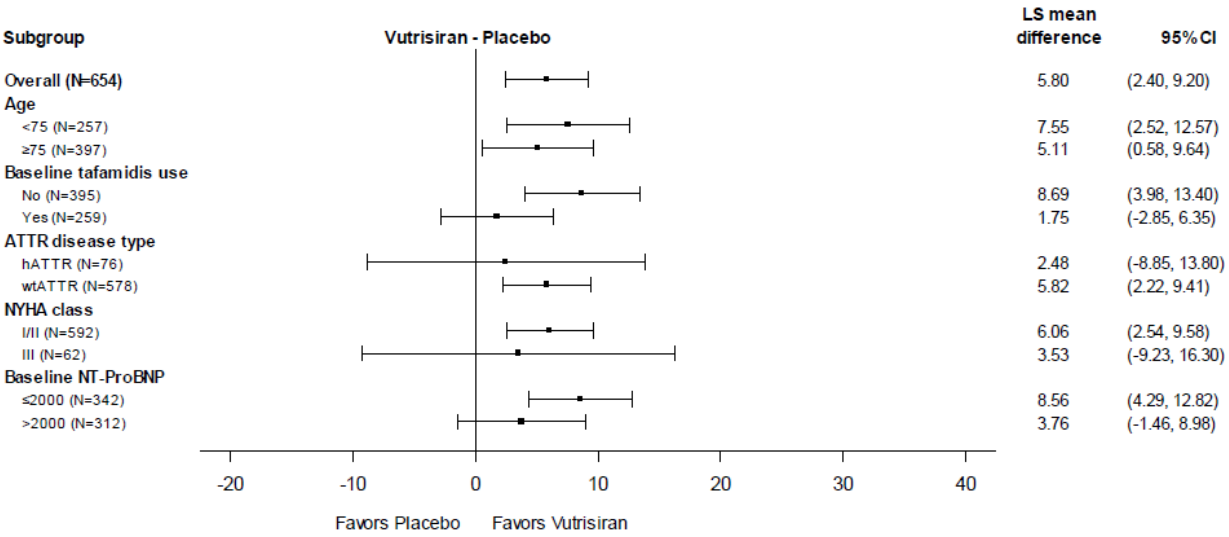


Source: CSR Figure 14.2.3.2.1.

3.2.8.3 Subgroup analyses change from baseline in KCCQ-OS score

Figure 3 shows that the efficacy for vutrisiran versus placebo may be greater for participants who are not receiving tafamidis at baseline compared to those who are, and also for participants with lower levels of NT-pro-BNP at baseline.

Figure 3 Forest plot of subgroup analyses: change from baseline in KCCQ-OS score

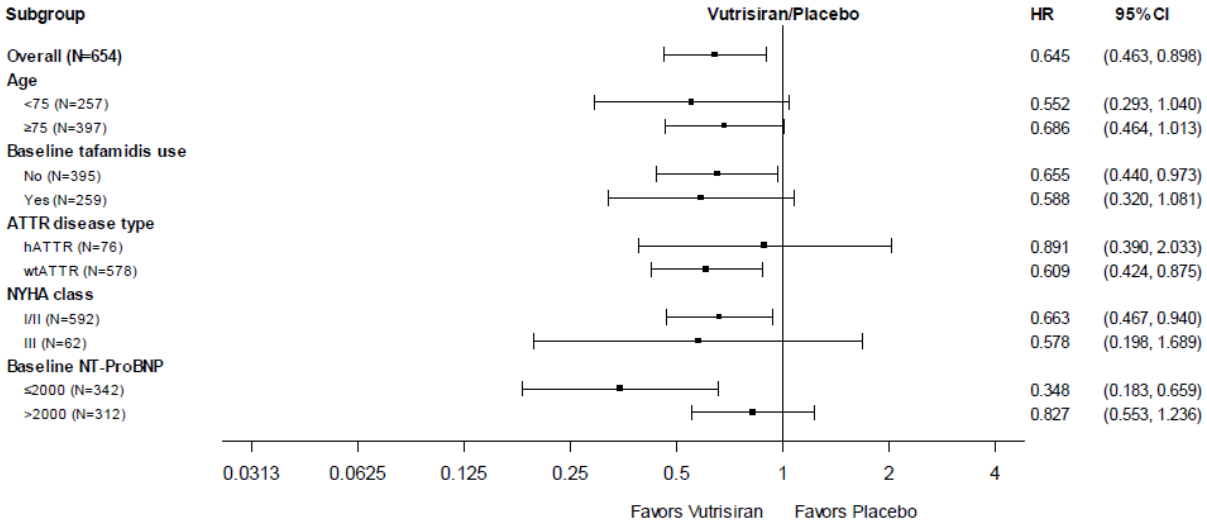


Source: CSR Figure 14.2.3.3.1.

3.2.8.4 Subgroup analyses ACM up to 42 months

Comparing up to 42 months, the effect estimate was less favourable for vutrisiran compared to placebo for participants with hATTR as opposed to wtATTR. The HR was also markedly higher for participants with a higher baseline NT-proBNP (HR 0.83, CI 0.55; 1.24) compared to a lower NT-proBNP level (HR 0.35, 95% CI 0.18; 0.66).

Figure 4 Forest plot of subgroup analyses: ACM up to 42 months

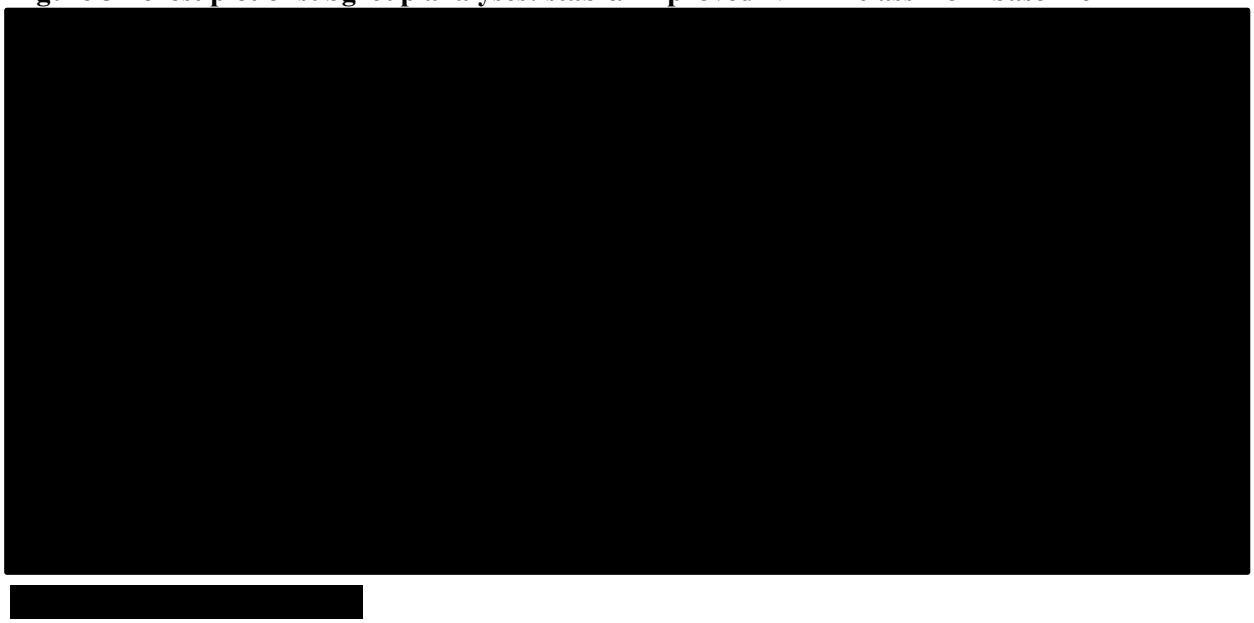


Source: CSR Figure 14.2.3.4.1.

3.2.8.5 Subgroup analyses stable/ improved NYHA class

[redacted]

Figure 5 Forest plot of subgroup analyses: stable/ improved NYHA class from baseline



3.3 Adverse events

3.3.1 Vutrisiran versus placebo

The company submission (Table 19, CS) provides very brief information on adverse events in the HELIOS-B trial, where the adverse event rates in the vutrisiran group are reported to be similar to those in the placebo group.

The CSR provides more extensive information on adverse events in the HELIOS-B trial. There were no meaningful differences between vutrisiran and placebo in the proportions with 'at least one AE', 'at least one serious AE', 'at least one severe AE', 'at least one AE leading to study interruption', 'at least one AE leading to discontinuation from study drug' or deaths. This was true whether these events were [redacted] (CSR, Table 26). There were also [redacted] in adverse events affecting ≥10% of patients (CSR, Table 27), [redacted] in serious adverse events affecting ≥2% of patients (CSR, Table 28). Specific injection site events, hepatic events, cardiac events, renal events, ocular events and malignancies were also [redacted] across groups.

Because vutrisiran reduces serum TTR, which has a role in transport of thyroxin and vitamin A, adverse events related to impaired thyroxin and vitamin A transport are plausible. These were not reported in the original submission and so the company was asked to provide further information.

In relation to thyroxin, the company reported evidence from HELIOS-B suggesting that thyroid-related AEs to vutrisiran do not occur [redacted] observed in the placebo group. The

company explain this by stating that TTR is only one of several thyroxin carrier proteins. Given this, the EAG agrees that thyroid-related AEs are unlikely.

In relation to vitamin A, the company provided evidence from HELIOS-B showing that eye disorders attributable to changes in vitamin A levels in the vutrisiran group [redacted] to those in the placebo group. The EAG note that the company have restricted their evidence to ocular adverse events, whereas vitamin A has potential effects on other body systems (for example excessive levels can lead to liver damage, and deficiency can lead to dermatological, cardiac, pulmonary and immunological effects). It is unclear if AEs in these systems were fully covered by the original AE evidence submitted.

3.3.2 Vutrisiran versus tafamidis

No adverse events were provided comparing the vutrisiran monotherapy subgroup and the tafamidis monotherapy subgroup. In response to a request for further information, the company provided a table of AE data in both sub-groups (Table 13, Company response to clarification). This demonstrated that the drugs lead to [redacted] of AEs, [redacted] of cardiac failure for vutrisiran ([redacted] compared to Tafamidis ([redacted]). The company explain this difference in terms of confounding secondary to non-randomised allocation. This is plausible, and so it would have been useful for the company to have also compared rates of cardiac failure in the propensity-matched groups (which they did not do). In the absence of such evidence and given the need to be vigilant for any signal of harm, the EAG would highlight this as a point for consideration by the committee.

3.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not supply any indirect treatment comparison evidence, either Matched Adjusted Indirect Comparison (MAIC) or network meta-analysis (NMA), to compare vutrisiran to tafamidis in its submission. The EAG therefore requested that these be supplied. The company only partly responded to this request. For full discussion see Section 3.5.

In response to the EAG's request, the company did supply a partial MAIC to compare vutrisiran in the HELIOS-B trial to tafamidis in the ATTR-ACT trial [10]. The EAG therefore briefly summarises the ATTR-ACT trial here.

The ATTR-ACT trial enrolled 441 patients across 13 countries. Patients were randomised to either tafamidis (20mg/day or 80mg/day) or placebo. Inclusion criteria appeared broadly similar to HELIOS-B and included patients with both hereditary and wild-type ATTR-CM, and patients across NYHA classes I to III. Patients were followed up for 30 months. Primary outcomes were all-cause

mortality and cardiovascular-related hospitalizations. Key secondary outcomes were the 6-MWT and the KCCQ-OS score.

The EAG has not performed a quality assessment of ATTR-ACT trial, but we note that EAG report for the NICE assessment of tafamidis (TA696/TA984, www.nice.org.uk/guidance/ta984) judged it to be of high-quality and raised no quality concerns.

There were substantial differences in the included populations between ATTR-ACT and HELIOS-B, that appear mainly to be due to improvements in clinical practice since ATTR-ACT was conducted. These are set out in CS Table 17. Briefly, patients in ATTR-ACT had more severe disease generally than those in HELIOS-B and were more likely to be in NYHA class III, and have poorer 6-MWT, KCCQ-OS and NT-pro-BNP.

3.5 Critique of the indirect comparison and/or multiple treatment comparison

As noted in Section 3.4, the company did not provide any indirect comparisons of vutrisiran and tafamidis. They justified this based on clinical expert opinion that: "HELIOS-B and ATTR-ACT have differing patient populations meaning that outcomes from these studies are not comparable. The patients enrolled in ATTR-ACT were much more advanced in terms of disease progression, vs. those enrolled in HELIOS-B, in which patients had milder disease." [*Quoted from company response to clarification question A12*]

3.5.1 Critique of company decision not to present any indirect comparison evidence

The assessment that the two studies had different populations with different disease severity is correct (see CS Table 17). However, the EAG does not accept that this represents a valid justification for not performing any indirect treatment comparisons. This is because the MAIC methodology is intended to correct for such imbalances between trials. Also, as both trials included a placebo arm, both anchored MAICs and an NMA should be feasible. Both of those methods are intended to reduce the possible bias arising from differences in trial populations. The EAG considers that indirect comparison will only be invalid if either:

- The matching in a MAIC is unsuccessful, with failure to adequately match trials across multiple key parameters
- Or, if any of the parameters where the trials differ are also treatment modifiers. For example, if tafamidis was more effective in populations with more advanced disease

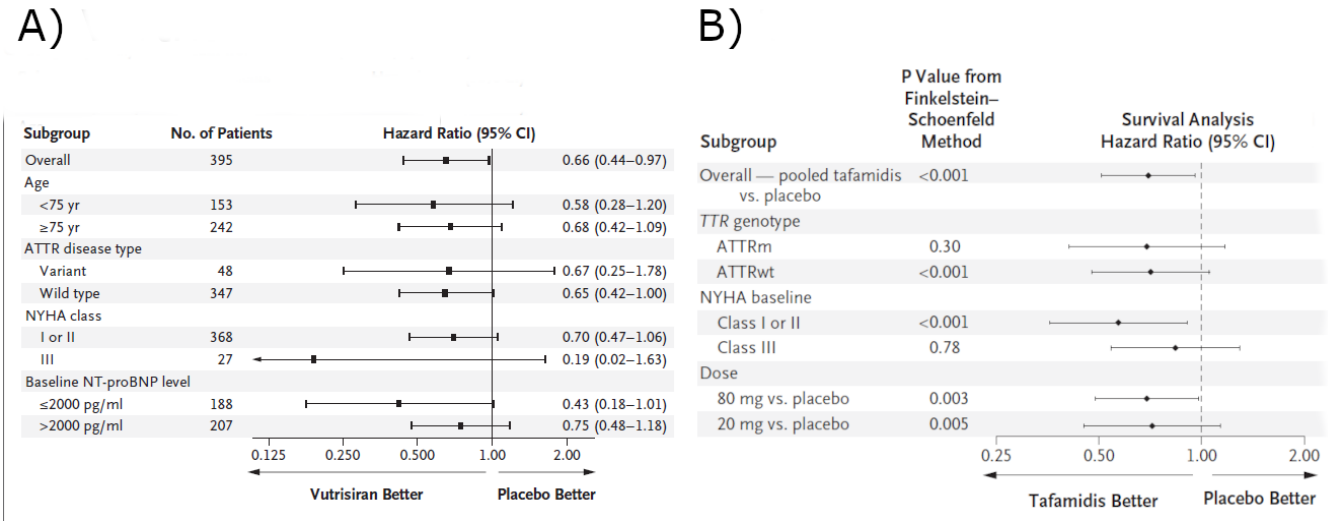
The company supplied details of the MAIC matching in CS Table 17. These results showed that, before MAIC adjustment there were considerable differences between the trials, with patients in ATTR-ACT being, older and with more advanced disease (e.g. more patients in NYHA class III,

poorer pro-BNP scores etc.). After MAIC adjustment, adjustment appeared successful [redacted] but was not fully successful for others including [redacted] The EAG notes there is therefore some concern that a MAIC comparison will not be fully fair. However, [redacted] the EAG still considers that performing a MAIC is reasonable, and that an anchored MAIC could further allay any imbalance concerns.

Evidence on whether key parameters are also treatment modifiers was available from subgroup analyses as reported for HELIOS-B [12] and ATTR-ACT [10]. These are reproduced here in Figure 6 (and see also Section 3.2.8). There is no compelling evidence that the effectiveness of tafamidis or vutrisiran varies with any key parameter. It is possible that tafamidis is more effective in people at NYHA class I or II. Vutrisiran might be more effective in people in NYHA class III or people with lower pro-BNP, but none of these are conclusive. On balance, there is no clear evidence that variation in the effectiveness of the treatments would lead to misleading results in either an NMA or an anchored MAIC.

In summary, although the EAG acknowledges that there are substantial differences between the populations in the HELIOS-B and ATTR-ACT trials, we consider that they do not mean that indirect comparison between the trials would therefore be invalid. The EAG thinks that both NMA and anchored MAIC could provide valuable evidence to compare vutrisiran with tafamidis. The EAG considers it to be unfortunate that the company declined to provide either analysis, despite our specific requests to do so.

Figure 6 Subgroup analysis of ACM for A) Vutrisiran in HELIOS-B and B) Tafamidis in ATTR-ACT



Source: HELIOS-B[12] and ATTR-ACT[10]

3.5.2 Summary of MAIC results comparing HELIOS-B with ATTR-ACT

The company did, on request, provide a limited unanchored MAIC to compare HELIOS-B to ATTR-ACT for all-cause mortality and stability or improvement in NYHA class. The results of these MAICs are presented in Table 13.

As discussed in Section 3.5.1 there were some concerns with imbalances between the two trials, both before and after weighting, so the MAIC may not represent a true comparison of vutrisiran and tafamidis if they were compared in a new trial.

The results show [redacted] We note that these findings are similar to the results found when comparing vutrisiran and tafamidis within HELIOS-B (see Section 3.2.6 and CS Table 16).

Given these findings, and because of the uncertainties arising when comparing HELIOS-B to ATTR-ACT, the EAG concludes that the MAIC demonstrates no clear evidence of any difference in effectiveness between vutrisiran and tafamidis.

Table 13 MAIC analyses comparing HELIOS-B to ATTR-ACT

Parameter	Unanchored MAIC
ACM HR, (vutrisiran vs. tafamidis; 95% CI)	[redacted]
Difference in proportion with stable/improved NYHA class from baseline to 30 months (vutrisiran – tafamidis; 95% CI)	[redacted]

3.6 Additional work on clinical effectiveness undertaken by the EAG

3.6.1 NMAs conducted by EAG

As discussed in Section 3.5 the EAG requested that the company supply NMAs and anchored MAICs to compare the HELIOS-B and ATTR-ACT trials. The company declined to supply these. The EAG has therefore conducted its own NMA analyses, where these were feasible, as we do not have the data to perform MAIC analyses.

NMAs were conducted for ACM, 6-MWT and KCCQ-OS. The EAG could not extract suitable data on tafamidis for any other outcomes. For all outcomes data were digitally extracted using WebPlotDigitizer software [https://automeris.io/] from the ATTR-ACT main publication [10]for tafamidis and from the CS (using the monotherapy data arms of HELIOS-B) for vutrisiran. For ACM data were extracted from Kaplan-Meier curves and raw survival data reconstructed from these using

the Guyot method [14]. Network meta-analyses were conducted in R using the multinma library [https://CRAN.R-project.org/package=multinma]. The EAG notes, therefore, that these analyses are based on imperfect data extraction, and may not precisely agree with a formal NMA conducted by the company or anyone else.

Results of the EAG's NMAs are presented in Table 14. For ACM there was no clear evidence of any difference between vutrisiran and tafamidis. Results were in the direction of favouring vutrisiran, but any benefit appears to be small and was not statistically significant. For 6-MWT and KCCQ-OS results were slightly in the direction of favouring tafamidis, but again, these results were not statistically significant. The benefit of tafamidis may be due to the larger changes in these outcomes observed in the ATTR-ACT trial.

Overall, the results of the NMAs were consistent with both the MAIC analyses provided by the company (see Table 13) and with the analyses performed within the HELIOS-B trial (see Section 3.2.6 and CS Table 16).

The EAG therefore concludes that there is no clear or conclusive evidence of any difference in effectiveness between vutrisiran or tafamidis for any main clinical outcome. While vutrisiran might have a slight benefit in reducing mortality, this appears to be small, and the evidence is insufficient to assume it is a genuine difference. The EAG thinks that assuming the vutrisiran and tafamidis have broadly the same effectiveness is the most reasonable conclusion, given the current evidence.

Table 14 Results of EAG network meta-analyses

Outcome	Analysis	Result of NMA: vutrisiran vs tafamidis
ACM	**Frequentist Cox model**	HR 0.90 (95% CI 0.54 to 1.52)
	Frequentist Weibull model	HR 0.93 (95% CI 0.63 4to 1.36)
	Bayesian NMA	HR 0.89 (95% CrI 0.53 to 1.43)
6MWT (at 30 months)	**Comparison of absolute change in 6MWT**	MD -12.16 (95% CrI -36.16 to 12.56)
KCCQ-OS (at 30 months)	**Comparison of absolute change in KCCQ-OS**	MD -4.80 (95% CrI -15.96 to 8.34)

3.6.2 Real-world evidence of tafamidis

The Transthyretin Amyloidosis Outcomes Survey (THAOS) study collected data on the natural history of TTR amyloidosis in 6718 patients from nineteen countries [15]. Analyses were conducted to

compare survival outcomes in 587 tafamidis-treated versus 854 tafamidis-untreated patients selected from the subset of symptomatic patients with a predominantly cardiac phenotype (N=1441) [16]. Analyses from the THAOS study estimate that survival rates for patients enrolled from 2019 at 42 months were 82.8% (95% CI 75.7–87.9) and 67.3% (95% CI 56.9–75.8) in tafamidis-treated and tafamidis-untreated patients, respectively.

The EAG compared results from post-2019 data from THAOS to the "monotherapy" data from the HELIOS-B trial, and to the ATTR-ACT trial. We note that demographic data was not available for THAOS, so we are uncertain as to how closely the patients match across data sets, but we have assumed that post-2019 data will be a reasonable match between THAOS and HELIOS B, but there may be some differences due to differing inclusion criteria.

Figure 7 presents smoothed ACM survival curves from THAOS patients treated with tafamidis and those who were untreated (dot-dash lines), alongside smoothed ACM survival curves for the HELIOS-B vutrisiran, tafamidis and placebo monotherapy subgroups (solid lines) and similarly for tafamidis and placebo arms in ATTR-ACT (dotted lines).

Survival on tafamidis was very similar between THAOS and HELIOS-B, and [redacted] (but note that no confidence intervals are supplied). Also, the THAOS trial does not show any decline in survival [redacted]. Untreated patients in THAOS had slightly poorer survival that placebo patients in HELIOS-B, but again, the THAOS data showed no decline in survival [redacted]. Survival rates for ATTR-ACT were poorer for both tafamidis and placebo across the board, confirming that there is evidence of general improvement in survival over time since ATTR-ACT was conducted.

An NMA comparing HELIOS-B to THAOS for ACM gave a hazard ratio of 1.17 in favour of tafamidis (95% CrI 0.73 to 1.90), but with no statistically significant difference between the treatments. We note that THAOS was not a randomised trial, so there may be bias in who was selected for tafamidis treatment, which would, in turn, bias any NMA. However, while it would not be appropriate to conclude that tafamidis is superior to vutrisiran based on this comparison, it raises further doubt over any claims of superiority of vutrisiran over tafamidis.

Figure 7 Comparison of ACM between HELIOS-B, ATTR-ACT and THAOS

3.7 Conclusions of the clinical effectiveness section

The evidence on vutrisiran as submitted is drawn entirely from HELIOS-B, a single RCT of 654 patients comparing vutrisiran to placebo. The EAG notes that the trial is of good quality, of appropriate size and with suitable analyses of its data. The trial shows clear and statistically significant evidence that vutrisiran produces clinically meaningful reductions in mortality and key morbidities (hospitalisation, 6-MWT etc.) when compared to placebo. It also shows that adverse events are generally manageable, and that vutrisiran is likely to be well-tolerated. The EAG therefore concludes that vutrisiran is an effective treatment for ATTR-CM. Although the company did not formally compare vutrisiran to best supportive care, the EAG concludes that patients in the placebo arm of HELIOS-B can reasonably be assumed to have been receiving best supportive care, so vutrisiran is clinically superior to best supportive care.

The company did not fully report the subgroup analyses as specified in the NICE scope. However, some were reported in the CS appendices, the HELIOS-B CSR and the publication of HELIOS-B[12]. Due to small numbers of patients in some subgroups it is difficult to draw firm conclusions. The effectiveness of vutrisiran might differ between hereditary and wild-type ATTR, but numbers were

small, and results were not consistent across different analyses. Vutrisiran might also be more effective in patients in NYHA class III, but numbers were small, and confidence intervals were wide, so this is not conclusive.

The company chose to compare vutrisiran to tafamidis using data from within the HELIOS-B trial, by separating patients who were receiving tafamidis at randomisation from those who were not (the "monotherapy" group). While the EAG agrees that this represents the most direct comparison of the therapies and avoids problems with changes in trial populations over time, it remains a non-randomised comparison, because the decision to prescribe tafamidis was not randomised. Also, some people were prescribed tafamidis after randomisation, which complicates the comparison. The company took reasonable steps, using propensity weighting, to correct for these issues, but the validity of the comparison remains uncertain. The company's analyses found that results for mortality generally were in the direction of favouring vutrisiran over tafamidis, but the hazard ratio was modest, and results were not statistically significant. However unadjusted analyses were sometimes in the direction of favouring tafamidis, although, again, results were not statistically significant.

The company declined to provide indirect comparisons of vutrisiran and tafamidis using ATTR-ACT, the primary randomised trial of tafamidis. The company argued that the trials were too dissimilar in their recruited populations to be comparable. The EAG agrees that the trials are very different, and this complicates any comparison. However, MAIC analysis, particularly anchored MAIC, and network meta-analysis are all designed to address such differences in trials, so this argument does not invalidate the value of indirect comparison between HELIOS-B and ATTR-ACT.

The company provided some limited unanchored MAICs comparing HELIOS-B and ATTR-ACT, and the EAG performed some NMAs using published trial data. Results from these were consistent with analyses within HELIOS-B alone, with all-cause mortality favouring vutrisiran over tafamidis, but with a modest hazard ratio, and no statistical significance. Similarly, there was no evidence of difference between vutrisiran and tafamidis for any other outcome.

The EAG therefore concludes that, given the current evidence, and the absence of randomised evidence to compare vutrisiran and tafamidis, the most reasonable assumption is that the two therapies are likely to be broadly similar in effectiveness across all major mortality and morbidity outcomes. The EAG therefore thinks that vutrisiran and tafamidis should be assumed to be equal in effectiveness for the purpose of this assessment. We note that this substantially conflicts with the company's preferred assumptions in their economic model, which incorporates some superiority of vutrisiran over tafamidis, both in overall survival and transitions between NYHA classes.

3.7.1 Outstanding areas of uncertainty

The EAG notes the following areas where it thinks some clinical uncertainties remain:

The submission has not formally included best supportive care as a comparator to vutrisiran, although this was in the NICE scope. The EAG notes that the placebo arm of HELIOS-B can broadly be considered to represent best supportive care but may not precisely represent this.

There was a general lack of subgroup analyses in the submission. Although numbers of patients in many key subgroups were small, there is a possibility that the effectiveness of vutrisiran and tafamidis might vary with key parameters such as ATTR type or NYHA class, which might affect the choice of therapy in clinical practice.

Comparison of vutrisiran with tafamidis was limited by difficulties of the non-randomised nature of tafamidis use within HELIOS-B. The EAG would like to have seen a broader evaluation of tafamidis use within HELIOS-B, such as presenting data for patients on both vutrisiran and tafamidis. We would also have liked to have seen a full indirect comparison of HELIOS-B with ATTR-ACT. The company largely declined to comply with the EAG's requests on both counts. The lack of a full analysis comparing the two treatments limits the ability to fairly compare them for this assessment.

Given the limitations of the evidence comparing vutrisiran to tafamidis, and the results seen, the EAG concludes that vutrisiran and tafamidis should be assumed to be equal in effectiveness for the purpose of this assessment. This conflicts substantially with the company's preferred assumptions in their economic model.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted an SLR to identify cost-effectiveness studies in ATTR-CM; this is detailed in Appendix E to the CS. The original database searches were carried out on 13th September 2023 with further searching of supplementary sources on 30th January 2024. An update search was undertaken on 5th November 2024.

The company considered 12 publications suitable for inclusion, which were summarised briefly in Table 20 of the CS and were used to inform the company's *de novo* model development.

Points for critique

The EAG notes that, while the information summarised by the company in Table 20 of the CS suggests a common model structure across the identified studies (i.e., reflecting cohort movement across health states defined by NYHA classes), the table does not explicitly indicate how survival outcomes were modelled. Since this is an important element of treatment effectiveness, the EAG describes here the survival modelling approach taken in previous NICE technology appraisals (TAs) of tafamidis in ATTR-CM. [17, 18] In the tafamidis TAs, background disease was explicitly accounted by using an excess hazard modelling approach, which directly incorporated general background mortality. The survival outcomes were estimated independently from NYHA class, and used to estimate the overall probability of death at each cycle, conditional upon being alive at the start of the model cycle, and this probability was converted to a total number of deaths expected. The contribution of each NYHA class to this total number of deaths was assumed to be proportional to the number of patients in the NYHA class at the start of the cycle and the relative hazard of mortality in that class. The EAG notes that modelling survival independently from NYHA class changes over the time horizon effectively omits an important structural link between disease progression across NYHA classes and mortality. The lack of this link which may introduce inconsistencies in the assumptions used for NYHA transitions and mortality estimates, leading to potentially implausible and optimistic survival extrapolations. This concern does not appear to have previously been raised in previous TAs, but may become an issue when in a population with lower mortality and disease severity at baseline than the population in previous models.

The EAG found that the searches for the cost-effectiveness SLR in Appendix E were overall appropriate, however, the comprehensiveness and transparency of the search could have been improved if separate searches had been undertaken for Embase and MEDLINE. Full details of the EAG appraisal of the searches for the cost-effectiveness SLR is reported in Appendix 1: EAG appraisal of review evidence and can be found in Table 39.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de novo* model to evaluate the cost-effectiveness of vutrisiran monotherapy versus tafamidis monotherapy for the treatment of ATTR-CM. The effectiveness evidence informing the model is largely based on HELIOS-B data from a non-randomised comparison of the outcomes of patients in the vutrisiran arm within the monotherapy population (n=196) and patients in the placebo arm who were on background tafamidis at baseline (n=129), adjusted for baseline characteristics imbalance by IPTW (see Section 3.2.5.2).

A Markov cohort-level model is used to estimate the long-term health outcomes and costs associated with ATTR-CM in the UK. Patients' movement (improvement, maintenance or worsening) across health states defined by NYHA class is captured by the model, with risk of transient (cardiovascular) events occurrence dependent on NYHA class. Transition probabilities across NYHA health states are time-dependent in the first 30 months in the model and become constant in the extrapolated period beyond that time point. The model also considers the time-dependent risk associated with death modelled by extrapolating ACM data from HELIOS-B with independent parametric survival functions to determine the proportion of patients alive over time for vutrisiran monotherapy and the comparator, tafamidis monotherapy. Extrapolated ACM was capped by general population age and sex adjusted mortality. OS was modelled independently from NYHA health state membership, with the total proportion of patients who died at each model cycle merely disaggregated across individual NYHA health states according to NYHA class specific mortality risks. Treatment discontinuation for vutrisiran and tafamidis monotherapy is informed by the same non-fatal time-to-treatment discontinuation (TTD) extrapolated curve as informed by observed data from the vutrisiran monotherapy arm of HELIOS-B. The company chose to apply the same discontinuation curve to both treatments under comparison due to evidence limitations, as tafamidis discontinuation was not systematically evaluated as an outcome in HELIOS-B. When patients discontinue treatment with vutrisiran monotherapy, treatment effectiveness (on impact on transition probabilities across NYHA health states, but not for ACM) is assumed to wane gradually over time to that of placebo in the HELIOS-B monotherapy subpopulation (assumed to be reflective of the effectiveness of BSC). For those treated with tafamidis monotherapy, treatment effectiveness becomes equivalent to that of BSC immediately after treatment discontinuation.

Vutrisiran monotherapy is modelled to impact on QALYs by delaying progression across NYHA class health states (with improved HRQoL for patients and carers) due to higher utility and fewer cardiovascular events (with associated disutility) in less severe health states compared to more severe ones and also improving survival relative to the comparator. SAEs for vutrisiran monotherapy are also modelled to result in less disutility than those with tafamidis monotherapy.

Compared to tafamidis monotherapy, vutrisiran monotherapy is modelled to impact on costs by [redacted] drug acquisition (including background medication) and administration costs while patients are on treatment, and by delaying progression across NYHA class health states (with lower costs associated with cardiovascular events and disease management). Vutrisiran monotherapy also reduces the costs associated with managing adverse events compared to tafamidis monotherapy. The largest component of cost difference between vutrisiran monotherapy and tafamidis monotherapy is the vutrisiran acquisition costs, followed by the costs of transient cardiovascular events and disease management costs. Cost differences across other categories of cost are marginal.

The company's *de novo* model uses a similar approach to that used in previous NICE TAs for ATTR-CM (TA696 and TA984).[17, 18]

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 15.

Table 15 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is partly appropriate. Health effects on carers are considered in the company's base case analysis, but their relevance to the current appraisal is uncertain, and it has not been considered in previous NICE TAs in ATTR-CM.
Perspective on costs	NHS and PSS	The CS is appropriate. A scenario analysis under the societal perspective is also presented.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate.
Synthesis of evidence on health effects	Based on systematic review	For the comparison against tafamidis monotherapy, the company uses a non-randomised comparison from HELIOS-B to inform the health effects of alternative treatments, rather synthesising effects across existing RCTs. The company considered that an indirect treatment comparison of vutrisiran (from HELIOS-B in the monotherapy population) vs. tafamidis

		(from ATTR-ACT,) was not feasible, due to the risk of bias from imbalances in the patient populations assessed in HELIOS-B and ATTR-ACT.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life (HRQoL) in adults.	The CS is appropriate.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The company developed a *de novo* Markov model to assess the cost-effectiveness of vutrisiran monotherapy compared to tafamidis monotherapy for the treatment of ATTR-CM.

The model structure consisted of four 'alive' health states, defined according to heart failure severity by NYHA class (from the least to the most severe: I to IV), and a 'death' health state (see Figure 21 of the CS). At the model entrance, the cohort is distributed across NYHA health states based on the NYHA class distribution at baseline of the *post-hoc* HELIOS-B trial population of patients on background tafamidis and those randomised vutrisiran monotherapy. At each subsequent cycle, patients can remain in the same health state or transition to a higher or lower NYHA class health state (i.e., the condition can remain stable, worsen or improve in severity) with transition probabilities varying by treatment group and time since model entrance. Furthermore, patients can also transition to the 'death' health state from any of the 'alive' health states; mortality is also time-dependent and treatment specific. The mortality risk is not conditional on NYHA class at each model cycle, i.e., mortality is modelled independently from NYHA class. The increased risk of death with NYHA class

is only used to adjust the proportion of patients alive at the subsequent model cycle; the total proportion of patients who died at each model cycle is disaggregated across individual NYHA health states according to NYHA class specific mortality risks. Patients remain on treatment until death or discontinuation from non-fatal causes. When treatment is discontinued due to non-fatal causes patients are assumed to have the survival outcomes and NYHA class transition probabilities, as well as background medication costs, of those treated with BSC (informed by the placebo arm of the HELIOS-B monotherapy), with the exception that when patients discontinue treatment with vutrisiran monotherapy, NYHA class transitions are assumed to wane gradually over time to that of placebo in the HELIOS-B monotherapy subpopulation.

Patients in any 'alive' health state are at risk of transient events (i.e., non-fatal CV-related hospitalisations and urgent heart failure visits); the risk of these events is conditional on NYHA class but not on treatment received. SAEs by treatment group are modelled as a one-off occurrence at model entrance.

The model has a cycle length of three months and a within-cycle correction using the Simpson's 1/3rd rule,[19] and a lifetime horizon.

Points for critique

The EAG considers the model structure broadly consistent with previous models in NICE TAs in ATTR-CM, even if the survival modelling does not follow the excess hazard modelling approach in TA696 and TA984 of tafamidis for ATTR-CM (see Section 4.1).[17, 18] The company justification for deviating to some extent from these previous appraisals when modelling survival outcomes seemed reasonable (see response to clarification question B2.b). Nevertheless, the EAG is concerned that the current structure does not appropriately link survival outcomes to the NYHA states or transient events, which may lead to inconsistent and potentially clinically implausible impacts on outcomes (also see Section 4.2.6.3).

The EAG notes that the within-cycle correction using Simpson's 1/3rd has not been used in NICE TAs in ATTR-CM, and that half-cycle corrections are a more conventional approach to handle potential inaccuracies in quantifying health and cost outcomes with discrete time modelling. The company's preferred within-cycle correction has been shown to provide the best approximation from a discrete time Markov model to the corresponding continuous-time Markov model in published literature,[19, 20] and the EAG considers the correction appropriate. However, this correction (similarly to the more routinely used half-cycle correction) should not be applied to all outcomes without consideration if their periodicity aligns or not with cycle length. The EAG comments on the implications of applying the within-cycle correction to vutrisiran acquisition and administration costs in Section 4.2.10.3.

4.2.3 Population

4.2.3.1 Summary of company's submission

The company defines the patient population in the model as the overall ATTR-CM patient population, which the company considers aligned with the population defined by the NICE scope and the marketing authorisation for vutrisiran. The baseline characteristics of the modelled population (see Table 23 of the CS) are informed by the population of individuals in HELIOS-B who received vutrisiran monotherapy and those who received placebo with background tafamidis (i.e. tafamidis monotherapy) prior to any IPTW adjustments. Treatment effectiveness estimates are informed by the IPTW adjusted vutrisiran vs. tafamidis monotherapy HELIOS-B population for the majority of parameters (see Section 4.2.6).

No separate subgroup populations are considered in the company's base case analysis.

Points for critique

The EAG considers the modelled population characteristics to be broadly in line with those of the monotherapy population (vutrisiran monotherapy vs. placebo without background tafamidis) in the HELIOS-B trial. The company did not present any cost-effectiveness subgroup analyses. Similarly, no subgroup clinical analyses were presented by the company for the population which informs the model. Given the uncertainties and limitations of the evidence used to inform the treatment effectiveness of vutrisiran vs. tafamidis monotherapy in the model (see Section 4.2.6.1), the EAG considers that it would not be appropriate to stratify this evidence into subgroups.

4.2.4 Intervention and comparator

4.2.4.1 Summary of company's submission

The intervention is vutrisiran monotherapy and the comparator is tafamidis monotherapy. Vutrisiran monotherapy is implemented as per its marketing authorisation for ATTR-CM, i.e., one 25 mg dose administered by subcutaneous (SC) injection every three months. Tafamidis monotherapy is also implemented in line with its marketing authorisation for ATTR-CM, which corresponds to a dose of 61mg delivered orally once daily. Patients on treatment with either the intervention or the comparator are also assumed to receive BSC consisting of background medication for symptomatic heart failure management.

The company did not compare vutrisiran monotherapy against BSC in the economic analysis, because established clinical management without vutrisiran, the alternative comparator listed in the NICE scope, was considered to equate to tafamidis monotherapy. At the clarification stage the EAG requested additional cost-effectiveness analyses comparing vutrisiran monotherapy to BSC (see response to question B1), but the company stated that *"there are no patients for whom BSC would be*

considered as an alternative choice to tafamidis currently or to vutrisiran in the future" and did not comply with the request. The company also presented, in response to the EAG request clinical expert statements to further support their claims that tafamidis monotherapy is the only relevant comparator. The company's clinical expert considers that this applies even in patients who have undergone disease progression while on treatment with tafamidis, as there are no other disease-modifying therapies currently available, and no stopping rules are in place for tafamidis. Both clinical advice to the company and the EAG suggest that the population ineligible for tafamidis due to intolerance is a small part of the population.

Points for critique

The EAG acknowledges that tafamidis monotherapy is the main comparator in this appraisal. However, the EAG considers that a comparison with BSC should also be included in the model to inform NICE committee decision making. The main reason for this is that the HELIOS-B trial was not designed or powered to assess the relative efficacy of vutrisiran (either as monotherapy or in combination with tafamidis) versus tafamidis monotherapy, and, therefore, the validity of the evidence used to inform treatment effects in the economic analysis and other approaches (e.g., unanchored MAICs and EAG NMAs) taken to compare the clinical outcomes of vutrisiran against tafamidis is severely limited (see Sections 3.7 and 4.2.6.1). In contrast, the EAG thinks that the HELIOS-B trial monotherapy subpopulation provides robust randomised controlled evidence of relative efficacy for vutrisiran monotherapy vs. placebo (without background tafamidis), a comparator that could reasonably be assumed similar to BSC in UK clinical practice (see Section 2.3.3). Furthermore, this comparison is unaffected by issues of differential timing of treatment initiation between treatment groups and for tafamidis drop-in was relatively balanced across treatment arms(see CS Section 2.6.9), and, thus, unlikely to be biased by these factors, unlike the evidence for vutrisiran vs. tafamidis monotherapy for which the impact of these potential sources of bias are uncertain (see Section 4.2.6.1).

The EAG also considers that the comparison against BSC remains relevant for the proportion of patients who are currently ineligible for tafamidis due to treatment intolerance, even if this comprises a small group of patients, as well as for patients who discontinue treatment with tafamidis due to lack of response. As noted above, clinical advice to the company highlighted that in the absence of other disease-modifying therapies for ATTR-CM, patients on treatment with tafamidis will carry on treatment even if disease progresses, at least until patients enter a palliative phase. However, this will change if another disease-modifying treatment, such as vutrisiran, becomes available. The EAG presents cost-effectiveness analyses for the BSC comparison in Section 6.

As highlighted in Section 2.3, the NICE scope does not restrict the use of vutrisiran in combination with tafamidis, and it is not anticipated that the marketing authorisation includes this restriction. The

company does not present cost-effectiveness results for the use of vutrisiran in combination with tafamidis, and, therefore, there is no evidence to inform decision making on resource use allocation for the use of vutrisiran as a combination therapy.

4.2.5 Perspective, time horizon and discounting

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales over a lifetime time horizon of [redacted]). A 3.5% annual discount rate is used for both costs and health effects.

Points for critique

The CS adheres to the NICE health technology evaluations manual [21] and the EAG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

The model includes two elements relating to treatment effectiveness and extrapolation of effects over time, for vutrisiran and tafamidis monotherapy:

- Health state transitions across different levels of disease severity as captured by NYHA classification, with the probability of transient events increasing with disease severity;
- ACM, i.e., the probability of dying of any cause.

The main data source informing these elements for each treatment was the IPTW adjusted HELIOS-B comparison of vutrisiran and tafamidis monotherapy. Time-dependent transition probabilities between NYHA class health states were derived from observed count data by NYHA class collected every 6-months in the double-blind period of the trial, with the probabilities in the extrapolation period (beyond 30 months) derived by averaging last two observed 6-month transition matrices; transition probabilities derived from these data is presented in Section 4.2.6.2 (see Table 16).

Parametric survival distributions were independently fitted to the ACM KM data observed (42-month follow-up) for each treatment of the IPTW adjusted HELIOS-B comparison of vutrisiran and tafamidis monotherapy, in order to extrapolate survival over the modelled lifetime horizon. The extrapolated ACM curves for the treatments under comparison used in the company's base case analysis in Figure 8, alongside the corresponding observed KM curves and general population mortality.

Figure 8 Modelled survival for vutrisiran and tafamidis monotherapy (Figure 27 of the CS)

The company's selection of extrapolation model was conducted by:

(i) Fitting seven standard parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma) to KM data from the trial.
(ii) Assessment of goodness-of-fit for each parametric distribution based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
(iii) Assessment of hazard functions for each parametric model compared to the observed hazard.
(iv) Assessment of clinical plausibility and visual goodness of fit of the long-term extrapolations based on clinical opinion obtained by structured expert elicitation (SEE).

The preferred extrapolation models for each treatment based on this assessment were capped by age and sex adjusted general population mortality in the model, to avoid clinically implausible scenarios.

The estimates of clinical effectiveness in the model are also informed by the HELIOS-B placebo arm of the monotherapy subpopulation (assumed to reflect the clinical effectiveness of BSC) for those patients who discontinue treatment with either vutrisiran or tafamidis monotherapy, as these are assumed to receive BSC once they discontinue their initial treatment. For patients on treatment with vutrisiran monotherapy, a gradual treatment effect waning over 21 months to that of BSC is modelled for the health state transition probabilities, whereas for those who discontinue tafamidis monotherapy, the transition probabilities are informed by the BSC transition matrices immediately upon treatment discontinuation. The gradual treatment waning effect was modelled solely for vutrisiran monotherapy,

as the company considered that serum TTR levels remain low for a sustained period after treatment discontinuation for this treatment, based on observed data on serum TTR levels over time following the final dose of vutrisiran received in the double-blind period of HELIOS-B. In contrast, when patients discontinue treatment with either vutrisiran or tafamidis, the ACM curves are informed by the BSC extrapolated curve from the point of treatment discontinuation (see Section 4.2.6.4). The company justified not modelling treatment effect waning for tafamidis, as this drug is not expected to maintain active pharmacodynamic levels without sustained daily administration.

Treatment discontinuation due to non-fatal causes was assumed to be treatment independent and was informed by observed data in the HELIOS-B double-blind period for vutrisiran monotherapy arm. The company chose to apply the same discontinuation curve to both treatments under comparison due to evidence limitations, as tafamidis discontinuation was not systematically evaluated as an outcome in HELIOS-B, and also due to concerns about bias introduced by differential timing of treatment initiation with tafamidis. These data were extrapolated by fitting parametric survival models to the observed data by a process similar to the points (i) and (ii) described above for ACM. The company's preferred extrapolation model (i.e., gamma distribution) is illustrated in Figure 9.

Figure 9 Modelled non-fatal treatment discontinuation (extracted from the model)

4.2.6.1 Evidence informing treatment effectiveness estimates in the model

As mentioned above, the main source of clinical effectiveness used by the company to inform was the IPTW adjusted HELIOS-B data for the comparison of vutrisiran and tafamidis monotherapy. Observed data in patients randomised in HELIOS-B to vutrisiran in the monotherapy subpopulation of HELIOS-B were adjusted for baseline characteristics using IPTW to allow for comparison with the group of patients randomised to the placebo arm and who were receiving background treatment with tafamidis at baseline (see Section 3.2.6). The transition probabilities matrices were informed by data for the double-blind period of HELIOS-B (30 months follow-up) and survival estimates by data from

the 42 months follow-up. For the transition probability, estimates for the period beyond 30 months were extrapolated by applying an average of the transition probabilities for the two last observed periods (i.e., 18-24 and 24-30 months) over the remainder of the time horizon. For the ACM data, independently fitted parametric functions were used to extrapolate the trial observed data for the vutrisiran and tafamidis monotherapy treatment groups.

The EAG notes that while the same observed data was used to derive the treatment effects on disease progression and ACM presented in Table 16 of the CS to inform clinical effectiveness in the economic model, these estimates were not directly implemented in the model and, therefore, the treatment effects implied by the model are different from those reported in the Section 3.2.6.

Points for critique

The EAG key concern is that the evidence used to inform the clinical effectiveness of vutrisiran vs. tafamidis monotherapy is subject to several important limitations and potential biases, as the HELIOS-B trial was not designed or powered to assess the relative efficacy of vutrisiran versus tafamidis, as noted by the company in response to clarification question A1.

The company's *post-hoc* approach to use data collected from patients in the placebo arm of HELIOS-B who were on background tafamidis at baseline as a proxy to inform the outcomes of patients treated with tafamidis monotherapy in the model presents several limitations. First, the approach breaks randomisation, which increases the risk of bias due to both observable and unobservable differences between the tafamidis and vutrisiran treated patients. Whilst the company's IPTW adjustment of the observed data allows reducing imbalances in observed patient characteristics between treatment groups, other observed differences between groups with potential impact on outcomes are not adjusted for, such as the differential timing for treatment initiation with tafamidis vs. vutrisiran monotherapy and the use of tafamidis drop-in by 23.4% of patients in the monotherapy group. Thus, the validity of the clinical evidence to inform treatment effectiveness for this comparison remains highly uncertain.

Second, the company's analysis for the vutrisiran vs. tafamidis monotherapy comparison (Table 17 of the CS) show that treatment effect estimates for all outcomes, including ACM and disease stabilisation/improvement, are statistically non-significant at 5% significance level, and hence, it is uncertain whether there are differences between the effectiveness of these treatments. The existence of treatment effect of vutrisiran vs. tafamidis monotherapy on ACM is particularly uncertain on both magnitude and on direction of treatment effect. [redacted] but depending on the analyses, the HR for this comparison is below or above 1. The unadjusted HR for the vutrisiran vs. tafamidis monotherapy and corresponding regression estimate adjusted for treatment

group suggest a detrimental effect ([redacted]) and [redacted], respectively; response to clarification question A8), while the regression estimated HR adjusted for treatment group, age group, ATTR disease type, baseline NYHA class, log-transformed NT-proBNP and Troponin, baseline 6-MWT, baseline KCCQ-OS, and baseline eGFR suggests a beneficial effect (HR=[redacted] The EAG notes that due to the way in which ACM is data is used in the model (i.e., by independently fitting parametric curves for each treatment group to the IPTW adjusted HELIOS-B survival data) implies a greater difference in treatment effects between treatment groups in the economic model than what is estimated in the company's covariate adjusted analysis HR of 0.81 for vutrisiran vs. tafamidis monotherapy in the observed period.

Third, the company considers that differences in the earlier timing of therapy initiation the tafamidis monotherapy group (who had been on treatment at baseline against with tafamidis for a median of 11.3 months [range: 1.1, 65.5]) are likely to have introduced against bias vutrisiran monotherapy, but did not provide further quantitative evidence to explore the potential impact of differential timing of treatment initiation with tafamidis and vutrisiran monotherapy on the survival estimates (see EAG clarification question B4). The company did, however, provide the vutrisiran monotherapy KM censored and uncensored for tafamidis drop-in use, which suggests that the impact of tafamidis drop-in on survival for those treated with vutrisiran monotherapy is [redacted] (see Figure 12 of the company's response to clarification question B3). The company did not quantitatively explore the impact of any of these unadjusted for observed differences between treatment groups on the treatment effect on disease progression, but considers that the beneficial effect of vutrisiran monotherapy suggested by their clinical analysis (OR for NYHA improvement or stabilisation over 30 months: [redacted] is also likely to be biased in favour of tafamidis due to the differential timing of treatment initiation with this drug.

The EAG believes that given the limitations of the evidence and the concerns highlighted above, the most reasonable assumption on the relative effectiveness of vutrisiran and tafamidis monotherapy is that there are no differences in treatment effects between the two drugs. This is also supported by the results of the company's unanchored MAIC comparing HELIOS-B and ATTR-ACT, and the EAG's NMA using published trial data for the ACM outcome (see Section 3.5 and 3.6.1), which were consistent with the company's analysis using evidence from HELIOS-B alone (i.e., showing a non-statistically significant effect for vutrisiran over tafamidis, the magnitude of which is uncertain).

Finally, the EAG notes that the THAOS study evidence [16] also provides important contextual on the survival outcomes with tafamidis in a more contemporaneous population (i.e., the post-2019 subpopulation) than the one in ATTR-ACT (see Section 3.6.2). Contrasting the survival outcomes for vutrisiran monotherapy with those of patients treated with tafamidis in the post-2019 subpopulation

suggests that survival with tafamidis in THAOS is similar to that of vutrisiran in HELIOS-B, as illustrated in

Figure 7. The EAG recognises the caveats of directly comparing the populations across the studies compared in

Figure 7, but the information provided is consistent with the EAG assessment of the clinical evidence (see Section 3.7) as suggesting broadly similar survival for vutrisiran and tafamidis.

4.2.6.2 Transition probabilities between NYHA class health states

The company details in Section 3.3.3 of the CS how the time-varying transition probabilities between NYHA class health states were estimated. The transition probabilities applied in the model at each time period are summarised in Table 16 for the treatments under comparison and for BSC; for transitions in the observed period (i.e., first 30 months in the model), [redacted]

Separate transition matrices were calculated for each treatment under comparison and informed by observed count data from the double-blind period of HELIOS-B, in which NYHA class was collected at each 6-month interval. During the first 30 months (10 cycles), 6-month transition matrices were estimated for each time interval in HELIOS-B and then converted to the corresponding 3-month transition matrices (assuming rates would remain constant within the 6-month interval) to align with the model's cycle length.

Beyond 30 months, the average of the last two observed 6-month transition matrices (i.e., months 18–24 and 24–30) from the observed period was converted to a 3-month transition matrix, and then carried forward for the remainder [redacted] of the time horizon ([redacted]) for each treatment group. The company justified this approach (as opposed to carrying forward the last observed transition matrix) as the probabilities of transitioning from any other health state to NYHA IV in the last observed period (24-30 month) were zero for vutrisiran monotherapy (but not for tafamidis monotherapy for transitions from NYHA II or III to IV). The company considered it would not be clinically plausible to apply these probabilities across the duration of the time horizon, given the progressive nature of the disease and the effects of ageing on cardiovascular health. It is worth noting that the probabilities for forward transitions to health state NYHA IV are [redacted] throughout the

observed period for BSC and more so for vutrisiran and tafamidis monotherapy, with many transition probabilities to [redacted].

In the transition matrix for the extrapolation period, which is applied for the majority of the time horizon, the main differences in the effect of vutrisiran monotherapy compared to tafamidis monotherapy are for the transitions from:

- NYHA III: patients treated with vutrisiran monotherapy [redacted]
- NYHA II to IV: the probability of this transition [redacted] with vutrisiran monotherapy (and almost [redacted]

Table 16 Three-month transition probabilities for the vutrisiran monotherapy vs. tafamidis monotherapy comparison

From NYHA class	To NYHA class health state											
	Vutrisiran monotherapy				Tafamidis monotherapy				BSC			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
Months 0–3 and 3–6 (Cycles 1 and 2)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 6–9 and 9–12 (Cycles 3 and 4)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 12–15 and 15–18 (Cycles 5 and 6)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 18–21 and 21–24 (Cycles 7 and 8)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 24–27 and 27–30 (Cycles 9 and 10)[*]												

From NYHA class	To NYHA class health state											
	Vutrisiran monotherapy				Tafamidis monotherapy				BSC			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 30+ (base-case extrapolation phase, cycles 11+)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											

*The company also presents a scenario whereby the Months 24-30 matrices are applied throughout the extrapolation (last observation carried forward)

Points for critique

The EAG reiterates that the key concern regarding the estimation of the transition probabilities between NYHA class health states applied in the model and the implied treatment effect for vutrisiran vs. tafamidis monotherapy on disease progression, stems from the limitations of the evidence used to inform these (see Section 4.2.6.1) given HELIOS-B was not designed to compare the clinical outcomes of treatment with vutrisiran vs. tafamidis.

In addition, the EAG is also concerned that the transition probability estimates applied in the model may not accurately reflect disease progression over the time horizon, and that, for some specific transitions, the estimates applied in the model may lack face validity. As noted above, the company considered it inappropriate to carry forward the matrix for the last observed period in recognition that it would not be clinically plausible to have transition probabilities from any less severe health state to NYHA IV equal to zero for vutrisiran monotherapy applied to the remainder of the time horizon. Whilst the EAG agrees that transition probabilities to health state NYHA IV in the company's extrapolation phase transition matrix seem less implausible than those in the transition matrix for the last observed period, [redacted] Importantly, looking across the transition matrices at different observed periods, there are instances in which transitions from NYHA class II to IV [redacted] NYHA class III to IV for both tafamidis and vutrisiran monotherapy. This is even more apparent when examining the NYHA transition matrices estimated from baseline to month 30 from HELIOS-B provided by the company in Tables 3 and 4 of the company's response to clarification question A1, which are reproduced in Table 17. The transition probabilities from NYHA class III to IV are [redacted] for all treatments under comparison, including for the randomised comparison of vutrisiran monotherapy to placebo monotherapy, while for transitions from NYHA class II to IV, they range from [redacted]

[redacted] This is not consistent with what would be expected for a progressive disease such as ATTR-CM even if active treatment slows disease progression, and is particularly implausible for those treated with placebo (assumed equivalent to BSC in the model).

Table 17 NYHA transition matrix from Baseline to Month 30 (IPTW adjusted comparisons)

From NYHA class	To NYHA class health state							
	Vutrisiran monotherapy				Tafamidis monotherapy			
	I	II	III	IV	I	II	III	IV
I	[redacted]							
II	[redacted]							
III	[redacted]							
IV	[redacted]							
	Vutrisiran monotherapy				Placebo monotherapy			
I	[redacted]							
II	[redacted]							
III	[redacted]							
IV	[redacted]							

The EAG believes that the implausible transition probabilities are in part driven by the distribution of disease severity at baseline in HELIOS-B (and the model, see Section 4.2.3), and results on fewer transition events occurring for patients at NYHA class III and IV compared to those in NYHA class II (see Table 18; values extracted from the economic model). While this is not unexpected given the distribution of patients at baseline [redacted] and the short duration of follow-up, it contributes to the uncertainty of the transition probability estimates and is compounded by the need to extrapolate these estimates over a modelled time horizon almost [redacted] longer than the observed follow-up. This contributes to the uncertainty of the transition probabilities extrapolation and the implied treatment effect on disease progression, vutrisiran monotherapy vs. tafamidis monotherapy, as a low number of events to higher severity NYHA classes in the observed period increases the risk that observed differences in progression between treatments are due to chance rather than treatment effects.

Table 18 Number of transition events by NYHA in each 6 months period in HELIOS-B

	NYHA distribution

HELIOS-B time interval	Vutrisiran monotherapy				Tafamidis monotherapy				BSC			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
0-6 months	[redacted]											
6-12 months	[redacted]											
12-18 months	[redacted]											
18-24 months	[redacted]											
24-30 months	[redacted]											

Overall, the EAG is concerned that the transition probabilities and the implied treatment effect on disease progression of vutrisiran monotherapy vs. tafamidis monotherapy are uncertain and lack clinical plausibility for transitions from health states NYHA class II and III to NYHA class IV.

4.2.6.3 All-cause mortality

The EAG described at the beginning of Section 4.2.6, how the company fitted parametric survival functions independently to IPTW adjusted all-cause mortality KM data for vutrisiran and tafamidis monotherapy from the HELIOS-B trial (42-month follow-up). In the base case analysis, the log-logistic and log-normal distributions were selected as the best fitting models for the vutrisiran and tafamidis monotherapy treatment groups, respectively. The capped extrapolated survival curves for each treatment are used to inform the probability of dying at each model cycle while patients are on treatment with tafamidis or vutrisiran monotherapy. Upon treatment discontinuation, this death probability is informed by a Weibull model fitted to observed data from the HELIOS-B placebo monotherapy (without background tafamidis at baseline) arm (see Appendix J of the CS for fit statistics and illustration of the observed survival and parametric survival functions for BSC) for both treatments under comparison.

The company's assessment of statistical and visual fit of alternative parametric models is detailed in Sections 3.3.4.1.4 to 3.3.4.2 of the CS. The company's choice of parametric distribution seems to be driven mostly by the assessment of (i) how well the hazard functions of each parametric model align with the observed hazard in HELIOS-B and (ii) the clinical plausibility of the extrapolated survival estimates. For the assessment of clinical plausibility, the company mostly referred to the results of the SEE report.[22] Briefly, the SEE exercise consisted of two rounds of elicitation (first individual and then in group) from clinical experts. Prior to the elicitation, the experts were provided with data from HELIOS-B (including the IPTW adjusted KM data for the vutrisiran and tafamidis comparison) and data from the ATTR-ACT trial and long-term extension. The quantities elicited by the experts consisted of proportion of patients alive at 8 years post-randomisation for vutrisiran and tafamidis

monotherapy with corresponding uncertainty. The company considers that the SEE showed good alignment between the survival predictions of the preferred parametric distributions (uncapped extrapolations for all fitted distributions shown in

Figure 10 and Figure 11) and the elicited 95% extrapolated intervals at 8 years post-randomisation ([redacted] and [redacted] for vutrisiran and tafamidis monotherapy, respectively).

Figure 10 Vutrisiran monotherapy ACM extrapolations uncapped by general population mortality

Figure 11 Tafamidis monotherapy ACM extrapolations uncapped by general population mortality

The company also states that the clinical plausibility of the extrapolations based on real-world evidence was also considered. This evidence was not presented in the CS.

Since the treatment specific ACM curves were estimated independently of patient's NYHA class, the probability of death at each model cycle determined by the survival curves was used to estimate the number of deaths expected at each model cycle (conditional upon being alive at the start of that cycle) and then different proportions of these deaths were attributed to each NYHA class health state. The contribution of each NYHA class to this total number of deaths is proportional to the number of patients in the NYHA class at the start of the cycle and the relative hazard of mortality in that class, assuming of 1.85-fold increase in HR for every increase in NYHA class (see Table 27 of the CS).

Points for critique

The EAG's main concerns are that (i) there is not sufficient evidence to robustly support the existence of a treatment effect for vutrisiran vs. tafamidis monotherapy on ACM, (ii) the company's preferred extrapolation distributions may result in overly optimistic survival projections and (ii) the company's approach to modelling ACM does not appropriately capture the relationship between disease progression across NYHA classes and mortality. The first key issue has been critiqued in Section 4.2.6.1; the remaining key issues are critiqued below.

The EAG considers that the company's preferred extrapolation models are likely to overestimate the long-term treatment effect on survival for vutrisiran and tafamidis monotherapy on the survival estimates and that the extrapolation is an additional source of uncertainty for the survival outcomes in the model to that stemming from the evidence limitations discussed in in Section 4.2.6.1. The EAG has concerns about the clinical plausibility of the extrapolated survival curves and the implications of this to the plausibility of the implied treatment effect on survival, in light of current evidence.

In Sections 3.7 and 4.2.6.1, the EAG highlighted that the clinical effectiveness evidence for the vutrisiran and tafamidis monotherapy comparison suggests that these treatments are broadly similar across several outcomes including ACM. This is in contrast with the modelled treatment effect on ACM implied by the company's extrapolation approach, which suggests that [redacted] (see Figure 1). The company's rationale for extrapolation model selection is partly based on how well the hazard functions for these curves fitted the observed hazard (Figure 12). Although the shape of the observed hazard for vutrisiran monotherapy seems consistent with the preferred log-logistic function [redacted]), the EAG does not consider that the hazards observed in HELIOS-B provide a suitable basis to establish clinical plausibility of the extrapolation. The observed hazards behaviour in HELIOS-B for vutrisiran and tafamidis is inconsistent with an underlying disease progression model that assumes patients continue to progress to more severe NYHA classes and will eventually result in an increase in

mortality. The EAG thinks that the hazards observed in the 42-month follow-up of HELIOS-B might be explained by the heterogeneity in the study population over this period. Patients in higher NYHA classes are more likely to die earlier in this period (hence the [redacted]), which in the short term may shift the distribution of disease severity towards lower NYHA classes with lower mortality compared to the starting population. Therefore, the EAG does not believe it to be clinically plausible to assume decreasing hazards in the long-term for either treatment under comparison. As shown in Figure 12, all survival functions fitted to vutrisiran monotherapy, but the exponential curve [redacted]

Figure 12 Comparison of hazard rates for parametric distributions fitted to survival

The EAG also considers that the company's assessment of clinical plausibility of the base-case extrapolated survival curves based on the SEE report results is potentially flawed for two reasons. The main limitation of the SEE exercise is that the clinical judgements were in part informed by the HELIOS-B IPTW adjusted comparison of survival outcomes between vutrisiran and tafamidis monotherapy, the limitations of which we have noted throughout the EAR, and which the EAG considers insufficient to support the existence of a treatment effect on survival between treatments.

Finally, the EAG is concerned with that the company's approach to model survival independently from the changes in NYHA class over the time horizon, does not appropriately reflect the structural link between NYHA progression and mortality. The company detailed in response to clarification question B2.c, that competing risks or multi-state survival analysis and modelling could have been used more formally link the survival extrapolation to NYHA class transitions. This was not implemented in the company's model due to data sparsity of data in NYHA classes I and III, and the absence of class IV overall survival data at baseline, and a relatively small number of mortality events in HELIOS-B. The company considered that there were insufficient data to reliably derive NYHA-specific survival estimates with competing risks for NYHA transitions. Nevertheless, the EAG believes that modelling a formal link between disease progression and mortality is a key limitation of

the model and that the evidence limitations highlighted by the company and reproduced above also affect the reliability of the treatment effects on disease progression and mortality considered in their modelling approach.

The omission of this key link between disease progression and mortality introduces the potential for inconsistencies in the assumptions used for NYHA transition and mortality estimates, leading to potentially implausible and optimistic survival extrapolations requiring logical constraints to be imposed over a relatively short time period (i.e., mortality hazard capped by general population hazards). The limitations described in Section 4.2.6.2 for the modelled transition probabilities will also contribute to exacerbating the potential for implausible health outcomes predictions in the model.

The company's base-case approach results in the predicted distributions of the modelled cohort in NYHA class health state membership over the time horizon shown in Figure 13 and Figure 14 (which reproduce Figures 2 and 3 in Appendix H of the CS, respectively). The EAG notes that predictions for tafamidis monotherapy suggest that patients spend proportionately more time in the health state NYHA class IV than III, which seems inconsistent with patients being at increased risk of death in NYHA class III than IV.

Figure 13 Health state distribution over model time horizon in the vutrisiran monotherapy arm

Figure 14 Health state distribution over model time horizon in the tafamidis monotherapy arm

4.2.6.4 Treatment discontinuation and treatment waning

In the base-case analysis, the company modelled treatment discontinuation due to non-fatal causes for patients in the alive health states, by fitting a parametric model (Gamma distribution; see Section B3.3.5 for details on extrapolation model selection) to the observed HELIOS-B KM data collected during double-blind period for the vutrisiran monotherapy treatment arm. The resulting extrapolated curve (see Figure 9) informed both treatments under comparison. The company initially justified the decision to use vutrisiran monotherapy non-fatal TTD discontinuation to inform the tafamidis group as it being unfeasible to use tafamidis specific data due to the extended period of time that patients were exposed to tafamidis prior to HELIOS-B baseline, as this could lead to selection bias for patients who did not discontinue tafamidis prior to enrolling in HELIOS-B. At the clarification stage (response to clarification question B7), the company further justified this choice due to tafamidis discontinuation data not being systematically evaluated as an outcome in HELIOS-B, as the study was not intended to assess the efficacy of tafamidis.

The proportion of patients who discontinue treatment stops incurring acquisition and administration costs for the primary treatment and corresponding costs of background medication (see Sections 4.2.10.3 and 4.2.10.4). The background medication costs applied beyond treatment discontinuation is then informed by the BSC background treatment distribution. Similarly, for patients who discontinue treatment with either vutrisiran or tafamidis, the ACM curves are informed by the BSC extrapolated curve from the point of treatment discontinuation.

For patients on treatment with vutrisiran monotherapy who discontinue treatment, a gradual treatment effect waning over 21 months to that of BSC is modelled for the health state transition probabilities, whereas for those who discontinue tafamidis monotherapy, the transition probabilities are informed by the BSC transition matrices immediately upon treatment discontinuation. The gradual treatment waning effect was modelled solely for vutrisiran monotherapy, as the company considered that serum TTR levels remain low for a sustained period after treatment discontinuation for this treatment. This was based on observed data on serum TTR levels over time following the final dose of vutrisiran received in the double-blind period of HELIOS-B (illustrated in Figure 15).

Figure 15 Mean change in serum TTR from pretreatment baseline following final dose of vutrisiran during the double-blind period in HELIOS-B (Figure 30, CS)

The company considered that an approximate 80% sustained reduction in serum TTR levels relative to pre-treatment baseline levels suggests that treatment benefit would remain, even in the absence of active treatment (threshold based on clinical opinion in the NICE highly specialised technology appraisal of patisiran in hATTR polyneuropathy),[23] and that the gradual reduction in serum TTR levels after treatment discontinuation would be associated with some level of treatment effect on transition probabilities over 21 months. This was implemented by basing NYHA class transition probabilities to remain the same as for those on treatment with vutrisiran [redacted] after discontinuation. Beyond those cycles, and as the mean percent TTR reduction relative to pre-treatment baseline during a post-discontinuation cycle was lower than 80% (based on the data in Figure 15), so a time-dependent weighted-average transition matrix, driven by the level of continued reduction of serum TTR relative to pre-treatment baseline, was used to estimate NYHA class transition matrices for patients who discontinued vutrisiran. The proportional contribution of BSC in the same cycle was calculated as 100% minus the proportional contribution of vutrisiran (estimated as the ratio between the percentual reduction in TTR at each time point and 80%). Treatment weights over time are reported in Table 29 of the CS.

Points for critique

The EAG is concerned that assuming the same treatment discontinuation from non-fatal causes for both vutrisiran and tafamidis monotherapy is not consistent with assuming treatment specific differences in health outcomes (e.g., on ACM and progression across NYHA class transitions). The EAG acknowledges the data limitations in HELIOS-B that precluded the company from providing a scenario analysis requested by the EAG where tafamidis monotherapy non-fatal TTD would be informed by treatment specific evidence from the double-blind period of HELIOS-B (consistently with assuming treatment specific ACM and disease progression in the model; see clarification question B7). Nevertheless, the EAG highlights that this is another consequence of HELIOS-B not being designed to assess the clinical effectiveness of vutrisiran vs. tafamidis monotherapy. It also means that it is not possible to ascertain that the time on treatment for tafamidis monotherapy that would lead to the health outcomes modelled by the company for this treatment.

The EAG is also concerned about the validity of the company's treatment effect waning on the transition probabilities. First, the company's approach does not account for the reason for discontinuation (other than death which was modelled separately). This is particularly a concern for those who may have discontinued due to loss or lack of treatment efficacy and may be included in the group of patients who discontinued for any of the following reasons: withdrawal by patient (n=[redacted]), clinician decision (n=[redacted]), lost to follow-up (n=[redacted]). For patients who discontinued treatment with vutrisiran due to loss or lack of treatment efficacy, the validity of assuming a continued treatment benefit lacks face validity. Second, the assumption that treatment effect wanes over a 21 months period based on a relationship between TTR levels reduction and treatment efficacy, for which the company does not present empirical data in the CS to support this quantitative relationship, is highly uncertain. Furthermore, the levels of TTR post treatment discontinuation in HELIOS-B only remain below the 80% TTR reduction from baseline threshold (suggested by clinical opinion) [redacted]. Third, clinical advice to the EAG also considered that gradual loss of treatment efficacy after discontinuation is plausible in the short-term, but not over 21 months as proposed for the company. The company has not explored the potential impact of this uncertain assumption on the estimates of cost-effectiveness. Hence, the EAG explores alternative assumptions for treatment effect waning for vutrisiran monotherapy in Section 6.

Finally, the EAG notes that the company's assumption that the mortality of patients who discontinue treatment with vutrisiran monotherapy is informed by the extrapolation curve of BSC is potentially conservative, as the observed survival for vutrisiran monotherapy should already account for not all patients remaining on treatment in the observed period. However, the EAG compared the survival curves with and without switching the source of survival estimates between vutrisiran and BSC at

treatment discontinuation and these were broadly similar, due to the relatively high proportion of patients on treatment over the time horizon.

4.2.7 Transient events

The company considered the occurrence of transient events comprising CV-related hospitalisations and urgent heart failure visits in the model, as these are associated with costs and HRQoL loss.

The probability of these events was assumed to depend on NYHA class, but not on treatment group. The company derived NYHA class-specific incidence rates at 3 months based on data from the IPTW-weighted HELIOS-B population pooled over vutrisiran and tafamidis monotherapy arms. The company justified the use of the pooled approach over using treatment-specific estimates to avoid very low event counts for some subgroups when stratifying by both treatment and NYHA class, which, leading to unreliable estimates with limited face validity (see response to clarification question B6). The per cycle incidence of transient events by NYHA classes applied in the model are summarised in Table 30 of the CS.

In the absence of data for patients in NYHA class IV, the company assumed that the relative risk of transient events in NYHA class IV was [redacted] that in NYHA III, according to clinical opinion received by the company.

Points for critique

The approach taken by the company is not entirely consistent with that of previous TAs of tafamidis in ATTR-CM (TA696 and TA984), as in these appraisals transient events were NYHA-specific and treatment-specific.[17, 18] Nevertheless, the company's approach for this seems appropriate, as applying a treatment effect on transient events by NHYA class could unduly magnify the impacts of vutrisiran vs. tafamidis monotherapy which are highly uncertain (see Section 4.2.6.1).

4.2.8 Adverse events

The model includes 10 treatment emergent SAEs experienced by at least 3% of the population in the vutrisiran monotherapy group or tafamidis monotherapy group during the double-blind period of HELIOS-B. the company chose this threshold in order to capture the treatment-emergent SAEs Treatment specific incidence rates for each SAE are presented in Table 31 of the CS.

SAEs were modelled as one-off impacts on costs and HRQoL (see Sections 4.2.10.7 and 4.2.9.4, respectively) in the first cycle in the model. This approach was preferred by the company (instead of modelling per cycle SAEs occurrence) to reflect observed treatment-emergent serious AEs in HELIOS-B and because clinical data indicate that AEs tend to cluster early in the course of treatment and become less frequent as patients continue therapy, rather than occurring consistently in each cycle. Furthermore, the company also considered that there was a lack of evidence supporting the

persistence of AEs over time. The approach is also consistent with the one taken in previous TAs of tafamidis in ATTR-CM (TA696 and TA984).[17, 18]

Points for critique

The EAG does not have concerns about the modelling of adverse events, as the incidence rates of these are unlikely to have more than a marginal impact on the estimates of cost-effectiveness.

4.2.9 Health-related quality of life

4.2.9.1 Summary of company's submission

The company conducted a systematic literature review to identify studies reporting HRQoL for adults with ATTR-CM (see Appendix F of CS). The company also conducted an SLR of HRQoL studies and cost and resource use studies in patients with ATTR-CM, Appendix B of the CS included the search strategies to identify these studies. The searches were part of a wider burden of illness SLR and were undertaken in December 2023 and updated in October 2024. Six studies were identified reporting EQ-5D data in patients with ATTR-CM (summarised in Table 33 of the CS). The company noted that only one study[24]reported EQ-5D-5L utilities by the NYHA class, and the study included only 3 patients in NYHA IV. Therefore, the company considered the health state utilities identified in the SLR unsuitable for use in the cost-effectiveness analysis.

The HELIOS-B, individual patient-level EQ-5D-5L data were used to inform NYHA class-specific utilities in the model. The health state utilities were derived from the HELIOS-B trial EQ-5D-3L data mapped to the EQ-5D-5L data using a published algorithm,[25] and using a linear mixed-effects model (LMEM). The utilities were modelled as treatment-independent estimates, i.e., a patient in a given NYHA class who is receiving vutrisiran is assumed to experience the same level of HRQoL compared with a patient in the same health states who is receiving tafamidis. Health state utilities were capped by age- and sex-matched UK general population utility. The model also accounts for utility decline over time associated with ageing by adjusting earlier-stage NYHA class utilities via age- and sex-matched utility decrement in NYHA class I and II.

HRQoL decrements (disutilities) are applied to transient events and for patients experiencing AEs while on treatment. The model includes CV-related hospitalisation and urgent HF visits as transient events. In the absence of the data from the HELIOS-B, disutilities for CV-related hospitalisation and urgent HF visits were sourced from previous studies.

4.2.9.2 Health State Utilities

Treatment independent utility values were estimated for each of the NYHA class health states (I, II, III, and IV), using HRQoL data collected from the ITT population of HELIOS-B. Longitudinal EQ-5D-5L data was mapped to EQ-5D-3L values was analysed using LMEM, adjusted for baseline EQ-

5D-3L, study visit, NYHA class at each visit, type of amyloidosis, age group, and sex (base LMEM). Missing EQ-5D data was assumed missing at random, and therefore, LMEMs were fitted to available measurements. For the NYHA class at each visit, last observation carried forward imputation was performed.

The company investigated further covariates (and interaction terms) for inclusion and fitted alternative model specifications, assessing their statistical goodness-of-fit based on AIC (see Table 18, response to clarification question B10). Although the best fitting model was, according to the company, LMEM (treatment-independent, excluding AEs), the preferred model used to derive base-case health state utilities was the LMEM including specific AEs. This was considered a more appropriate model specification by the company, given the importance of estimating AE disutilities for the economic model. The company did not provide NYHA health state utility values derived by any of the alternative LMEM specifications.

The health state utilities in estimates company applied in the model were capped for the UK age- and sex-matched general population corresponding to the model population at baseline, because the utilities estimated from HELIOS-B data were higher than the general population's. This was done by adjusting all utility values by a fixed value ([redacted]) corresponding to the difference between the regression estimated utility in NYHA class I at the model baseline age- and sex-matched UK general population utility. Utilities before and after capping are presented in Table 19.

Table 19: NYHA class-specific utility values (Tables 32 and 34, CS)

Utility estimates by NYHA class	Utilities estimated using HELIOS-B LMEM analysis	Utilities in the model* Mean input value (95% CI)
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]

*Capped by age- and sex-matched UK general population utility

The model also adjusted for the utility loss associated with ageing by applying a utility decrement to the HRQoL accrued in NYHA classes I and II every year of the model (i.e., first cycle of that year), using an additive approach. Disutilities for ageing were not applied to patients in NYHA classes III or IV, as the company assumed that the impact of ageing on utilities for these patients would be negligible compared to the detrimental effects of the disease on HRQoL.

Points for critique

The EAG considers the company's approach to be consistent with previous NICE TA984 for tafamidis, as health states utilities (NYHA classes) were modelled as treatment-independent estimates, and utilities were age-and sex- adjusted to the general population utility. Furthermore, the EAG considers that the company's capping of health state utilities to avoid estimates above those of the age and sex matched general population appropriate and in line with NICE guidance.[21] However, the company preference for an additive approach perform general population adjustments to the utilities was not justified. At the request of the EAG, the company provided a number of scenario analyses using the multiplicative approach (in response to clarification question B9, table 17), which is generally preferred for age- and sex-matched utility adjustments in line with general population utility over time[21, 26] with and without capping health state utilities by the matched general population utility at baseline. The EAG considers that, in the absence for a strong rationale to use the additive approach, the company should have used the method recommended by the NICE manual, i.e., the multiplicative approach. The EAG further notes that the decision to only adjust utilities to utilities accrued in NYHA classes I and II, is not consistent with previous NICE TAs in ATTR-CM (TA696 and TA984)[17, 18] and would have preferred to see analyses where the adjustments are extended to all health states. Nevertheless, the EAG considers that extending the general population utility adjustment to all NYHA is unlikely to have a sizeable impact on the estimates of cost-effectiveness and that the company's rationale for only adjusting NYHA class I and II may be valid.

The EAG has some concerns regarding the methods used by the company to estimate health state utilities. Despite the additional information provided by the company at the clarification stage, the EAG has not been able to verify the robustness of the model to alternative health states utilities derived by these alternative LMEM model specifications, as these values were not provided. As shown in Table 20, which reports the regression output for the company's preferred LMEM model, the provided coefficients on many of the specified AEs lack face validity as these suggest HRQoL improvements rather than decrements for a number of AEs. The coefficients on AEs also lack statistical significance, making them highly uncertain. Thus, the EAG is not persuaded by the company's rationale for LMEM selection. Overall, the EAG considers the information provided by the company insufficiently detailed to critique the suitability of the chosen model for deriving NYHA class-specific utilities from the HELIOS-B data and would have liked to see the results of the base LMEM without adjustments for specific AEs. This notwithstanding, the EAG considers that the health state utility estimates applied in the company's base case seem to have face validity (i.e., decreasing utility estimates with increased NYHA class; see Table 19). The EAG was not able to compare the health state utility values with those of previous NICE TAs in ATTR-CM, as these are redacted in the documentation. However, the estimates in the company's model are similar to those applied in a recent HTA in ATTR-CM by the Institute for Cost-Effectiveness Review.[27] Thus, the EAG is

reassured that the utility values are consistent with other estimates used to inform decision making in this indication even if in another jurisdiction.

Table 20 LMEM model coefficients used to derive the base-case health state utilities (Table 19, response to clarification question B10) model

Covariate	Estimate	SE	t value	95% CI lower limit	95% CI upper limit
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study visit (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study visit (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study visit (Month 30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnosis (wtATTR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group (>=75 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial flutter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB: Estimates represent the change in EQ5D-3L for a unit change in the covariate.

For the searches conducted for the HRQoL studies and cost and resource use studies SLR, the EAG has no concerns; the searches are appropriate, high quality, and clearly reported. Full details of the EAG appraisal of the searches can be found in Table 40 of Appendix 1: EAG appraisal of review evidence.

4.2.9.3 Disutility associated with transient events

The company's model considers HRQoL loss associated with transient events, namely CV-related hospitalisation and urgent heart failure visits. In each model cycle, QALY losses were applied to the proportion of patients who experienced a CV-related hospitalisation or urgent heart failure visit.

The company states that it was not possible to derive utility decrements for these events from HELIOS-B EQ-5D-5L data, because these data were typically not available from patients at the time they were experiencing these events. Utility decrements for CV-related hospitalisation were sourced from the published literature (see Table 35 of the CS) and are not specific to ATTR-CM, but rather to

heart failure. The disutility estimate for CV-related hospitalisation reflects utility decrements over a 4-week window, and thus, QALY loss per CV-related hospitalisation was determined by multiplying the disutility value by a proportion of 1 year represented by a 4-week period (yielding a QALY loss of -0.005). A similar assumption on the duration of the event was applied to estimate the QALY loss associated with urgent heart failure, resulting in a QALY loss of –0.003.

Table 21: Transient and SAE event disutility applied in the company's model (CS Tables 35 and 36)

Item	Disutility	Source
Disutility estimates		
CV-related hospitalisation	-0.070	McEwan et al. (2021)[28]
Urgent HF visit	-0.036	TA679[29]
Serious adverse event		
Atrial fibrillation	[redacted]	HELIOS-B LMEM analysis
Osteoarthritis	–0.149	McEwan et al. (2020) [30]
Pneumonia	–0.100	McEwan et al. (2021) [28]
Acute kidney injury	[redacted]	HELIOS-B LMEM analysis
Atrial flutter	[redacted]	HELIOS-B LMEM analysis
Ventricular tachycardia	[redacted]	HELIOS-B LMEM analysis
Syncope	–0.048	Wehler et al. (2018)[31]
Chest pain	–0.050	Davies et al. (2015) [32]
Hyponatraemia	–0.121	TA797[33]
Urinary retention	[redacted]	HELIOS-B LMEM analysis

Points for critique

The EAG noted the discrepancies in the disutility value for CV-related event reported in the CS (page 90, section 3.4.5.1) and Table 35. The model was implemented using values reported in Table 35. The disutility value associated with CV-related hospitalisation was sourced from McEwan et al. (2021). The study utilized data from the AFFIRM-AHF trial and included more severe patients compared to HELIOS-B. Notably, the overall population at baseline in HELIOS-B with NYHA classes I and II comprised ~90% of the study population opposed to 47% in the AFFIRM-AHF study. [28]

4.2.9.4 Disutility associated with serious adverse events

The company modelled the disutility associated with the included SAEs (see Section 4.2.8). The disutilities associated with SAEs was informed by the same LMEM used to derive health state utilities (see Section 4.2.9.2) for those AEs for which HRQoL was available and the coefficients did not imply an improvement in HRQoL. The company preferred using AE disutilities from HELIOS-B whenever

possible, because HELIOS-B represents the population of interest (i.e., contemporary patients with ATTR-CM). For the remaining SAEs, disutilities were informed by the published literature. The duration of the SAEs was informed by HELIOS-B data and QALY loss associated with SAEs was estimated by multiplying the proportion of patients who experience the SAE in each treatment arm by the disutility estimate for the SAE (see Table 22). The resulting treatment-specific QALY loss was applied as a one-off impact in the first model in the cycle [redacted] for vutrisiran and tafamidis, respectively).

Table 22 SAE disutility applied in the company's model (CS Table 36)

Serious adverse event	Disutility	Source	Median duration, days (range)
Atrial fibrillation	[redacted]	HELIOS-B LMEM analysis (assumed the same as atrial flutter)	[redacted]
Osteoarthritis	–0.149	McEwan et al. (2020) [30]	[redacted]
Pneumonia	–0.100	McEwan et al. (2021) [28]	[redacted]
Acute kidney injury	[redacted]	HELIOS-B LMEM analysis	[redacted]
Atrial flutter	[redacted]	HELIOS-B LMEM analysis	[redacted]
Ventricular tachycardia	[redacted]	HELIOS-B LMEM analysis	[redacted]
Syncope	–0.048	Wehler et al. (2018)[31]	[redacted]
Chest pain	–0.050	Davies et al. (2015) [32]	[redacted]
Hyponatraemia	–0.121	TA797[33]	[redacted]
Urinary retention	[redacted]	HELIOS-B LMEM analysis	[redacted]

Points for critique

As noted above in Section 4.2.9.2, the EAG the company's preferred LMEM, which provides the disutility values for some of the SAEs in the model, produced statistically insignificant coefficients for all SAEs specified in the model, and some of these coefficients implied a utility gain rather than a loss. Given this, the EAG is not persuaded by the company's source of disutility values for any of the SAEs included in the model. The EAG also notes that the values applied in the model for atrial flutter does not match the corresponding coefficient of the LMEM output (see Table 20), but the difference is small.

The EAG also considers it inconsistent to assign the disutility associated with SAEs based on data from HELIOS-B but not for CV transient events. The company's response to clarification question B10, suggests that it is possible and appropriate to capture the impact on HRQoL of transient events like SAEs using HELIOS-B data. It is not clear why the company considered it inappropriate to derive disutility for the CV events which are also transient.

The EAG considers that overall, the disutility estimates applied in the model to capture the impact of SAEs on HRQoL are highly uncertain. Nevertheless, the EAG does not believe that this uncertainty is

likely to impact substantially the estimates of cost-effectiveness and as noted in Section 4.2.8 the incidence rates of SAEs are unlikely to have more than a marginal impact on the estimates of cost-effectiveness.

4.2.9.5 Caregiver disutilities

The company included caregiver disutilities in all of their cost-effectiveness analyses, as they considered that ATTR-CM is burdensome and has detrimental impacts on the HRQOL of informal caregivers.

The NYHA class specific caregiver disutility estimates applied in the company's model were sourced from a study that estimated compared EQ-5D-3L scores in 36 caregivers of patients with hATTR, reported by ambulatory status of the patient (as indicated stage).[34] with those of general population matched controls. These utilities are reported by familial amyloid polyneuropathy [FAP] stage, defined by ambulatory status, in CS Table 47. Some of the patients in the study had ATTR-CM (62%), but carer disutilities were not reported by NYHA class. The model company used these values as a proxy for caregiver disutilities by the NYHA class, i.e., caregiver disutility for FAP stage 1 is assumed to correspond to NYHA class I, FAP 2 to NYHA II, and FAP 3 to NYHA IV. For NYHA class III, the company assumed that FAP 3 to NYHA IV and caregiver disutility for NYHA III was assumed to be 80% of NYHA IV. To estimate the caregiver utility per cycle, the company also took into account the proportion of patients requiring a caregiver and the number of caregivers per patient at each NYHA class; this evidence was sourced from clinical expert opinion. The EAG has summarised the information used to estimate caregiver disutilities per cycle (which are then weighed by the proportion of patients in each NYHA class health state to derive QALY losses for carers) in Table 23.

Table 23 Estimation of utilities applied in the model per NYHA class and cycle

NYHA class	Disutility mean value	Proportion of patients with caregivers	Number of caregivers	Disutility per cycle
I	-0.031	10%	1	-0.0031
II	-0.096	30%	1	-0.0288
III	-0.104	80%	2*	-0.0832
IV	-0.130	100%	2*	-0.13

* was assumed to be [redacted], so this is modelled as only one caregiver incurring the disutility.

Points for critique

The EAG considered it reasonable to expect the disease to have an impact on the HRQoL of caregivers beyond what is captured by movements across NYHA classes, but it is uncertain whether

the extent of this impact is greater than would be expected in other disease areas where carer burden is not routinely accounted for in the QALY estimates (e.g., in oncology in adult patients). While there is no formal guidance to determine when is it relevant to include in NICE appraisals,[21, 35]it has been recommend that evidence should be provided to show that a condition is associated with a substantial impact on carer's health-related quality of life to help mitigate the issue that the carer effects associated with the portfolio of standard NHS treatments is not included in the usual cost-effectiveness threshold.[26] The EAG considers that the company has not provided sufficient evidence to support their case for inclusion of caregiver utilities, but acknowledges that this is an area of uncertainty.

Furthermore, the use of caregiver utilities is not consistent with previous NICE TAs in ATTR-CM (TA696 and TA984).[17, 18] The company also had to rely on a number of assumptions in order to derive caregiver disutilities by NYHA class from a population of patients with hATTR of which 62% had hATTR-CM (vs. less 15% than in the HELIOS-B population which only included patients with ATTR-CM), as the evidence by NYHA class in a contemporaneous, predominantly wtATTR-CM population was not available.

The EAG considers that there is uncertainty as to whether i) caregiver disutilities should be considered for the modelled population and ii) the disutilities applied in the model are reflective of caregiver disutility by NYHA class in a contemporaneous ATTR-CM population. The EAG presents analyses with and without carer disutilities in Section Table 1 Summary of Key Issues6.

4.2.10 Resource use and costs

4.2.10.1 Confidential pricing arrangements

The EAG notes that there are confidential commercial arrangements in place for tafamidis consisting of s confidential Patient Access Scheme (PAS) price for this drug which differs from the publicly available list price used to generate the results in this report. The drug acquisition cost used in the CS and in Sections 5 and 6 of this report includes only the PAS price for vutrisiran, which consists of a [redacted] over the vutrisiran list price (see Section 4.2.10.3).

The confidential price for tafamidis was made available to the EAG and used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee; these are reported in a separate appendix to the EAR. The price is correct as of February 25, 2025.

4.2.10.2 Summary of company's submission

The company's economic model includes costs related to (i) drug acquisition, (ii) drug administration, (iii) background medication, (iv) SAEs, (v) transient CV events, (vi) non-hospitalisation disease management, and (vii) terminal care. Unit costs are mostly informed by national published sources,

such as NHS reference costs 2023/2024 [36] , the Personal Social Services Research Unit (PSSRU) costs 2023 [37] , and the British National Formulary (BNF) where appropriate and discounted at an annual rate of 3.5%. Costs per 3-month model cycle in the company's base-case analysis are summarised by category in Table 24.

Table 24 Summary of costs included in the company's base-case analysis

Item	Model input	EAR Section
Drug acquisition costs per cycle		
Vutrisiran	[redacted]	Section 4.2.10.3
Tafamidis	£32,525.14	
Drug administration costs per cycle		
Vutrisiran	First cycle: £108.90 Subsequent cycles: £0	Section 4.2.10.3
Tafamidis	£0	
Background medication costs per cycle		
Vutrisiran	[redacted]	Section 4.2.10.4
Tafamidis	[redacted]	
SAEs costs per cycle		
Vutrisiran	[redacted]	Section 4.2.10.7
Tafamidis	[redacted]	
Transient events costs per cycle		
Vutrisiran	NYHA I: £[redacted] NYHA II: £[redacted] NYHA III: £[redacted] NYHA IV: £[redacted]	Section 4.2.10.5
Tafamidis		
Non-hospitalisation disease management costs per cycle		
Vutrisiran	NYHA I: £[redacted] NYHA II: £[redacted] NYHA III: £[redacted] NYHA IV: £[redacted]	Section 4.2.10.6
Tafamidis		
Terminal care costs (one-off cost reflecting in the cycle patients die)		
Vutrisiran	£8,051	Section 4.2.10.8
Tafamidis		

4.2.10.3 Drug acquisition costs and administration costs

The company based the acquisition unit cost for vutrisiran on the PAS price of [redacted] for one individually packed pre-filled syringe containing 25mg of vutrisiran, which corresponds to a [redacted] discount over the list price of £95,862.36). For tafamidis, the unit cost was informed by the list price for tafamidis 61 mg (£10,685.00) per 30 capsules pack.[8] Vutrisiran acquisition costs were applied once every 3 months, and tafamidis once every day taken orally for tafamidis. No drug wastage was considered for vutrisiran or tafamidis, and both drugs were assumed to have a relative dose intensity

of 100%. The annual acquisition costs of vutrisiran and tafamidis are £[redacted] and £130,100.56, respectively.

Administration costs were included for vutrisiran in the first cycle in the model to account for the delivery of one SC by a nurse in a hospital setting (£108.90 (see Section 3.5.1.2 of the CS) [36]. [redacted] For tafamidis, administration costs are not included, as the drug is administered orally.

The drug acquisition and administration costs are incurred while patients remain alive and on treatment, with treatment duration for both treatments under comparison informed by the extrapolated (non-fatal) TTD based on HELIOS-B for the vutrisiran monotherapy arm (see Section 4.2.6.4).

Points for critique

The EAG is concerned that the vutrisiran acquisition and administration costs may have been underestimated in the company's cost-effectiveness analysis due to the application of the within-cycle correction (see Section 4.2.2). The EAG considers that this within-cycle correction (or other more routinely applied cycle corrections like the half-cycle correction) should not be applied to the vutrisiran acquisition and administration costs, given that the periodicity of drug administration completely aligns with the modelled cycle length. Given this, it is not reasonable to assume that not all patients treated with vutrisiran would have incurred these costs if they were to stop treatment at some point within the model cycle, as is implied when assuming a cycle correction. For tafamidis, which is taken once a day, the within-cycle correction is appropriate (although it may have been more appropriate to also include a wastage assumption for this treatment when including the within-cycle correction for this treatment). The EAG presents total drug acquisition and administration costs for vutrisiran and tafamidis with and without within-cycle correction in Table 25, to illustrate the impact of this in treatment costs over the time horizon.

Table 25 Drug acquisition and administration costs with and without within-cycle correction

	Total acquisition cost		Total administration cost	
	Vutrisiran	Tafamidis	Vutrisiran	Tafamidis
(a) With within-cycle correction	[redacted]	[redacted]	[redacted]	£0
(b) Without within-cycle correction	[redacted]	[redacted]	[redacted]	£0
Difference: (a)-(b)	[redacted]	[redacted]	[redacted]	£0

Another issue of concern stems from the company's assumptions on [redacted] Therefore, the EAG considers that administration costs should be in line with the SmPC,[1] which states that vutrisiran should be administered by a health care professional throughout the time on treatment.

Finally, the EAG reiterates that the assumption that time on treatment is the same for both treatments under comparison is inconsistent with the company's modelling of differential treatment effectiveness for vutrisiran and tafamidis monotherapy (see Section 4.2.6.4), but notes that there is no available alternative source of evidence to inform treatment duration for tafamidis monotherapy.

4.2.10.4 Background medication costs

In the model, all patients received medications to manage the associated cardiac symptoms of the disease. Treatment specific per-cycle use rates were informed by HELIOS-B data for vutrisiran and tafamidis monotherapy, and are reported in Table 41 of the CS. The model also considers the background medication use derived from the monotherapy placebo arm of HELIOS-B to inform the corresponding estimates for patients who have discontinued treatment with either vutrisiran or tafamidis monotherapy to reflect use while on BSC; these values are reported in Table 9 of Appendix J. Unit costs of background medication and posology was sourced from the BNF (see Table 42 of the CS).

Points for critique

The EAG considers the company's approach generally appropriate, although it is unclear whether the differences in background costs should be treatment specific for vutrisiran and tafamidis monotherapy, given the limitations of the clinical evidence informing these treatments (see Section 4.2.6.1). The actual cost estimates per cycle are, however, quite similar between treatments (£[redacted] and £[redacted] for vutrisiran and tafamidis monotherapy, respectively) so this is a minor issue. The EAG was also unable to completely reconcile the unit costs in the company's model with those in the most

recent version of the BNF. However, differences were minor and are unlikely to impact on the estimates of cost-effectiveness.

4.2.10.5 Costs of transient events

The model considers the costs of patients who are hospitalised for CV-related reasons or have urgent HF visits. The rates of these events are only NYHA class specific (see Section 4.2.7). The unit costs for each of these two transient events are informed by the NHS 2023/2024 National Schedule of Costs [36] and reported in Table 43 of the CS.

Points for critique

The EAG has no concerns about the parameterisation of this category of costs.

4.2.10.6 Non-hospitalisation disease management costs

The company's model considers the costs of healthcare services use in ATTR-CM, beyond that of hospitalisation. These include outpatient visits, community care and monitoring laboratory and imaging tests. The estimates of resource use (reported in Tabel 45 of the CS and informed by expert clinical opinion) are conditional on NYHA class, with resource use increasing with disease severity for some but not all categories of cost. The resulting health state costs per NYHA class are reported in Table 46 of the CS.

Points for critique

The EAG has no concerns about the parameterisation of this category of costs.

4.2.10.7 Costs of associated with SAEs

The company considers the costs associated with managing the SAEs included in the model (see Section 4.2.8). The unit costs for these SAEs are informed by the NHS 2023/2024 National Schedule of Costs[36] and reported in Table 47 of the CS. The one-off cost of managing SAEs applied at the first cycle in the model was estimated by weighing the unit costs by the treatment specific incidence rates and corresponded to [redacted] and [redacted] for vutrisiran and tafamidis monotherapy, respectively.

Points for critique

The EAG has no concerns about the parameterisation of this category of costs, other than those raised in Section 4.2.8.

4.2.10.8 Costs of terminal care

The company include the costs associated with terminal care for the proportion of patient who died at each model cycle. The unit cost applied (£8,051) was sourced from publicly available national source.[37]

Points for critique

The EAG has no concerns about the parameterisation of this category of costs.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of the company's submission

A summary of the inputs and variables used in the company's base case analysis is presented in Table 50 of CS and the assumptions used in the model are summarised in Table 51 of CS. All analyses presented in the CS include the confidential simple PAS discount of [redacted] over the vutrisiran list price (see Section4.2.10.3). The analyses with confidential PAS prices are presented in a confidential appendix separate to the EAR for the company's base-case analysis. The company's base-case results are not adjusted by any severity modifier, as the criteria for this to hold are not met (see Section 7).

Table 26 shows the company's base case probabilistic and deterministic cost-effectiveness results. The probabilistic ICER for vutrisiran relative to tafamidis is [redacted], while the deterministic ICER is [redacted]. The cost effectiveness plane and cost effectiveness acceptability curve are presented in Figures 31, 32 of CS, respectively. The results of the company's probabilistic base case analysis show that the probability of vutrisiran being cost-effective compared to tafamidis is [redacted] at cost-effectiveness thresholds of £20,000 and £30,000/QALY.

Table 26 Company's base case results (reproduced from Tables 52 and 53 of the CS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Probabilistic							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years;

The EAG noted in Section 4.2.9.5, that the company did not present the cost-effectiveness results excluding caregiver disutilities in the CS. The EAG considers this to be an area of uncertainty and one with a potentially large impact on the estimates of cost-effectiveness. Therefore, the EAG reports in Section 6 results for the company's base-case deterministic results without caregiver disutilities.

Table 27 Company's base case results excluding carer disutilities (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To aid understanding of the key drivers of the cost-effectiveness results, Table 28 and Table 29 provide a summary of the disaggregated costs and health outcomes, respectively. The additional costs of vutrisiran compared to tafamidis monotherapy are predominantly driven by the drug acquisition costs of vutrisiran, with some of this cost offset by reduced costs associated with non-hospital disease management, transient events, SAE management and terminal care. It also shows that vutrisiran yields the higher total LYs with incremental LYs compared to tafamidis of [redacted] in NYHA class I, II and III and lower LYs in the most severe health state (NYHA class IV) compared to tafamidis. The QALY gain for vutrisiran is driven by the gains in HRQoL associated with a higher proportion of vutrisiran patients in the less severe health states (NYHA class I and II and less) over time and lower caregiver disutilities compared to tafamidis.

Table 28 Disaggregated costs (discounted) for vutrisiran and tafamidis (adapted from Appendix H, CS)

Costs	Vutrisiran (£)	Tafamidis (£)	Incremental costs (£)	% of total incremental costs
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Background medication	[redacted]	[redacted]	[redacted]	[redacted]
Non-hospitalisation disease management	[redacted]	[redacted]	[redacted]	[redacted]
Transient events	[redacted]	[redacted]	[redacted]	[redacted]
SAE management	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SAE, serious adverse event.

Table 29 Disaggregated health outcomes (discounted) for vutrisiran and tafamidis (adapted from Appendix H, CS)

Outcome	Vutrisiran	Tafamidis	Incremental	% of total incremental
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	Vutrisiran	Tafamidis	Incremental	% of total incremental
NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
SAE disutilities	[redacted]	[redacted]	[redacted]	[redacted]
Transient event disutilities	[redacted]	[redacted]	[redacted]	[redacted]
Age-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver disutilities	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SAE, serious adverse events; LY, life years; NYHA, New York Heart Association; QALY, quality-adjusted life years. Note: Total may be off due to rounding.

5.2 Company's sensitivity analyses

5.2.1 Summary of the company's submission

The company conducted a deterministic OWSA by varying the base-case values of input parameters and plotting those with the greatest impact on ICERs on a tornado plot and in a tabular format (Figure 33 and Table 54 of the CS, respectively. The company considered the most influential parameters to be the probability of remaining in for NYHA health state II to NYHA at Months 24–27 and 27–30 for the tafamidis arm.

The CS also reports deterministic results for sixteen scenario analyses, with three additional scenarios presented at the clarification state; results are summarised in Table 30. The company's results are generally robust to the assumptions varied in scenario analyses, with all but one analysis (which used hypothetical acquisition costs for vutrisiran and tafamidis) yielding ICERs well above the range of cost-effectiveness thresholds usually considered by NICE. [redacted] The EAG also notes that there are numerous areas of uncertainty highlighted by the EAG throughout Section 4 that were not explored in the company's sensitivity analysis; the EAG presents further analyses in Section 6.

Table 30 Scenario analysis results (From Table 57 of the CS, and Table 17 of the company clarification questions response)

Scenario	Incremental discounted costs (£)	Incremental discounted QALYs	Discounted ICER (£/QALY)	% of discounted base case ICER
Base Case	[redacted]	[redacted]	[redacted]	–
Discounting				
Costs=0%, effects=0%	[redacted]	[redacted]	[redacted]	[redacted]
Costs=0%, effects=5%	[redacted]	[redacted]	[redacted]	[redacted]
Costs=5%, effects=0%	[redacted]	[redacted]	[redacted]	[redacted]
Costs=5%, effects=5%	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental discounted costs (£)	Incremental discounted QALYs	Discounted ICER (£/QALY)	% of discounted base case ICER
Time horizon				
5 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]
Transition matrix				
Extrapolated TPs based on TPs in M24–27 and 27–30	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of full societal perspective				
Include caregiver lost productivity	[redacted]	[redacted]	[redacted]	[redacted]
Include caregiver and patient lost productivity (full societal perspective)	[redacted]	[redacted]	[redacted]	[redacted]
Per-cycle transient event incidence rates in NYHA class IV				
Rate in NYHA IV is four times rate in NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
Rate in NYHA IV is five times rate in NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
Baseline age				
72 years old	[redacted]	[redacted]	[redacted]	[redacted]
Survival				
Similar survival in vutrisiran and tafamidis arms	[redacted]	[redacted]	[redacted]	[redacted]
Annual acquisition costs for vutrisiran and tafamidis				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-related utility decrement method				
Use multiplicative approach of applying age-related utility decrement rather than an additive approach	[redacted]	[redacted]	[redacted]	[redacted]
Utility capping				
Disable capping of health state utilities by UK age- and sex- matched general population utility (additive approach)	[redacted]	[redacted]	[redacted]	[redacted]
Disable capping of health state utilities by UK age- and sex- matched general population utility (multiplicative approach)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life year; TP, transition probability.

The company did not conduct subgroup analysis.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company undertook technical validation internally and externally of the model. For internal validation, the CS states that an independent quality assessment was conducted to ensure the model is error-free and correctly programmed; an internal peer reviewer who was not involved in the original programming checked on the computational framework of the model, including model input, calculation, reference formulas, and VBA code. For external validation, the company states that the model outputs, including survival parameters, estimated life years, QALYs, and costs, were validated

against observed data in ATTR-CM clinical trials, a real-world UK clinical practice study,[39] and tafamidis HTA submissions. The company did not, however, present in the CS any outcomes of this external validation exercise. The company also used SEE to validate the modelled survival (see Section 4.2.6.3). Feedback on key clinical model inputs and assumptions is summarised in Table 48 of the CS.

Points for critique

The EAG considers the company's technical validation procedure to be reasonable. However, the EAG reviewed the company model in detail and identified two errors in the calculation and implementation of the severity modifier (these are detailed in Section 7), but do not impact the estimates of cost-effectiveness. Both of these errors were corrected by the EAG, so that the severity modifier could be correctly calculated for the analysis presented in Section 6.

The EAG cannot comment on the external validation conducted by the company, given that the company did not present its results in the CS, other than the information provided by the SEE report (discussed in Section 4.2.6.3).

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the main issues identified and critiqued in Section 6, along with the scenario where the EAG addresses each issue in its additional analyses, is shown in Table 31. The EAG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where possible, the EAG explored alternative assumptions and model inputs in scenario analyses to the company's base-case analysis (EAG Scenarios 1-7). The EAG's base case consists of the set of assumptions and model inputs that the EAG considers to be more appropriate for assessing the cost-effectiveness of vutrisiran monotherapy relative to (i) tafamidis monotherapy and (ii) BSC. Where the EAG is unable to provide a judgment in the absence of evidence [redacted], the EAG have presented results of alternative scenarios to the EAG base case. Thorough descriptions of the EAG scenario analyses are presented in Section 6.1.1, while the impact on the cost-effectiveness results is presented in Section 6.2. All scenario results are presented with and without including carer disutilities, as the EAG considers it uncertain whether these apply to ATTR-CM. The severity modifier does not apply to any of the EAG's analyses (see Section 7).

Table 31 Summary of the main issues identified by the EAG in Section 4 and EAG scenarios

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
1	***It may not be appropriate to include caregiver impacts on health outcomes in ATTR-CM***	Sc. 1-7	Yes	Yes	Yes
2	***BSC should have been included as comparator***	Sc. 1-7	Yes	Yes	Yes
3	***Treatment waning effect for vutrisiran monotherapy conditional on TTR levels is uncertain***	Sc. 2 & 4	Yes	Yes	No
4	***Implausible long-term hazard (decreasing over time) for the vutrisiran monotherapy ACM extrapolation***	Sc. 3 & 4	Yes	Yes	No
5	***Differences in treatment effectiveness of vutrisiran vs. tafamidis monotherapy are highly uncertain***	Sc. 4	Yes	Yes	Yes
6	***The lack of structural link between disease progression***	NA	NA	Yes	Unknown
7	***Assuming the same treatment duration for tafamidis and vutrisiran monotherapy is inconsistent with the assumption that these treatments have a differential impact on clinical effectiveness***	Sc. 4	Yes	Yes	NA
8	***Health state utilities should be adjusted by general population utility using a multiplicative approach***	Sc.5	Yes	Yes	Yes
9	***The within cycle correction should not apply to vutrisiran administration and acquisition costs***	Sc. 6	Yes	No	No
10	***The administration costs for vutrisiran monotherapy should be in line with SmPC.***[1]	Sc. 7	Yes	Yes	No

Abbreviations: NA, not applicable; Sc., scenario

6.1.1 Issues explored by the EAG in additional analyses

6.1.1.1 Scenario 1: Comparison with BSC

As detailed in Section 4.2.4, the EAG considers that the comparison of vutrisiran monotherapy vs. BSC should not have been excluded from the cost-effectiveness analysis in the CS, as the only robust relative effectiveness evidence for vutrisiran monotherapy in ATTR-CM has been established against placebo (without background tafamidis) in the HELIOS-B trial and placebo can be assumed to reasonably reflect the effectiveness of BSC. Furthermore, there is a proportion of patients for whom tafamidis is not a treatment option due to treatment intolerance or lack of effectiveness (i.e., those whose treatment with tafamidis has not achieved the expected response).

As the company did not provide a version of the model with functionality to select BSC as an alternative comparator (see response to clarification question B1), the EAG updated the model to utilise effectiveness data for BSC informed by the placebo arm of the monotherapy population of HELIOS-B as reported in Appendix J of the CS for the NYHA class transition probabilities (Table 7) and the survival extrapolation (Figure 6 in Appendix J of the CS and reproduced in Figure 16). Treatment costs of BSC were also included based on the distribution of therapies for symptom management with BSC reported in Table 9 of Appendix J of the CS.

These data were included in the company's version of the model to inform the health and cost outcomes of patients who discontinued vutrisiran or monotherapy, and not for the purpose of establishing a direct comparison with vutrisiran monotherapy. Furthermore, the vutrisiran monotherapy effectiveness data in the model was IPTW adjusted to allow for comparison with tafamidis monotherapy. Therefore, the EAG notes that the clinical effectiveness used to inform comparison in this scenario does not correspond to the clinical effectiveness for the HELIOS-B monotherapy population, as would have been the EAG's preference. However, the EAG considers the approach taken reasonable, given that the company's model was not set up to allow for the comparison with BSC.

In scenario 1, all the company's base case assumptions, except for the relevant comparator, were retained. For the BSC survival extrapolation, the Weibull distribution is assumed in line with the company's assessment of the best fitting distribution. Whilst the EAG was not able to validate the company's assessment of alternative survival functions, but the Weibull seemed a reasonable choice.

Figure 16 Parametric functions fit to survival in the placebo monotherapy arm in HELIOS-B (Figure 6, Appendix J of the CS)

The EAG notes that information on the incidence of SAEs for BSC is not considered in the company's model, and the information presented in the CS for the safety in the placebo arm of the HELIOS-B monotherapy population is too aggregated to be incorporated in the model. Therefore, the EAG assumed that there were no SAEs for BSC, which may be conservative towards vutrisiran monotherapy, but unlikely to have more than a marginal impact on the estimates of cost-effectiveness.

In subsequent EAG scenarios varying the company's assumptions for the vutrisiran vs. tafamidis monotherapy, the corresponding analysis for the comparison against BSC is also presented; the only exceptions are for scenarios 4.1 and 4.2, as the assumptions varied in these analyses only pertain to tafamidis monotherapy.

6.1.1.2 Scenario 2: Treatment effect waning with vutrisiran monotherapy

In Section 4.2.6.4, the EAG highlighted the uncertainties underpinning the company's base-case assumptions on the persistence of vutrisiran monotherapy's effect over time (i.e., treatment effect waning) on NYHA class transition probabilities as a function of the TTR levels observed after the last dose of vutrisiran in HELIOS-B. In this scenario, the EAG explores alternative assumptions, namely that:

- Scenario 2.1: The vutrisiran monotherapy treatment effect persists in full for [redacted] after vutrisiran monotherapy discontinuation, as by that time point, patients' average TTR level reduction compared to baseline values would have gone below the 80% threshold.

- Scenario 2.2: There is no treatment effectiveness persistence for vutrisiran monotherapy beyond discontinuation.

The scenarios are implemented in the model by changing the weights for the contributions of vutrisiran monotherapy (and BSC) transition probability matrices in each cycle after discontinuation, as per Table 32.

Table 32 Application of treatment waning effects on transition matrices based on weighted contributions from vutrisiran monotherapy

Cycles after vutrisiran monotherapy discontinuation (months)	Mean % TTR reduction*	Transition matrix weights (% contribution of the vutrisiran monotherapy matrices)		
		Company's BC	EAG Sc. 2.1	EAG Sc. 2.2
1 (0–3)	[redacted]	[redacted]	[redacted]	0%
2 (3–6)	[redacted]	[redacted]	[redacted]	0%
3 (6–9)	[redacted]	[redacted]	0%	0%
4 (9–12)	[redacted]	[redacted]	0%	0%
5 (12–15)	[redacted]	[redacted]	0%	0%
6 (15–18)	[redacted]	[redacted]	0%	0%
7 (18–21)	[redacted]	[redacted]	0%	0%
8 (21+)	[redacted]	[redacted]	0%	0%

Abbreviations: BC, base-case; BSC, best supportive care; EAG, evidence assessment group; Sc., scenario; TTR, transthyretin. *Average TTR reduction was calculated by digitising the curve presented in Figure 30 of the CS. †Serum TTR levels are assumed to be at pretreatment baseline level after 21 months from the last dose of vutrisiran.

6.1.1.3 Scenario 3: ACM extrapolation for vutrisiran monotherapy

In Scenario 3, the EAG explores the use of an alternative ACM extrapolation curve for vutrisiran monotherapy, that does not impose decreasing mortality hazards over most of the long-term extrapolation. In Section 4.2.6.3, the EAG discussed how mortality hazard in the modelled population are likely to increase over time in the long-term period beyond 42 months of observed data. Therefore, the exponential distribution is applied in Scenario 1 for vutrisiran monotherapy instead of the company's preferred extrapolation (i.e., log-logistic), as it is the only function that does not imply decreasing hazards in the extrapolated period for this treatment group. Although all other extrapolation distributions fitted to vutrisiran monotherapy's ACM data are considered too optimistic by the EAG, extrapolating with the exponential distribution may still be optimistic, as it assumes a constant hazard throughout the model.

For tafamidis monotherapy, the EAG is less concerned about the plausibility of the long-term extrapolation, given the lack of robustness and the high level of uncertainty affecting the relative effectiveness data for this comparison. Hence, the EAG does not explore alternative ACM

extrapolation functions for tafamidis monotherapy, but rather alternative assumptions on the relative effectiveness of tafamidis vs. vutrisiran monotherapy in Scenario 4.

6.1.1.4 Scenario 4: Treatment effect of vutrisiran monotherapy

The key issue affecting the comparison of vutrisiran and tafamidis monotherapy is the lack of robust evidence to inform the clinical effectiveness for these treatments, as the HELIOS-B trial was not designed or powered to inform this comparison (see Section 4.2.6.1). Given the evidence available to establish a comparison between vutrisiran and tafamidis monotherapy and the absence of randomised evidence to inform this comparison (see Sections 3.7 and 4.2.6.1), the EAG considers that the evidence is not robust enough to support the existence of differences in relative effectiveness between these treatments.

In scenario 4, the EAG explores the cumulative impact of assuming no differences in treatment effect for vutrisiran vs. tafamidis monotherapy. In Scenario 4.1., the ACM curve for tafamidis monotherapy is informed by the vutrisiran monotherapy ACM curve using the exponential distribution as extrapolation model (as this is the only extrapolation model that does not assume decreasing hazards in the long-term for vutrisiran), thus assuming no differences in survival between treatments. In Scenario 4.2, we add the assumption of no differences in rate of disease progression/stabilisation to that of no differences in survival between treatments. In this scenario, the survival estimates are set as for scenario 4.1, and the tafamidis monotherapy time-dependent NYHA class transition matrices are set equal to those of vutrisiran monotherapy. Scenario 4.2 still allows for some differences in clinical effectiveness between vutrisiran and tafamidis monotherapy due to (i) treatment effect waning over time with vutrisiran but not tafamidis, and (ii) treatment specific SAEs incident rates, the company's model assumes a treatment waning effect. Scenarios 4.3 and 4.4 add the assumptions on vutrisiran's treatment effect waning explored in Scenarios 2.1 and 2.2, respectively, to the assumptions in Scenario 4.2. In scenario 4.4, the only difference in clinical effectiveness between vutrisiran and tafamidis monotherapy is due to differences in SAE rates between treatments.

6.1.1.5 Scenario 5: Age and sex adjusted utilities using multiplicative approach

In Scenario 5, the health state utilities are adjusted to reflect decreases in HRQoL in the age and sex-matched general population, using a multiplicative approach in line with NICE guidance (see Section 4.2.9.2). The EAG notes that this adjustment is only applied to health states NYHA class I and II in line with the company's assumption that the impact of ageing on utilities for patients in health states NYHA class III and IV would be negligible compared to the detrimental effects of the disease on HRQoL.

6.1.1.6 Scenario 6: Vutrisiran monotherapy acquisition and administration costs without within-cycle correction

In scenario 6, the within-cycle correction is not applied to the acquisition and administration costs of vutrisiran, as these costs are incurred every three months in line with the model cycle length and, therefore, do not require correction. The within-cycle correction is maintained for these categories of costs for tafamidis, as this treatment is delivered daily. The EAG acknowledges that these costs for tafamidis may be underestimated if the assumption of no drug wastage for this drug does not hold, but is unclear what is reasonable to assume in terms of tafamidis wastage given the model's short cycle length and within-cycle correction approach.

6.1.1.7 Scenarios 7: Vutrisiran monotherapy administration costs in line with SmPC[1]

In scenario 7, the EAG assumes that the administration costs for vutrisiran monotherapy are in line with the SmPC,[1] which states that the injections should be delivered by a healthcare professional. Therefore, the vutrisiran administration cost assumed by the company to apply only to patients in the first cycle in the model (i.e., £108.90 per administration by a nurse at the hospital) is applied at every cycle, while the patient remains on treatment with vutrisiran.

6.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Table 33 shows deterministic cost-effectiveness results of the EAG scenarios, when including caregiver utilities; corresponding results excluding these disutilities are presented in Table 34.

For the analysis including caregiver disutilities scenarios with the largest impact on the company's base case ICER comparing vutrisiran vs. tafamidis monotherapy are those where the clinical effectiveness of both treatments is assumed the same (Scenario 4.4) or similar (Scenarios 4.2. and 4.3), with ICERs ranging between [redacted] per additional QALY. This considerable increase of the ICER compared to the company's base-case is driven by the reduction in incremental QALYs, which decrease to [redacted] QALYs when the survival and transition probability matrices are set equal for the two treatments (Scenario 4.2.) and become [redacted] when also no treatment effect waning is also assumed for vutrisiran monotherapy (Scenario 4.4). In the latter case, the differences are driven exclusively by differences in safety profile between vutrisiran and tafamidis monotherapy. The EAG notes that, when only the survival is assumed the same for vutrisiran and tafamidis monotherapy, the ICER actually decreases to [redacted] (Scenario 4.1) compared to the company's base-case ([redacted]) and to the EAG scenario where the vutrisiran survival is extrapolated with an exponential distribution (Scenario 3, [redacted]). This is because, despite the decrease in incremental QALYs to [redacted] QALYs compared to [redacted] QALYs for scenario 3 and company's base case, respectively. This is because the total costs with tafamidis is substantially increased when the survival is assumed the same as for vutrisiran ([redacted]

compared to [redacted] in the company's base case) while for vutrisiran these decrease ([redacted] compared to [redacted] in the company's base case) due to the less optimistic survival extrapolation in Scenario 4.1 (and 3), resulting in an incremental cost of [redacted]. The analyses suggest that the QALY gains for vutrisiran vs. tafamidis monotherapy are driven by the differences between the transition probability matrices between the two treatments.

The other assumption with large impact on the ICER is the inclusion of a pairwise comparison with BSC in Scenario 1. The ICER for vutrisiran monotherapy vs. BSC is [redacted] per additional QALY. While the incremental QALY for this comparison are larger than for the comparison with tafamidis ([redacted]), these are offset by the increase in incremental costs from [redacted] against tafamidis to [redacted] against BSC.

The use of the multiplicative approach when adjusting health state utilities to reflect decreases in HRQoL in the age and sex-matched general population (Scenario 5 also increases the ICERs for the comparison against tafamidis monotherapy ([redacted] per additional QALY) and against BSC [redacted] per additional QALY) compared to corresponding analysis using the additive approach [redacted] per additional QALY for the comparisons against tafamidis monotherapy and BSC, respectively.

The removal of the within-cycle correction for vutrisiran monotherapy acquisition and administration costs in Scenario 6 is also impactful; the ICER increases to [redacted] and to [redacted] for the comparison against tafamidis monotherapy and against BSC, respectively.

The interpretation of the scenario analysis is similar when caregiver utilities are excluded from the vutrisiran vs. tafamidis monotherapy; ICERs increase substantially in all scenarios where vutrisiran and tafamidis monotherapy are assumed to have differences in clinical effectiveness. For the comparison against BSC the exclusion of caregivers disutilities consistently decreases the ICERs compared to the corresponding analysis with caregiver disutilities. This is due to the lower survival with BSC resulting in shorter times in health states with high carer disutilities (i.e., NYHA class III and IV) compared to vutrisiran monotherapy. This means that for the comparison with BSC, the QALY gains for vutrisiran monotherapy are reduced by the inclusion of caregivers disutilities, as these are accrued for longer periods.

Table 33 Cost-effectiveness results of the EAG scenario analyses (including caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs*	Inc. QALYs*	ICER, /QALY*
	Company's base-case results	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Comparison of vutrisiran monotherapy vs. BSC (with company's base assumptions)	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.1	Treatment effect waning over 6 months for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	No treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.1	Treatment effect of vutrisiran monotherapy - No effect on survival	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.2	Treatment effect of vutrisiran monotherapy - No effect on survival and transition probabilities between NYHA class	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.3	Treatment effect of vutrisiran monotherapy - No effect on survival and transition probabilities between NYHA class, with treatment effect waning over 6 months for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.4	Treatment effect of vutrisiran monotherapy - No effect on survival and transition probabilities between NYHA class, with no treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Age and sex adjusted utilities using multiplicative approach	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Vutrisiran monotherapy administration costs in line with SmPC[1]	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*compared to vutrisiran monotherapy

Table 34 Cost-effectiveness results of the EAG scenario analyses (excluding caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs*	Inc. QALYs*	ICER, /QALY*
	Company's base-case results	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Comparison of vutrisiran monotherapy vs. BSC (with company's base assumptions)	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.1	Treatment effect waning over 6 months for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	No treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.1	Treatment effect of vutrisiran monotherapy - No effect on survival	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.2	Treatment effect of vutrisiran monotherapy - No effect on survival and transition probabilities by NYHA class	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.3	Treatment effect of vutrisiran monotherapy - No effect on survival and transition probabilities between NYHA class, with treatment effect waning over 6 months for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.4	Treatment effect of vutrisiran monotherapy - No effect on survival and transition probabilities between NYHA class, with no treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Age and sex adjusted utilities using multiplicative approach	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Vutrisiran monotherapy administration costs in line with SmPC[1]	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*compared to vutrisiran monotherapy

6.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes from the company's base case:

- Include a comparison between vutrisiran monotherapy and BSC in line with NICE scope and given that it is one of the comparisons that can be informed by randomised evidence in HELIOS-B - **Scenario 1**
- Vutrisiran monotherapy curve extrapolated with exponential distribution, as this is the only fitted parametric model that does not imply increasing hazards over the long-term - Scenario 3
- No treatment effect waning for vutrisiran monotherapy, given the uncertainty of the company's approach to model the treatment effect persistence - **Scenario 2.2**
- No difference in survival between vutrisiran and tafamidis monotherapy, given the lack of robust evidence to support the existence of a treatment effect on survival - **Scenario 4.1**
- No difference in transition probabilities between NYHA health states between vutrisiran and tafamidis monotherapy, given the lack of robust evidence to support the existence of a treatment effect on movement across NYHA health states - **Scenario 4.2**
- Use of a multiplicative approach to reflect decreases in HRQoL in the age and sex-matched general population in line with NICE guidance.[21] This assumption is not added cumulatively to the EAG base-case for the comparison against tafamidis monotherapy, as this as no impact when equal clinical effectiveness for vutrisiran and tafamidis monotherapy is assumed - **Scenario 5**
- Removal of the within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy, to avoid underestimation of costs that are incurred at a periodicity that aligns with the model cycle length - **Scenario 6**
- Vutrisiran monotherapy administration costs in line with SmPC[1] - **Scenario 7**

Table 35 and Table 36 shows the cumulative impact of the EAG's preferred assumptions on the deterministic ICER when comparing vutrisiran monotherapy against tafamidis monotherapy and BSC, respectively. Probabilistic and deterministic results for both pairwise comparisons are presented in Table 37. These results do not include caregiver disutilities as the EAG considers that the company has not made a robust case for the inclusion of these disutilities, particularly when these have not been included in previous NICE TAs for tafamidis in ATTR-CM (TA696 and TA984).[17, 18] The EAG acknowledges that the results of corresponding analyses including caregiver disutilities may be relevant to the appraisal committee and presents these in Appendix 2 (except for analysis against tafamidis monotherapy, assuming no difference in clinical effectiveness between treatment groups).

Table 35 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the tafamidis comparison (excluding caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	+No treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3	+ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1	+ No treatment effect on survival	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2	+No effect on transition probabilities between NYHA class	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6	+Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6+7 (EAG base case)	+ Vutrisiran monotherapy administration costs in line with SmPC[1]	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 36 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the BSC comparison (excluding caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
1	Company's base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2	No treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3	ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5	Age and sex adjusted utilities using multiplicative approach	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6	Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6+7 (EAG base case)	Vutrisiran monotherapy administration costs in line with SmPC[1]	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 37 Deterministic and probabilistic cost-effectiveness results for the EAG's base case (excluding caregiver disutilities)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
Probabilistic comparison to tafamidis							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic comparison to tafamidis							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic comparison to BSC							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic comparison to BSC							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The selection of changes made to the EAG base case is based on the available evidence; however, uncertainty remains on whether [redacted] in the near future. Therefore, the results for a scenario over the EAG base case is presented in Table 38, excluding caregiver utilities (results including caregiver utilities are presented in Appendix 2).

Table 38 Cost-effectiveness results for alternative assumption on vutrisiran administration over the EAG's base case (excluding caregiver disutilities)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
Probabilistic comparison with tafamidis							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic comparison with tafamidis							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic comparison to BSC							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic comparison to BSC							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost-effectiveness section

The company submitted a Markov model to assess the cost-effectiveness of vutrisiran monotherapy compared to tafamidis monotherapy for the treatment of ATTR-CM. The model captures the impact on costs and HRQoL outcomes of cohort movement across NYHA class health states; treatment effects are applied on transition probabilities between NYHA class health states and on survival outcomes. The use of vutrisiran in combination with tafamidis was not considered in the company's cost-effectiveness analysis, as the company was concerned that this would not result in a cost-effective use of NHS resources. The cost-effectiveness analysis presented by the company did not include BSC as a comparator, despite established clinical management without vutrisiran being specified in the NICE scope; the EAG considers this to be an important limitation of the company's cost-effectiveness analysis.

The main source of treatment effectiveness evidence informing the economic model is the IPTW adjusted HELIOS-B data for the comparison of patients treated in the trial with vutrisiran monotherapy and those randomised to the placebo arm who were already receiving tafamidis at baseline (i.e., patients in the placebo arm receiving background tafamidis). The HELIOS-B trial was not designed or powered to assess the relative efficacy of vutrisiran versus tafamidis, and therefore, the company had to perform a *post-hoc* adjustment (IPTW of baseline characteristics) to try to address possible biases. This notwithstanding, the IPTW approach does not address other differences between groups that may impact on patient outcomes, such as the differences in timing of treatment initiation between treatment groups (i.e., patients in the tafamidis group had already had pre-exposure for this treatment prior to randomisation) and use of tafamidis drop-in in the vutrisiran group after the double-blind period. Hence, the results for this comparison remain subject to potential biases, the magnitude and direction of which are uncertain. Given current evidence (see Sections 3.7 and 4.2.6.1) and the limitations of the IPTW adjusted data, the EAG believes that the most reasonable assumption on the relative effectiveness of vutrisiran and tafamidis monotherapy is that there are no differences in treatment effects between the two drugs.

The HELIOS-B trial monotherapy subpopulation provides robust randomised controlled evidence of relative efficacy for vutrisiran monotherapy vs. placebo (without background tafamidis), a comparator that could reasonably be assumed similar to BSC in UK clinical practice, and this population is not affected by the limitations of the evidence informing the vutrisiran vs. tafamidis monotherapy comparison in the model. The EAG also considers that, despite agreeing that the main comparison is against tafamidis, the comparison against BSC is relevant for the proportion of patients who are currently ineligible for tafamidis due to treatment intolerance, , as well as for patients who discontinue treatment with tafamidis due to lack of response. The EAG has therefore presented additional cost-effectiveness analyses to compare vutrisiran monotherapy against BSC.

The EAG considers that the model structure used to assess the cost-effectiveness of vutrisiran monotherapy, while broadly consistent with previous TAs of tafamidis in ATTR-CM,[17, 18] has a key limitation. This limitation is the lack of an important structural link between disease progression across NYHA classes and mortality, given that survival is modelled independently from NYHA class changes over the time horizon. This omission may introduce inconsistencies in the assumptions used for NYHA transitions and mortality estimates, leading to potentially implausible and optimistic survival extrapolations, requiring logical constraints (i.e., general population mortality cap) to be imposed at relatively early time points of the model horizon. This feature of the model may also lead to inconsistent and potentially clinically implausible impacts on other outcomes. One such inconsistency is the implied higher proportion of patients treated with tafamidis spending time in NYHA class IV health state over the model time horizon compared to health state NYHA III in the company's base analysis.

Further to the concerns about the robustness of the IPTW adjusted HELIOS-B data detailed in Section 4.2.6.1, the EAG also considers that, due to the need to extrapolate these data beyond the trial observed period results implies a greater difference in treatment effects between treatment groups in the economic model compared to those estimated in the clinical effectiveness analyses section. This further contributes to uncertainties in the treatment effects implied by the economic model over the time horizon for the transition probabilities between NYHA class health states and for ACM.

The EAG is concerned that the transition probabilities between NYHA class health states may not accurately reflect disease progression over the time horizon, and that, for some specific transitions, the estimates applied in the model may lack face validity. For example, over the observed period, transitions to NYHA class IV from any other NYHA class health state probabilities are generally low across the observed period and in some cases transitions [redacted] for both tafamidis and vutrisiran monotherapy. The EAG discusses in Section 4.2.6.2, how this may be caused of the observed low events counts for forward transitions to higher severity health states, which is to be expected as the distribution of patients at baseline [redacted] The short follow-up duration in HELIOS-B may have been insufficient to accurately capture transitions for patients across all levels of disease severity and that differences between these transition probabilities (particularly at higher disease severity) may be due to chance and amplified over the modelled time horizon (almost [redacted] longer than the observed follow-up).

For the ACM modelling, the EAG's main concern is that the company's preferred extrapolation distributions may result in overly optimistic survival projections, as outlined in Section 4.2.6.3. The company's selection of the ACM extrapolated curve is partially driven by the hazards observed in HELIOS-B, but these imply decreasing hazards in the long-term for both treatments under

comparison. The EAG thinks that it is inconsistent with an underlying disease progression model that assumes patients continue to progress to more severe NYHA classes and will eventually result in an increase in mortality. The clinical implausibility of the extrapolated curves is mitigated to some extent as these are capped by general population mortality, but may still contribute to overly optimistic estimates of treatment effect on mortality, particularly as mortality is modelled independently from NYHA class.

The company's approach to model treatment waning effect over time on NYHA class transition probabilities for vutrisiran monotherapy relies on a number of assumptions on how treatment effect persistence relates to levels of TTR, which are not supported by empirical data and are highly uncertain (see Section 4.2.6.4). The EAG notes that this uncertainty does not have a sizeable on the estimates of cost-effectiveness for the vutrisiran vs. tafamidis monotherapy in part because the time to treatment discontinuation from non-fatal causes is assumed to be the same for vutrisiran and tafamidis monotherapy. The EAG also highlights that this approach is not consistent with the company's assumption of treatment specific differences in health outcomes between vutrisiran and tafamidis monotherapy, albeit necessary given that HELIOS-B did not systematically evaluate discontinuation data for tafamidis.

The company has taken an additive approach to reflect the decrease in HRQoL in the general population in the health state utilities rather than a multiplicative approach, as recommended by current guidance.[21, 26] The use of the additive approach is also not in line with previous NICE TAs in ATTR-CM (TA696 and TA984).[17, 18] Despite this and the impact on the estimates of cost-effectiveness of different adjustment approaches, the company did not justify their preference for the additive approach. The EAG is thus concerned that the company's preferred approach may not be appropriate.

The company included in all their cost-effectiveness analyses, NYHA class specific caregiver disutilities. While the EAG acknowledges that ATTR-CM imposes a considerable carer burden, the evidence provided by the company does not allow ascertaining whether this impact is greater than would be expected in other disease areas where carer burden is not routinely accounted for in the QALY estimates (e.g., in oncology in adult patients). There is also no precedent of including caregiver disutilities in previous NICE TAs in ATTR-CM (TA696 and TA984).[17, 18] The company also had to rely on a number of assumptions in order to derive caregiver disutilities by NYHA class, as the evidence by NYHA class in a contemporaneous, predominantly wtATTR-CM population was not available. Therefore, the EAG considers that there is uncertainty as to whether i) caregiver disutilities should be considered for the modelled population and ii) the disutilities applied in the model are reflective of caregiver disutility by NYHA class in a contemporaneous ATTR-CM population.

The vutrisiran acquisition and administration costs in the company's cost-effectiveness analysis may have been underestimated. The EAG thinks that, given that the periodicity of drug administration completely aligns with the modelled cycle length. these costs should not have been subject to any within-cycle correction. The administration costs for vutrisiran are also not in line with the SmPC,[1] which does not allow for self-administration. While the EAG acknowledges that this may change, it is not yet appropriate to assume that the cost of administration by a nurse at a hospital only applies at the first cycle in the model, as it will underestimate this cost.

The EAG additional analyses address the majority of the issues highlighted above. For the analysis including caregiver disutilities, scenarios with the largest impact on the company's base case ICER comparing vutrisiran vs. tafamidis monotherapy are those where the clinical effectiveness of both treatments is assumed the same (Scenario 4.4) or similar (Scenarios 4.2. and 4.3), with ICERs ranging between [redacted] per additional QALY. The magnitude of these ICERs for these analyses is driven by the sharp reduction in incremental QALYs accrued when vutrisiran is assumed to have equivalent treatment effectiveness to tafamidis. The inclusion of a comparison with BSC in the EAG scenarios is also impactful, with the ICER for vutrisiran monotherapy vs. BSC being [redacted] per additional QALY in the scenario holding all other company's assumptions constant (Scenario 1). The remaining EAG scenarios for both comparisons are also less favourable compared to the company's base-case analysis, but less impactful than the scenarios above.

The interpretation of the scenario analysis is similar when caregiver utilities are excluded from the vutrisiran vs. tafamidis monotherapy; ICERs consistently increase in all scenarios where vutrisiran and tafamidis monotherapy are assumed to have differences in clinical effectiveness. For the comparison against BSC, the exclusion of caregivers disutilities consistently decreases the ICERs compared to the corresponding analysis with caregiver disutilities.

The EAG base-case analysis considers two separate pairwise comparisons to vutrisiran monotherapy, namely against (i) tafamidis monotherapy and (ii) BSC. The EAG's preferred assumptions for both these comparisons include the following changes from the company's base case: (i) no treatment effect waning for vutrisiran, (ii) ACM extrapolation for vutrisiran with exponential distribution, (iii) a multiplicative approach to reflect decreases in HRQoL in the age and sex-matched general population, iv) removal of the within-cycle correction for the acquisition and administration costs of vutrisiran, and (v) administration costs for vutrisiran in line with the SmPC. [1] For the comparison against tafamidis monotherapy, the EAG further assumes that there are no differences in clinical effectiveness between this treatment and vutrisiran monotherapy. The interpretation of the EAG base-case analysis is consistent with the EAG additional analysis. The EAG probabilistic base case analysis suggests an ICER for vutrisiran vs. tafamidis monotherapy of [redacted] per additional QALY (regardless of whether caregiver utilities are included). For the comparison against BSC, the base-case probabilistic ICER is [redacted] and [redacted] per additional QALY, when excluding and including caregiver utilities, respectively.

7 SEVERITY MODIFIER

The CS presents an assessment of whether the severity modifier applies using current NICE guidance,[21] which was provided upon request by the EAG (see response to clarification question B11). The severity modifier does not apply in the company's base case or scenario analyses.

Points for critique

The company's implementation of the QALY shortfall calculated the QALY gains for the standard of care (assumed to correspond to tafamidis monotherapy) included caregiver disutilities, which is not in line with current NICE guidance as only patient health impacts should be considered in these calculations.[21] Furthermore, the estimated severity weight was not incorporated into the incremental QALYs estimates in the model. The EAG corrected both these issues, but notes that, given that the severity weight was equal to 1 across all the company's and EAG's analyses, this has no impact on the estimates of cost-effectiveness (including those for the BSC comparison).

8 REFERENCES

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9 APPENDICES

Appendix 1: EAG appraisal of review evidence

Table 39 EAG appraisal of evidence identification for SLR of cost-effectiveness

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	In the original submission it was unclear which databases had been searched and the full search strategy for NHS EED had not been reported These points were clarified in company response to the PfCs. There was a lack of clarity with the search of MEDLINE as it was searched via Embase.com. In addition, the use of the /syn command in Embase.com does not allow readers to view and assess the MeSH and Emtree terms that were used within the search.
Were appropriate sources searched?	PARTLY	A range of relevant databases and conference proceedings were searched. However, the following weaknesses were noted: - INAHTA and the HTA database were not searched and may have contained additional relevant HTAs. In addition, only a selection of major HTA websites were searched. - Reference checking of included studies or relevant reviews was not undertaken. - MEDLINE was searched via Embase.com. A more comprehensive and transparent approach would have been to search MEDLINE separately to allow for the inclusion of MeSH within the search.
Was the timespan of the searches appropriate?	YES	Databases: inception to 5th November 2024 HTA website searches: to 5th November 2024 Conference proceedings: 1st January 2021 to 5th November 2024
Were appropriate parts of the PICOS included in the search strategies?	YES	**MEDLINE and Embase** [P] ATTR-CM AND [S] economic evaluations **EconLit** [P] ATTR-CM **NHS EED** [P] ATTR-CM AND [I] tafamidis OR patisiran OR vutrisiran OR eplontersen OR acoramidis
Were appropriate search terms used?	PARTLY	Text word searches in the title and abstracts of records were appropriate. However, it was not possible for the EAG to confirm whether the correct MeSH and Emtree terms were used in the search of Embase.com due to the lack of clarity in the search strategies reported and a lack of access to Embase.com.
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	PARTLY	The search in PubMed was limited to economic evaluations using a study design filter by CADTH and was referenced within the company response to the PfCs.The filter had been translated by CADTH from their validated search filter for use in MEDLINE.

		The search in Embase.com (covering MEDLINE and Embase records) was limited to economic evaluations using a combination of 1) a study design filter by CADTH and 2) an unvalidated study design filter from the Scottish Intercollegiate Guidelines Network (SIGN). The SIGN filter only was referenced with the company response to the PfCs. It was unclear whether all relevant MeSH headings were included within the search filter used.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 40 EAG appraisal of evidence identification for SLR of HRQoL studies and SLR of cost and resource use studies

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	
Were appropriate sources searched?	YES	The main databases searched (MEDLINE, Embase, PsycINFO, NHS EED, CPCI-S) were appropriate for identifying HRQoL studies and cost and resource use studies. Supplementary searches consisted of handsearching of specific conference proceedings and searching of selected HTA agency websites (NICE, SMC, CADTH and ICER).
Was the timespan of the searches appropriate?	YES	Databases: 2013 to 10th October 2024 HTA website searches: 2013 to 10th October 2024 Conference proceedings: 2022 to October 2024
Were appropriate parts of the PICOS included in the search strategies?	YES	MEDLINE and Embase*: Population* (ATTR-CM) AND *Outcomes* (HRQoL/patient outcome instruments or measures OR costs/resource use). PsycINFO, NHS EED and CPCI-S: *Population* (ATTR-CM).
Were appropriate search terms used?	YES	Subject headings (MeSH, Emtree) to cover ATTR-CM were missing from the search strategies for MEDLINE and Embase. However, for this particular SLR, this was appropriate given the lack of directly relevant subject headings for ATTR-CM and trying to achieve a good balance of comprehensiveness without large numbers of irrelevant hits.
Were any search restrictions applied appropriate?	YES	A date limit to studies from 2013 onwards was applied to the searches.
Were any search filters used validated and referenced?	YES	

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Appendix 2: Additional cost-effectiveness results

Table 41 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the tafamidis comparison (including caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	+No treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3	+ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1	+ No treatment effect on survival	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2	+No effect on transition probabilities between NYHA class	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6	+Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6+7 (EAG base case)	+ Vutrisiran monotherapy administration costs in line with SmPC[1]	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 42Cumulative cost-effectiveness results for the EAG's preferred assumptions for the BSC comparison (including caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY

1	Company's base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2	No treatment effect waning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+ 2.2+3	ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5	Age and sex adjusted utilities using multiplicative approach	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6	Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6+7 (EAG base case)	Vutrisiran monotherapy administration costs in line with SmPC[1]	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 43 Deterministic and probabilistic cost-effectiveness results for the EAG's base case (including caregiver disutilities)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (/QALY)
Probabilistic							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 44 Cost-effectiveness results for company's assumption on vutrisiran administration over the EAG's base case (including caregiver disutilities)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (/QALY)
Probabilistic							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic							
Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Single Technology Appraisal

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 22 July 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Descriptions of EAG assumptions regarding administration of vutrisiran in relation to the current SmPC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 13, 22, 23, 24, 96, 97, 106, 111, 114, 116, 117, 118, 119, 120, 124, 125, 132, and 133. The EAG's preferred assumption related to the modelling of administration costs for vutrisiran, which is described as having "vutrisiran monotherapy administration costs in line with current SmPC".	For accuracy, whenever this preferred assumption is mentioned in the report, it should instead be described as an assumption where costs are applied to every administration of vutrisiran, and any mention of alignment with the current Summary of Product Characteristics (SmPC) should be removed. Descriptions of the "potential update" for the inclusion of patient/caregiver administration in the SmPC on pages 22, 96, 97, and 120 should be modified to note that as of the date of the EAG report, these updates had been made in both the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) updated SmPCs.	The EAG raised a concern that administration costs for vutrisiran—applied for the first dose in the hospital setting and assumed to be zero cost for all subsequent doses (which would be administered at home by the patient or a caregiver)—in the company pharmacoeconomic model were not in line with the requirement for hospital administration in the SmPC.[1] However, the SmPC for vutrisiran states that *"Amvuttra may be administered by a healthcare professional, the patient, or a caregiver."*.[1] It should be noted that the inclusion of patient/caregiver administration in the SmPC for vutrisiran was recently added (February 18th, 2025 update),[1] meaning the timing of the EAG report in relation to the SmPC update could have led to this discrepancy. In line with this update to the SmPC, administration with vutrisiran in the company submission is assumed to be performed by the patient or caregiver at home at zero cost for all administrations subsequent to the initial administration. The updated MHRA SmPC included the allowance for patient/caregiver administration prior to the date on the EAG	At the FAC stage, the EAG was not able to validate the date at which the SmPC wording was updated to allow for people other than a healthcare professional, as only the latest version of the SmPC is available on the MHRA website. Given that the EAG was explicit in the report that an update to the wording was expected and to avoid inconsistencies throughout the report, we have made it explicit which version of the SmPC[2] we are referencing, and updated the text to ensure accuracy. We also note that scenario analysis over the EAG base-case allowing for self administration were also included in the report (see Tables 38 and 44, EAR) Furthermore, we note that while the most up to date SmPC allows

		report (April 15, 2025), meaning these SmPC amendments were publicly available prior to the finalisation of the EAG report.	for self-administration, this does not exclude the possibility that in clinical practice vutrisiran will be administered by health care professionals (with associated costs).

Issue 2 Lack of accuracy in the EAG assumption related to within-cycle correction for acquisition costs for vutrisiran

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 22, 96, 111, 117, and 124. The EAG has assumed that only the periodicity of vutrisiran administration aligns with the model cycle length (3 months), leading to the removal of within-cycle correction from the calculation of acquisition costs in the vutrisiran arm. The EAG did not comment on the prescription volume usually supplied for tafamidis, and whether this would	In the areas where the EAG has noted that the periodicity of administration for vutrisiran aligns with model cycle length, leading to the preferred assumption that within-cycle correction for acquisition costs be removed, a statement similar to below should also be added as a caveat: "The EAG also notes that if tafamidis is usually supplied in quantities that are sufficient for treatment lengths similar to the model cycle length (3 months), then within-cycle correction should also be	The EAG noted that the model's 3-month cycle length aligned with the dosing schedule of vutrisiran administration and therefore recommended removing the within-cycle correction from the calculation of acquisition costs for vutrisiran. However, Alnylam believes the within-cycle correction for tafamidis also needs to be removed to reflect the factual reality that patients treated with tafamidis in the UK are currently prescribed tafamidis on a 12-month basis and supplied on a 3-month supply basis (confirmed by the NAC[3]), effectively mirroring vutrisiran.	The EAG does not consider this to be a matter of factual accuracy. The EAG noted in Section 4.2.10.3, EAR, that it is appropriate to keep the within-cycle correction for tafamidis drug acquisition and administration costs due to its posology, caveating that wastage might have been more appropriate to also have included wastage assumptions for tafamidis. At the FAC stage, the company cites email correspondence with NAC clinicians on how tafamidis is supplied in clinical practice. The EAG was not able to verify this source due to it referring to personal

have an effect on the use of within-cycle correction for the calculation of tafamidis acquisition costs.	removed from the calculation of tafamidis acquisition costs."		communications between the company and clinical experts, which was not shared by the company. The EAG acknowledges that if tafamidis is supplied on a 3-month supply basis (rather than one-month), then the within-cycle correction should be removed for both tafamidis and vutrisiran acquisition and administration costs. Therefore, additional analysis to this effect are presented in the EAG review of the company's targeted response to the EAR.

Issue 3 Description of EAG-preferred modelling assumptions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 "**No treatment effect** for vutrisiran vs. tafamidis monotherapy on transition probabilities between NYHA class health states;"	This should be corrected to: "**No difference in treatment effect** for vutrisiran vs. tafamidis monotherapy on transition probabilities between NYHA class health states;"	This is a more accurate description of what is modelled in the EAG-preferred scenario.	This has been amended as suggested by the company, for clarity.

Issue 4 Description of safety outcomes in company model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17 "Assuming the same effect on all-cause mortality and NYHA class transitions probabilities (**and only accounting for differences in safety outcomes**)..."	This should be corrected to: "Assuming the same effect on all-cause mortality and NYHA class transitions probabilities (**and only accounting for a benefit in safety outcomes with vutrisiran**)..."	Vutrisiran was associated with a gain in incremental quality-adjusted life years (QALYs) over tafamidis associated with the occurrence of serious adverse events (SAEs).	Not a matter of factual accuracy

Issue 5 Nomenclature related to eplontersen appraisal in ATTR-CM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28 The nomenclature for the potential appraisal of eplontersen is labelled as "ID12105".	Nomenclature for this potential appraisal should be "TSID12105".	This potential appraisal is still in topic selection and the appraisal has not been formally scheduled.	This has been amended

Issue 6 Nomenclature related to TTR variants

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39 The nomenclature for the "threonine to alanine at amino acid position 80 (T80A)" in Table 7 does not align with naming conventions used elsewhere in the document. Also, there are published data from HELIOS-B with the	This should be modified to "T60A" to align with other variant nomenclature in the report (i.e., V122I is currently used, as opposed to V142I). Further, the following data are published regarding baseline proportions of patients with the T60A variant:[4] • HELIOS-B, vutrisiran (overall population): n=2 (5%)	The valine to isoleucine substitution at amino acid position 122 (V122I) and threonine to alanine at amino acid position 60 (T60A) are two common variants in patients with hereditary transthyretin amyloidosis with cardiomyopathy (hATTR-CM). These variants have been historically referred to as V122I and T60A; however, nomenclature has been updated (for all TTR variants) due to the incorporation of a signal peptide comprising 20 amino acids into the codon count for the TTR gene (i.e., resulting in "V142I" and "T80A"). The	This is because "T80A" was the terminology used in the data source (EAG report ref 12). We have edited Table 7 to "T80A/T60A" to represent differences in nomenclature between the source and the rest of the report. The HELIOS-B data have been added to Table 7

baseline proportions of patients with this variant.	• HELIOS-B, placebo (overall population): n=6 (15%)	previous nomenclature is still commonly used. Consistent nomenclature should be used throughout the document.	

Issue 7 Description of potential bias in comparison of vutrisiran and tafamidis monotherapy from HELIOS-B

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 43 "The interpretation of these results is complicated by the comparison of a subgroup with **known** exposure to vutrisiran, to a subgroup with **unknown** exposure to tafamidis."	The descriptions of known exposure to therapy need to be reversed: "The interpretation of these results is complicated by the comparison of a subgroup with **unknown** exposure to vutrisiran, to a subgroup with **known** exposure to tafamidis." If this statement is referring to the lack of follow-up related to tafamidis treatments in HELIOS-B, then the statement should be altered to more accurately reflect this: "The interpretation of these results is complicated since detailed data regarding tafamidis dose administrations in patients receiving tafamidis monotherapy were not collected post-baseline in HELIOS-B."	Patients in HELIOS-B on tafamidis were aware they were on an active treatment for ATTR-CM (i.e., tafamidis), whereas patients randomized to vutrisiran were blinded, and did not have known if they were receiving vutrisiran or placebo. If the statement was not referring to patient awareness of their treatment status in HELIOS-B, then altering the statement would reduce any potential misunderstanding.	As the sentence after this on page 43/44 makes clear, this is about EAG/trialist knowledge of exposure, not patient knowledge. The sentence is correct, but has been edited to avoid confusion

Issue 8 Description of potential bias in comparison of vutrisiran and tafamidis monotherapy from HELIOS-B

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Page 57
 	
Descriptions of the EAG mortality analysis of tafamidis-treated patients in the Transthyretin Amyloidosis Outcomes Survey (THAOS) versus HELIOS-B:
 	
"We note that demographic data was not available for THAOS, so we are uncertain as to how closely the patients match across data sets, **but we have assumed that post-2019 data should be a reasonable match between THAOS and HELIOS B.**"
	The text should more accurately describe the issues associated with this comparison:
	
	"We note that demographic data was not available for THAOS, so we are uncertain as to how closely the patients match across data sets**. Further, considering eligibility criteria, the patient population in the THAOS analysis was restricted to patients without neuropathy manifestations,[5] and this differed from HELIOS-B (in which only patients with more severe neuropathy manifestations were considered ineligible).[4] Given that worse levels of neuropathy severity are associated with worse survival in ATTR,[6, 7] the potential neuropathy-related differences between populations significantly**
		The EAG compared mortality between patents in HELIOS-B, ATTR-ACT, and the Transthyretin Amyloidosis Outcomes Survey (THAOS; a global, multicentre, observational study),[5] which suggested a nonsignificant survival benefit in patients who were treated with tafamidis in the THAOS study who enrolled after 2019, compared to patients who received vutrisiran monotherapy in HELIOS-B. While the EAG noted this comparison was associated with limitations, the following issues should also be noted for this comparison:
		
		• There were clinically relevant differences in the populations included in the THAOS analysis and in HELIOS-B.
		  ○ The THAOS analysis was restricted to patients with ATTR-CM without neuropathy, such that patients with neurological and gastrointestinal symptoms related to ATTR were excluded, while also requiring patients to have a modified polyneuropathy disability (PND) score of <I or missing.
		  ○ Conversely, patients were only excluded from HELIOS-B if they had
			Not a factual accuracy
			
			This is an EAG assumption, not a claim of truth about the data. For clarity we have added "…but there may be some differences due to differing inclusion criteria" on page 57

	limits conclusions taken from the comparison of tafamidis-treated patients in THAOS and vutrisiran-treated patients in HELIOS-B. In addition to this caveat, the THAOS analysis also included patients who had been receiving tafamidis prior to enrolment, meaning these patients were already likely accruing an efficacy benefit from pre-baseline treatment (similar to patients with background tafamidis treatment at baseline in HELIOS-B).”	a PND score of III or IV and specific neurological symptoms were not an exclusion criterion. ○ The potential differences in neurological disease status at baseline between these patient populations cannot be ignored when comparing survival in these populations. • The THAOS analysis included patients who had been receiving tafamidis prior to enrolment (i.e., baseline of the mortality assessment), meaning these patients were already likely accruing an efficacy benefit from pre-baseline treatment.	

Issue 9 NYHA class outcomes in patients who discontinue vutrisiran in the pharmacoeconomic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65 The following statement needs to be amended for accuracy: “When treatment is discontinued due to non-fatal causes	Adjusted to: “When treatment is discontinued due to non-fatal causes patients are assumed to have the survival outcomes and NYHA class transition probabilities, as well as	This is stated elsewhere in the report, but should also be clarified on page 65.	We have amended as suggested by the company to enhance clarity.

patients are assumed to have the survival outcomes and NYHA class transition probabilities, as well as background medication costs, of those treated with BSC (informed by the placebo arm of the HELIOS-B monotherapy)."	background medication costs, of those treated with BSC (informed by the placebo arm of the HELIOS-B monotherapy)**, with the exception that when patients discontinue treatment with vutrisiran monotherapy, NYHA class transitions are assumed to wane gradually over time to that of placebo in the HELIOS-B monotherapy subpopulation**."		

Issue 10 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57 There are typographical errors: *"*…and similarly for tafamidis and placebo arms in **ATRR-ACT** (dotted lines)."	Both should be adjusted to: "**ATTR-ACT**"	There are typographical errors in these sentences.	We have corrected the typographical errors in Issues 10 to 12.

"…over time since **ATRR-ACT** was conducted."			

Issue 11 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment
Page 57 There is a typographical error: "The EAG compared results from post-**2109** data…"	Adjusted to: "The EAG compared results from post-**2019** data…"	There is a typographical error in this sentence.

Issue 12 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment
Pages 12, 20, 23, 24, 113, 114, 115, 118, 119, 132, and 133. "Wanning" is used 16 times in the report.	This should be corrected to "waning", to align with the other 27 times it is used in the report.	Repeated typographical error.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). *AMVUTTRA (vutrisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; Date 18 Feb 2025*. In.

2. *Summary of Product Characteristics (SPC) amvuttra 25 mg solution for injection in pre-filled syringe*. London: Medicines & Healthcare products Regulatory Agency (MHRA); 2023.

3. Alnylam Pharmaceuticals. *Data on file. Email correspondance with NAC clinicians.* In; 2025.

4. Fontana M, Berk JL, Gillmore JD, Witteles R, Grogan M, Drachman B, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med* 2025;**392**:33–44. Available from: https://www.ncbi.nlm.nih.gov/pubmed/39213194

5. Garcia-Pavia P, Kristen AV, Drachman B, Carlsson M, Amass L, Angeli FS, et al. Survival in a real-world cohort of patients with transthyretin amyloid cardiomyopathy treated with tafamidis: an analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS). *J Card Fail* 2025;**31**:525–33. Available from: https://www.ncbi.nlm.nih.gov/pubmed/38909877

6. Russo M, Gentile L, Di Stefano V, Di Bella G, Minutoli F, Toscano A, et al. Use of drugs for ATTRv amyloidosis in the real world: how therapy is changing survival in a non-endemic area. *Brain Sci* 2021;**11**:545.

7. Ungerer MN, Hund E, Purrucker JC, Huber L, Kimmich C, Aus dem Siepen F, et al. Real-world outcomes in non-endemic hereditary transthyretin amyloidosis with polyneuropathy: a 20-year German single-referral centre experience. *Amyloid* 2021;**28**:91–9.

8. Sheikh FH, Habib G, Tang WHW, Gillmore JD, Egolum UO, Longhi S, et al. Impact of vutrisiran on functional capacity and quality of life in transthyretin amyloidosis with cardiomyopathy. *J Am Coll Cardiol* 2025. Available from: https://www.ncbi.nlm.nih.gov/pubmed/40099774

NICE National Institute for Health and Care Excellence

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

Targeted company response to EAG report

Additional evidence / analysis requested

Please provide additional evidence and analyses that have been requested for the following key issues.

EAG report key issue	Evidence / analysis requested	Company response
1. Best supportive care is not included as a comparator	1. The company should formally model the comparison of vutrisiran monotherapy vs. BSC, as informed by randomised evidence from the HELIOS-B trial. 2. The company should elicit clinical advice (or other evidence) on the proportions who receive tafamidis and BSC in NHS clinical practice, including the proportion for whom tafamidis cannot be	The final NICE scope for vutrisiran included tafamidis and "*established clinical management without vutrisiran*" as comparators. According to this scope, modelling of the comparison between vutrisiran monotherapy and best supportive care (BSC) would only inform decision-making in situations in which "*established clinical management without vutrisiran*" was equivalent to BSC. However, clinical experts from the National Amyloidosis Centre (NAC), the sole treatment centre for transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in the UK, state that "*established clinical management without vutrisiran*" is equivalent to tafamidis for all patients in the UK. Specifically, NAC clinical experts highlight that **tafamidis is currently the standard of care for essentially all ATTR-CM patients in the UK eligible for disease-modifying therapy**. The NAC estimates that currently only [redacted] of the approximately [redacted] ATTR-CM patients eligible for disease-modifying therapy do not receive tafamidis due to intolerance

EAG report key issue	Evidence / analysis requested	Company response
	used (e.g. due to intolerance or lack of treatment response).	or lack of treatment response. This represents only 1% of all patients with ATTR-CM who are eligible for a disease-modifying treatment. Furthermore, expert clinicians, [redacted] and [redacted] from the NAC also clearly state that tafamidis should be the sole comparator in this appraisal and that BSC is not an appropriate comparator:[1] *"Tafamidis only has one contra-indication (hypersensitivity), which has a very low level of occurrence in our patient population, so in reality there are no patients for which we would consider 'best supportive care' as an alternative choice to disease modifying therapy currently.* ***Therefore, in our expert view, best supportive care is not an appropriate comparator to vutrisiran in the treatment of ATTR-CM****."* This highlights that in the real-world clinical treatment of ATTR-CM in the UK, essentially the only treatment choice will be whether patients receive vutrisiran (if made available) or tafamidis. Finally, despite a trend towards better efficacy for vutrisiran versus tafamidis (see response to Question #4 below), the EAG-preferred analysis assumes equivalent efficacy for these two therapies. Therefore, the EAG-preferred analysis is effectively a cost comparison, where, based on other NICE cost-comparison appraisals, BSC would not be considered a relevant comparator.[2] Therefore, Alnylam views the company base-case analysis that is focused solely on tafamidis as a comparator as the only real-world clinically relevant basis for decision-making, and that a cost-effectiveness analysis versus BSC would not be informative.

EAG report key issue	Evidence / analysis requested	Company response
2. Limited evidence on key patient subgroups	Formal modelling and testing for subgroup differences in both HELIOS-B and ATTR-ACT would be desirable. Further trial data on small subgroups would be helpful.	Neither HELIOS-B nor ATTR-ACT were powered to draw definitive conclusions about the efficacy of vutrisiran or tafamidis versus placebo in specific subgroups. Rather, the aim of the prespecified subgroup analyses in these trials was to explore the consistency of clinical benefits across these patient populations. As discussed in greater detail below, subgroup analyses from ATTR-ACT suggest that tafamidis may have worse efficacy in patients in (New York Heart Association) NYHA class III compared to patients in NYHA class I/II,[3] whereas vutrisiran demonstrated a consistent clinical benefit across all prespecified subgroups.[4] Modelling differential treatment effects by patient subgroup would require either subgroup-specific indirect treatment comparisons (ITC) or subgroup-specific within-trial analyses from HELIOS-B. Considering the small patient numbers that would be included in either of these analyses (especially for the within-trial comparison), the uncertainty of these estimates would only increase compared to analyses across the overall trial populations. When specifically considering subgroup-specific ITCs, it should be again noted that Alnylam views that it is not feasible to conduct an ITC of vutrisiran in HELIOS-B and tafamidis in ATTR-ACT in an unbiased manner due to imbalances in the patient populations assessed in HELIOS-B and ATTR-ACT, which were driven by recent advancements in the ATTR-CM management landscape (i.e., improvements in diagnosis, disease awareness, and background supportive care therapies).[5-7] Please note this is not only a conclusion made by Alnylam, but has also been stated in a review of clinical trials in ATTR-CM,[8] by the United States Institute for Clinical and Economic Review in their review of therapies for ATTR-CM,[9] and by expert clinicians at the NAC, [redacted] and [redacted], who state:

EAG report key issue	Evidence / analysis requested	Company response
		"HELIOS-B and ATTR-ACT have differing patient populations meaning that outcomes from these studies are not comparable. The patients enrolled in ATTR-ACT were much more advanced in terms of disease progression, vs. those enrolled in HELIOS-B, in which patients had milder disease. This was primarily driven by the advances in cardiovascular health in recent years, meaning HELIOS-B was much more reflective of current clinical practice with more intensive use of cardiovascular medications, vs. ATTR-ACT, in which there was under utility of cardiovascular medications vs. current clinical practice." This resulted in patient populations in HELIOS-B and ATTR-ACT with vastly different baseline characteristics, including differences in multiple parameters that could not be adjusted for (as described in the company submission). Despite the inability to assess subgroups within an ITC or a within-trial comparison of vutrisiran and tafamidis, the following are important to consider regarding the efficacy of these therapies within key subgroups: • The EAG has already assumed vutrisiran is at least as efficacious as tafamidis across the entire ATTR-CM population. • Vutrisiran demonstrated a consistent clinical benefit versus placebo for all primary and secondary endpoints in HELIOS-B across all prespecified subgroups, including age, baseline tafamidis use, disease type (wild-type [wtATTR] vs. hereditary [hATTR]), NYHA class, and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP).[4] • Noting the limitations of comparing subgroups across trials, tafamidis demonstrated limited benefit versus placebo over 30 months from baseline in patients in NYHA III

EAG report key issue	Evidence / analysis requested	Company response
		in ATTR-ACT, with significantly higher rates of cardiovascular (CV) hospitalisations for tafamidis versus placebo (76.9% vs. 58.7%).[3,10] In contrast, in the HELIOS-B monotherapy group, NYHA III patients treated with vutrisiran showed a nominally significant reduction in recurrent CV event risk compared to placebo ([redacted]% reduction; relative rate reduction [RRR]=[redacted] [95% CI: [redacted]]).
3. Comparison of vutrisiran with tafamidis is based on non-randomised data	More in-depth modelling of the HELIOS-B trial, such as regression modelling adjusting for confounding factors and use of tafamidis treatment both before and after randomisation would be useful. A full indirect comparison of HELIOS-B with ATTR-ACT using both anchored MAIC and NMA methods, would also be useful.	A within-trial comparison of vutrisiran and tafamidis monotherapy from HELIOS-B provided the most robust possible assessment of the relative efficacy of these therapies in a contemporary ATTR-CM population and was therefore used to inform the company model. Because this within-trial comparison was not randomised, stabilised inverse probability of treatment weighting (IPTW) was used to balance baseline differences between the vutrisiran and tafamidis monotherapy groups. As demonstrated in the clarification responses to NICE, none of the baseline parameters designated as high-priority (in terms of prognostic significance) had a standardised mean difference of >10% between the vutrisiran monotherapy and tafamidis monotherapy groups after stabilised IPTW, indicating good balance between groups and thus supporting the robustness of the comparison.[11-13] The IPTW analysis could not be adjusted for baseline use of tafamidis since there is no overlap for this covariate between treatment arms. As noted in the company submission, this pre-baseline time on treatment for tafamidis (median of 11.3 months [range: 1.1, 65.5]) meant that these patients were already deriving some degree of efficacy benefit from tafamidis at baseline of HELIOS-B. In contrast, patients in the vutrisiran group were not receiving vutrisiran until entry into HELIOS-B and thus did not derive efficacy benefit from vutrisiran until after HELIOS-B baseline. As noted in the company responses to clarification questions, shifting the “definition of baseline” for vutrisiran by 11.3 months in the IPTW analysis was considered; however, it was deemed to be inappropriate due to important methodological limitations which were described in clarification response to question B4.

EAG report key issue	Evidence / analysis requested	Company response
		When considering tafamidis use post-randomisation, in alignment with the methods used in the primary prespecified analyses in HELIOS-B, the IPTW analysis used to inform the company model did not censor for drop-in tafamidis use in the vutrisiran monotherapy arm. A post hoc analysis of vutrisiran versus placebo showed that results in the vutrisiran monotherapy group remained consistent after censoring for tafamidis drop-ins (Alnylam, data on file). Thus, given that the treatment effects of vutrisiran were insensitive to tafamidis drop-in, censoring for drop-in in the vutrisiran arm in the IPTW analysis would not meaningfully impact model results. As noted in response to #2 above, an ITC of vutrisiran and tafamidis was not feasible to conduct in an unbiased manner. Nonetheless, while noting the methodological limitations of an ITC, Alnylam provided an exploratory unanchored MAIC in our response to EAG clarification questions. Regarding the request for further indirect comparison data consisting of an anchored matching-adjusted indirect comparison (MAIC), Alnylam wishes to highlight that the validity of an anchored MAIC would be predicated on the existence of a common comparator between HELIOS-B and ATTR-ACT, to allow “bridging” of results between the two trials. Nominally, the placebo arms from the two trials would serve as this common comparator, but as discussed in section 2.10 of the company evidence submission document, [redacted] While Alnylam continues to note that an ITC of vutrisiran and tafamidis is not feasible to conduct in an unbiased manner, in response to the EAG request for an anchored MAIC of

<table>
<tr><th>EAG report key issue</th><th>Evidence / analysis requested</th><th>Company response</th></tr>
<tr><td></td><td></td><td>vutrisiran in HELIOS-B versus tafamidis in ATTR-ACT, Alnylam has provided results for this anchored comparison (Table 1).

Table 1: Unanchored and anchored MAIC results
<table>
<tr><th>Outcome*</th><th>Anchored result</th><th>Unanchored result</th><th>Interpretation</th></tr>
<tr><td>ACM, HR (95% CI)</td><td>  </td><td>  </td><td>There is a trend towards improved survival with vutrisiran.</td></tr>
<tr><td>CV events, IRR (95% CI)</td><td>  </td><td>  </td><td>There is a trend towards reduced frequency of CV events with vutrisiran.</td></tr>
<tr><td>NHYA class, difference in proportion stable/improved vs. baseline (95% CI)</td><td>  </td><td>  </td><td>There is a trend towards greater likelihood of maintenance or improvement in NYHA class with vutrisiran.</td></tr>
</table>
ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; MAIC, matching-adjusted indirect comparison; NYHA, New York Heart Association. *For each study included in the cross-trial ITC, these endpoints were assessed using the primary methodology used in that study's statistical analysis plan.
Source: Alnylam, data on file

Alnylam also notes that the EAG performed their own network meta-analyses (NMA) comparing vutrisiran (HELIOS-B) and tafamidis (ATTR-ACT), which showed a consistent numerical benefit for vutrisiran in ACM.</td></tr>
<tr><td>5. Modelled treatment effectiveness implies greater</td><td>Consider alternative survival extrapolations which allow for modelling a range of long-term treatment benefits with vutrisiran.</td><td>Vutrisiran arm: Goodness-of-fit criteria show comparable Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) estimates across parametric functions, with the lowest estimates coming from the exponential function. Despite having the lowest AIC and BIC, the hazard rate from the exponential function did not align with the observed hazard from the vutrisiran monotherapy arm in HELIOS-B, and accordingly, the</td></tr>
</table>

EAG report key issue	Evidence / analysis requested	Company response
difference between treatments than the clinical data suggests		extrapolated curve using the exponential function was found to not follow the observed overall survival curve. Consequently, as per the Structured Elicitation Exercise (SEE) performed with UK clinical experts, the log-logistic function was selected to model survival in the vutrisiran arm in the base-case analysis. Alternative extrapolations, including Weibull and Gamma, were identified in the SEE as plausible, and were explored in scenario analyses. **Tafamidis arm**: Similarly, goodness-of-fit criteria show comparable AIC and BIC estimates across all functions assessed. The lowest AIC and BIC estimates were observed with the Gompertz function. However, visual inspection of hazard rates over 42 months showed that the log-normal function was best aligned with the observed hazard from HELIOS-B for the tafamidis monotherapy arm. Furthermore, SEE resulted in the selection of the log-normal function as the most appropriate to model survival in the tafamidis arm in the base-case analysis. Alternative survival extrapolations suggested by SEE were log-logistic and Gamma, which were explored in scenario analysis.
9. The appropriateness of considering caregiver disutilities in the cost-effectiveness analysis is uncertain.	EQ-5D data collected from carers of a contemporaneous (predominantly wtATTR) ATTR-CM population across NYHA health classification. The company could also present evidence to allow ascertaining whether the caregiver burden in ATTR-CM is greater than would be expected in other disease areas where carer burden is not	In the absence of published EQ-5D data collected from caregivers of a contemporaneous ATTR-CM population across NYHA classes, caregiver disutilities by NYHA class in the cost-effectiveness analysis were derived from a study in which EQ-5D data were collected from caregivers for patients with hATTR. In that study, 62% of patients had hATTR-CM and 72% reported cardiac symptoms. Since NYHA classification is based on limitations in physical activity (due to heart failure), applying caregiver disutilities based on impairments in patients' ambulatory and functional status (via familial amyloid polyneuropathy [FAP] stage) is an appropriate proxy for caregiver disutilities based on the NYHA class of the patient they provide care for. The need for physical assistance (and thus the burden to the caregiver) is expected to be driven by the severity of the patient's physical limitations, and

EAG report key issue	Evidence / analysis requested	Company response
	routinely accounted for in the QALY estimates.	is unlikely to differ depending on the cause of these limitations (i.e., heart failure or other ATTR-related symptoms). Given the significant burden experienced by caregivers of patients with ATTR-CM, Alnylam considered the inclusion of caregiver health-related quality of life (HRQoL) impacts in the cost-effectiveness analysis to be both relevant and aligned with the NICE Manual on Health Technology Evaluations. Alnylam notes the burden on caregivers in ATTR-CM was highlighted to NICE by the UK ATTR Amyloidosis Patients' Association during the appraisal of tafamidis:[14] *"The burden on caregivers is significant too. Most caregivers are partners or spouses, sometimes children. Caregivers also complain of chronic fatigue; apart from caring for their spouse they also gradually assume more and more of the household duties as their spouse/parent becomes less and less able to help. Caregivers may also suffer isolation as they are either afraid or unable to leave their spouses alone. Caregivers also suffer from low mood and depression as a result of the impact of the disease on them and their families."* Also noted from the NICE appraisal of tafamidis in ATTR-CM, the company, in response to clarification questions about caregiver benefits, noted two studies in heart failure that showed that worsening heart failure severity (assessed via NYHA class) was associated with poorer quality of life in caregivers.[14] Given the substantial evidence that highlights the burden of caregiving in ATTR-CM, Alnylam is unsure as to why the sponsor for tafamidis did not include caregiver disutilities in their submitted pharmacoeconomic model, and, based on available evidence, believes they should have been included.

EAG report key issue	Evidence / analysis requested	Company response
		Notably, in hATTR with polyneuropathy (hATTR-PN), where TTR accumulation manifests primarily as polyneuropathy, caregiver disutilities were accepted in the NICE appraisal of patisiran.[15] From the perspective of the caregiver, providing care in ATTR-CM is similarly if not potentially more burdensome than providing care in hATTR-PN, as patients with ATTR-CM face burdensome signs and symptoms related to heart failure such as fatigue and loss of physical capacity.[16-20] These severely limit patients' ability to perform daily activities (e.g., walking, social/leisure activities, chores),[21] leading to even further dependence on caregiver support. Patients with ATTR-CM may also have symptoms of neuropathy,[22-27] which based on the appraisal of patisiran, would partially justify the inclusion of caregiver disutilities in the current submission on its own. Additionally, based on the abbreviated lifespan after diagnosis in ATTR-CM (2.1–5.8 years.[16,18,28-36]) compared to hATTR-PN (4.7 years[29]), there is anticipated to be a more rapid increase in the demands on placed on caregivers as patients progress in disease in ATTR-CM, further highlighting the relevance of caregiver disutilities. Beyond the burdens of caregiving in ATTR-CM that were described in the company submission, it is important to consider the age and demographics of caregivers of patients with ATTR-CM. Caregivers of patients with ATTR-CM are predominantly female (81–85%) and most often a partner/spouse (58–78%).[37,38] In addition, while both hATTR-PN and ATTR-CM substantially diminish patients' physical function and ability to perform everyday activities, patients with ATTR-CM are typically of more advanced age at disease onset (e.g., median age in HELIOS-B [ATTR-CM] was ~77 years and in HELIOS-A [hATTR-PN] was ~65 years).[4,39] This means caregivers of patients with ATTR-CM are typically senior women. The particularly substantial burden that caregiving places on older female caregivers has been highlighted in Canadian caregivers.[40] Specifically, a report by Statistics Canada shows that senior female caregivers experience greater stress, a stronger sense of responsibility burden, and more negative health impacts compared to their male

EAG report key issue	Evidence / analysis requested	Company response
		counterparts.[40] These effects intensify as caregiving demands increase,[40] which is highly applicable to the company submission, which modelled caregiver HRQoL to worsen as patients' NYHA class increased (therefore demanding greater levels of support). In light of the fact that NICE has already considered caregiver disutilities in an appraisal in hATTR-PN, and that the burden of caregiving is similar if not potentially elevated in ATTR-CM compared to hATTR-PN, Alnylam maintains that caregiver disutility is a substantial and relevant contributor to the overall impact of ATTR-CM and should be incorporated into quality-adjusted life year (QALY) calculations. However, to support Committee decision-making, in view of the uncertainty expressed by the EAG, updated cost-effectiveness results are now provided with and without caregiver disutilities.

Brief responses to other EAG report key issues

Please share a brief response to other EAG report key issues.

4. **Clinical evidence comparing vutrisiran to tafamidis shows no evidence of difference in effectiveness**

Alnylam acknowledges the EAG's concerns regarding the uncertainty in the relative efficacy of vutrisiran and tafamidis, given the absence of a randomised head-to-head comparison. Alnylam acknowledges that the Committee may adopt a conservative stance aligned with the EAG's preferred analysis, and if needed, [redacted].

However, Alnylam highlights the following key considerations:

- A consistent trend (across analyses of multiple different data sources) suggests superior efficacy of vutrisiran over tafamidis.

- The EAG's preferred analysis assuming equivalent efficacy requires factual corrections.

Trend towards an efficacy benefit for vutrisiran over tafamidis

The IPTW analysis conducted within the HELIOS-B population showed the following results in the vutrisiran monotherapy group relative to the tafamidis monotherapy group:

- A numerical relative reduction of approximately 17% in the composite risk of ACM and CV events (HELIOS-B primary composite endpoint; HR: 0.831 [95% CI: 0.54, 1.29]) over a follow-up duration of up to 36 months.

- A numerical relative reduction of 18% in CV event rate (component analysis of HELIOS-B primary composite endpoint; RRR: 0.82 [95% CI: 0.62, 1.08]) over a follow-up duration of up to 36 months.

- A numerical relative reduction of approximately 19% in ACM risk (HELIOS-B secondary endpoint; HR: 0.81 [95% CI: 0.494, 1.340]) over a follow-up duration of up to 42 months (including up to 6 months of follow-up during the open-label extension phase of HELIOS-B).

While Alnylam emphasises that an ITC of vutrisiran and tafamidis is not feasible to conduct in an unbiased manned for the reasons stated in company submission, in response to clarification questions and in this document, we note that:

- The EAG's NMA comparing vutrisiran (HELIOS-B) and tafamidis (ATTR-ACT) showed a numerical benefit for vutrisiran in ACM across all three statistical models: frequentist Cox, frequentist Weibull, and Bayesian NMA.

- Similar findings were observed via anchored and unanchored MAIC using data from HELIOS-B and ATTR-ACT, as presented in Table 1.

Thus, although they were not adequately powered to demonstrate a statistical difference between patients receiving vutrisiran monotherapy and patients receiving tafamidis monotherapy, all these analyses are consistent in suggesting that vutrisiran provides clinical benefit over tafamidis.

In addition, the Institute for Clinical and Economic Review, in its recent assessment of treatments for ATTR-CM, has highlighted that vutrisiran is the only therapy approved for ATTR-CM that has demonstrated a mortality benefit in the contemporary ATTR-CM population.[9]

Finally, while acknowledging that the EAG's preferred analysis assumes equivalent clinical efficacy between vutrisiran and tafamidis, the EAG report, reflecting the EAG's opinion itself states "…*vutrisiran might have a slight benefit in reducing mortality…*".

Factual corrections to the EAG-preferred analysis which assumes equivalent efficacy

While these are discussed fully in Alnylam's response to issue #10 below, fundamentally, the EAG's preferred analysis needs factual correction to account for:

- Tafamidis being prescribed on a 12-month basis and supplied on a 3-month basis (as confirmed by clinical experts at the NAC[1]).

- Vutrisiran administration costs reflecting the current Summary of Product Characteristics (SmPC; which allows for patient self-administration or administration by a caregiver), NAC intentions for all patients on vutrisiran to initiate and continue treatment at home, and the availability of company-funded homecare.

6. All-cause mortality (ACM) is modelled independently from New York Heart Association (NYHA) classification and transient cardiovascular events

The current approach for modelling survival is similar to the approach applied in the NICE technology appraisal of tafamidis in ATTR-CM (TA696 and TA984).[14,41]

Competing risks or multi-state survival analysis and modelling could formally link overall survival extrapolation to NYHA class transitions; however, this approach is not advisable for the following reasons:

- Trial data from HELIOS-B are limited, as in the relevant subset of the trial dataset, baseline NYHA class distribution was highly skewed ([redacted]% in NYHA class II, [redacted]% in NYHA class I, [redacted]% in NYHA class III, and no patients in NYHA class IV). The sparsity of patients in NYHA classes I and III and the absence of any patients in class IV at baseline, together with the relatively small number of mortality events in HELIOS-B, means that there were insufficient data to derive robust NYHA-specific survival estimates with competing risks for NYHA transitions.

- With ATTR-ACT having <10% in NYHA I and no patients in NYHA IV,[3] TA696/TA984 did not adopt a competing risk or multi-state survival analysis approach.[42] Instead, a "*survival model derived from all patients unconditional upon NYHA class was preferred over a NYHA-specific survival model, as it requires estimation of fewer direct parameters (for the NYHA-specific risk of mortality) and indirect parameters (for NYHA state transition) that would affect the precision of the overall survival estimate*".

Using the current modelling approach, patients who die are allocated across NYHA class health states according to NYHA class mortality HRs, reflecting what would be expected in real-world environments (i.e., higher NYHA classes are associated with higher mortality). Since transient events (including CV events) were also modelled to increase in likelihood as patients entered worse NYHA classes, patients are expected to be more likely to both incur a transient event and die as their NYHA class worsens. This relationship is consistent with clinical understanding of the disease course and would not be expected to change if the model were to formally link overall survival to NYHA class transitions.

7. Treatment effect waning with vutrisiran is uncertain

In ATTR, misfolded transthyretin (TTR) protein leading to TTR amyloid deposition in the heart leads to cardiomyopathy (ATTR-CM), which ultimately results in heart failure.[43] As TTR protein is the main driver of the disease process, silencing the expression of the TTR gene with vutrisiran and thus lowering serum TTR protein levels has been shown to be disease modifying, as evidenced in HELIOS-B in patients with ATTR-CM.[4] Accordingly, clinical experts agree there is a relationship between the extent of TTR lowering and clinical outcomes in patients with ATTR.[1]

Pharmacodynamic modelling data from HELIOS-B (Figure 30 in the company submission) showed the trajectory of serum TTR level reversal following discontinuation of vutrisiran, with these levels on average reverting to pre-treatment baseline approximately 21 months after discontinuing vutrisiran. Clinician experts suggest this would lead to a waning residual treatment effect of vutrisiran during the interval over which serum TTR remained below baseline levels post-discontinuation.[1] Patients treated with vutrisiran in clinical trials have consistently shown median reductions in serum TTR of 80+% relative to their pretreatment baseline levels,[4,39] and therefore, the clinical efficacy observed in these trials is representative of the impact of an 80+% reduction in serum TTR levels. Considering the relationship between TTR lowering and clinical outcomes, it is expected that a smaller magnitude of TTR reduction would still result in clinical efficacy, although proportionally less than that observed in association with 80+% serum TTR lowering. This principle was followed in modelling the residual treatment effect of vutrisiran after discontinuation.

Alnylam notes that the approach employed in the company evidence submission to model this treatment effect waning was conservatively only applied to NYHA class transition rates and had no effect on mortality (i.e., after discontinuing vutrisiran, patients immediately were assumed to have the same per-cycle mortality risk as patients receiving BSC).

While modelling a treatment waning effect after discontinuing vutrisiran is supported by expert opinion and has been implemented conservatively, Alnylam appreciates the EAG's opinion that a gradual loss of treatment efficacy after discontinuation is plausible, but not over the full length of time originally modelled (page 85 of the EAG report). Therefore, Alnylam has:

- Taken a more conservative assumption of modelling treatment waning over a shorter 12-month period in the updated company base-case analysis (versus a 21-month period in the original submission).

- Modelled other scenarios to support Committee decision-making, which reflect the EAG's preference to explore the uncertainty regarding the waning of treatment effects, as follows:

    - [redacted] of treatment effect waning

    - No treatment effect waning

8. General population utility adjustments are additive rather multiplicative

Alnylam thanks the EAG for noting the multiplicative approach is preferred when adjusting for general population utility decreases and has incorporated this into the updated company base case.

10. The vutrisiran acquisition and administration costs may have been underestimated

The EAG noted that the model's 3-month cycle length aligned with the dosing schedule of vutrisiran administration and therefore recommended removing the within-cycle correction from the calculation of acquisition costs for vutrisiran. Alnylam acknowledges this recommendation and has implemented this in the updated company base-case.

However, Alnylam believes the within-cycle correction for tafamidis also needs to be removed to reflect the factual reality that patients treated with tafamidis in the UK are currently prescribed tafamidis on a 12-month basis and supplied on a 3-month supply basis (confirmed by the NAC[1]), effectively mirroring vutrisiran.

Accordingly, in the updated company base-case analysis and EAG-preferred analysis that Alnylam has corrected for factual errors (company-corrected EAG-preferred analysis), the within-cycle correction has been removed when calculating acquisition costs for both vutrisiran and tafamidis.

Separately, the EAG raised a concern that administration costs for vutrisiran—applied for the first dose in the hospital setting and assumed to be zero cost for all subsequent doses (which would be administered at home by the patient or a caregiver)—in the company pharmacoeconomic model were not in line with the requirement for hospital administration in the Summary of Product Characteristics (SmPC).[44]

However, the SmPC for vutrisiran states that *"Amvuttra may be administered by a healthcare professional, the patient, or a caregiver."*.[44] It should be noted that the inclusion of patient/caregiver administration in the SmPC for vutrisiran was recently added (February 18th, 2025 update),[44] meaning the timing of the EAG report in relation to the SmPC update could have led to this discrepancy. In line with this update to the SmPC, administration with vutrisiran in the company submission is assumed to be performed by the patient or caregiver at home at zero cost for all administrations subsequent to the initial administration.

Alnylam further importantly notes:

- The preference and confirmed plans from the NAC for all patients to administer vutrisiran at home, including their first dose.[1]
- The availability of company-funded homecare for all patients.

Therefore, Alnylam views the company base-case analysis which assumes an administration cost for the first dose as likely to overestimate costs in the vutrisiran arm.

Therefore, in the updated company base-case analysis and company-corrected EAG-preferred analysis, only the first administration of vutrisiran is associated with a cost and subsequent administrations are assumed to have zero cost, even though this likely overestimates the administration cost in the vutrisiran arm.

Economic analysis

Please provide an updated base case and full set of scenario analyses using the updated proposed discount and incorporating any other changes made to the base case in response to this request.
Please note it is not necessary to provide scenario analyses including an estimate of the confidential discount for comparator treatments.

In response to the issues and preferred assumptions noted by the EAG, Alnylam has prepared a company-corrected EAG-preferred analysis and an updated company base-case analysis. In line with how the EAG presented results from their preferred analyses, Alnylam has included results with and without caregiver disutilities.

Company-corrected EAG-preferred analysis

- All EAG key assumptions are kept consistent with the EAG preferred analysis, except for the following modifications which Alnylam considers to be factual accuracy corrections required to mirror clinical reality:
    - Within-cycle correction has been removed from the calculation of acquisition costs for both vutrisiran and tafamidis.
    - Administration costs are only applied for the first administration of vutrisiran.
    - The [redacted] treatment effect waning scenario has been updated so that treatment effects of vutrisiran persist for [redacted] after treatment discontinuation, instead of [redacted] as reflected in the EAG model.

Updated company base case

- The following changes have been made in the updated company base case:
    - Utility changes associated with ageing in the general population follow a multiplicative approach, which is aligned to the EAG preference.
    - A 12-month treatment waning effect in the vutrisiran arm following vutrisiran discontinuation was incorporated, instead of the originally modelled 21-month treatment waning effect.
    - Within-cycle correction has been removed from the calculation of acquisition costs for both vutrisiran and tafamidis.

Results from these analyses are presented in Table 2 and Table 3. Pack costs included in the analyses are listed below:

- Vutrisiran: £[redacted] per prefilled syringe
- Tafamidis: List price of £10,685.00 per pack (30 x 61 mg capsules)

Table 2: Company-corrected EAG-preferred analysis

Analysis	Inc. cost (£)	Including caregiver utilities		Excluding caregiver disutilities	
		Inc. QALYs	ICER	Inc. QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: [redacted] waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: 12-month waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 3: Updated company base-case analysis

Analysis	Inc. cost (£)	Including caregiver utilities		Excluding caregiver disutilities	
		Inc. QALYs	ICER	Inc. QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: [redacted] waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Vutrisiran alternative survival extrapolation: Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Vutrisiran alternative survival extrapolation: gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Tafamidis alternative survival extrapolation: log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Tafamidis alternative survival extrapolation: gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

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EAG review of the company's additional evidence
Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]

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Declared competing interests of the authors

None

Note on the text

All commercial-in-confidence (CON) data have been highlighted in blue and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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1 OVERVIEW

This document presents the External Assessment Group's (EAG) review and critique of the *"Targeted company response to EAG report".* The company's document (referred to henceforth as the company's response) was provided before the first appraisal committee meeting (ACM1) and includes the company's response to the key issues identified by the EAG in the evidence review report (EAR), as requested by the NICE technical team. In addition to this, the company also included in the document:

1. Additional deterministic cost-effectiveness analyses inclusive of a Patient Access Scheme (PAS) price for vutrisiran (i.e., [redacted] per individually packed 25mg syringe, corresponding to a discount of approximately [redacted] over vutrisiran's list price). This PAS price has not been formally approved (to the EAG's best knowledge); for simplicity this PAS price is henceforth referred to as the hypothetical PAS price for vutrisiran. [redacted] The company did not present any corresponding results for these analyses at the approved PAS price (i.e., [redacted] per individually packed 25mg syringe, corresponding to a discount of [redacted] over vutrisiran's list price).
2. Two updated versions of the electronic model (one with parameters set to the values of the company's updated base-case analysis and the other set to the company's corrected EAG base-case analyses).

In Section 2, the EAG reviews and critiques the additional evidence presented by the company, and presents, in Section 3, cost-effectiveness analyses conducted by the EAG. The cost-effectiveness results presented by the EAG in Section 3, are inclusive of the two alternative PAS discounts: i) the hypothetical PAS discount, and ii) the formally approved PAS discount on the list price of vutrisiran (~[redacted] and [redacted] respectively). The corresponding results for analyses including the tafamidis confidential PAS price are presented in a separate confidential appendix. Given the constrained timelines, all analyses in this document and its confidential appendix are deterministic.

2 ADDITIONAL EVIDENCE PRESENTED BY THE COMPANY

2.1 Best supportive care is not included as a comparator

The company details in their response the reasons why it does not consider best supportive care (BSC) to be a relevant comparator in the current appraisal, and do not present any cost-effectiveness analyses

for this comparison. The company also reports that clinical advice received suggests that approximately [redacted] of the UK ATTR-CM patients eligible for disease-modifying therapy do not receive tafamidis due to intolerance or lack of treatment response.

The EAG notes that the NICE scope for this assessment clearly lists two comparators of interest:

- Tafamidis
- Established clinical management without vutrisiran

The EAG therefore considers that these are intended to be separate comparators, and so management without tafamidis (i.e. BSC) is a comparator that should have been fully assessed, particularly as it is the only comparison for which randomised evidence exists. The EAG notes that the selection of comparators for the assessment rests with the NICE committee; the EAG report is simply recognising that the company submission does not strictly match the scope.

The EAG acknowledges that tafamidis is in widespread use, and so BSC might only apply to patients who are intolerant to tafamidis or have a lack of treatment response. The EAG also acknowledges that this may be a small subset of patients. However, the EAG believes that those patients should not be excluded from consideration, and vutrisiran may be a useful therapy in such patients, particularly if vutrisiran cannot be shown to be cost-effective when compared to tafamidis.

2.2 Limited evidence on key patient subgroups

The company states in their response the reasons why no formal modelling and testing for subgroup differences in both HELIOS-B and ATTR-ACT or further trial data on small subgroups are presented.

The EAG notes that the NICE scope for this assessment clearly lists two key subgroups of interest:

- Severity of heart failure (such as by New York Heart Association classification class)
- Wild type or hereditary ATTR-CM

The EAG report noted simply that very limited evidence on these required subgroups was presented, and mostly had to be drawn from appendices and the HELIOS-B CSR. These results showed a possibility of variation in the effectiveness of vutrisiran across subgroups. The EAG therefore considers that more in-depth regression analyses to compare vutrisiran, tafamidis and placebo within and across these subgroups, particularly in HELIOS-B, would be desirable. The EAG acknowledges the limitations of such analyses, given small sample sizes, but does not think this sufficient justification for not fully investigating the subgroups specified in the scope.

The EAG has neither requested nor suggested that indirect treatment comparisons between HELIOS-B and ATTR-ACT by subgroup should be performed. The EAG agrees that this would be impractical. The EAG disagrees with the reasoning presented for not performing indirect treatment comparisons in general. Our reasons are given in detail in Section 3.5.1 of the EAG report, so are not repeated here.

The EAG disagrees with the company's claim that "Vutrisiran demonstrated a consistent clinical benefit versus placebo for all primary and secondary endpoints in HELIOS-B across all prespecified subgroups". Based on EAG report Figures 2-5 (Section 3.2.8), we concluded that "there is no evidence of a benefit of vutrisiran in the small subgroup of participants with hATTR". Although we acknowledge that this subgroup is small and the confidence intervals are very wide.

2.3 Comparison of vutrisiran with tafamidis is based on non-randomised data

The company's response provides the results of an anchored matching-adjusted indirect comparison (MAIC) for key HELIOS-B outcomes (Table 1, of the company's response) alongside those of the unanchored MAIC.

The EAG notes that, as HELIOS-B was conducted by the company, wide-ranging regression analyses could be performed on the trial data to regress outcomes against all treatments (vutrisiran, tafamidis and placebo), timing of treatment, subgroup membership etc. Such additional analysis would give a fuller picture of the outcomes of HELIOS-B alongside the company's IPTW analysis. The EAG is not suggesting that results from further regression models would conflict with the IPTW analysis, only that they would provide additional reassurance.

The EAG disagrees with the reasoning presented for not performing indirect treatment comparisons between HELIOS-B and ATTR-ACT in general. Our reasons are given in detail in Section 3.5.1 of the EAG report, so are not repeated here. The EAG thanks the company for supplying the requested anchored MAIC to compare HELIOS-B and ATTR-ACT. The EAG notes that the results of the anchored MAIC [redacted]

Consequently, the EAG is unchanged in its opinion about the relative effectiveness of vutrisiran and tafamidis, as given in Section 3.7 of the EAG report. Namely, that results for mortality generally were in the direction of favouring vutrisiran over tafamidis, but the hazard ratio was modest, results were not statistically significant, and all comparisons are either indirect or non-randomised so are at risk of bias. The EAG also notes that the unadjusted mortality hazard ratio (HR) for the vutrisiran vs. tafamidis monotherapy and corresponding regression estimate adjusted for treatment group suggest a detrimental effect ([redacted]) and [redacted], respectively; response to clarification question A8), while the regression estimated HR adjusted for treatment

group, age group, ATTR disease type, baseline NYHA class, log-transformed NT-proBNP and Troponin, baseline 6-MWT, baseline KCCQ-OS, and baseline eGFR suggests a beneficial effect (HR= This contributes to the uncertainty in the size and the direction of treatment effect on mortality. Therefore, it remains the EAG's opinion that the most reasonable assumption is that the two therapies are likely to be broadly similar in effectiveness across all major mortality and morbidity outcomes and vutrisiran and tafamidis should be assumed to be equal in effectiveness for the purpose of this assessment.

Clinical evidence comparing vutrisiran to tafamidis shows no evidence of difference in effectiveness.

The EAG does not dispute that the data from HELIOS-B and ATTR-ACT suggest However, for the reasons set out in Section 3.7 and 4.2.6.1 of the EAR and the section above, the EAG do not consider that the evidence is sufficient to assume superiority of vutrisiran over tafamidis. for the purpose of cost-effectiveness analysis. Given current evidence and the limitations of the IPTW adjusted data, the EAG's position remains that the most reasonable assumption on the relative effectiveness of vutrisiran and tafamidis monotherapy is that there are no differences in treatment effects between the two drugs. The EAG cost-effectiveness analyses in the EAR include a range of scenarios modelling alternative assumptions on the treatment effectiveness of vutrisiran vs. tafamidis (see Section 6.1.1, EAR).

2.4 Modelled treatment effectiveness implies greater difference between treatments than the clinical data suggests

The company reiterated the reasons for their preferred survival modelling approach and presented cost-effectiveness scenario analysis using alternative parametric survival models to extrapolate the all-cause mortality for a) vutrisiran and b) tafamidis. The parametric models tested were those considered plausible in the context of the Structured Elicitation Exercise (SEE) of UK experts conducted by the company (report included in the company's original submission). In the company's extrapolation scenarios over their updated base-case, the incremental QALYs range between , including caregiver disutilities, and between excluding caregiver disutilities (see Table 3 of the company's response).

The EAG considers that the scenario analysis does not address the issue raised in the EAR that, whilst the company's clinical effectiveness evidence from HELIOS-B for the comparison between vutrisiran and tafamidis monotherapy (and broader evidence identified by the EAG) showed no conclusive evidence of difference between the treatments, the modelled outcomes suggest considerable incremental health gains with vutrisiran vs. tafamidis (LYs and QALYs in the company's original probabilistic base case analysis).

The EAG reiterates that this issue is only partly driven by the extrapolation of treatment effects over a time horizon considerably greater than the observed data follow-up. Other contributing factors relate to:

- the data observed in the trial follow-up, which may not accurately reflect the outcomes of ATTR-CM across the full spectrum of disease severity;
- all-cause mortality being modelled independently from progression across NYHA classes;
- the observed mortality hazards, which are likely to be heterogeneous and display trends (decreasing hazards in the long-term) that are implausible to persist over the modelled time horizon for a progressive and fatal disease.

The EAG acknowledged in the EAR (Section 1.5) that this issue cannot be handled without jointly addressing the contributing factors, and that this is not possible with the evidence currently available.

2.5 The appropriateness of considering caregiver disutilities in the cost-effectiveness analysis is uncertain.

The company reiterated their approach and rationale for including caregiver disutilities in the cost-effectiveness analysis. The company did not present any additional EQ-5D data collected from carers of a contemporaneous (predominantly wild type ATTR) ATTR-CM population across NYHA health classification. The company also presents contextual information to further support the preference for including caregiver disutilities in the cost-effectiveness analysis. The company presents updated analysis with and without caregiver disutilities to support the Committee decision making.

The EAG position on this matter remains unchanged and welcomes the company's decision to include cost-effectiveness analyses with and without caregiver disutilities, in line with the EAG's approach.

2.6 Clinical evidence comparing vutrisiran to tafamidis shows no evidence of difference in effectiveness and trend towards an efficacy benefit for vutrisiran over tafamidis

The EAG response in Section 2.3 and 2.4 relates to these two issues and the EAG has no further comments on the related clinical effectiveness evidence. The company's corrections to the EAG-preferred analysis assuming similar clinical effectiveness between vutrisiran and tafamidis relate strictly to costs and are discussed in Section 2.9.

2.7 All-cause mortality is modelled independently from New York Heart Association (NYHA) classification and transient cardiovascular events

The company states that while competing risks or multi-state survival analysis and modelling could formally link overall survival extrapolation to NYHA class transitions, this would not have been

advisable in the current appraisal. The company asserts that this is due to the baseline NYHA class distribution being highly skewed in the relevant subset of the HELIOS-B dataset, which combined with the small number of mortality events in the trial, precludes the estimation of robust NYHA-specific survival estimates with competing risks for NYHA transitions. Furthermore, the company notes that this approach was also not taken in the previous NICE appraisal of tafamidis in ATTR-CM (TA696/984) where the survival model was also independent of NYHA classification.

The EAG agrees with the company's assessment that the data issues in the subset of the HELIOS-B dataset for the vutrisiran vs. tafamidis monotherapy, could have hindered the estimation of robust NYHA-specific survival estimates. We have updated the EAR at the factual accuracy stage to better characterise our position on the matter, as we detected an error in the box describing the EAG's alternative approach preferences. This field now reads:

- "The use of a state transition modelling approach with competing risks, could allow overcoming this limitation. However, the HELIOS-B evidence is <u>not</u> sufficient to appropriately parameterise such model and external evidence in a contemporaneous ATTR-CM population is not available."

The EAG acknowledged in the EAR that the model in TA696/984 also did not condition survival on NYHA class and noted that no concerns were raised that the lack of this link would introduce inconsistencies in the assumptions used for NYHA transitions and mortality estimates, leading to potentially implausible and optimistic survival extrapolations (see Section 4.1, EAR). However, the EAG also highlighted that this might become an issue when in a population with lower mortality and disease severity at baseline than the population in previous models, as is the case for the HELIOS-B population.

The EAG key concern remains that the modelled survival estimates appear to be overly optimistic, based on the observed data in the post-hoc non-randomised analysis of HELIOS-B which informs the model, and that failure to accurately capture the link between disease progression mortality is likely to be a contributing factor to these potentially overly optimistic differences in health outcomes between treatments (see Section 4.2.6.3, EAR).

2.8 Treatment effect waning with vutrisiran is uncertain

The company reiterated their rationale for applying treatment effect waning on the transition probabilities across NYHA health states for vutrisiran, based on the observed serum transthyretin (TTR) levels after treatment discontinuation. The company presents no additional evidence to support their approach, but state that they have taken a more conservative assumption of modelling treatment

waning over a shorter 12-month period in the updated company base-case analysis (versus a 21-month period in the original submission).

In the absence of additional evidence provided by the company to support their position, the EAG considers that the critique presented in Section 4.2.6.4 of the EAR remains appropriate. The EAG also notes that, while the company has reduced the duration of treatment effect waning from 21 to 12 months in the updated analysis, the percentual contribution of the vutrisiran monotherapy transition matrices has also increased in the period between 6- and 12-months post-discontinuation compared to the original base-case (see Table 1). The company does not justify this change to its base-case analysis.

Table 1 Application of treatment waning effects on transition matrices based on weighted contributions from vutrisiran monotherapy

Cycles after vutrisiran monotherapy discontinuation (months)	Mean % TTR reduction*	Transition matrix weights (% contribution of the vutrisiran monotherapy matrices)		
		Company's original BC	Company's updated BC	EAG's BC
1 (0–3)	[redacted]	[redacted]	[redacted]	0%
2 (3–6)	[redacted]	[redacted]	[redacted]	0%
3 (6–9)	[redacted]	[redacted]	[redacted]	0%
4 (9–12)	[redacted]	[redacted]	[redacted]	0%
5 (12–15)	[redacted]	[redacted]	0%	0%
6 (15–18)	[redacted]	[redacted]	0%	0%
7 (18–21)	[redacted]	[redacted]	0%	0%
8 (21+)	[redacted]	[redacted]	0%	0%

Abbreviations: BC, base-case; EAG, evidence assessment group; TTR, transthyretin. *Average TTR reduction was calculated by digitising the curve presented in Figure 30 of the CS. †Serum TTR levels are assumed to be at pretreatment baseline level after 21 months from the last dose of vutrisiran.

2.9 General population utility adjustments are additive rather multiplicative

The company has accepted the use of a multiplicative approach to adjust health state utilities to reflect decreases in health-related quality of life in the age and sex-matched general population, in line with the EAG's preference.

2.10 The vutrisiran acquisition and administration costs may have been underestimated

The company considers that the EAG's preferred assumptions for the vutrisiran acquisition and administration costs result in factual inaccuracies, due to the:

1. Inclusion of a within-cycle correction on the drug acquisition and administration costs for vutrisiran, but not for tafamidis;
2. Assumption that vutrisiran would only be administered by a healthcare professional throughout treatment duration, and thus, incur administration costs over this period.

The company "corrected" the EAG base-case analysis for these assumptions (presented in Table 2 of the company's response). The EAG does not consider that the corrections conducted by the company to be appropriate. The rationale for this is detailed below, alongside the information provided by the company to support their position.

In its response document, the company states that patients treated with tafamidis in the UK are currently prescribed tafamidis on a 12-month basis and supplied on a 3-month supply basis; this was based on clinical opinion received by the company through personal communication (referenced in the company's response). The EAG has not been able to verify this claim but considers that if the new information provided is factually correct, then it would be appropriate to exclude the within cycle correction on the drug acquisition and administration costs for both tafamidis and vutrisiran. Thus, the EAG presents additional scenario analyses in Section 3 to explore the impact of this on the estimates of cost-effectiveness.

In regard to the assumption that vutrisiran is administered by a healthcare professional, the EAG noted in the EAR (see Section 4.2.10.3) that the SmPC included in the company's submission did not allow for caregivers or patients to self-administer vutrisiran and that the company stated that an update of the SmPC allowing for self-administration of vutrisiran was anticipated by April 2025. Therefore, the EAG preferred to assume in the base-case analysis that every administration of the drug would incur the cost of delivery of one subcutaneous injection by a nurse in a hospital setting. The company states that by 18th of February 2025, the SmPC had been updated to allow for self-administration, and, therefore, the EAG should have excluded this cost from the base-case analyses. Furthermore, the company provided the following information in its response document:

a) National Amyloidosis Centre (NAC) clinicians expressed a preference and confirmed plans from the NAC for all patients to administer vutrisiran at home, including their first dose. The EAG was not given access to the personal communication containing this information.
b) Company-funded homecare for all patients is available.

Given that the EAG could not independently verify the information above, we consider that there is uncertainty on how vutrisiran will be administered in UK clinical practice. Thus, the EAG maintains the assumption that patients treated with vutrisiran incur the cost of administration as per our original base-case, and explores alternative assumptions in Section 3.

2.11 Company's updated analyses

The company updated its base case analysis, as illustrated in Table 2.

Table 2 Comparison of preferred assumptions in the company's original and updated

	Original BC	Updated BC
Treatment effect waning on NYHA class transitions for vutrisiran	Assumed to occur gradually over 21 months after discontinuation, with weights derived based on TTR serum levels post treatment discontinuation (see Table 1).	Assumed to occur over 12 months after discontinuation, and with different weights applied in the period between [redacted] and 12 months after discontinuation compared to the original preferred assumption (see Table 1)
Age and sex matched general population adjustments to health state utilities	Additive approach	Multiplicative approach
Within cycle correction on drug acquisition and administration costs	Included for both vutrisiran and tafamidis	Excluded for both vutrisiran and tafamidis

Abbreviations: BC, base-case; NYHA, New York Heart Association; TTR, transthyretin

The company presents deterministic cost-effectiveness results for the updated base-case analysis in Table 3 of the response document, alongside the results of scenario analysis on the treatment effect waning for vutrisiran and alternative survival extrapolations for tafamidis and vutrisiran. These analyses all incorporate the hypothetical PAS price for vutrisiran ([redacted]% discount over the list price); the EAG presents in Table 3 corresponding results at the approved PAS price for vutrisiran ([redacted] discount over the list price).

Table 3 Updated company base-case analysis versus tafamidis at approved PAS price for vutrisiran

Analysis	Inc. cost (£)	Including caregiver utilities		Excluding caregiver disutilities	
		Inc. QALYs	ICER (/QALY)	Inc. QALYs	ICER (/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: [redacted] waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: No waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Vutrisiran alternative survival extrapolation: Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Vutrisiran alternative survival extrapolation: gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Tafamidis alternative survival extrapolation: log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Tafamidis alternative survival extrapolation: gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

3 EAG'S ADDITIONAL ANALYSES

The EAG updated the cumulative base-case analyses presented in the EAR, including the company's hypothetical PAS for vutrisiran; these are reported in Table 5 and Table 4 (with and without caregiver disutilities, respectively) for the comparison versus tafamidis, and in Table 7 and Table 6 (with and without caregiver disutilities, respectively) for the comparison versus BSC. Corresponding analyses at the approved PAS for vutrisiran can be found in the EAR (Tables 35-36 and Table 41-42).

Table 4 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the tafamidis comparison with vutrisiran's hypothetical PAS price (excluding caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's original base-case results	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	+No treatment effect wanning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3	+ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1	+ No treatment effect on survival	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2	+No effect on transition probabilities between NYHA class	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6	+Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6+7 (EAG base case)	+ Vutrisiran monotherapy administration costs included assuming delivery by nurse in hospital setting*	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Description updated to enhance clarity

Abbreviations: ACM, all-cause mortality; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; PAS, patient access scheme; QALY, quality-adjusted life year

Table 5 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the tafamidis comparison with vutrisiran's hypothetical PAS price (including caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's original base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	+No treatment effect wanning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3	+ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1	+ No treatment effect on survival	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2	+No effect on transition probabilities between NYHA class	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6	+Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2+3+4.1+4.2+6+7 (EAG base case)	+ Vutrisiran monotherapy administration costs included assuming delivery by nurse in hospital setting*	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Description updated to enhance clarity

Abbreviations: ACM, all-cause mortality; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 6 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the BSC comparison with vutrisiran's hypothetical PAS price (excluding caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
1	Company's original base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2	No treatment effect wanning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3	ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5	Age and sex adjusted utilities using multiplicative approach	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6	Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6+7 (EAG base case)	Vutrisiran monotherapy administration costs included assuming delivery by nurse in hospital setting*	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Description updated to enhance clarity

Abbreviations: ACM, all-cause mortality; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 7 Cumulative cost-effectiveness results for the EAG's preferred assumptions for the BSC comparison with vutrisiran's hypothetical PAS price (including caregiver disutilities)

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
1	Company's original base-case assumptions	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2	No treatment effect wanning for vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+ 2.2+3	ACM extrapolation for vutrisiran monotherapy with exponential distribution	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5	Age and sex adjusted utilities using multiplicative approach	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6	Without within-cycle correction for the acquisition and administration costs of vutrisiran monotherapy	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2.2+3+5+6+7 (EAG base case)	Vutrisiran monotherapy administration costs included assuming delivery by nurse in hospital setting*	Vutrisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Description updated to enhance clarity

Abbreviations: ACM, all-cause mortality; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; PAS, patient access scheme; QALY, quality-adjusted life year.

The EAG presents additional scenario analyses over the EAG base-case for the vutrisiran vs. tafamidis exploring the impact of the company's preferred assumptions on the i) administration costs of vutrisiran (scenario 1), and ii) removal of the within cycle correction from drug acquisition and administration costs (scenario 2) are varied independently and jointly (Scenario 1+2). These analyses are reported at the approved and hypothetical PAS price for the vutrisiran in Table 8 and Table 9, respectively. Since the EAG base-case analysis for this comparison assumes no differences in mortality and transition probability matrices between NYHA classes, results remain the same regardless of whether caregiver utilities are included or not.

Table 8 EAG's scenario analyses results at approved vutrisiran PAS price – vutrisiran vs. tafamidis

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
EAG base-case							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Vutrisiran assumed to incur no administration costs beyond first cycle							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Within-cycle correction removed from the acquisition and administration costs of both treatments							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 + 2							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 9 EAG's scenario analyses results at hypothetical vutrisiran PAS price– vutrisiran vs. tafamidis

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
EAG base-case							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Vutrisiran assumed to incur no administration costs beyond first cycle							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Within-cycle correction removed from the acquisition and administration costs of both treatments							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1 + 2							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

The EAG presents an additional scenario analysis over the EAG base-case for the vutrisiran vs. BSC exploring the impact of the company's preferred assumptions on the administration costs of vutrisiran (scenario 1). These analyses were performed excluding caregiver disutilities and are reported at the approved and hypothetical PAS price for the vutrisiran in Table 10 and Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 11, respectively. Corresponding analyses, including caregiver disutilities, are reported in Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 12 and Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 13.

Table 10 EAG's scenario analyses results at approved vutrisiran PAS price excluding caregiver disutilities– vutrisiran vs. BSC

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
EAG base-case							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Vutrisiran assumed to incur no administration costs beyond first cycle							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 11 EAG's scenario analyses results at hypothetical vutrisiran PAS price excluding caregiver disutilities – vutrisiran vs. BSC

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
EAG base-case							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Vutrisiran assumed to incur no administration costs beyond the first cycle							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 12 EAG's scenario analyses results at approved vutrisiran PAS price including caregiver disutilities– vutrisiran vs. BSC

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
EAG base-case							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Vutrisiran assumed to incur no administration costs beyond the first cycle							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 13 EAG's scenario analyses results at hypothetical vutrisiran PAS price including caregiver disutilities – vutrisiran vs. BSC

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (/QALY)
EAG base-case							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Vutrisiran assumed to incur no administration costs beyond the first cycle							
Vutrisiran	[redacted]	[redacted]	[redacted]				
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.