Medicinrådet

Bilag til Medicinrådets vurdering af vutrisiran til behandling af vildtype eller hereditær transthyretin amyloidose hos voksne patienter med kardiomyopati

Vers. 1.1

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. vutrisiran
2. Ansøgers endelige ansøgning vedr. vutrisiran

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

12.08.2026

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	Revurdering
Leverandør	Genesis Pharma (første ansøgning fra Alnylam Pharmaceuticals)
Lægemiddel	Amvuttra (vutrisiran)
Ansøgt indikation	Behandling af vildtype eller hereditær transthyretin-amyloidose hos voksne patienter med kardiomyopati
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (revurdering)

Prisinformation

Amgros har forhandlet følgende pris på Amvuttra (vutrisiran):

Tabel 1: Forhandlingsresultat, betinget pris ved revurdering.

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Amvuttra	25 mg (1 stk.)	[redacted]	[redacted]	[redacted]
[redacted]				

Tabel 2: Forhandlingsresultat marts 2026.

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Amvuttra	25 mg (1 stk.)	812.054,57	[redacted]	[redacted]

[redacted]

Aftaleforhold

[redacted]

[redacted]

[redacted]

[redacted]

Information fra forhandling

Det er en ny leverandør, som har overtaget markedsføringsrettighederne på Amvuttra.

[redacted]

[redacted]

Konkurrencesituationen

To andre lægemidler er anbefalet i Medicinrådet til behandling af transthyretin amyloidose med kardiomyopati: Vyndaqel (tafamidis), november 2024 og Beyonttra (acoramidis), maj 2025.

[redacted]

Tabel 3 viser de årlige lægemiddeludgifter for hhv. Amvuttra, Beyonttra og Vyndaqel.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient pr. år.

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Amvuttra	25 mg (1 stk.)	25 mg hver 3. måned, s.c.	[redacted]	[redacted]
Beyonttra	356 mg (120 stk.)	712 mg 2 gange daglig, oral	[redacted]	[redacted]
Vyndaqel	61 mg (30 stk.)	61 mg daglig, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
England	Anbefalet	Link til anbefaling
Sverige	Ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of vutrisiran (Amvuttra®) for treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

Contact information	
Name	**Anees Malik, Alnylam Pharmaceuticals**
Title	Senior Director Market Access, International
Phone number	+44 7917 820 691
E-mail	amalik@alnylam.com

Table of contents

Contact information **2**

Overview of Tables **7**

Overview of Figures **9**

Abbreviations **10**

1. Regulatory information on the medicine **12**

2. Summary table **13**

3. The patient population, intervention, choice of comparator(s) and relevant outcomes **15**

3.1 The medical condition 15
3.1.1 Disease overview 15
3.1.2 Pathophysiology 15
3.1.3 Types of ATTR-CM 17
3.1.4 Staging and disease severity 17
3.1.5 New York Heart Association classification of heart failure 18
3.2 Patient population 18
3.3 Current treatment options 19
3.3.1 Limitations associated with TTR stabilizers 19
3.4 The intervention 20
3.4.1 Description of ATMP 21
3.4.2 The intervention in relation to Danish clinical practice 21
3.5 Choice of comparator(s) 21
3.6 Cost-effectiveness of the comparator(s) 22
3.7 Relevant efficacy outcomes 22
3.7.1 Definition of efficacy outcomes included in the application 22

4. Health economic analysis **26**

4.1 Model structure 26
4.2 Model features 26

5. Overview of literature **28**

5.1 Literature used for the clinical assessment 28
5.2 Literature used for the assessment of health-related quality of life 29
5.3 Literature used for inputs for the health economic model 30

6. Efficacy **31**

6.1 Efficacy of vutrisiran compared to tafamidis for adults with ATTR-CM 31
6.1.1 Relevant studies 31
6.1.2 Comparability of studies 33
6.1.2.1 Comparability of patients across studies 33
6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment 35
6.1.4 Efficacy – results per HELIOS-B (primary analysis) 35
6.1.5 Efficacy – results per HELIOS-B – monotherapy vutrisiran and tafamidis subgroups 38

7. Comparative analyses of efficacy 38
7.1.1 Differences in definitions of outcomes between studies 39
7.1.2 Method of synthesis in the within trial analysis 39
7.1.2.1 Weighting of monotherapy populations 39
7.1.2.2 Analysis of outcomes 40
7.1.3 Efficacy – results of composite analysis of recurrent CV events and ACM over up to 36 months 46
7.1.3.1 Vutrisiran vs. placebo (ITT) 46
7.1.3.2 Vutrisiran vs. placebo (monotherapy) 46
7.1.3.3 Vutrisiran vs. tafamidis (monotherapy) 46
7.1.4 Efficacy – results of recurrent CV events over up to 36 months 46
7.1.4.1 Vutrisiran vs. placebo (ITT) 46
7.1.4.2 Vutrisiran vs. placebo (monotherapy) 46
7.1.4.3 Vutrisiran vs. tafamidis (monotherapy) 47
7.1.5 Efficacy – results of ACM over up to 42 months 47
7.1.5.1 Vutrisiran vs. placebo (ITT) 47
7.1.5.2 Vutrisiran vs. placebo (monotherapy) 47
7.1.5.3 Vutrisiran vs. tafamidis (monotherapy) 47
7.1.6 Efficacy – Results of the 6-MWT 47
7.1.6.1 Vutrisiran vs. placebo (ITT) 47
7.1.6.2 Vutrisiran vs. placebo (monotherapy) 47
7.1.7 Efficacy – KCCQ overall score 48
7.1.7.1 Vutrisiran vs. placebo (ITT) 48
7.1.7.2 Vutrisiran vs. placebo (monotherapy) 48
7.1.8 Efficacy – NYHA class 48
7.1.8.1 Vutrisiran vs. placebo (ITT) 48
7.1.8.2 Vutrisiran vs. placebo (monotherapy) 48
7.1.8.3 Vutrisiran vs. tafamidis (monotherapy) 48

8. Modelling of efficacy in the health economic analysis 48
8.1 Presentation of efficacy data from the clinical documentation used in the model 48
8.1.1 Extrapolation of efficacy data 49
8.1.1.1 Extrapolation of [effect measure 1] 49
8.1.2 Calculation of transition probabilities 50

8.2 Presentation of efficacy data from [additional documentation] 50
8.3 Modelling effects of subsequent treatments 50
8.4 Other assumptions regarding efficacy in the model 50
8.5 Overview of modelled average treatment length and time in model health state 50

9. Safety 51
9.1 Safety data from the clinical documentation 51
9.2 Safety data from external literature applied in the health economic model 54

10. Documentation of health-related quality of life (HRQoL) 56
10.1 Presentation of the health-related quality of life measured by [instrument] 56
10.1.1 Study design and measuring instrument 56
10.1.2 Data collection 56
10.1.3 HRQoL results 56
10.2 Health state utility values (HSUVs) used in the health economic model 57
10.2.1 HSUV calculation 57
10.2.1.1 Mapping 57
10.2.2 Disutility calculation 57
10.2.3 HSUV results 57
10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy 57
10.3.1 Study design 57
10.3.2 Data collection 57
10.3.3 HRQoL Results 57
10.3.4 HSUV and disutility results 58

11. Resource use and associated costs 58
11.1 Medicines - intervention and comparator 58
11.2 Medicines– co-administration 59
11.3 Administration costs 59
11.4 Disease management costs 59
11.5 Costs associated with management of adverse events 60
11.6 Subsequent treatment costs 61
11.7 Patient costs 61
11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost) 62

12. Results 62
12.1 Base case overview 62
12.1.1 Base case results 63
12.2 Sensitivity analyses 64
12.2.1 Deterministic sensitivity analyses 64
12.2.2 Probabilistic sensitivity analyses 64

13. Budget impact analysis 64

14. List of experts 66

15. References 67

Appendix A. Main characteristics of studies included 71

Appendix B. Efficacy results per study 77

Appendix C. Comparative analysis of efficacy 81

Appendix D. Extrapolation 83

D.1 Extrapolation of [effect measure 1] 83
D.1.1 Data input 83
D.1.2 Model 83
D.1.3 Proportional hazards 83
D.1.4 Evaluation of statistical fit (AIC and BIC) 83
D.1.5 Evaluation of visual fit 83
D.1.6 Evaluation of hazard functions 83
D.1.7 Validation and discussion of extrapolated curves 83
D.1.8 Adjustment of background mortality 83
D.1.9 Adjustment for treatment switching/cross-over 83
D.1.10 Waning effect 83
D.1.11 Cure-point 83

Appendix E. Serious adverse events 83

Appendix F. Health-related quality of life 87

Appendix G. Probabilistic sensitivity analyses 88

Appendix H. Literature searches for the clinical assessment 89

Appendix I. Literature searches for health-related quality of life 90

Appendix J. Literature searches for input to the health economic model 91

Overview of Tables

Table 1 Incidence and prevalence in the past 5 years 18
Table 2 Estimated number of patients eligible for treatment 19
Table 3 Efficacy outcome measures relevant for the application 23
Table 4 Features of the economic model 27
Table 5 Relevant literature included in the assessment of efficacy and safety 29
Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10) 30
Table 7 Relevant literature used for input to the health economic model 30
Table 8 Overview of study design for studies included in the comparison 32
Table 9 Baseline characteristics of patients in HELIOS-B in the overall population 33
Table 10 Characteristics in the relevant Danish population and in the health economic model 35
Table 11 Results from HELIOS-B 36
Table 12 Baseline characteristics of weighted monotherapy populations of HELIOS-B 42
Table 13 Results from the comparative analysis of vutrisiran vs. placebo/tafamidis for ATTR-CM patients 44
Table 14 Summary of assumptions associated with extrapolation of [effect measure] 49
Table 15 Transitions in the health economic model 50
Table 16 Estimates in the model 50
Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model) 50
Table 18 Overview of safety events – primary analysis, all patients at least 33 months follow-up 51
Table 19 Serious adverse events during double-blind period 53
Table 20 Adverse events used in the health economic model 53
Table 21 Adverse events that appear in more than X % of patients 55
Table 22 Pattern of missing data and completion 56
Table 23 HRQoL summary statistics 56
Table 24 Overview of health state utility values [and disutilities] 57
Table 25 Overview of health state utility values [and disutilities] 58
Table 26 Overview of literature-based health state utility values 58
Table 27 Medicines used in the model 59
Table 28 Administration costs used in the model 59
Table 29 Disease management costs used in the model 60
Table 30 Cost associated with management of adverse events 60
Table 31 Medicines of subsequent treatments 61
Table 32 Patient costs used in the model 61
Table 33 Base case overview 62
Table 34 Base case results, discounted estimates 63
Table 35 One-way sensitivity analyses results 64

Table 36 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) 65
Table 37 Expected budget impact of recommending the medicine for the indication 65
Table 38 Main characteristic of studies included 71
Table 39 Results per study 77
Table 40 Comparative analysis of studies comparing vutrisiran and tafamidis monotherapy for patients with ATTR-CM 81
Table 41 Serious adverse events during double-blind period 83
Table 42. Overview of parameters in the PSA 88

Overview of Figures

Figure 1 Pathophysiology of ATTR-CM 16
Figure 2 Distribution of propensity scores by monotherapy treatment group in HELIOS-B 81

Abbreviations

Abbreviations	Description
6-MWT	6 minutes walking test
ACM	All-cause mortality
AIP	Apotekets indkøbspris
(h/wt) ATTR-CM	(Hereditary/wild-type) transthyretin amyloidosis cardiomyopathy
ATTR-PN	transthyretin amyloidosis polyneuropathy
CI	Confidence interval
CMA	Cost-minimisation analysis
CV	Cardiovascular
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Danish Medicines Council
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
HRQoL	Health-related Quality of Life
IQR	Interquartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
LS	Least squares
MDI	Major Depression Inventory
mg	milligram
MMRM	Mixed effects model with repeated measures
mL	Millilitre
NAC	National Amyloidosis Centre;

NCT	National clinical trial
NYHA	New York Heart Association
QoL	Quality of life
SC	Subcutaneous
SD	Standard deviation
TTR	Transthyretin

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Amvuttra®
Generic name	Vutrisiran
Therapeutic indication as defined by EMA	Vutrisiran is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). EMEA/H/C/005852
Marketing authorization holder in Denmark	Alnylam Netherlands B.V.
ATC code	N07XX18
Combination therapy and/or co-medication	Vitamin A supplementation is advised.
(Expected) Date of EC approval	09-06-2025 (actual)
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, EU/3/18/2026
Other therapeutic indications approved by EMA	Yes, vutrisiran is indicated for the treatment of hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (hATTR-PN).
Other indications that have been evaluated by the DMC (yes/no)	No.
Joint Nordic assessment (JNHB)	No, different treatment landscape across Nordics.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	25 mg (0.5 mL in 50 mg/mL solution in pre-filled syringe)

2. Summary table

Summary	
Indication relevant for the assessment	Wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM), in line with EMA indication.
Dosage regiment and administration	The recommended dose of vutrisiran is 25 mg administered via subcutaneous injection once every 3 months.
Choice of comparator	Tafamidis 61mg, which has been approved by the Medicinraadet (1) would be considered the comparator for this submission. The recommendation applies to patients in NYHA class I-III and NAC stage I or II, and who meet the Danish Medicines Council's initiation criteria (2). The recommended dose of tafamidis is 61 mg orally once daily.
Prognosis with current treatment (comparator)	ATTR-CM is a rapidly progressive and fatal disease (3). Even with currently approved treatment, tafamidis 61mg, patients continue to experience worsening of physical capacity, health-related quality of life (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) (4-6).
Type of evidence for the clinical evaluation	HELIOS-B, a phase 3, randomised, double-blind, placebo-controlled, multicentre study that evaluated the efficacy and safety of vutrisiran in patients with ATTR-CM. HELIOS-B compared treatment with vutrisiran against treatment with placebo, with possible tafamidis background therapy. Evidence includes a post hoc comparison of patients receiving vutrisiran monotherapy (i.e., patients in the vutrisiran arm within the monotherapy population) and patients receiving tafamidis monotherapy (i.e., patients in the placebo arm who were on background tafamidis at baseline).
Most important efficacy endpoints (Difference/gain compared to comparator)	Composite of ACM and recurrent CV events (up to 36 months), favouring vutrisiran over tafamidis with a hazard ratio of 0.83 (95% CI: 0.54, 1.29). ACM (up to 42 months), favouring vutrisiran over tafamidis with a hazard ratio of 0.81 (95% CI: 0.49, 1.34). CV events (up to 36 months), favouring vutrisiran over tafamidis with a hazard ratio of 0.82 (95% CI: 0.62, 1.08).

Summary	
Most important serious adverse events for the intervention and comparator	Vutrisiran had an acceptable safety profile in HELIOS-B. Higher proportions of patients in the placebo group compared to the vutrisiran group experienced a serious adverse event (7). [redacted]
Impact on health-related quality of life	Clinical documentation: In HELIOS-B patients treated with vutrisiran showed preservation of HRQoL relative to pretreatment baseline (5). Health economic model: NA
Type of economic analysis that is submitted	Cost-comparison
Data sources used to model the clinical effects	NA
Data sources used to model the health-related quality of life	NA
Life years gained	NA
QALYs gained	NA
Incremental costs	[redacted]
ICER (DKK/QALY)	NA
Uncertainty associated with the ICER estimate	NA
Number of eligible patients in Denmark	Incidence: 100 patients per year, of which 70 eligible Prevalence: 550 patients
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Disease overview

Transthyretin amyloidosis (ATTR) is a rare, rapidly progressive, and fatal disease, which is characterised by the deposition of TTR amyloid fibrils in multiple organs and tissues (e.g., heart, nerves, gastrointestinal tract, and kidneys), with corresponding clinical manifestations (8). The formation of TTR amyloid fibrils is the result of an accumulation of toxic misfolded TTR-protein (8).

In transthyretin amyloid cardiomyopathy (ATTR-CM), these TTR-derived amyloid fibrils accumulate in the heart and cause progressive loss of cardiac function, ultimately resulting in heart failure (inability to pump an adequate supply of blood to body systems) and premature death (9-11). As such, ATTR-CM is an increasingly recognised cause of heart failure (HF) in older adults (12). Due to the advancement of imaging techniques, ATTR-CM is expected to be detected more frequently than previously anticipated (13, 14).

TTR-derived amyloid fibrils can also accumulate in nerves, in a condition known as ATTR with polyneuropathy (ATTR-PN) resulting in sensory neuropathy, motor dysfunction, and autonomic dysfunction (including gastrointestinal and cardiac autonomic dysfunction) (15, 16).

Some patients can present with both cardiomyopathy and polyneuropathy (i.e., mixed phenotype), due to the systemic deposition of TTR amyloid in both the myocardium and the peripheral and autonomic nerves (8, 17-20).

3.1.2 Pathophysiology

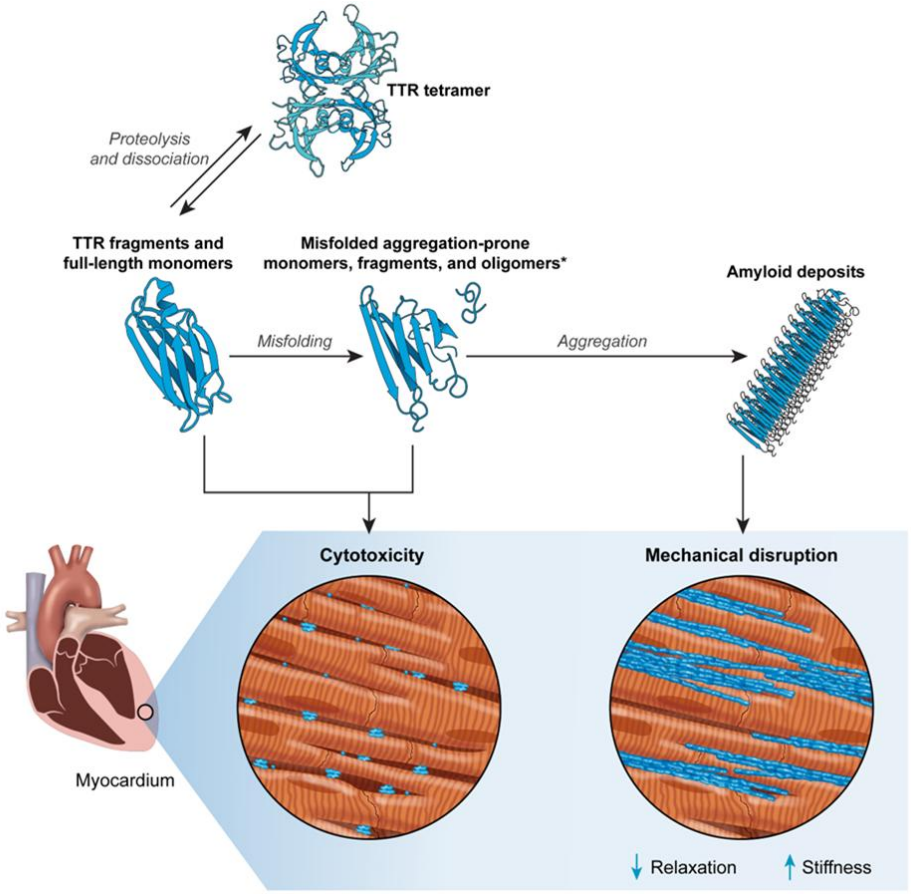
TTR is primarily produced in the liver, and its normal physiological function is to serve as a transport protein for thyroxine and vitamin A (8, 21, 22). In its normal configuration, the TTR protein is found in homotetramers in circulation; however, in ATTR, the TTR tetramer disaggregates into unstable monomers and other TTR protein fragments that are prone to misfolding and structural reorganisation into amyloid fibrils in various tissues (8, 23).

The potential clinical manifestations of ATTR are highly varied, as TTR-protein is carried in circulation and may deposit as amyloid throughout the body (8, 17, 19, 20, 24). As such, affected patients may experience a range of manifestations depending on where amyloid deposits form in the body (8, 17, 19, 24), with manifestations being predominantly limited

to a single organ or tissue type, or being multisystemic in nature (8, 17, 19, 20, 24). The two predominant clinical manifestations associated with ATTR are cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) (8).

In ATTR-CM, TTR-derived amyloid fibrils occupy the interstitial space in the myocardium, making this myocardial tissue thicker and more rigid and therefore preventing normal physiological functioning (22, 25), as illustrated by Figure 1 In addition to the physical disruption to the myocardium caused by amyloid deposition, *in vitro* studies have shown that unstable TTR-monomers and short oligomers also damage cardiac cells via interactions with membrane proteins, triggering apoptotic mechanisms via activation of caspase 3/7 and the generation of superoxide species (25, 26). Collectively these processes, driven by misfolded TTR-protein, result in progressive cardiomyopathy with multiple associated signs and symptoms.

Figure 1 Pathophysiology of ATTR-CM



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; TTR, transthyretin.
*Oligomers smaller than 100 kDa contribute to cytotoxic effects. Source: Griffin et al, 2021 (25)

Aside from causing rapidly progressive cardiomyopathy, cardiac TTR amyloid deposition may also disrupt electrical signalling (cardiac conduction) 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 (27-29).

3.1.3 Types of ATTR-CM

The pathogenic process of TTR amyloid depositions may be nonhereditary ("wild type", wtATTR) or hereditary (variant, hATTR) in origin (12, 30) With regard to aetiology, ATTR-CM is more commonly of wild-type origin than of hereditary origin (31). In Denmark, 38 hATTR-CM patients and 400-500 wtATTR-CM patients were estimated in the tafamidis and acoramidis submissions (32, 33).

In the case of wtATTR, the disease process is associated with aging; in particular, TTR tetramer instability results from age-associated changes in cellular functions, including protein oxidative modification and protein repair (25, 31, 34). Cardiomyopathy, caused by deposition of TTR amyloid in the heart, is the central clinical manifestation of wtATTR (wtATTR-CM) (31).

In hATTR, the pathological deposition of TTR-derived amyloid occurs due to mutations in the TTR gene. In particular, specific mutations in the TTR gene promote instability of TTR tetramers, making the tetramers more prone to dissociation into unstable monomers and other TTR protein fragments that can accumulate as amyloid deposits in body tissues (25). Over 150 reported TTR genetic variants are associated with hATTR (15). The central clinical manifestations of hATTR include polyneuropathy (hATTR-PN) and cardiomyopathy (hATTR-CM) (8).

3.1.4 Staging and disease severity

Due to the progressive and ultimately fatal nature of ATTR-CM, assessment of disease severity at the time of diagnosis, and subsequent monitoring of disease progression are critical.

Initial staging provides insight into the extent of disease progression that has already occurred by the time of diagnosis, and thus allows understanding of patients' prognostic outlook, as well as the degree of morbidity present, and will guide disease management. Because ATTR-CM causes progressive, irreversible morbidity, the identification of treatment opportunities is especially important, allowing clinicians to take rapid action to attempt to slow or halt disease progression in a timely manner and thus minimise any accumulation of irreversible morbidity, so that patients are maintained in the best clinical and functional state possible.

A panel of experts with experience in treating ATTR-CM developed consensus recommendations for monitoring the initial severity and ongoing progression ATTR-CM (35), highlighting that patients should be assessed along three dimensions, on the basis of 1) clinical and functional measures; 2) measures involving laboratory biomarkers of cardiac morbidity; and 3) measures involving imaging and ECG-based indicators of cardiac morbidity.

New York Heart Association (NYHA) class is a mainstay in the initial assessment and ongoing monitoring of patients with ATTR-CM. In addition, there is a body of emerging research demonstrating the specific value of longitudinal changes in certain other measures—namely, loop diuretic dose and serum N-terminal pro-B-type natriuretic peptide (NT-proBNP)(36-39).

3.1.5 New York Heart Association classification of heart failure

The NYHA functional classification has been a commonly used classification system for heart failure in general (40) and has also been used for staging the condition of patients with ATTR-CM, as it is predictive of both health-related quality of life (HRQoL) and mortality. The NYHA classes assess the patients' functional status based on the level of physical activity that gives rise to heart failure symptoms.

3.2 Patient population

ATTR-CM is a rare disease (8, 22). Globally, the estimated number of affected patients is 240,000–340,000, including 40,000 patients with hATTR-CM (8) and 200,000–300,000 patients with wtATTR-CM. In Denmark, incidence has been estimated at approximately 100 new patients yearly and prevalence at 550 patients (33). Almost all patients in Denmark are NYHA I-III, with less than 1% being categorized as NYHA IV (33).

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	100	100	100	100	100
Prevalence in Denmark	550	550	550	550	550
Global prevalence *	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence.

Abbreviations: N/A, not applicable.

The Danish Medicines Council (DMC) estimated that based on the initiation criteria that DMC has set in the treatment guidelines, 60-80% of patients are eligible for treatment with acoramidis, so the mid-point of this assumption is assumed for vutrisiran (33).

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	70	70	70	70	70

3.3 Current treatment options

The Danish framework presents a clear clinical pathway: early non-invasive diagnosis, conventional symptom relief and timely initiation of disease-modifying therapies (41).

Patients with ATTR-CM are currently recommended TTR stabilizers, such as tafamidis, which has been shown to improve survival and is recommended by the DMC according to a set criterion (i.e., NYHA class I-III) (41). In addition to this, Danish treatment guidelines recommend management of resultant heart failure tailored to the restrictive physiology of ATTR-CM, including diuretics and lifestyle measures, while avoiding digitalis and calcium-channel blockers that may bind amyloid (41).

3.3.1 Limitations associated with TTR stabilizers

Acoramidis and tafamidis are TTR stabilizers, acting downstream of liver-mediated TTR production in the ATTR-CM disease pathway. Several efficacy limitations associated with TTR stabilizers have been identified in their respective pivotal phase 3 trials in patients with ATTR-CM (4, 42). For instance, despite the benefits of TTR stabilizers relative to placebo, patients receiving these therapies may continue to experience worsening in physical capacity, HRQoL, and cardiac injury relative to their own pre-treatment baseline. They also continue to experience substantial rates of mortality and, in the case of acoramidis, showed no statistically significant mortality benefit versus placebo. In addition, TTR stabilizers appear to provide only limited benefit compared to placebo in certain patient types (4, 42).

Of relevance, neither TTR stabilizer therapy has demonstrated a mortality benefit in a contemporary ATTR-CM population (i.e., current real-world patients who more often are diagnosed earlier in the disease course and have access to improved supportive care) (43) (44). As ATTR-ACT took place between 2013–2018, the trial population from ATTR-ACT therefore no longer represents the contemporary ATTR-CM population, which questions whether the observed magnitude of the mortality benefit versus placebo would be reflected in current real-world practice (4). Acoramidis, on the other hand, was studied in a contemporary ATTR-CM population in the ATTRibute-CM pivotal trial (2019–2023) but did not show a statistically significant survival benefit versus placebo (secondary endpoint analysis of all-cause mortality [ACM]) in this population (42).

The efficacy limitations associated with TTR stabilizers in ATTR-CM have been recognized by independent regulatory authorities (such as the EMA (45)) and non-profit research institutes (such as the Institute for Clinical and Economic Review [ICER]) (46).

Furthermore, patients with ATTR-CM who are treated with tafamidis in real-world clinical practice continue to experience clinically evident cardiac worsening (reflected by cardiovascular events, cardiovascular hospitalizations, mortality, and increased rates of diuretic initiation) in addition to showing biochemical evidence of disease progression (reflected by increased NT-proBNP levels and decreased estimated glomerular filtration rate [eGFR]) (44). A separate analysis of real-world tafamidis use in US patients with ATTR-CM also showed a substantial 30% mortality rate 30 months after initiating treatment (43).

3.4 The intervention

Amvuttra®, an RNAi therapeutic that is administered subcutaneously every three months, 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) (47).

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 (13).

The rapid and sustained knockdown of serum TTR by vutrisiran is anticipated to lead to disease modification, resulting in reduced morbidity and mortality, thus addressing the limitations of the current Danish standard of care for ATTR-CM, i.e., tafamidis 61 mg (5).

As described in Section 6, in HELIOS-B, 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 a significant reduction in the composite risk of mortality and recurrent cardiovascular events, and in mortality risk separately (5). Further, over 30 months of treatment, patients treated with vutrisiran maintained their baseline levels of HRQoL and physical capacity (via analyses of observed values), in addition to preserving their baseline cardiac well-being, with consistent efficacy versus placebo across all predefined subgroups.

Overview of intervention	
Indication relevant for the assessment	Wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM), in line with EMA indication.
ATMP	N/A
Method of administration	Subcutaneous injection
Dosing	The recommended dose of vutrisiran is 25 mg once every 3 months.
Dosing in the health economic model (including relative dose intensity)	In the cost-minimization analysis, the recommended dose of 25 mg once every 3 months was used.

Overview of intervention	
Should the medicine be administered with other medicines?	Vitamin A supplementation is advised.
Treatment duration / criteria for end of treatment	Continuous treatment
Necessary monitoring, both during administration and during the treatment period	NA.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Treatment is to be used in patients with NYHA stage I – III. The NYHA functional class is a tool currently applied in Danish clinical practice (41).
Package size(s)	25 mg/0.5 mL - 1 pre-filled syringe

Abbreviations: NYHA, New York Heart Association; mg, milligram.

3.4.1 Description of ATMP

Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

Vutrisiran is expected to be used as a first-line new standard-of-care treatment option for ATTR-CM patients in Danish clinical practice.

3.5 Choice of comparator(s)

Overview of comparator	
Generic name	Tafamidis 61mg
ATC code	N07XX08
Mechanism of action	Tafamidis is a selective stabilizer of TTR. Tafamidis binds to the two thyroxine binding sites on the native tetrameric form of TTR, stabilizing the tetramer and preventing dissociation into monomers, the rate-limiting step in the amyloidogenic process. The inhibition of TTR tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression in patients with TTR amyloid cardiomyopathy.
Method of administration	Oral administration
Dosing	61 mg taken orally once daily.

Overview of comparator	
Dosing in the health economic model (including relative dose intensity)	In the cost-minimization analysis, the recommended daily dose of 61 mg orally was used.
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Continuous treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	Treatment is to be used in patients with NYHA stage I – III. The NYHA functional class is a tool currently applied in Danish clinical practice (41).
Package size(s)	30 x 1 soft capsules – each capsule contains 61 mg of micronized tafamidis

Abbreviations: NYHA, New York Heart Association; mg, milligram.

3.6 Cost-effectiveness of the comparator(s)

Tafamidis has been previously assessed by the DMC for both hereditary and wild-type ATTR-CM. DMC's recommendation for tafamidis was restricted to patients with NYHA class I-III or NAC stage I or II (48).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The clinical value of vutrisiran in ATTR-CM is supported by results from the HELIOS-B trial, a phase 3, randomized, double-blind, placebo-controlled, multicenter study. In HELIOS-B, participants were randomized 1:1 to receive 25 mg of vutrisiran or placebo every 3 months via subcutaneous injection, with double-blind follow-up for up to 36 months from baseline.

The overall population in HELIOS-B (N=654) included patients receiving background tafamidis at baseline and those not receiving background tafamidis at baseline. In addition to the overall population, a separate monotherapy population was defined comprising patients in the overall population who were not receiving tafamidis at baseline (N=395).

The pre-specified clinical outcomes of HELIOS-B are presented in this section, of which the results are presented in section 6.

The primary endpoints of HELIOS-B were:

1) A composite endpoint of ACM and recurrent cardiovascular events (comprising cardiovascular hospitalisations and urgent heart failure visits) observed among all patients (overall population [with and without background tafamidis use at baseline]) observed over up to 36 months during the double-blind period.
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) (49, 50). For analysis of this endpoint, heart transplantation and/or receipt of a ventricular assist device were categorised as deaths (49).

Secondary endpoints included change from baseline in functional exercise capacity as measured by 6- MWT distance over 30 months, change from baseline in HRQoL as measured by Kansas City Cardiomyopathy Questionnaire – Overall Summary (KCCQ-OS) over 30 months, ACM up to 42 months (including up to the first 6 months of open-label extension data following the double-blind period), and change from baseline in heart failure severity as measured by NYHA class changes at 30 months (49).

Each of these secondary endpoints was assessed among all patients (overall population), and among patients not on tafamidis at baseline (monotherapy population) (49). In addition to the secondary endpoints, quality of life was also assessed using the EQ-5D-5L instrument.

Findings from the HELIOS-B trial indicate that vutrisiran is an efficacious therapy for patients with ATTR-CM. Vutrisiran treatment led to statistically and clinically significant benefits versus placebo for all primary and secondary endpoints in the overall population and in the monotherapy population (Table 3).

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Composite of ACM and recurrent CV events*	Up to 36 months	Composite outcome of ACM and recurrent cardiovascular events assessed up to Month 36	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).
Change in 6MWT†	30 months	Change from baseline to Month 30 in 6-MWT distance.	Mixed effects model with repeated measures (MMRM) which included baseline 6-MWT distance as a covariate and treatment (vutrisiran vs. placebo), visit, treatment-by-visit interaction, ATTR disease

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			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.
Change in KCCQ-OS score‡	30 months	Change from baseline to Month 30 in KCCQ-OS score.	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.
ACM (stand-alone)§	Up to 42 months	Stand-alone ACM assessed up to Month 42.	• 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 logarithmic transformation) as covariates used to estimate the overall HR and 95% CI.
Change in NYHA class¶	30 months	Percentage of patients with stable/improved NYHA class from baseline to Month 30.	• CMH method applied, with stratification by baseline NT-proBNP (continuous variable with logarithmic transformation) and

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			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.

Abbreviations: 6MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Score; LS, least square; NYHA, New York Heart Association.

Notes: *No imputation was performed for early dropouts. Deaths collected after study discontinuation were not included in the composite analysis. †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]. §All deaths collected were included in the analysis, including deaths after treatment and study discontinuation. ¶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.

Validity of outcomes

The primary efficacy endpoint in the HELIOS-B trial, a composite of ACM and recurrent CV events (CV hospitalizations and urgent heart failure visits), is both clinically meaningful and aligned with treatment goals for patients with ATTR-CM (51). [redacted]. This endpoint reflects the high morbidity and mortality associated with the disease and allows for a comprehensive evaluation of the therapeutic benefit across both survival and disease burden. The use of recurrent events, rather than time-to-first event alone, offers a more sensitive and relevant measure in this chronic, progressive condition, particularly for older patients frequently hospitalized due to worsening heart failure.

In HELIOS-B, functional capacity and quality of life (QoL) were assessed using the 6MWT, the KCCQ-OS, and changes in NYHA functional class. These endpoints are consistent with those recognized as meaningful by clinical experts in ATTR-CM and heart failure management more broadly. The 6MWT is an objective and reproducible measure that

reflects submaximal exercise capacity and has been shown to detect changes in disease severity, treatment effect, and progression in ATTR-CM populations. KCCQ-OS is a disease-specific QoL instrument validated in heart failure and previously used in ATTR-CM trials such as ATTR-ACT. It captures patient-reported outcomes across key domains including physical limitation, symptom burden, and social function. While inherently subjective, the KCCQ is sensitive to meaningful changes over time and can be used alongside clinical markers to help confirm stabilization or deterioration of disease (52). When considered together, the 6MWT, KCCQ-OS, and NYHA class provide a complementary, clinically relevant view of patient function and quality of life, supporting their inclusion as valid endpoints in the assessment of vutrisiran for ATTR-CM.

DMC has previously accepted similar efficacy endpoints for the treatment of the same patient population in its assessment of tafamidis (1, 32).

To estimate the efficacy of vutrisiran versus tafamidis, a post hoc analysis of two treatment arms within HELIOS-B was conducted, where the vutrisiran arm was represented by the vutrisiran monotherapy (patients initiating with vutrisiran treatment and not on background tafamidis treatment at baseline) and the tafamidis arm was represented by the patients within the placebo arm who were treated with tafamidis at baseline (5). This comparison showed a numerical efficacy benefit favouring vutrisiran over tafamidis, demonstrating that vutrisiran has at the least equivalent if not better clinical benefit relative to tafamidis in the treatment of ATTR-CM. These analyses are discussed fully in section 6.

4. Health economic analysis

The within-trial comparison showed vutrisiran is at least as efficacious as tafamidis is in the treatment of ATTR-CM (see section 6.1). A cost-minimization analysis (CMA) is therefore considered appropriate to evaluate the economic value of vutrisiran versus tafamidis, accounting for costs related to drug acquisition, drug administration, treatment of adverse events, and patient time and travel for treatment associated with vutrisiran and tafamidis.

4.1 Model structure

The CMA considers a time horizon of 2 years, to capture the costs of the different treatment regimens in the first and second year of treatment with vutrisiran or tafamidis. The different safety profiles are included by costing adverse events in the first year, based on the incidence observed in HELIOS-B.

4.2 Model features

In Table 4 below, the features of the economic analysis are presented.

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) NYHA stage I – III with symptoms or a history of symptomatic disease	In line with recommendations of tafamidis
Perspective	NA	Not applicable in CMA setting.
Time horizon	Two years	This is an adequate time horizon to capture the costs associated with the two different treatment regimens in years one and two of treatment.
Cycle length	One year	Annual treatment costs are estimated.
Half-cycle correction	No	-
Discount rate	3.5%	The DMC applies a discount rate of 3.5% for all years
Intervention	Vutrisiran	-
Comparator(s)	Tafamidis	In alignment with the national treatment guideline and validated by Danish clinical experts (53, 54).
Outcomes	Treatment costs Administration costs Adverse events costs Patient time and travel costs	-

5. Overview of literature

5.1 Literature used for the clinical assessment

The application is based on results from HELIOS-B including a within-trial monotherapy comparison between vutrisiran and tafamidis. Tafamidis represents the current standard-of-care treatment in the Danish clinical practice.

No additional literature search was conducted.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Fontana M, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025 Jan 2;392(1):33-44. doi: 10.1056/NEJMoa2409134. Epub 2024 Aug 30. PMID: 39213194. (5)	HELIOS-B	NCT04153149	Study start date: 2019-11-26 Primary completion: 2024-05-08 Data cut-off: 8th of May 2024	Vutrisiran vs. placebo
Data on file. Post hoc within-trial analysis of vutrisiran vs. tafamidis in HELIOS-B.(55)	HELIOS-B	NCT04153149	Study start date: 2019-11-26 Primary completion: 2024-05-08 Data cut-off: 8th of May 2024	Vutrisiran monotherapy vs. tafamidis monotherapy

5.2 Literature used for the assessment of health-related quality of life

Not applicable in the context of cost-comparison. HRQoL results from HELIOS-B are described in section 10.

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
NA	NA	NA

5.3 Literature used for inputs for the health economic model

Not applicable in the context of cost comparison. Drug acquisition, administration, and patient time and travel costs were included as per Danish costing manual.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NA	NA	NA	NA

6. Efficacy

6.1 Efficacy of vutrisiran compared to tafamidis for adults with ATTR-CM

6.1.1 Relevant studies

The efficacy of vutrisiran was measured in HELIOS-B, of which a description of design and trial outcomes is described in Section 3.7.1). Additionally, the within-trial analysis of vutrisiran monotherapy versus tafamidis monotherapy compared the clinical outcomes between the treatments relevant to the Danish context.

Data presented in this submission is from the data cut-off on the 8th of May 2024.

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
HELIOS-B (NCT04153149) (7)	Randomized, double blinded, placebo controlled, phase III study of vutrisiran versus placebo.	Double-blind follow-up was up to 36 months.	Adult patients with wtATTR-CM or hATTR-CM. All sexes eligible.	Amvuttra® (vutrisiran): 25 mg subcutaneously every 12 weeks.	Placebo	The primary end point was a composite of death from any cause and recurrent cardiovascular events (defined as hospitalisations for cardiovascular causes or urgent visits for heart failure) during the double-blind period (up to 36 months), assessed in the overall population and monotherapy population. Secondary endpoints were assessed in the overall population and monotherapy population, namely: death from any cause through 42 months (including up to 6 months of OLE treatment), and change from baseline to 30 months in: • Functional capacity, as assessed with 6-MWT • HRQoL, as assessed via KCCQ-OS score • Severity of clinical heart failure symptoms, as determined by NYHA class

Abbreviations: 6MWT, 6 minites walking test; HRQoL, Health-related qualify of life; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; mg, milligram; NCT, National Clinical Trial; NYHA, New York Heart Association; wt/hATTR, wild-type/hereditary transthyretin amyloidosis cardiomyopathy.

6.1.2 Comparability of studies

Not applicable as only one study is included.

6.1.2.1 Comparability of patients across studies

The baseline characteristics of total study population are presented in Table 9. The baseline characteristics of the vutrisiran monotherapy vs. tafamidis monotherapy analysis included in Section 7.1.2.1 in Table 12.

Table 9 Baseline characteristics of patients in HELIOS-B in the overall population

	HELIOS-B	
	Vutrisiran (n=326)	Placebo (n=328)
Age at randomisation, median, years (range)	77.0 (45.0–85.0)	76.0 (46.0–85.0)
Male, n (%)	299 (91.7)	306 (93.3)
Race		
White	277 (85.0)	275 (83.8)
Asian	18 (5.5)	19 (5.8)
Black/African American	23 (7.1)	24 (7.3)
Other/not reported	8 (2.5)	10 (3.0)
Disease type		
hATTR, n (%)	37 (11.3)	39 (11.9)
V122I, n (%)	24 (7.4)	25 (7.6)
wtATTR, n (%)	289 (88.7)	289 (88.1)
Time since diagnosis, median, years (range)	0.9 (0–11.1)	1.0 (0–10.8)
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, n (%)		
I	49 (15.0)	35 (10.7)
II	250 (76.7)	258 (78.7)
III	27 (8.3)	35 (10.7)

	HELIOS-B	
	Vutrisiran (n=326)	**Placebo (n=328)**
NAC stage, n (%)		
1	208 (63.8)	229 (69.8)
2	100 (30.7)	87 (26.5)
3	18 (5.5)	12 (3.7)
6MWT, mean, meters (SD)*	372.0 (103.7)	377.1 (96.3)
KCCQ-OS score, mean, points (SD)*	73.0 (19.4)	72.3 (19.9)
NT-proBNP, median, ng/L (IQR)	2,021 (1,138, 3,312)	1,801 (1,042, 3,082)
Troponin I, median, ng/L (IQR)	71.9 (44.9, 115.9)	65.2 (41.0, 105.5)
eGFR, median, mL/min/1.73m^2 (IQR)	64 (50, 81)	65 (53, 81)
Coexisting conditions, n (%)		
Hypertension	185 (57)	187 (57)
Diabetes mellitus**	56 (17)	55 (17)
Atrial fibrillation	197 (60)	196 (60)

Abbreviations: 6MWT, 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. *Baseline 6MWT 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 (5) **Includes categories diabetes mellitus, steroid diabetes and type 2 diabetes mellitus.

Source: Fontana 2024, article and supplementary materials (5).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In order to validate the patient characteristics from the HELIOS-B trial with the Danish population, two ATTR-CM treating clinicians were interviewed (53, 54). Additionally, the findings were cross-checked with the recent DMC assessment of acoramidis (33).

Both experts agreed that the trial population of HELIOS-B reflects the Danish population better than the ATTR-ACT trial. The HELIOS-B population reflective of the Danish ATTR-CM was found to be in less severe NYHA class resulting from earlier diagnosis and management of the disease (53, 54). Baseline characteristics from the HELIOS-B trial were assumed to represent the expected Danish population as confirmed by the two interviewed clinicians (53, 54).

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (33, 53, 54)	Value used in health economic model
Age	75 to 77 years	NA
Male (%)	90%	NA
NYHA class, n (%)		NA
I	~10%	
II	~80%	
III	~10%	
NT-proBNP, ng/L (IQR)	~2,000	NA
6MWT, mean, meters	~370 meter	NA
KCCQ-OS score, points	~70	NA

Abbreviations: 6MWT, 6 minutes walking test; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; ng/L, nanograms per liter; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Neither tafamidis nor vutrisiran have weight-dependent dosing. The time horizon of two years also does not require any mortality adjustments. Considering these aspects, there are no patient characteristics incorporated in the model, since none of the baseline patient characteristics lend themselves to be time- or treatment-dependent.

6.1.4 Efficacy – results per HELIOS-B (primary analysis)

Findings from the HELIOS-B trial indicate that vutrisiran is an efficacious therapy for patients with ATTR-CM. Vutrisiran treatment led to statistically and clinically significant benefits versus placebo for all primary and secondary endpoints in the overall population and in the monotherapy population, including a significant reduction in mortality risk, and in the composite risk of mortality and recurrent cardiovascular events. Further, over 30 months of treatment, patients treated with vutrisiran maintained their baseline levels of

HRQoL and physical capacity (via analyses of observed values), in addition to preserving their baseline cardiac well-being, with consistent efficacy versus placebo across all predefined subgroups. Results of HELIOS-B and monotherapy populations (vutrisiran only, and placebo only) are presented in Table 11 (5).

Table 11 Results from HELIOS-B

Measure	Overall population (N=654)		Monotherapy population (N=395)	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran monotherapy (n=196)	Placebo monotherapy (no tafamidis) (n=199)
Primary endpoint: composite of ACM and recurrent CV events over 36 months*				
Patients with at least one event, n (%)	125 (38.3)	159 (48.5)	76 (38.8)	105 (52.8)
HR (vutrisiran vs. 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 6MWT over 30 months†				
LS mean change over 30 months, meters (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), meters (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 up to 42 months§				
Deaths, n (%)	60 (18.4)	85 (25.9)	43 (21.9)	58 (29.1)
HR (vutrisiran vs. placebo) (95% CI)	0.65 (0.46, 0.90) p=0.01		0.66 (0.44, 0.97) p=0.045	

Measure	Overall population (N=654)		Monotherapy population (N=395)	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran monotherapy (n=196)	Placebo monotherapy (no tafamidis) (n=199)
Secondary endpoint: change in NYHA class at 30 months¶				
Stable/improved over 30 months, %	67.8	60.5	66.3	56.4
Adjusted difference in % stable/improved (vutrisiran – placebo), % (95% CI)	8.7 (1.3, 16.1) p=0.02		12.5 (2.7, 22.2) p=0.01	

Abbreviations: 6MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Score; LS, least square; NYHA, New York Heart Association.

Notes: *No imputation was performed for early dropouts. Deaths collected after study discontinuation were not included in the composite analysis. †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]. §All deaths collected were included in the analysis, including deaths after treatment and study discontinuation. ¶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.

In the primary endpoint analysis of HELIOS-B, vutrisiran treatment led to 28% and 33% reductions in the composite risk of ACM and cardiovascular (CV) events in the overall and monotherapy populations, respectively, during double-blind follow-up. Considering ACM on its own up to Month 42 (secondary endpoint analysis), vutrisiran treatment also led to substantial reductions in mortality risk in the overall and monotherapy populations, by 35% and 34%, respectively. Notably, the efficacy observed on these key measures, which capture the risk of death and severe morbidity in ATTR-CM, was consistent across all prespecified subgroups, including age, baseline tafamidis use, ATTR disease type, NYHA class, and baseline NT-proBNP (5).

In addition to the benefits demonstrated on the primary composite endpoint and on the secondary endpoint of ACM, vutrisiran also demonstrated statistically significant and clinically meaningful benefits over placebo in terms of physical capacity (via 6-MWT), HRQoL (via KCCQ-OS score), and heart failure severity (via NYHA class) over 30 months in HELIOS-B. Analyses of observed 6-MWT and KCCQ-OS score values without imputation of missing data demonstrated preservation of baseline physical capacity and HRQoL in vutrisiran-treated patients over 30 months, which is a clinically relevant outcome considering the substantial declines that occur in these domains in untreated patients with ATTR-CM. Consistent with this pattern of preserved physical capacity and quality of life,

the percentage of patients who showed stabilisation or improvement in NYHA class was significantly higher in the vutrisiran group compared to the placebo group. Similarly, an exploratory endpoint analysis in HELIOS-B showed that patient outcomes in terms of cardiac injury (as measured by NT-proBNP) were significantly improved with vutrisiran relative to placebo over 30 months, with vutrisiran-treated patients exhibiting relative stabilisation of NT-proBNP levels in comparison to their own pre-treatment baseline (5).

In the prespecified secondary endpoint analysis of ACM in HELIOS-B, survival was assessed over a period of up to 42 months (including a maximum of 6 months of treatment in the OLE). Therefore, depending on patients' time of enrolment in HELIOS-B, vital status data were collected over a period of 33–42 months from baseline. An updated analysis of ACM from baseline to 42 months (including 6 months of OLE treatment for all eligible patients) demonstrated consistent findings with results from the prespecified secondary endpoint analysis, with vutrisiran treatment reducing mortality risk by 36% in the overall population (HR: 0.64 [95% CI: 0.46, 0.88]; p=0.007) and 39% in the monotherapy population (HR: 0.61 [95% CI: 0.42, 0.90]; p=0.16) (56).

6.1.5 Efficacy – results per HELIOS-B – monotherapy vutrisiran and tafamidis subgroups

In a post hoc analysis of HELIOS-B (55), vutrisiran monotherapy (i.e., patients in the vutrisiran arm within the monotherapy population; n=196) was compared to tafamidis monotherapy (i.e., patients in the placebo arm who were on background tafamidis at baseline; n=129). This is reported in the next section.

7. Comparative analyses of efficacy

As described in Section 3.5, in the Danish setting tafamidis 61 mg is the most suitable comparator, which is the recommended treatment for ATTR-CM in the clinical guidelines, alongside the clinically equivalent acoramidis.

Therefore, a post hoc analysis of HELIOS-B monotherapy populations was performed, which compared patients who were randomised to receive vutrisiran and had no tafamidis background therapy (i.e., patients receiving vutrisiran monotherapy), and patients who were randomised to placebo but had tafamidis background treatment at baseline (i.e., patients receiving tafamidis monotherapy). Results showed consistent trends toward improved survival and fewer recurrent cardiovascular events among individuals receiving vutrisiran compared to tafamidis.

This analysis presents a conservative estimate of the relative efficacy of vutrisiran and tafamidis, considering the timing of therapy initiation between these two groups in HELIOS-B, which likely biased against vutrisiran. 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. 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 outcomes favouring the tafamidis monotherapy arm due to the duration of time needed (as observed in trials of multiple ATTR-CM therapies) for survival benefit to emerge after ATTR-CM treatment initiation, for which tafamidis-treated patients in HELIOS-B had an approximate 1-year lead time over vutrisiran-treated patients due to pre-baseline exposure to tafamidis. Due to these biases, clinical outcomes from the analysis are likely to be biased in favour of tafamidis, resulting in conservative estimates of relative efficacy for vutrisiran.

Despite not being a prespecified analysis, the post hoc within-trial comparison was considered by the sponsor to be the best available data to compare vutrisiran monotherapy to tafamidis monotherapy in a contemporary ATTR-CM population. The feasibility of an indirect treatment comparison (ITC) of vutrisiran monotherapy from HELIOS-B and tafamidis monotherapy from ATTR-ACT was also explored, despite these populations representing contemporary and non-contemporary populations, respectively. However, as expected, it was not feasible to conduct an unbiased ITC using data from these trials, due to differences in trial endpoints and baseline characteristics, as well as differences in clinical practice (i.e., background supportive heart failure therapy use) between the time periods in which HELIOS-B and ATTR-ACT were conducted. This was contextualised by Girard et al. (57) which noted that ACM in the contemporary population of vutrisiran-treated patients in HELIOS-B approached that of the healthy age-matched general population suggesting that vutrisiran largely eliminates the burden of excess mortality in ATTR-CM.

In addition to the post hoc within-trial analysis from HELIOS-B, the benefits of vutrisiran are further supported by the EMA maintenance of Orphan Drug Designation (ODD) for vutrisiran (58).

Therefore, based on findings from the HELIOS-B post hoc analysis, vutrisiran has demonstrated evidence of providing a relative efficacy benefit compared to tafamidis 61 mg. Therefore, it can be conservatively assumed that vutrisiran and tafamidis 61 mg have at least comparable efficacy in patients with ATTR-CM, which would support the feasibility of a cost-comparison analysis.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis in the within trial analysis

7.1.2.1 Weighting of monotherapy populations

Unlike the pre-specified comparisons across the randomized vutrisiran and placebo arms of HELIOS-B, the vutrisiran and tafamidis monotherapy groups did not constitute a

randomized comparison within HELIOS-B. As such, these analyses need to be appropriately statistically adjusted and interpreted. Adjustment for baseline differences between the vutrisiran and tafamidis monotherapy groups was done using the stabilized inverse probability of treatment weighting (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.

[redacted]

Selection of the final adjustment factors prioritized 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, standardized 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 and <25% for other baseline parameters is considered to indicate good balance between the groups (59-61).

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 stabilized IPTW weights as described above. As such, in order to allow the use of all available data, there was no matching procedure implemented.

[redacted]

Weighted baseline characteristics are presented in Table 12.

7.1.2.2 Analysis of outcomes

For the primary composite endpoint of ACM and recurrent CV events, a hazard ratio was estimated using the weighted Andersen-Gill model.

For ACM up to 42 months from HELIOS-B baseline, a weighted Cox regression model was used to estimate the hazard ratio between treatment groups.

For NYHA class change from baseline (categorized as stable or improved vs. worsened relative to baseline), a weighted Cochran-Mantel-Haenszel test was used and the difference in proportion with stable or improved NYHA class between treatment groups was reported.

For the primary outcome, weighted regression models had an indicator for the vutrisiran monotherapy vs. prevalent tafamidis monotherapy groups as an independent variable and were adjusted for baseline differences between group. To account for uncertainty in the estimation of the weights based on the data, SEs and 95% CIs based on robust variance estimators were used.

The baseline characteristics of the weighted monotherapy populations on vutrisiran-only or tafamidis-only at baseline are presented in Table 12. The standardized differences are displayed, demonstrating the weighting was effective.

The within-trial comparison of vutrisiran monotherapy versus tafamidis monotherapy showed a trend for an efficacy benefit for vutrisiran monotherapy versus tafamidis, which suggests that vutrisiran has at least equivalent clinical efficacy to tafamidis in ATTR-CM.

The post hoc analysis (adjusted to balance the two groups being compared) demonstrated 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: 0.83 [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; HR: 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: 0.49, 1.34]) 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).

A summary of the weighted results in the monotherapy populations is presented in Table 12.

Table 12 Baseline characteristics of weighted monotherapy populations of HELIOS-B

	Weighted		
	Vutrisiran (n=196)	On tafamidis – receiving placebo (n=129)	Standardized difference (%)
Age*, n (%)			
<75	[redacted]	[redacted]	[redacted]
>=75	[redacted]		
Male, n (%)	[redacted]	[redacted]	[redacted]
Race			
White	[redacted]	[redacted]	[redacted]
Black/African American			
Other/not reported			
Disease type			
hATTR, n (%)	[redacted]	[redacted]	[redacted]
V122I, n (%)			
wtATTR, n (%)			
Time since diagnosis, median, years (range)	[redacted]	[redacted]	[redacted]
Tafamidis baseline use, n (%)	[redacted]	[redacted]	[redacted]
Time on tafamidis prior to start of study, median, months (range)	[redacted]	[redacted]	[redacted]
NYHA class, n (%)			
I	[redacted]	[redacted]	[redacted]
II			
III			
NAC stage, n (%)			
1	[redacted]	[redacted]	[redacted]
2			
3			
6MWT, mean, meters (SD)*	[redacted]	[redacted]	[redacted]

Weighted			
	Vutrisiran (n=196)	On tafamidis – receiving placebo (n=129)	Standardized difference (%)
KCCQ-OS score, mean, points (SD)*	[redacted]	[redacted]	[redacted]
NT-proBNP, median, ng/L (IQR)	[redacted]	[redacted]	[redacted]
eGFR, median, mL/min/1.73m^2 (IQR)	[redacted]	[redacted]	[redacted]
Coexisting conditions, n (%) Hypertension Diabetes mellitus** Atrial fibrillation	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 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. *Baseline 6MWT 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 (5) **Includes categories diabetes mellitus, steroid diabetes and type 2 diabetes mellitus.Source: Within-trial comparison (5).

Table 13 Results from the comparative analysis of vutrisiran vs. placebo/tafamidis for ATTR-CM patients

HELIOS-B (Primary analysis)			
Overall population			
Outcome measure	**Vutrisiran (N = 326)**	**Placebo (N = 328)**	**Result**
Composite of ACM and recurrent CV events over 36 months*, patients with at least one event, n (%)	125 (38.3)	159 (48.5)	HR: 0.72 (0.56, 0.93), p = 0.01
Recurrent CV events over up to 36 months, patients with at least one event, n (%)	112 (34)	133 (41)	Relative rate ratio: 0.73 (0.61, 0.88), p = 0.001
Change in 6MWT over 30 months†	–45.4 (–54.5, –36.3)	−71.9 (−81.3, −62.4)	LS Mean: 26.5 (13.4, 39.6), p < 0.001
Change in KCCQ-OS score over 30 months‡	-9.7 (-12.0, -7.4)	-15.5 (18.0 to 13.0)	LS Mean: 5.8 (2.4, 9.2), p < 0.001
ACM up to 42 months§, patients with at least one event, n (%)	60 (18.4)	85 (25.9)	HR: 0.65 (0.46, 0.90), p = 0.01
Stable or improved in NYHA class over 30 months¶, Adjusted % (95% CI)	67.8	60.5	Adjusted difference: 8.7 (1.3, 16.1), p = 0.022

Monotherapy population			
	Vutrisiran monotherapy (N = 196)	**Placebo monotherapy (no tafamidis (N = 199)**	**Result**
Composite of ACM and recurrent CV events over 36 months, patients with at least one event, n (%)	76 (38.8)	105 (52.8)	HR: 0.67 (0.49, 0.93), p = 0.02
Recurrent CV events over up to 36 months, patients with at least one event, n (%)	66 (34)	87 (44)	Relative rate ratio: 0.68 (0.53, 0.86), p = 0.001

Change in 6MWT over 30 months	−59.7 (−72.7, −46.7)	−91.8 (−104.4, −79.2)	LS Mean: 32.1 (14.0, 50.2), p < 0.001
Change in KCCQ-OS score over 30 months	−10.8 (−14.1, −7.5)	−19.5 (−22.9, −16.1)	LS Mean: 8.7 (4.0, 13.4), p < 0.001
ACM up to 42 months, patients with at least one event, n (%)	43 (21.9)	58 (29.1)	HR: 0.66 (0.44, 0.97), p = 0.0045
Stable or improved in NYHA class over 30 months Adjusted % (95% CI)	66.3	56.4	Adjusted difference: 12.5 (2.7, 22.2), p=0.012
HELIOS-B (Within trial post hoc analysis)			
Outcome measure	**Vutrisiran monotherapy (n=196)**	**Tafamidis monotherapy (n=129)**	**Results**
Composite of ACM and recurrent CV events over up to 36 months, patients with at least one event, n (%)	Only reported for ACM and CV events separately	Only reported for ACM and CV events separately	HR (95% CI): 0.83 (0.54, 1.29)
ACM over up to 42 months, patients with at least one event, n (%)	43 (21.9)	[redacted]	HR (95% CI): 0.81 (0.49, 1.34)
Recurrent CV events over up to 36 months, patients with at least one event, n (%)	66 (33.7)	[redacted]	Relative rate ratio (95% CI): 0.82 (0.62, 1.08)
Stable or improved in NYHA class over 30 months Adjust % (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: LS Mean, Least Squares Mean; SEM, Standard Error of the Mean; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; CI, Confidence Interval; NR, Not Reported; ITT, Intention to Treat; ACM, All-Cause Mortality; CV, Cardiovascular; HR, Hazard Ratio.

Notes: *No imputation was performed for early dropouts. Deaths collected after study discontinuation were not included in the composite analysis. †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]. §All deaths collected were included in the analysis, including deaths after treatment and study discontinuation. ¶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.

Note on within-trial analysis: 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.

7.1.3 Efficacy – results of composite analysis of recurrent CV events and ACM over up to 36 months

7.1.3.1 Vutrisiran vs. placebo (ITT)

In the primary analysis comparing vutrisiran with placebo, 125 patients (38%) receiving vutrisiran and 159 patients (48%) receiving placebo experienced death from any cause or recurrent CV events. Vutrisiran was associated with a 28% lower risk of ACM and/or cardiovascular events compared to placebo, indicated by a statistically significant hazard ratio (HR) of 0.72 (95% CI: 0.56–0.93).

7.1.3.2 Vutrisiran vs. placebo (monotherapy)

Among the monotherapy groups, 76 patients (39%) on vutrisiran alone and 105 patients (53%) on placebo alone experienced death from any cause or recurrent cardiovascular events. In this population, vutrisiran reduced the risk of ACM and/or cardiovascular events by 33% relative to placebo, as shown by a statistically significant HR of 0.67 (95% CI: 0.49–0.93).

7.1.3.3 Vutrisiran vs. tafamidis (monotherapy)

In the within-trial analysis, vutrisiran demonstrated a 17% reduction in risk compared to tafamidis, with an HR of 0.83 (95% CI: 0.54–1.29), though this finding was not statistically significant.

7.1.4 Efficacy – results of recurrent CV events over up to 36 months

7.1.4.1 Vutrisiran vs. placebo (ITT)

In the primary analysis comparing the vutrisiran and placebo groups, 112 patients (34%) receiving vutrisiran and 133 patients (41%) receiving placebo experienced at least one CV event. The incidence of CV events was reduced by 27% among patients treated with vutrisiran relative to placebo, as indicated by a statistically significant rate ratio of 0.73 (95% CI: 0.61–0.88).

7.1.4.2 Vutrisiran vs. placebo (monotherapy)

Among the monotherapy populations (vutrisiran-only and placebo-only), 66 patients (34%) on vutrisiran and 87 patients (44%) on placebo had at least one CV event. This corresponds to a 32% reduction in the rate of CV events for vutrisiran compared to placebo, supported by a statistically significant rate ratio of 0.68 (95% CI: 0.53–0.86).

7.1.4.3 Vutrisiran vs. tafamidis (monotherapy)

In the within-trial analysis, 66 patients (34%) receiving vutrisiran-only and [redacted] receiving tafamidis-only experienced at least one CV event. The rate of CV events was 18% lower in the vutrisiran group compared to tafamidis according to the point estimate, with a rate ratio of 0.82 (95% CI: 0.62–1.08).

7.1.5 Efficacy – results of ACM over up to 42 months

7.1.5.1 Vutrisiran vs. placebo (ITT)

In the primary analysis of the vutrisiran and placebo groups, 60 (18%) patients on vutrisiran and 85 (26%) on placebo died from any cause through 42 months of follow-up. The risk of death from any cause is 35% less for patients on vutrisiran compared to placebo, as demonstrated by a statistically significant HR of 0.65 (95% CI: 0.46-0.90).

7.1.5.2 Vutrisiran vs. placebo (monotherapy)

In the monotherapy populations (vutrisiran only and placebo only), 43 (22%) patients on vutrisiran-only and 58 (29%) patients on placebo-alone died from any cause through 42 months of follow-up. The risk of death from any cause is 34% less for patients on vutrisiran compared to placebo, as demonstrated by an HR of 0.66 (95% CI: 0.44-0.97).

7.1.5.3 Vutrisiran vs. tafamidis (monotherapy)

In the within-trial analysis, 43 (22%) patients on vutrisiran-only and [redacted] patients on tafamidis-only died from any cause through 42 months of follow-up. The risk of death from any cause is 19% less for patients on vutrisiran compared to tafamidis, according to the point estimate (HR of 0.81 [95% CI: 0.49-1.34]).

7.1.6 Efficacy – Results of the 6-MWT

7.1.6.1 Vutrisiran vs. placebo (ITT)

In the primary analysis comparing the vutrisiran and placebo groups, patients receiving vutrisiran demonstrated a 45.4-metre decrease in their 6MWT distance, whereas those on placebo experienced a 71.9-metre decrease. The LS mean difference was 26.5 metres (95% CI: 13.4–39.6), indicating a statistically significant benefit in favour of vutrisiran.

7.1.6.2 Vutrisiran vs. placebo (monotherapy)

Among monotherapy populations (vutrisiran only and placebo only), participants treated with vutrisiran exhibited a 59.7-metre decrease in 6MWT scores, compared to a 91.8-metre decrease observed in the placebo group. The LS mean difference was 32.1 metres (95% CI: 14.0–50.2), further supporting a statistically significant effect favouring vutrisiran.

7.1.7 Efficacy – KCCQ overall score

7.1.7.1 Vutrisiran vs. placebo (ITT)

In the primary analysis comparing vutrisiran and placebo, patients receiving vutrisiran had a change of --9.7 in KCCQ-OS, while those on placebo experienced a -15.5-change. The LS mean difference was 5.8 (95% CI: 2.4-9.2), indicating a statistically significant difference favoring vutrisiran.

7.1.7.2 Vutrisiran vs. placebo (monotherapy)

In the monotherapy groups (vutrisiran only and placebo only), patients in the vutrisiran group experienced a -10.8-change compared to a -19.5-change in the placebo group. The LS mean difference was 8.7 (95% CI: 4.0-13.4), demonstrating a statistically significant result for vutrisiran.

7.1.8 Efficacy – NYHA class

7.1.8.1 Vutrisiran vs. placebo (ITT)

In the primary analysis comparing vutrisiran with placebo, 68% of patients receiving vutrisiran and 61% on placebo achieved stable or improved NYHA class at 30 months. The adjusted between-group difference was 8.7% (95% CI: 1.3–16.1), indicating a statistically significant benefit in favour of vutrisiran.

7.1.8.2 Vutrisiran vs. placebo (monotherapy)

Among the monotherapy populations (vutrisiran-only versus placebo-only), 66% of patients on vutrisiran and 56% on placebo experienced a stable or improved NYHA class at 30 months. Here, the adjusted difference was 12.5% (95% CI: 2.7–22.2), again favouring vutrisiran with statistical significance.

7.1.8.3 Vutrisiran vs. tafamidis (monotherapy)

[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Not applicable.

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 14 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.2 Calculation of transition probabilities

Not applicable.

Table 15 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Not applicable.

Table 16 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
N/A	N/A	N/A	N/A

9. Safety

9.1 Safety data from the clinical documentation

Vutrisiran had an acceptable safety profile in HELIOS-B. 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 (5).

Table 18 Overview of safety events – primary analysis, all patients at least 33 months follow-up

	Vutrisiran (N=326)	Placebo (N=328)	Vutrisiran monotherapy (N=196)	Tafamidis monotherapy (N=126)
Number of adverse events, n	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	322 (99)	323 (98)	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	201 (62)	220 (67)	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR	NR
Number and proportion of patients with ≥ 1	NR	NR	NR	NR

	Vutrisiran (N=326)	Placebo (N=328)	Vutrisiran monotherapy (N=196)	Tafamidis monotherapy (N=126)
CTCAE grade ≥ 3 events[§], n (%)				
Number of treatment-related adverse reactions, n	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 treatment-related adverse reactions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	NR	NR	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NR	NR	NR	NR
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	10 (3)	13 (4)	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

The frequency of serious adverse events during the double-blind period of HELIOS-B that occurred in 5% or more of the patients are reported in Table 19. All serious adverse events that occurred in 1% or more of the patients are reported in Appendix E.

Table 19 Serious adverse events during double-blind period

Adverse events	Vutrisiran (N=326)		Placebo (N=328)		Vutrisiran monotherapy – unweighted (n=196)		Tafamidis monotherapy - unweighted(n=126)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	201 (62)	[redacted]	220 (67)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	38 (12)	[redacted]	57 (17)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	26 (8)	[redacted]	20 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure acute	13 (4)	[redacted]	18 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The cost comparison includes all SAEs occurring in 3% or more of patients in the HELIOS-B monotherapy subgroups. It is assumed that SAEs only occur in the first year of treatment.

Table 20 Adverse events used in the health economic model

Adverse events	Vutrisiran	Tafamidis		
	Frequency used in economic	Frequency used in economic	Source	Justification

Adverse events	Vutrisiran model for intervention	Tafamidis model for comparator		
Adverse event, n (%)				
Cardiac failure	[redacted]	[redacted]	HELIOS-B	SAEs occurring ≥3% of patients in HELIOS-B monotherapy populations
Atrial fibrillation	[redacted]	[redacted]	HELIOS-B	Same as above.
Osteoarthritis	[redacted]	[redacted]	HELIOS-B	Same as above
Pneumonia	[redacted]	[redacted]	HELIOS-B	Same as above
Acute kidney injury	[redacted]	[redacted]	HELIOS-B	Same as above
Atrial flutter	[redacted]	[redacted]	HELIOS-B	Same as above
Ventricular tachycardia	[redacted]	[redacted]	HELIOS-B	Same as above
Syncope	[redacted]	[redacted]	HELIOS-B	Same as above
Chest pain	[redacted]	[redacted]	HELIOS-B	Same as above
Hyponatremia	[redacted]	[redacted]	HELIOS-B	Same as above
Urinary retention	[redacted]	[redacted]	HELIOS-B	Same as above

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 21 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA	NA	NA	NA	NA	NA	NA	NA

10. Documentation of health-related quality of life (HRQoL)

As this application for reimbursement is based on a cost comparison, the HRQoL outcomes from the HELIOS-B trial were not used to inform health state utilities. The change in KCCQ-OS score is reported for the primary analysis in Table 13.

10.1 Presentation of the health-related quality of life measured by [instrument]

10.1.1 Study design and measuring instrument

Not applicable.

10.1.2 Data collection

Not applicable.

Table 22 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
-				

10.1.3 HRQoL results

Not applicable.

Table 23 HRQoL summary statistics

	X		Y		Difference
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline					

10.2 Health state utility values (HSUVs) used in the health economic model

Not applicable.

10.2.1 HSUV calculation

Not applicable.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

Not applicable.

Table 24 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	NA	NA	NA	NA

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 25 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	NA	NA	Na	NA

Table 26 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	NA	NA	NA	NA

11. Resource use and associated costs

The cost categories included in this pragmatic cost comparison are categories where a difference is expected between the two treatments. As treatment regimens and administration routes are different, medicine acquisition and administration costs are included. As the different treatment regimens require different healthcare resource use, the patient time and travel costs related to healthcare visits are also incorporated. Finally, given the difference in safety profiles between vutrisiran and tafamidis, the costs of adverse events are also included.

11.1 Medicines - intervention and comparator

For the medicine acquisition costs, the apotekets indkøbspris (AIP) were sourced from medicinprisker.dk.

Vutrisiran is administered with a subcutaneous (SC) injection, once every three months (AIP: 812,054.57 DKK per 1 syringe pack).

Tafamidis 61 mg is reimbursed for ATTR-CM and administered orally every day (AIP: 59,166.43 DKK per 30 capsule pack).

For both products no wastage and equal relative dose intensity (RDI) of 100% is assumed.

Table 27 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Vutrisiran	25 mg	100% (assumed)	Every three months	No
Tafamidis	61 mg daily	100% (assumed)	Daily	No

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Vutrisiran is administered through a SC injection every three months. It is assumed the first administration is in the hospital, whereafter 90% of the administrations are self-administered and 10% are administered through primary care.

No administration cost is assumed for tafamidis, as it is administered orally.

Table 28 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
SC injection in hospital	Once (First administration at treatment initiation)	1,268.00	DRG 05MA98, MDC05 1-dagsgruppe, pat. mindst 7 år	DRG 2025
SC injection home*	Every three months	0.00	-	-
SC injection primary care**	Every three months	167.93	-	Konsultation - Almen praksis. Takstkort April 2025.

*90% of all administrations

**10% of all administrations

11.4 Disease management costs

Not applicable.

Table 29 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
[Activity]	NA	NA	NA	NA

11.5 Costs associated with management of adverse events

Costs associated with the management of adverse events were sourced from DRG 2025 (62). The costs presented in Table 30 were included in the CMA.

Table 30 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Cardiac failure	DRG 10MA06 Hjertesvigt UNS	31,177
Atrial fibrillation	DRG 05MA07, Hjertearytmi og synkope	21,047
Osteoarthritis	DRG 08MA17, Øvrige sygdomme i knogler og led	2,267
Pneumonia	DRG 04MA14, Lungebetændelse og pleuritis, pat. 18-59 år	34,955
Acute kidney injury	DRG 11MA01, Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese	51,134
Atrial flutter	DRG 05MA07, Hjertearytmi og synkope	21,047
Ventricular tachycardia	DRG 05MA07, Hjertearytmi og synkope	21,047
Syncope	DRG 05MA07, Hjertearytmi og synkope	21,047
Chest pain	DRG 05MA03, Stabil iskæmisk hjertesygdom/brystsmerter	2,877
Hyponatremia	DRG 10MA06, Andre ernærings- og stofskiftesygdomme	31,177
Urinary retention	DRG 11MA10, Andre sygdomme, mistanke om sygdom, eller symptomer fra nyrer eller urinveje	19,050

11.6 Subsequent treatment costs

Not applicable.

Table 31 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
NA	NA	NA	NA	NA

11.7 Patient costs

Given the difference in administration and thereby healthcare visits, there will be patient time and travel costs incurred for patients treated with vutrisiran, whereas tafamidis is an oral, at-home treatment. Travel costs are also incurred for healthcare visits, which are estimated to cost 152 DKK per healthcare visit.

Table 32 Patient costs used in the model

Activity	Time spent
SC injection at healthcare facility	2 hours, including travel time
Cardiac failure	48 hours, including travel time
Atrial fibrillation	24 hours, including travel time
Osteoarthritis	4 hours, including travel time
Pneumonia	24 hours, including travel time
Acute kidney injury	24 hours, including travel time
Atrial flutter	24 hours, including travel time
Ventricular tachycardia	24 hours, including travel time
Syncope	24 hours, including travel time
Chest pain	4 hours, including travel time
Hyponatremia	24 hours, including travel time
Urinary retention	4 hours, including travel time

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

An overview of the base case of the model and its features is given below in Table 33.

Table 33 Base case overview

Feature	Description
Comparator	Tafamidis 61 mg
Type of model	Cost comparison
Time horizon	Two years
Treatment line	NA
Measurement and valuation of health effects	NA
Costs included	Medicine costs Administration costs Costs of adverse events Patient costs
Dosage of medicine	Vutrisiran: 25 mg every three months Tafamidis: 61 mg daily
Average time on treatment	NA
Parametric function for PFS	NA
Parametric function for OS	NA
Inclusion of waste	NA
Average time in model health state Health state 1 Health state 2 Health state 3	NA

Feature	Description
Death	

12.1.1 Base case results

The base case results of the CMA comparing vutrisiran and tafamidis in ATTR-CM are presented below in Table 34.

Table 34 Base case results, discounted estimates

	Vutrisiran	Tafamidis	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	NA	NA	NA
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	NA	NA	NA
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	NA	NA	NA
Patient time and travel costs	[redacted]	[redacted]	[redacted]
Palliative care costs	NA	NA	NA
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (health state A)	NA	NA	NA
Life years gained (health state B)	NA	NA	NA
Total life years	**NA**	**NA**	**NA**
QALYs (state A)	NA	NA	NA
QALYs (state B)	NA	NA	NA
QALYs (adverse reactions)	NA	NA	NA

	Vutrisiran	Tafamidis	Difference
Total QALYs	**NA**	**NA**	**NA**
Incremental costs per life year gained		**NA**	
Incremental cost per QALY gained (ICER)		**NA**	

12.2 Sensitivity analyses

Not applicable.

12.2.1 Deterministic sensitivity analyses

Not applicable.

Table 35 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA	NA	NA	NA	NA

12.2.2 Probabilistic sensitivity analyses

Not applicable.

13. Budget impact analysis

This overview of budget impact projects the estimated costs and savings of recommending vs. not recommending vutrisiran in ATTR-CM in Denmark.

Number of patients (including assumptions of market share)
The expected number of patient eligible for treatment with vutrisiran is described in section 3.2. It is expected that there are 550 prevalent patients, and 70 incident eligible patients with ATTR-CM every year in Denmark.

If vutrisiran is recommended, it was assumed that vutrisiran would have a market share of 15% in year 1 (2025), 25% in year 2 (2026), 35% in year 3 (2027), 40% in year 4 (2028) and 45% in year 5 (2029). It was assumed that due to at least equivalent clinical efficacy for vutrisiran relative to tafamidis, market share uptake will be relatively consistent and peak at 45% of the market over the forecasted horizon. However, if vutrisiran is not recommended, it was assumed that tafamidis (and acoramidis) would have a market share of 100% during the entire five-year period. It is assumed that the recommendation of

vutrisiran does not lead to additional patients treated, i.e., it is assumed that patients treated with vutrisiran would have been treated with tafamidis or acoramidis, in the case of no recommendation.

In line with the budget impact estimates made in the acoramidis assessment, a patient starting treatment with vutrisiran was assumed to continue treatment with vutrisiran in the following years without switching treatment. The expected cumulative patient numbers, adjusted for market share, are presented in Table 36.

Table 36 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Vutrisiran	58	114	184	238	299
Tafamidis	327	341	341	357	366
			Non-recommendation		
Vutrisiran	0	0	0	0	0
Tafamidis	385	455	525	595	665

Budget impact

The estimated budget impact based on the expected number of patients to be treated in the next five years was obtained by taking the modelled treatment costs for year 1 in the first year of their treatment, and the second-year costs for further years of treatment. Costs for patients entering their first year of treatment were halved to account for starting treatment at any point during the year. The introduction of vutrisiran for ATTR-CM in Denmark is expected to have a budget impact of DKK [redacted] in 2029, as presented in Table 37.

Table 37 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

[redacted]

15. References

1. Medicinrådet. Medicinrådets anbefaling vedr. tafamidis til behandling af vildtype transthyretinmedieret amyloidose med kardiomyopati (Version 5). 2024.
2. Medicinrådet. Kriterier vedr. behandling med tafamidis til patienter med transthyretin amyloidose med kardiomyopati (ATTR-CM). 2024.
3. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. Circulation. 2019;140(1):16-26.
4. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. New England Journal of Medicine. 2018;379(11):1007-16.
5. 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. 2024.
6. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail. 2021;23(2):277-85.
7. Fontana M, Berk JL, Gillmore JD, Witteles RM, Grogan M, Drachman B, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. New England Journal of Medicine. 2025;392(1):33-44.
8. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Ann Med. 2015;47(8):625-38.
9. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation. 2012;126(10):1286-300.
10. Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. Circulation. 2016;133(3):282-90.
11. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol. 2016;68(10):1014-20.
12. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(22):2872-91.
13. Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the american college of cardiology solution set oversight committee. J Am Coll Cardiol. 2023;81(11):1076-126.
14. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075.
15. Ando Y, Adams D, Benson MD, Berk JL, Plante-Bordeneuve V, Coelho T, et al. Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosis. Amyloid. 2022;29(3):143-55.
16. Liu Q, Chen D, Wang Y, Zhao X, Zheng Y. Cardiac autonomic nerve distribution and arrhythmia. Neural Regen Res. 2012;7(35):2834-41.
17. Conceicao I, Gonzalez-Duarte A, Obici L, Schmidt HH, Simoneau D, Ong ML, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21(1):5-9.
18. Gonzalez-Duarte A, Berk JL, Quan D, Mauermann ML, Schmidt HH, Polydefkis M, et al. Analysis of autonomic outcomes in APOLLO, a phase III trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. J Neurol. 2020;267(3):703-12.

19. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol. 2016;68(2):161-72.
20. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry. 2015;86(9):1036-43.
21. Eisele YS, Monteiro C, Fearns C, Encalada SE, Wiseman RL, Powers ET, et al. Targeting protein aggregation for the treatment of degenerative diseases. Nat Rev Drug Discov. 2015;14(11):759-80.
22. Jain A, Zahra F. Transthyretin amyloid cardiomyopathy (ATTR-CM). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
23. Tsoi MR, Lin JH, Patel AR. Emerging therapies for transthyretin amyloidosis. Curr Oncol Rep. 2023;25(6):549-58.
24. Gonzalez-Duarte A. Autonomic involvement in hereditary transthyretin amyloidosis (hATTR amyloidosis). Clin Auton Res. 2019;29(2):245-51.
25. Griffin JM, Rosenblum H, Maurer MS. Pathophysiology and therapeutic approaches to cardiac amyloidosis. Circ Res. 2021;128(10):1554-75.
26. Manral P, Reixach N. Amyloidogenic and non-amyloidogenic transthyretin variants interact differently with human cardiomyocytes: insights into early events of non-fibrillar tissue damage. Biosci Rep. 2015;35(1):e00172.
27. Hartnett J, Jaber W, Maurer M, Sperry B, Hanna M, Collier P, et al. Electrophysiological manifestations of cardiac amyloidosis: JACC: cardiooncology state-of-the-art review. JACC CardioOncol. 2021;3(4):506-15.
28. Chiaro G, Stancanelli C, Koay S, Vichayanrat E, Sander L, Ingle GT, et al. Cardiovascular autonomic failure in hereditary transthyretin amyloidosis and TTR carriers is an early and progressive disease marker. Clin Auton Res. 2024.
29. Ioannou A, Chacko L, Kotecha T, Patel RK, Razvi Y, Porcari A, et al. Myocardial ischaemia in cardiac amyloidosis: a change of perspective [Presented at ESC Congress 2022, Barcelona, Spain, 26–29 August]. Eur Heart J. 2022;43:1761.
30. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR amyloidosis: current and emerging management strategies: JACC: cardiooncology state-of-the-art review. JACC CardioOncol. 2021;3(4):488-505.
31. Porcari A, Fontana M, Gillmore JD. Transthyretin cardiac amyloidosis. Cardiovasc Res. 2023;118(18):3517-35.
32. Medicinrådet. Medicinrådets anbefaling vedrørende tafamidis til behandling af arvelig transthyretinmedieret amyloidose med polyneuropati stadie 1. 2021.
33. Medicinrådet. Medicinrådets anbefaling vedr. acoramidis til behandling af transthyretin amyloidose med kardiomyopati. 2025.
34. Zhao L, Buxbaum JN, Reixach N. Age-related oxidative modifications of transthyretin modulate its amyloidogenicity. Biochemistry. 2013;52(11):1913-26.
35. Garcia-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. Eur J Heart Fail. 2021;23(6):895-905.
36. Kristen AV, Maurer MS, Rapezzi C, Mundayat R, Suhr OB, Damy T, et al. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - Report from the Transthyretin Amyloidosis Outcome Survey (THAOS). PLoS One. 2017;12(4):e0173086.
37. Ioannou A, Cappelli F, Emdin M, Nitsche C, Longhi S, Masri A, et al. Stratifying disease progression in patients with cardiac ATTR amyloidosis. J Am Coll Cardiol. 2024;83(14):1276-91.
38. Slama M, Charron P, Algalarrondo V, Lairez O, Pelcot F, Durand-Zaleski I, et al. Development of an algorithm using the dispensed daily doses of loop diuretics to assess survival of patients with transthyretin amyloid cardiomyopathy (ATTR-CM) according to

the disease severity [Presented at ISPOR Europe, virtual, Nov 19–Dec 20, 2020]. Value Health. 2020;23:S487.
39. Cheng RK, Levy WC, Vasbinder A, Teruya S, De Los Santos J, Leedy D, et al. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. JACC CardioOncol. 2020;2(3):414-24.
40. American Heart Association. Classes and Stages of Heart Failure 2023 [Available from: https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure.
41. Selskab DC. Myokardiesygdomme 2025 [Available from: https://www.cardio.dk/myokardiesygdomme.
42. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. New England Journal of Medicine. 2024;390(2):132-42.
43. Masri A, Bhattacharya P, Medoff B, Ejaz AU, Elman MR, Chandrashekar P, et al. A Multicenter Study of Contemporary Long-Term Tafamidis Outcomes in Transthyretin Amyloid Cardiomyopathy. JACC CardioOncol. 2025;7(3):282-93.
44. Fontana M, Kumar V, Sheridan P, Rubens L, Toyip A, Boehme A, et al. Unmet Need In A Contemporary Cohort Of Tafamidis-Treated Transthyretin Amyloid Cardiomyopathy Patients. Journal of Cardiac Failure. 2025;31(1):318.
45. (EMA) EMA. SUMMARY OF PRODUCT CHARACTERISTICS. 2025.
46. (ICER) IfCaER. Disease modifying therapies for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) 2024.
47. Habtemariam BA, Karsten V, Attarwala H, Goel V, Melch M, Clausen VA, et al. Single-dose pharmacokinetics and pharmacodynamics of transthyretin targeting N-acetylgalactosamine-small interfering ribonucleic acid conjugate, vutrisiran, in healthy subjects. Clin Pharmacol Ther. 2021;109(2):372-82.
48. Medicinrådet. Tafamidis (Vyndaqel) - revurdering. 2024.
49. Alnylam Pharmaceuticals. HELIOS-B Clinical Study Protocol. 2024.
50. ClinicalTrials.gov. HELIOS-B: A study to evaluate vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy (NCT04153149) [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04153149.
51. Alnylam Pharmaceuticals I. Data on file. 2025.
52. Garcia-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. European Journal of Heart Failure. 2021;23(6):895-905.
53. Mads Kristian Ersbøll. Clinical validation of use of vutrisiran in ATTR-CM in Denmark [Data on file]. 2025.
54. Mølgaard H. **Clinical validation of use of vutrisiran in ATTR-CM in Denmark**. 2025.
55. Bender S, Alnylam Pharmaceuticals I. Data on file - Medical Affairs Post Hoc Statistical Report. 2024.
56. R. Witteles PG-P, T. Damy, M. Grogan, F. H. Sheikh, C. Morbach, S. Bender, J. Exter, , S. Eraly MF. Vutrisiran Reduces All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis from the HELIOS-B Tria2025.
57. Girard AA, Sperry BW. Contextualizing the results of HELIOS-B in the broader landscape of clinical trials for the treatment of transthyretin cardiac amyloidosis. Heart Fail Rev. 2024.
58. European Medicines Agency (EMA). Amvuttra (vutrisiran) - EMA/COMP position on review of criteria for orphan designation (Data on file). 2025.
59. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107.

60. Mamdani M, Sykora K, Li P, Normand SL, Streiner DL, Austin PC, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. Bmj. 2005;330(7497):960-2.
61. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010;25(1):1-21.
62. Sundhedsdata-styrelsen. Takstsystem 2025. 2024.
63. Witteles RM, Garcia-Pavia P, Damy T, Grogan M, Sheikh FH, Morbach C, et al. Vutrisiran Improves Survival and Reduces Cardiovascular Events in ATTR Amyloid Cardiomyopathy: HELIOS-B. J Am Coll Cardiol. 2025.
64. Fontana M, Maurer MS, Gillmore JD, Bender S, Aldinc E, Eraly SA, et al. Outpatient Worsening Heart Failure in Patients With Transthyretin Amyloidosis With Cardiomyopathy in the HELIOS-B Trial. J Am Coll Cardiol. 2025;85(7):753-61.
65. Maurer MS, Witteles RM, Garcia-Pavia P, Sheikh FH, Morbach C, Rodriguez Duque D, et al. Impact of Heart Failure Severity on Vutrisiran Efficacy in Transthyretin Amyloidosis With Cardiomyopathy. J Am Coll Cardiol. 2025;85(20):1927-39.
66. European Medicines Agency (EMA). Protocol Assistance. Vutrisiran (ALN-TTRSC02). 2019.
67. Food and Drug Administration (FDA). Memorandum of meeting minutes. 2019.

Appendix A. Main characteristics of studies included

Table 38 Main characteristic of studies included

Trial name: HELIOS-B	NCT number: NCT04153149
Objective	To evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM
Publications – title, author, journal, year	Fontana M, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025 Jan 2;392(1):33-44. doi: 10.1056/NEJMoa2409134. Epub 2024 Aug 30. PMID: 39213194. (5) Witteles RM, et al. Vutrisiran Improves Survival and Reduces Cardiovascular Events in ATTR Amyloid Cardiomyopathy: HELIOS-B. J Am Coll Cardiol. 2025 Apr 30:S0735-1097(25)06170-4. doi: 10.1016/j.jacc.2025.04.008. Epub ahead of print. PMID: 40380962.(63) Fontana M, et al. Outpatient Worsening Heart Failure in Patients With Transthyretin Amyloidosis With Cardiomyopathy in the HELIOS-B Trial. J Am Coll Cardiol. 2025 Feb 25;85(7):753-761. doi: 10.1016/j.jacc.2024.11.015. Epub 2024 Nov 18. PMID: 39566871. (64) Maurer MS, et al. Impact of Heart Failure Severity on Vutrisiran Efficacy in Transthyretin Amyloidosis With Cardiomyopathy. J Am Coll Cardiol. 2025 May 27;85(20):1927-1939. doi: 10.1016/j.jacc.2025.03.477. Epub 2025 Mar 17. PMID: 40099776. (65)
Study type and design	HELIOS-B was a phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated the efficacy and safety of vutrisiran in patients with ATTR-CM. Randomization was stratified by:(49) • 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 are >75 years old]) The double-blind period of HELIOS-B was up to 36 months in duration; specifically, patients received double-blind treatment (vutrisiran or placebo) for 30 months after the last enrolled patient in the study was randomized or for 33 months after their own randomization, whichever occurred first, and then underwent 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 randomization) receive treatment with vutrisiran every 3 months for up to 2 years, beginning immediately at the conclusion of double-blind follow-up.

Trial name: HELIOS-B	NCT number: NCT04153149
Sample size (n)	The 654 patients randomized to vutrisiran or placebo made up the overall population. This population of patients included patients receiving background tafamidis at baseline, as well as those not receiving background tafamidis at baseline. In addition to 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.

Main 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).

Trial name: HELIOS-B	NCT number: NCT04153149
	▪ 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 hospitalization 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 pressures 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 randomization. • In stable clinical status with no cardiovascular-related hospitalization in the 6 weeks prior to randomization. • 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 meters or more on the 6-MWT at screening. • KPS ≥60%.
Main 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 randomization.
- 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 stabilizers, 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 randomization) a heart, liver, or other organ transplant or implantation of left-ventricular assist device.

Trial name: HELIOS-B	NCT number: NCT04153149
	▪ 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.
Intervention	25 mg of vutrisiran Q3M via subcuteanous injection
Comparator(s)	Placebo, via subcuteanous injection.
Follow-up time	Up to 36 months.
Is the study used in the health economic model?	Yes, it informs the adverse events.
Primary, secondary and exploratory endpoints	The primary endpoints of HELIOS-B were 1) a composite endpoint of ACM and recurrent cardiovascular events (comprising cardiovascular hospitalizations 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).(49, 50) The EMA and the United States Food and Drug Administration (FDA) both stated in their formal guidance to Alnylam that a composite endpoint of mortality and cardiovascular events was an acceptable primary endpoint for HELIOS-B.(66, 67) For analysis of this endpoint, heart transplantation and/or receipt of a ventricular assist device were categorized as deaths.(49) Secondary endpoints included change from baseline in functional exercise 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 OLE data following the double-blind period), and change from baseline in heart failure severity as measured by NYHA class changes at 30 months.(49) Each of these secondary endpoints was assessed among all patients (overall

Trial name: HELIOS-B		NCT number: NCT04153149
	population), and among patients not on tafamidis at baseline (monotherapy population).(49)	
Method of analysis	ITT, monotherapy subgroups (vutrisiran-only vs. placebo-only, and vutrisiran-only vs. tafamidis-only). See Table 39 for methods per outcome.	
Subgroup analyses	Monotherapy groups (vutrisiran only, placebo only)	
Other relevant information	Post hoc analysis of vutrisiran monotherapy vs. tafamidis monotherapy.	

Appendix B. Efficacy results per study

Results per study

Table 39 Results per study

Results of HELIOS-B (NCT04153149); Primary analysis											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Composite of ACM and recurrent CV events over 36 months (Overall population)	Vutrisiran	326	125 (38.3)	N/A	N/A	N/A	HR: 0.72	0.56–0.93	0.01	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)	(5)
	Placebo	328	159 (48.5)								
Composite of ACM and recurrent CV events over 36 months (Monotherapy population)	Vutrisiran monotherapy	196	76 (38.8)	N/A	N/A	N/A	HR: 0.67	0.49–0.93	0.02		
	Placebo monotherapy (no tafamidis)	199	105 (52.8)								
Change in 6MWT over 30 months (Overall population)	Vutrisiran	326	–45.4 (–54.5, –36.3)	LS Mean: 26.5	13.4, 39.6	<0.001	N/A	N/A	N/A	Mixed effects model with repeated measures (MMRM) which included baseline 6-MWT distance as a covariate and treatment (vutrisiran vs. placebo), visit, treatment-by-	(5)
	Placebo	328	−71.9 (−81.3, −62.4)								

Results of HELIOS-B (NCT04153149); Primary analysis											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in 6MWT over 30 months (Monotherapy population)	Vutrisiran monotherapy	196	−59.7 (−72.7, −46.7)	LS Mean: 32.1	14.0, 50.2	<0.001	N/A	N/A	N/A	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	
	Placebo monotherapy (no tafamidis)	199	−91.8 (−104.4, −79.2)								
Change in KCCQ-OS score over 30 months (Overall population)	Vutrisiran	326	-9.7 (-12.0, -7.4)	LS Mean: 5.8	2.4, 9.2	<0.001	N/A	N/A	N/A	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	(5)
	Placebo	328	-15.5 (-18.0, -13.0)								
Change in KCCQ-OS score over 30 months (Monotherapy population)	Vutrisiran monotherapy	196	−10.8 (−14.1, −7.5)	LS Mean: 8.7	4.0, 13.4	<0.001	N/A	N/A	N/A		
	Placebo monotherapy (no tafamidis)	199	−19.5 (−22.9, −16.1)								
ACM up to 42 months (Overall population)	Vutrisiran	326	60 (18.4)	N/A	N/A	N/A	HR: 0.65	0.46, 0.90	0.01	Log-rank test stratified by baseline tafamidis use (yes vs. no) and baseline NT-proBNP group (≤3000	(5)
	Placebo	328	85 (25.9)								

Results of HELIOS-B (NCT04153149); Primary analysis											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ACM up to 42 months **(Monotherapy population)**	Vutrisiran monotherapy	196	43 (21.9)	N/A	N/A	N/A	HR: 0.66	0.44, 0.97	0.0045	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 logarithmic transformation) as covariates used to estimate the overall HR and 95% CI	
	Placebo monotherapy (no tafamidis)	199	58 (29.1)								
Change in NYHA class at 30 months **(Overall population)**	Vutrisiran	326	67.8	Adjusted difference: 8.7	1.3, 16.1	0.02	N/A	N/A	N/A	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	(5)
	Placebo	328	60.5								
Change in NYHA class at 30 months	Vutrisiran monotherapy	196	66.3		2.7, 22.2	0.01	N/A	N/A	N/A		

Results of HELIOS-B (NCT04153149); Primary analysis											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
(Monotherapy population)	Placebo monotherapy (no tafamidis)	199	56.4	Adjusted difference: 12.5						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	

Note: ATTR-CM, transthyretin amyloid cardiomyopathy; N/A, not applicable; CI, confidence intervals; NYHA, New York Heart Association; CMH, Cochran-Mantel-Haenszel method; HR, hazard ratio; 6-MWT, 6-Minute-Walk-Test.

Appendix C. Comparative analysis of efficacy

The methods for the comparative analysis have been described in Section 7.1.2. Additional relevant information is presented in this section.

Figure 2 Distribution of propensity scores by monotherapy treatment group in HELIOS-B

[redacted]

Note: Tafamadis monotherapy indicates that patients in the placebo arm were on tafamadis at baseline.

Table 40 Comparative analysis of studies comparing vutrisiran and tafamidis monotherapy for patients with ATTR-CM

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Composite of ACM and recurrent CV events over up to 36 months	HELIOS-B (post hoc analysis)	N/A	N/A	N/A	Weighted – HR: 0.83	Weighted: 0.54, 1.29		[redacted]	

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
ACM over up to 42 months		N/A	N/A	N/A	Weighted – HR: 0.81	Weighted: 0.49, 1.34	Not reported	[redacted]	
Recurrent CV events over up to 36 months		N/A	N/A	N/A	Weighted – relative rate ratio: 0.82	Weighted: 0.62, 1.08		[redacted]	
Change in proportion with stable or improved NYHA class over 30 months		Weighted: [redacted]	Not reported	Not reported	[redacted]	[redacted]	N/A	[redacted]	

Appendix D. Extrapolation

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

Appendix E. Serious adverse events

Table 41 Serious adverse events during double-blind period

Adverse events	Vutrisiran (N=326)		Placebo (N=328)		Vutrisiran monotherapy - unweighted (n=196)		Tafamidis monotherapy – unweighted (n=129)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events

Adverse events	Vutrisiran (N=326)		Placebo (N=328)		Vutrisiran monotherapy - unweighted (n=196)		Tafamidis monotherapy – unweighted (n=129)	
Adverse event, n (%)	201 (62)	[redacted]	220 (67)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	38 (12)	[redacted]	57 (17)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	26 (8)	[redacted]	20 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure acute	13 (4)	[redacted]	18 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial flutter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ventricular tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrioventricular block complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events	Vutrisiran (N=326)		Placebo (N=328)		Vutrisiran monotherapy - unweighted (n=196)		Tafamidis monotherapy – unweighted (n=129)	
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hip fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrioventricular block first degree	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac pacemaker insertion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gout	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lumbar spinal stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events	Vutrisiran (N=326)		Placebo (N=328)		Vutrisiran monotherapy - unweighted (n=196)		Tafamidis monotherapy – unweighted (n=129)	
Acute respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arrythmia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebral infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypervolaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Staphylococcal sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Not applicable.

Table 42. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
NA	NA	NA	NA	NA

Appendix H. Literature searches for the clinical assessment

Not applicable, as comparison of vutrisiran against relevant comparator in Danish clinical practice included in pivotal trial.

Appendix I. Literature searches for health-related quality of life

Not applicable.

Appendix J. Literature searches for input to the health economic model

Not applicable.

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk