Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy

Part 1: for screen – contains redacted CON information

Technology appraisal committee C [09 September 2025]

Chair: James Fotheringham

Lead team: Pedro Saramago Goncalves, Ugochi Nwulu, David Foreman

External assessment group: York Technology Assessment Group

Technical team: Chris Shah, Albany Chandler, Lorna Dunning

Company: Alnylam Pharmaceuticals

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on transthyretin amyloidosis with cardiomyopathy (ATTR-CM)

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

Causes

- Abnormal transthyretin protein produced in the liver → accumulates as amyloid deposits in the heart tissue → tissue thickens and stiffens → heart unable to pump blood efficiently

Epidemiology

- ~1200 to 1300 people with a diagnosis of ATTR-CM in UK, likely to be underdiagnosed
- Awareness and improvements in imaging have led to earlier diagnosis and increased number of cases

Diagnosis and classification

- **Wild type:** TTR protein becomes unstable with age-related breakdown in homeostatic mechanisms. Onset usually after 70 years
- **Hereditary:** Inherited mutations in TTR gene. Onset usually after 60 years

Symptoms and prognosis

- Shortness of breath, palpitations and arrythmias, ankle swelling, fatigue and chest and limb pain
- Median survival is around 2 to 6 years (differs by type)

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; TTR, transthyretin

Patient perspectives

ATTR-CM is a progressive, debilitating and fatal disease that affects every aspect of life and has a significant burden on caregivers

Submissions from Amyloidosis UK and Cardiomyopathy UK

- ATTR-CM has severe physical, financial, social, emotional and psychological impacts
- ATTR-CM also has a major impact on the lives of carers and loved ones
- Despite recent progress, delayed and inaccurate diagnosis and lack of access to care close to home remain major challenges
- Availability of tafamidis welcomed, but condition remains progressive and ultimately fatal and not all people respond to or tolerate tafamidis
- Vutrisiran would be second disease-modifying treatment for ATTR-CM and having an additional option would be a significant advantage
- For some, subcutaneous injection administration route may be a disadvantage if requires hospital appointment every 3 months. Self-administration would be preferrable
- Vutrisiran could open the door to combination therapy with tafamidis, which could further improve outcomes

"Participants in the focus group described a feeling that their body was wearing away, or losing a little bit of life every day"

"The burden on caregivers is significant… In addition to the financial burden, caregivers often experience chronic fatigue"

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Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy

Clinical perspectives

There remains a high unmet need despite the availability of tafamidis in the NHS

Submission from British Cardiovascular Society

- In an ageing cohort of people with ATTR-CM, QoL measures and functional status are more important than traditional outcome measures such as all-cause mortality
- Both TTR stabilisers (tafamidis) and siRNA therapies (vutrisiran) are now proven to be effective in ATTR-CM
- There appears to be no significant difference in terms of safety between the existing available NHS treatment (tafamidis) and vutrisiran
- Administration preference would influence first-line choice of therapy (tafamidis is an oral capsule, vutrisiran is a subcutaneous injection)
- Other factors that would influence choice of therapy include ability to check compliance (through blood serum TTR levels) and what package of care if any, is available alongside the basic administration of the drug
- Important to consider role of combination therapy

"Many of these patients are the main carers for their spouses. Do not underestimate the importance of drug therapy which would prevent hospital admissions in an elderly co-morbid population."

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; TTR, transthyretin; QoL, quality of life

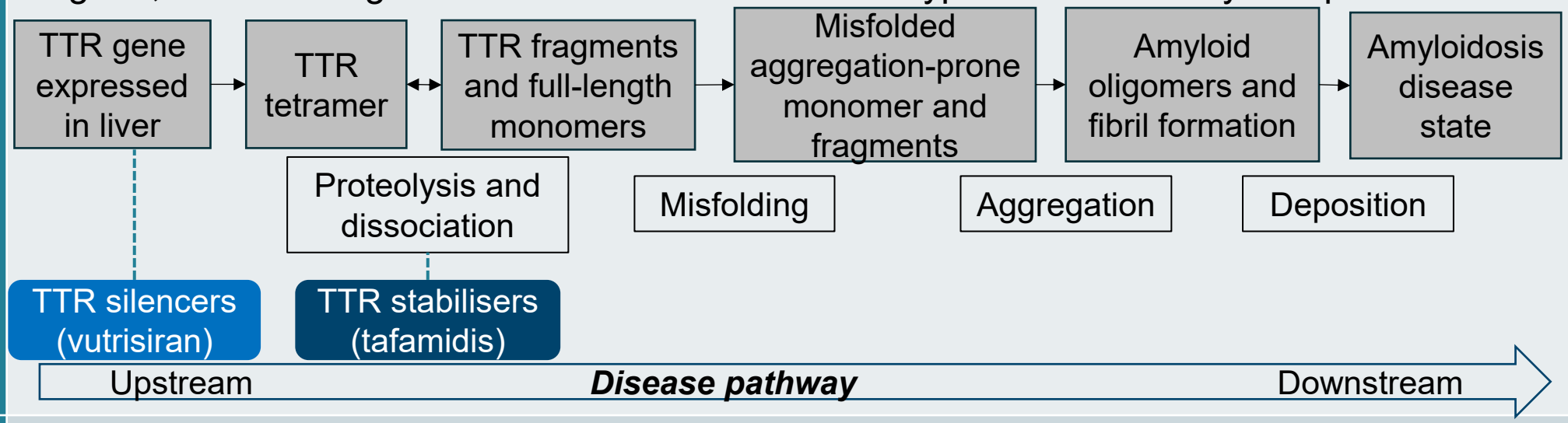
Equality considerations

- **Hereditary ATTR-CM disproportionately affects certain ethnic groups:**
  - People from African or Caribbean and Hispanic family backgrounds have a higher prevalence of hereditary ATTR-CM compared to the general population
  - The most common hereditary ATTR mutation, V122I, is found predominantly in people of West African ancestry
- **Wild-type and hereditary ATTR-CM primarily affect older people:**
  - The average age of people likely to be suitable for this treatment is around 60-80 years
  - Wild-type ATTR-CM is typically diagnosed later than hereditary ATTR-CM (wild-type onset usually after 70 years vs hereditary onset usually after 60 years)

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy

Vutrisiran (AMVUTTRA, Alnylam Pharmaceuticals)

Marketing authorisation	• For the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy • GB marketing authorisation granted in July 2025
Mechanism of action	• Vutrisiran is a chemically stabilised double-stranded siRNA that specifically targets variant and wild-type transthyretin mRNA • Causes degradation of transthyretin mRNA in liver, silencing expression of transthyretin gene, and resulting in reduction of variant and wild-type serum transthyretin protein levels
Administration	• Subcutaneous injection of 25mg vutrisiran every 3 months
Price	• List price: £95,862 per pre-filled syringe of vutrisiran (25 mg in 0.5 mL solution for injection) • List price for 12 months of treatment: £383,449 • A patient access scheme has been agreed



Abbreviations: TTR, transthyretin

Key issues

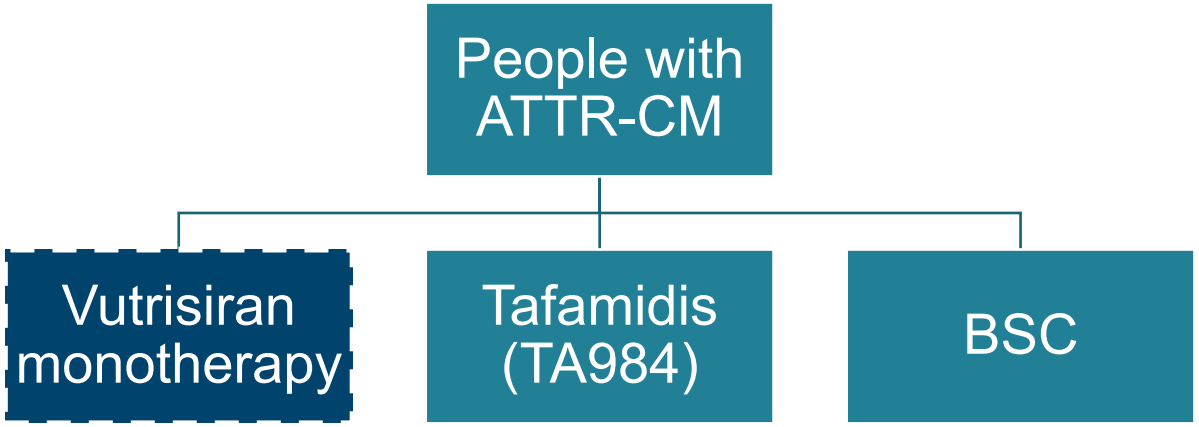
Issue	Resolved?	ICER impact
Intervention and comparator(s)	No – for discussion	Unknown
Uncertainty in the comparative clinical evidence	No – for discussion	Large
Modelling of treatment effectiveness	No – for discussion	Large
Vutrisiran treatment effect waning	No – for discussion	Small
Caregiver disutilities	No – for discussion	Small

Other issues (in appendix):

- Tafamidis and vutrisiran costs
- Modelling of all-cause mortality independently from NYHA classification
- Limited evidence on key subgroups

Key issue: Intervention and comparator(s)

Current treatment pathway and proposed positioning of vutrisiran



Company

- Considers tafamidis to be only relevant comparator
- Clinical experts from National Amyloidosis Centre (NAC) note tafamidis is standard care for almost all (approximately [redacted]) people with ATTR-CM eligible for disease-modifying therapy
- Tafamidis has only one contraindication with low level of occurrence, so BSC not relevant comparator

EAG:

- Comparison to BSC relevant for people with ATTR-CM who are eligible for disease-modifying therapy but do not receive tafamidis
- RCT data available for comparison against BSC

- Would vutrisiran be used as monotherapy or would vutrisiran be used in combination with tafamidis in clinical practice?
- Is BSC an appropriate comparator?
- If yes, how is BSC defined?
- Is tafamidis supplied on a 3-month basis?
- In what setting(s) would treatment with vutrisiran be initiated and administered?

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Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; BSC, best supportive care; RCT, randomised controlled trial

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Key clinical trial: HELIOS-B

[For baseline characteristics see appendix]

	HELIOS-B (NCT04153149)
Design	Phase 3, randomised, double-blind placebo-controlled study
Population	People with ATTR-CM (N=654), excluding people with NYHA class IV heart failure
Intervention	Vutrisiran
Comparator(s)	Placebo
Duration	Double-blind period up to 36 months followed by OLE for up to 24 months

Primary outcome	• Composite outcome of ACM and recurrent CV events over up to 36 months:
	  • ACM includes death, heart transplant, or receiving ventricular assist device
	  • CV events include CV hospitalisations and urgent heart failure visits

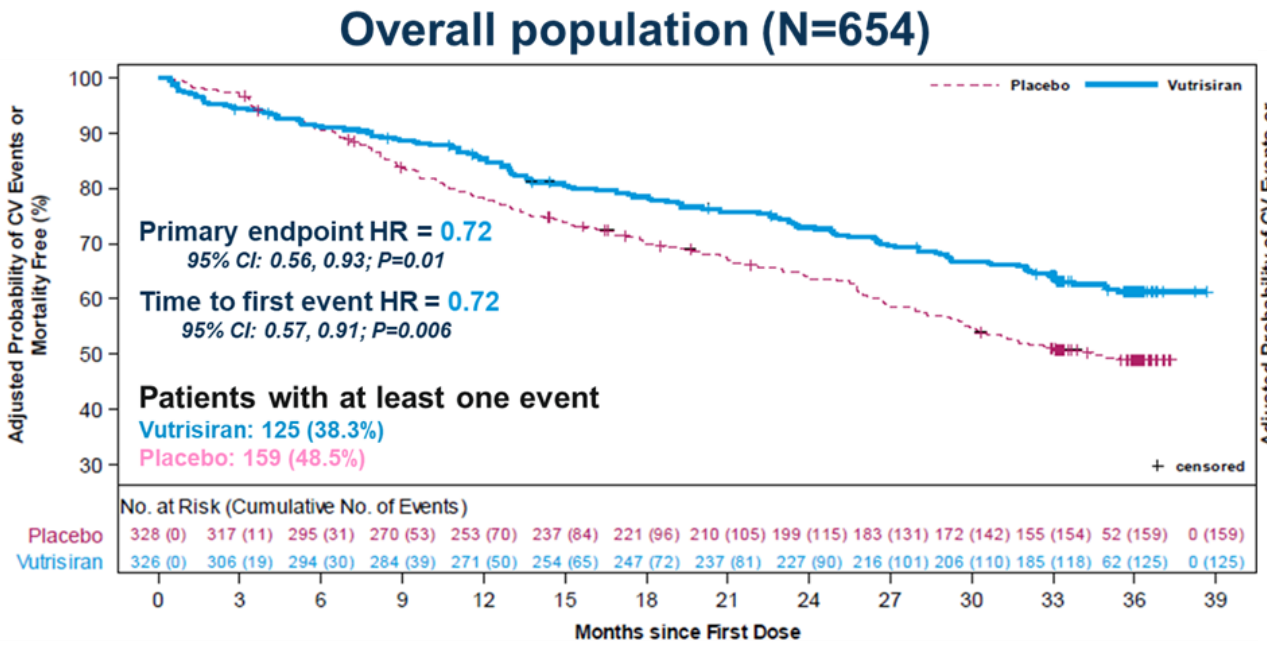
Key secondary outcomes	• Change from baseline to Month 30 in 6-MWT • Change from baseline to Month 30 in KCCQ-OS • ACM over up to 42 months • Proportion stabilised or improved in NYHA class from baseline to Month 30
Locations	87 sites in 26 countries, including United Kingdom (n=151, 23.1% of participants)
Used in model?	Yes, vutrisiran monotherapy group compared with placebo group receiving tafamidis at baseline

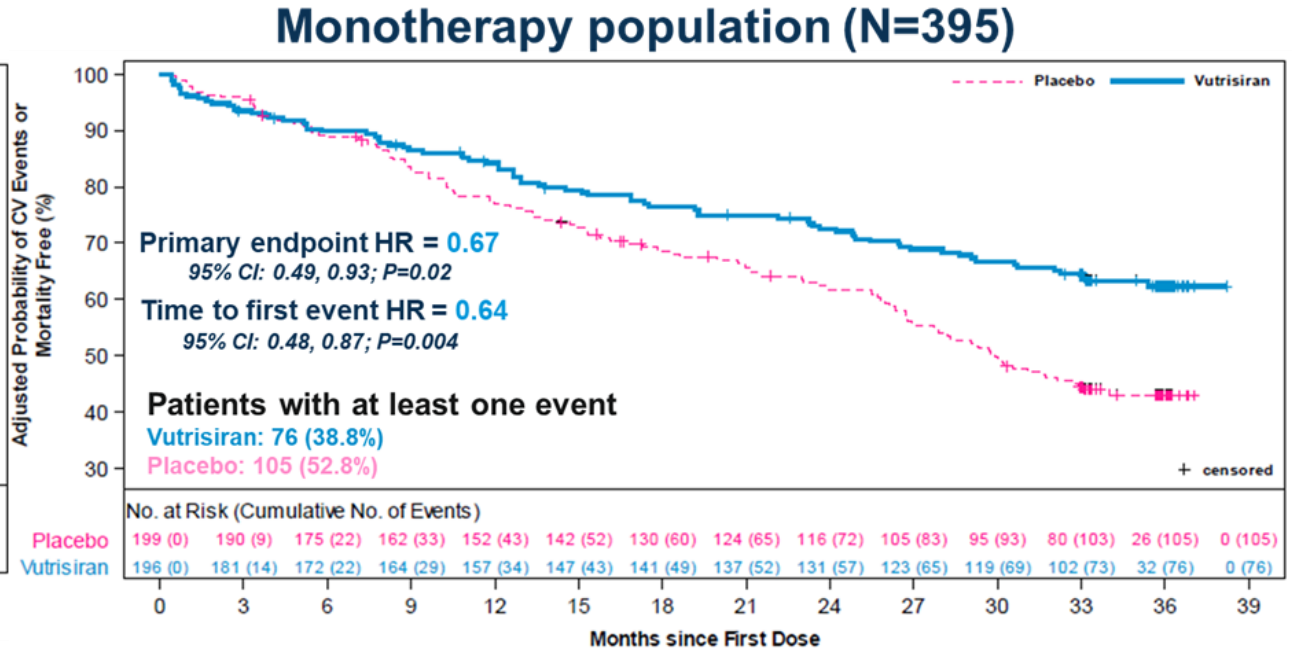
Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; OLE, open-label extension

Key clinical trial results: HELIOS-B

Vutrisiran resulted in a significant reduction in the risk of mortality and recurrent CV events vs placebo

HELIOS-B primary endpoint analysis: time to ACM or first CV event (whichever occurred first)





Note:

- Overall population includes participants receiving background tafamidis at baseline
- Monotherapy population excludes participants receiving background tafamidis at baseline
- Tafamidis “drop-in”: in monotherapy population similar numbers started treatment with tafamidis during the trial (44 (22.4%) in vutrisiran arm and 41 (20.6%) in placebo arm)

Abbreviations: ACM, all-cause mortality, CV cardiovascular; HR, hazard ratio

Survival results for HELIOS-B populations used in model

Overview of trial populations

Overall population	Vutrisiran (n=326)
	Placebo (n=328)
Monotherapy population	Vutrisiran (n=196)
	Placebo (n=199)
Background tafamidis population	Vutrisiran (n=130)
	Placebo (n=129)

Modelled as tafamidis monotherapy

Modelled as vutrisiran monotherapy

Note:

- Monotherapy population: excludes people receiving tafamidis at baseline
- Background tafamidis population: only includes people receiving tafamidis at baseline

HELIOS-B KM curves for vutrisiran and tafamidis monotherapy arms

Company

- Potential for bias in favour of tafamidis since tafamidis monotherapy arm had been receiving tafamidis for a median of 11.3 months at HELIOS-B baseline and may have been deriving survival benefit

EAG:

- Company did not provide evidence to explore impact of differential timing of treatment initiation

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Abbreviations: KM, Kaplan-Meier

Link to KM curves

Key issue: Uncertainty in comparative clinical evidence (1/2)

Background

- Company's preferred comparison for vutrisiran and tafamidis is non-randomised comparison between two groups that HELIOS-B was not designed to compare:
  i. People randomised to vutrisiran arm who were not receiving tafamidis prior to randomisation
  ii. People randomised to placebo arm who were receiving tafamidis prior to randomisation
- Results of the company's preferred comparison are not statistically significant

Company: Results indicate consistent trend of efficacy benefit for vutrisiran

- Within-trial comparison of vutrisiran and tafamidis provided most robust assessment of relative efficacy
- Since within-trial comparison not randomised, IPTW used to balance baseline differences between groups
- IPTW analysis did not censor for tafamidis "drop-in" use - results insensitive to this
- Indirect comparison not appropriate because the populations in HELIOS-B and ATTR-ACT (tafamidis trial) were not comparable. ATTR-ACT more advanced in terms of disease progression vs HELIOS-B likely due to improvement in heart failure management in ATTR-CM
- Provided results of unanchored and anchored MAIC in response to EAG request
- Company IPTW analysis, unanchored and anchored MAICs and EAG NMA indicate consistent trend of efficacy benefit for vutrisiran over tafamidis

Abbreviations: EAG, external assessment group; IPTW, inverse probability of treatment weighting; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

Key issue: Uncertainty in comparative clinical evidence (2/2)

EAG: Most reasonable assumption is that vutrisiran and tafamidis are similar in effectiveness

- Agrees company-preferred comparison avoids problems with changes in trial populations over time, but it is non-randomised and some people were prescribed tafamidis after randomisation
- Agrees HELIOS-B and ATTR-ACT had different populations but disagrees that this invalidates any ITCs
- MAIC adjustment appeared successful across many key variables in company unanchored MAIC
- Conducted NMA to compare HELIOS-B vs ATTR-ACT trial and vs RWE from contemporary THAOS study
- No conclusive evidence that vutrisiran is more effective than tafamidis: no analyses statistically significant with some results suggesting potential modest clinical benefit for vutrisiran but others for tafamidis

ACM results (vutrisiran vs tafamidis), not used directly in model:

	ACM HR (95% CI)
Company within-trial comparison (adjusted)	0.81 (0.50-1.34)
Company unanchored MAIC*	[redacted]
Company anchored MAIC*	[redacted]
Within-trial comparison (unadjusted)	[redacted]
Within-trial comparison (adjusted only for treatment group)	[redacted]
EAG NMA, Bayesian (HELIOS-B vs ATTR-ACT)	0.89 (0.53-1.43)
EAG NMA (HELIOS-B vs THAOS)	1.17 (0.73-1.90)

*Unclear which covariates were included in adjustment

Link to additional information on THAOS study

What is committee's view on the effectiveness of vutrisiran vs tafamidis?

Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; EAG, external assessment group; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RWE, real world evidence; THAOS, Transthyretin Amyloidosis Outcomes Survey

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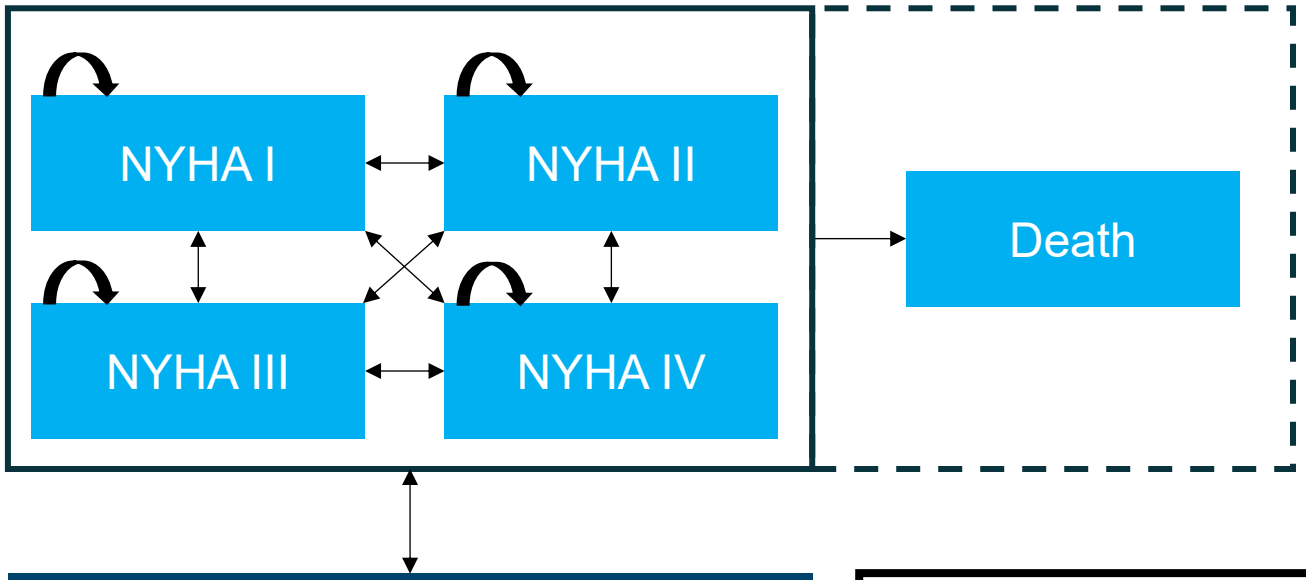
Overview of company's model

Model structure (based on NYHA classification)



- Lifetime horizon, 3.5% discounting rate
- 3-month cycle length
- Vutrisiran modelled to affect **QALYs** by:
  i. Delaying progression across NYHA class health states
  ii. Improving survival
  iii. Reducing incidence of AEs
- Treatment-independent health state utilities from EQ-5D-5L in HELIOS-B mapped to EQ-5D-3L
- Caregiver disutilities included
- Parametric extrapolation of IPTW-adjusted survival observed in HELIOS-B

EAG

- Model structure broadly consistent with previous models in NICE appraisals for ATTR-CM
- Concerned that model structure does not appropriately link survival outcomes to NYHA states or transient events

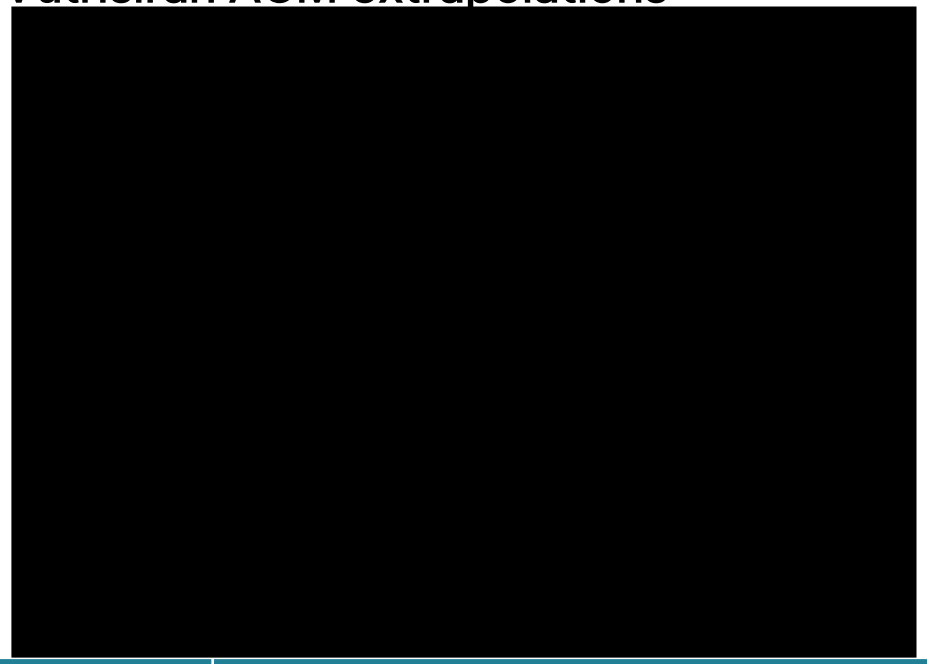
Abbreviations: AE, adverse event; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association; IPTW, inverse probability of treatment weighting; SAEs, serious adverse events; QALYs, quality-adjusted life years

Key issue: Modelling of treatment effectiveness (1/3)

Link to hazard rates

Parametric extrapolation of survival

Vutrisiran ACM extrapolations



Tafamidis ACM extrapolations

	Company preferred approach	EAG preferred approach
Vutrisiran	Log-logistic, capped by gen. population mortality	Exponential, capped by gen. population mortality
Tafamidis	Log-normal, capped by gen. population mortality	Same curve as vutrisiran (no treatment effect)

Company

- Preferred curves chosen using SEE and align with observed hazards in HELIOS-B

EAG

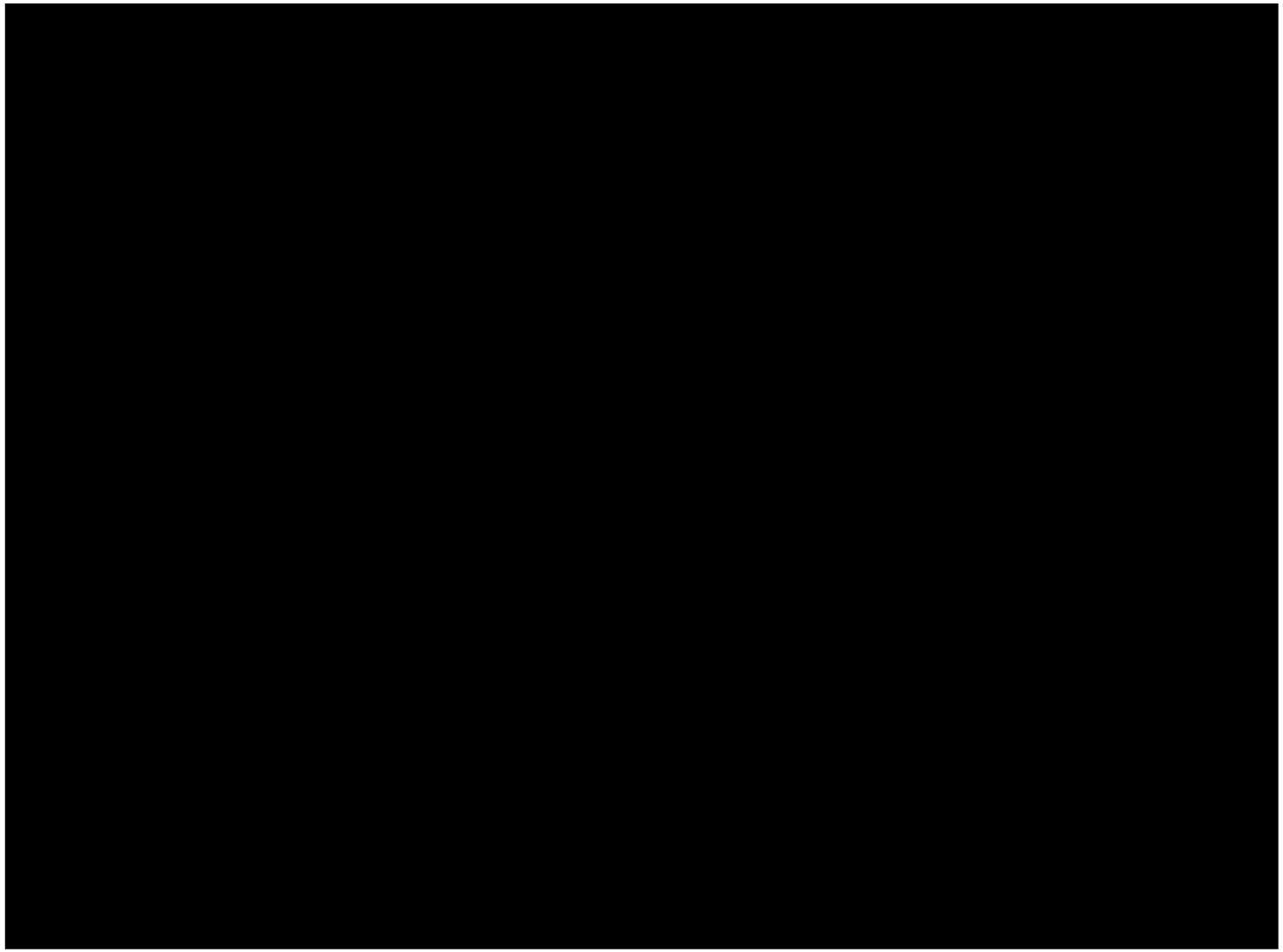
- Assumption of decreasing hazards implausible in long term
- Company approach likely overestimates difference in effect

- What are committee's preferred assumptions for extrapolation of survival?

Abbreviations: ACM, all-cause mortality; EAG, external assessment group; gen., general; SEE, structured expert elicitation

Key issue: Modelling of treatment effectiveness (2/3)

Company modelling of survival for vutrisiran and tafamidis monotherapy



Committee considerations:

1. Trajectory of individual vutrisiran monotherapy and tafamidis monotherapy KM curves considering baseline tafamidis use
2. Extrapolation of vutrisiran and tafamidis curves beyond trial period
3. Relationship between extrapolations and general population mortality curve

Abbreviations: KM, Kaplan-Meier

Link to transition matrices

Key issue: Modelling of treatment effectiveness (3/3)

NYHA health state transition probabilities

Background

- Company calculated transition matrices separately for vutrisiran and tafamidis informed by observed data from double-blind period of HELIOS-B, in which NYHA class was collected at each 6-month interval
- First 30 months (10 cycles): 6-month transition matrices estimated for each time interval in HELIOS-B and converted to corresponding 3-month transition matrices to align with cycle length
- Beyond 30 months: average of the last two observed 6-month transition matrices converted to 3-month transition matrix, and carried forward for remainder of time horizon – didn't use last observed period as transition probabilities from NYHA I, II or III to NHYA IV were implausible (all 0 for vutrisiran)

EAG

- Modelled treatment effectiveness implies greater effect than clinical data suggests → prefers to assume no treatment effect (same transition probabilities for tafamidis and vutrisiran)
- Transition probabilities may not accurately reflect disease progression over time horizon
- Some transition probabilities lack face validity and likely driven by distribution of disease severity at baseline → results in [redacted] transition events occurring in NYHA III and IV than NYHA I and II
- Transition probabilities to NYHA IV remain [redacted] from 30 months

- Are the observed transition probabilities applied in the model clinically plausible?
- What is committee's preferred approach to NYHA health state transition probabilities?

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association; SAEs, serious adverse events; QALYs, quality-adjusted life years

Key issue: Vutrisiran treatment effect waning

Background

Upon treatment discontinuation:

- Tafamidis: NYHA transitions based immediately on BSC
- Vutrisiran: treatment waning applied for NYHA transitions
- Mortality informed by BSC for both treatments

Company

- TTR trajectory after stopping suggests waning effect
- ~80% reduction in serum TTR vs baseline indicates remaining treatment effect
- Provided scenarios with 6-month and no waning effect

EAG

- Lack of empirical evidence for 80% TTR assumption
- Gradual treatment effect loss plausible but TTR levels below 80% only up to [redacted] after discontinuation
- Company base case implies treatment effect lost at 12 months rather than gradual treatment effect waning. Link to application of waning effect transition matrices

	Company base case	EAG base case
Vutrisiran effect waning point	12 months	0 months

Mean change in serum TTR from baseline following final dose of vutrisiran in double-blind period in HELIOS-B

[redacted]

- Is an 80% reduction in serum TTR from baseline appropriate to indicate clinical benefit?
- Is 12-month waning point, indicating continued treatment benefit beyond an 80% reduction in TTR, appropriate?
- Is gradual or sudden treatment effect waning after stopping vutrisiran and tafamidis appropriate?

Abbreviations: BSC, best supportive care; EAG, external assessment group; TTR, transthyretin

Key issue: Caregiver disutilities

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin amyloidosis; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NYHA, New York Heart Association

Background

- Caregiver disutilities sourced from study estimating EQ-5D-3L in 36 carers of people with hATTR used in HST9 (Inotersen, hATTR-PN)
- FAP stage utilities used as proxy for NYHA class utilities
- TA984 (Tafamidis, ATTR-CM): carer disutilities not included

NYHA class	Disutility mean value	Proportion with caregivers	Number of caregivers	Disutility per cycle per caregiver
I	-0.031	10%	1	-0.0031
II	-0.096	30%	1	-0.0288
III	-0.104	80%	2	-0.0832
IV	-0.130	100%	2	-0.13

EAG

- Uncertain whether caregiver disutilities should be considered
- Uncertain if disutilities are reflective of caregiver disutility by NYHA class in ATTR-CM population

Company

- Disutilities applied are appropriate proxy for ATTR-CM by NYHA class in absence of evidence for ATTR-CM
- Carer burden in ATTR-CM similar if not elevated compared with hATTR-PN, where caregiver disuilities were accepted in previous appraisals (HST9, HST10)

Patient, carer and clinical organisations

- ATTR-CM has significant impact on lives of carers who are often elderly spouses or children. Includes financial, emotional and psychological impact. Caregivers often experience chronic fatigue and isolation.

- Is it appropriate to consider caregiver disutilities in this evaluation?
- Is the carer burden in ATTR-CM comparable to that in hATTR-PN?
- If so, are the caregiver disutilities applied in the model likely to be reflective of ATTR-CM population?

Link to FAP and NYHA stages [22]

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Other considerations

Managed access

- Company has not made a managed access proposal

Uncertainty

- EAG notes uncertainty associated with modelling survival independently from changes in NYHA class since it does not appropriately reflect link between NYHA progression and mortality → leads to implausible survival extrapolations needing logical constraints (e.g. mortality capped by general population mortality)

Uncaptured benefits

Company notes:

- Vutrisiran is administered less frequently than tafamidis, which may be convenient for some people
- Health states based on NYHA classification do not fully capture the burden of neuropathy-related clinical manifestations present due to systemic TTR amyloid deposition in the peripheral and autonomic nerves in some people with ATTR-CM
- Vutrisiran has received a positive NICE recommendation for treating hereditary transthyretin-related amyloidosis in adults with stage 1 or stage 2 polyneuropathy (TA868)

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; EAG, external assessment group; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NYHA, New York Heart Association; TTR, transthyretin

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Summary of company and EAG base case assumptions

Assumption	Updated company base case	EAG base case
Appropriate comparator(s)	Tafamidis	Tafamidis and BSC
Modelling survival	Uses non-randomised HELIOS-B data from tafamidis and vutrisiran arms • Vutrisiran: Log-logistic, capped • Tafamidis: Log-normal, capped	No treatment effect between vutrisiran and tafamidis • Vutrisiran: Exponential, capped • Tafamidis: same curve as vutrisiran
Modelling NYHA health state transitions	Informed by observed data from HELIOS-B	No difference in transition probabilities between vutrisiran and tafamidis
Vutrisiran treatment effect waning	• Vutrisiran: 12-month waning point • Tafamidis: no waning period	No waning period for vutrisiran or tafamidis
Caregiver disutilities	Analyses presented with and without caregiver disutilities	Analyses presented with and without caregiver disutilities
Tafamidis and vutrisiran costs	• Excludes within-cycle correction for tafamidis • Treatment initiation in hospital and subsequent administration at home	• Includes within-cycle correction for tafamidis • Treatment initiation and administration by clinician

Abbreviations: BSC, best supportive care; EAG, external assessment group; NYHA, New York Heart Association

Summary of key issues and questions for committee (1/2)

Issue	ICER impact
Intervention and comparator(s) • Would vutrisiran be used as monotherapy or would vutrisiran be used in combination with tafamidis in clinical practice? • Is BSC an appropriate comparator? • If yes, how is BSC defined? • Is tafamidis supplied on a 3-month basis? • In what setting(s) would treatment with vutrisiran be initiated and administered?	Unknown
Uncertainty in the comparative clinical evidence • What is committee's view on the effectiveness of vutrisiran vs tafamidis?	Large
Modelling of treatment effectiveness • What are committee's preferred assumptions for extrapolation of survival? • Are the observed transition probabilities applied in the model clinically plausible? • What is committee's preferred approach to NYHA health state transition probabilities?	Large

Abbreviations: BSC, best supportive care; NYHA, New York Heart Association

Summary of key issues and questions for committee (2/2)

Issue	ICER impact
Vutrisiran treatment effect waning • Is an 80% reduction in serum TTR from baseline appropriate to indicate clinical benefit? • Is 12-month gradual waning period, indicating continued treatment benefit beyond an 80% reduction in TTR, appropriate? • Is gradual or sudden treatment effect waning after stopping vutrisiran and tafamidis appropriate?	Small
Caregiver disutilities • Is it appropriate to consider caregiver disutilities in this evaluation? • Is the carer burden in ATTR-CM comparable to that in hATTR-PN? • If so, are the caregiver disutilities applied in the model likely to be reflective of ATTR-CM population?	Small

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; ICER, incremental cost effectiveness ratio; TTR, transthyretin

Cost-effectiveness results are presented in Part 2 of the committee meeting because of confidential comparator discounts

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy

Supplementary appendix

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Issue: Tafamidis and vutrisiran costs

	Company base case	EAG base case
Tafamidis and vutrisiran acquisition cost within-cycle correction	• Excludes within-cycle correction for tafamidis and vutrisiran acquisition cost • Tafamidis supplied every 3 months (ref: NAC); vutrisiran administered every 3 months	• Align on vutrisiran within-cycle correction • Cannot verify that tafamidis supplied every 3 months – so includes within-cycle correction for tafamidis • Would be appropriate to exclude within-cycle correction if 3-month supply confirmed
Treatment initiation and administration costs for vutrisiran	• Aligned with updated SmPC (February 2025) which allows for patient self-administration or administration by caregiver • NAC intends for all patients on vutrisiran to initiate and continue treatment at home with availability of company-funded homecare	• Assumed to be administered by healthcare professional throughout time on treatment since it could not independently verify information provided by the company

- Is tafamidis supplied on a 3-month basis?
- In what setting(s) would treatment with vutrisiran be initiated and administered?

Abbreviations: EAG, external assessment group; NAC, National Amyloidosis Centre; SmPC, summary of product characteristics

Link to health state distributions over model time horizon

Issue: Modelling of ACM independently from NYHA classification

Background

- In each model cycle, contribution of each NYHA class to number of deaths is proportional to the number of people in the NYHA class at the start of the cycle and the relative hazard of mortality in that class, assuming 1.85-fold increase in HR for every increase in NYHA class (derived from the literature)

EAG

- Company's approach to model survival independently from changes in NYHA class does not appropriately reflect link between NYHA progression and mortality → introduces potential for inconsistencies in assumptions used for NYHA transition and mortality, leading to implausible survival extrapolations needing logical constraints over a relatively short time (e.g. mortality capped by general population mortality)
- Competing risks or multi-state survival analysis could formally link survival and NYHA class transitions – but HELIOS-B data insufficient to conduct this

Company

- Approach to modelling survival similar to NICE TA984 (Tafamidis in ATTR-CM)
- Approach to formally link survival and NYHA class transitions not advisable because:
  - Small numbers in NYHA classes I and III and no NYHA class IV at baseline
  - Relatively small number of mortality events in HELIOS-B so insufficient data to derive robust NYHA-specific survival estimates with competing risks for NYHA transitions

- Is company approach to modelling survival independently from NYHA classification acceptable?

Abbreviations: ATTR-CM, transthyretin amyloidosis cardiomyopathy; ACM, all-cause mortality; CV, cardiovascular; HR, hazard ratio; NYHA, New York Heart Association

Issue: Limited evidence on key subgroups

Link to HELIOS-B subgroup analyses

Background

- Final scope included the following subgroups: (i) severity of heart failure (by NYHA class); (ii) wild-type or hereditary ATTR-CM

Company

- Did not present modelling for subgroups listed in scope
- Neither HELIOS-B nor ATTR-ACT were powered to draw conclusions about efficacy in different subgroups
- HELIOS-B and ATTR-ACT are not comparable due to differences in populations; small participant numbers, so uncertainty of subgroup-specific ITCs or within-trial analyses would be high
- Vutrisiran demonstrated consistent clinical benefit vs placebo for all primary and secondary endpoints across all prespecified subgroups
- For NYHA III population, ATTR-ACT showed limited benefit of tafamidis vs placebo; HELIOS-B showed significant reduction in recurrent CV event risk for vutrisiran vs placebo

EAG

- Although the evidence is uncertain, variation in effectiveness across NYHA class and ATTR type may affect the choice of treatment for some patients.
- Formal modelling for subgroups would be desirable, but acknowledges limitations of such analyses

- Is modelling by NYHA class and ATTR type subgroup feasible and desirable?

NICE

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; ITC, indirect treatment comparison; NYHA, New York Heart Association

Summary of other issues and questions for committee

Issue	ICER impact
Limited evidence on key subgroups • Would modelling for NYHA class and ATTR type subgroups be plausible and desirable?	Unknown
Modelling of all-cause mortality independently from NYHA classification • Is the company approach to modelling survival independently from NYHA classification acceptable?	Unknown

Abbreviations: ATTR , transthyretin amyloidosis; ICER, incremental cost effectiveness ratio; NYHA, New York Heart Association

HELIOS-B baseline patient characteristics (1/2)

Link to main slides

	Includes participants receiving background tafamidis at baseline		Excludes participants receiving background tafamidis at baseline		Only participants receiving background tafamidis at baseline	
Parameter at baseline	**Overall population (N=654)**		**Monotherapy population (N=395)**		**Background tafamidis population (N=259)**	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=130)	Placebo (n=129)
Age at randomisation, median, years (range)	77.0 (45.0–85.0)	76.0 (46.0–85.0)	77.5 (46.0–85.0)	76.0 (53.0–85.0)	77.0 (45.0, 85.0)	75.0 (46.0, 85.0)
Male, n (%)	299 (91.7)	306 (93.3)	178 (90.8)	183 (92.0)	121 (93.1)	123 (95.3)
Disease type						
hATTR, n (%)	37 (11.3)	39 (11.9)	23 (11.7)	25 (12.6)	14 (10.8)	14 (10.9)
V122I, n (%)	24 (7.4)	25 (7.6)	13 (6.7)	16 (8.0)	[redacted]	[redacted]
wtATTR, n (%)	289 (88.7)	289 (88.1)	173 (88.3)	174 (87.4)	116 (89.2)	115 (89.1)
Time since diagnosis, median, years (range)	0.9 (0–11.1)	1.0 (0–10.8)	0.5 (0–8.3)	0.6 (0–6.2)	1.26 (0.0, 11.1)	1.53 (0.1, 10.8)
Tafamidis baseline use, n (%)	130 (39.9)	129 (39.3)	–	–	130 (100)	129 (100)
Time on tafamidis prior to start of study, median, months (range)	9.2 (1.1–65.3)	11.3 (1.1–65.5)	–	–	9.18 (1.1, 65.3)	11.30 (1.1, 65.5)

Used in model

Abbreviations: hATTR, hereditary transthyretin amyloidosis; wtATTR, wild-type transthyretin amyloidosis

HELIOS-B baseline patient characteristics (2/2)

Link to main slides

	Includes participants receiving background tafamidis at baseline		Excludes participants receiving background tafamidis at baseline		Only participants receiving background tafamidis at baseline	
	Overall population (N=654)		**Monotherapy population (N=395)**		**Background tafamidis population (N=259)**	
Parameter at baseline	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=130)	Placebo (n=129)
Tafamidis drop-in use, n (%)	44 (13.5)	41 (12.5)	44 (22.4)	41 (20.6)		
NYHA class						
I, n (%)	49 (15.0)	35 (10.7)	15 (7.7)	12 (6.0)	34 (26.2)	23 (17.8)
II, n (%)	250 (76.7)	258 (78.7)	172 (87.8)	169 (84.9)	78 (60.0)	89 (69.0)
III, n (%)	27 (8.3)	35 (10.7)	9 (4.6)	18 (9.0)	18 (13.8)	17 (13.2)
NAC stage						
1, n (%)	208 (63.8)	229 (69.8)	113 (57.7)	138 (69.3)	95 (73.1)	91 (70.5)
2, n (%)	100 (30.7)	87 (26.5)	68 (34.7)	55 (27.6)	32 (24.6)	32 (24.8)
3, n (%)	18 (5.5)	12 (3.7)	15 (7.7)	6 (3.0)	3 (2.3)	6 (4.7)
6-MWT, mean, metres (SD)	372.0 (103.7)	377.1 (96.3)	362.7 (102.7)	372.8 (98.1)	[redacted]	[redacted]
KCCQ-OS score, mean, points (SD)	73.0 (19.4)	72.3 (19.9)	70.3 (20.2)	69.9 (20.8)	[redacted]	[redacted]

Used in model

Abbreviations: 6-MWT, 6-minute walk test; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NAC, National Amyloidosis Centre; NYHA, New York Heart Association;

Link to main slides

Results for comparison between vutrisiran and tafamidis

	Vutrisiran vs tafamidis				
	Company-preferred within-trial comparison	Company unanchored MAIC	Company anchored MAIC	EAG NMA, Bayesian (HELIOS-B vs ATTR-ACT)	EAG NMA (HELIOS-B vs THAOS)
All-cause mortality HR (95% CI)	0.81 (0.50, 1.34)	[redacted]	[redacted]	0.89 (0.53, 1.43)	1.17 (0.73, 1.90)
Cardiovascular events IRR (95% CI)	0.82 (0.62, 1.08)	[redacted]	[redacted]	-	-
NYHA class, Difference in proportion with stable/improved from baseline (95% CI)	[redacted]	[redacted]	[redacted]	-	-
Comparison of absolute change in 6MWT, MD at 30 months (95% CI)	-	-	-	-12.16 (-36.16, 12.56)	-
Comparison of absolute change in KCCQ-OS, MD at 30 months (95% CI)	-	-	-	-4.80 (-15.96-8.34)	-

Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; MAIC, matching-adjusted indirect comparison; MD, mean difference; NMA, network meta-analysis; NYHA, New York Heart Association

Link to main slides

Additional information on THAOS study

- THAOS study collected ATTR natural history data in 6718 patients from 19 countries. Not clear if UK included.
- Analyses from THAOS looked at non-randomised 587 tafamidis-treated vs 854 tafamidis-untreated patients selected from the subset of symptomatic patients with a predominantly cardiac phenotype (N=1441).
- EAG analyses used survival results from post-2019 data in patients who received tafamidis monotherapy.
- Demographic data was not available for THAOS post 2019 data.

Abbreviations: ATTR, transthyretin amyloidosis; EAG, external assessment group; THAOS, Transthyretin Amyloidosis Outcomes Survey

Link to main slides

Health state distribution over model time horizon

Vutrisiran monotherapy arm

Tafamidis monotherapy arm

Application of treatment waning effects on transition matrices for vutrisiran monotherapy

Link to main deck

Cycles after vutrisiran monotherapy discontinuation (months)	Mean % TTR reduction from pretreatment baseline	Transition matrix weights (% contribution of the vutrisiran monotherapy matrices)		
		Company's original base case	Company's updated Base case	EAG's Base case
1 (0–3)	[redacted]	[redacted]	[redacted]	0%
2 (3–6)	[redacted]	[redacted]	[redacted]	0%
3 (6–9)	[redacted]	[redacted]	[redacted]	0%
4 (9–12)	[redacted]	[redacted]	[redacted]	0%
5 (12–15)	[redacted]	[redacted]	0%	0%
6 (15–18)	[redacted]	[redacted]	0%	0%
7 (18–21)	[redacted]	[redacted]	0%	0%
8 (21+)	[redacted]	[redacted]	0%	0%

Abbreviations: EAG, evidence assessment group; TTR, transthyretin

Link to main slides

FAP stages and NYHA classification

FAP stage	Criteria
0	No symptoms
1	Unimpaired ambulation; mostly mild sensory and motor neuropathy in the lower limbs
2	Assistance with ambulation needed; mostly moderate impairment progression to the lower limbs, upper limbs and trunk
3	Wheelchair-bound or bedridden; severe sensory and motor neuropathy of all limbs

Proxy (80%)

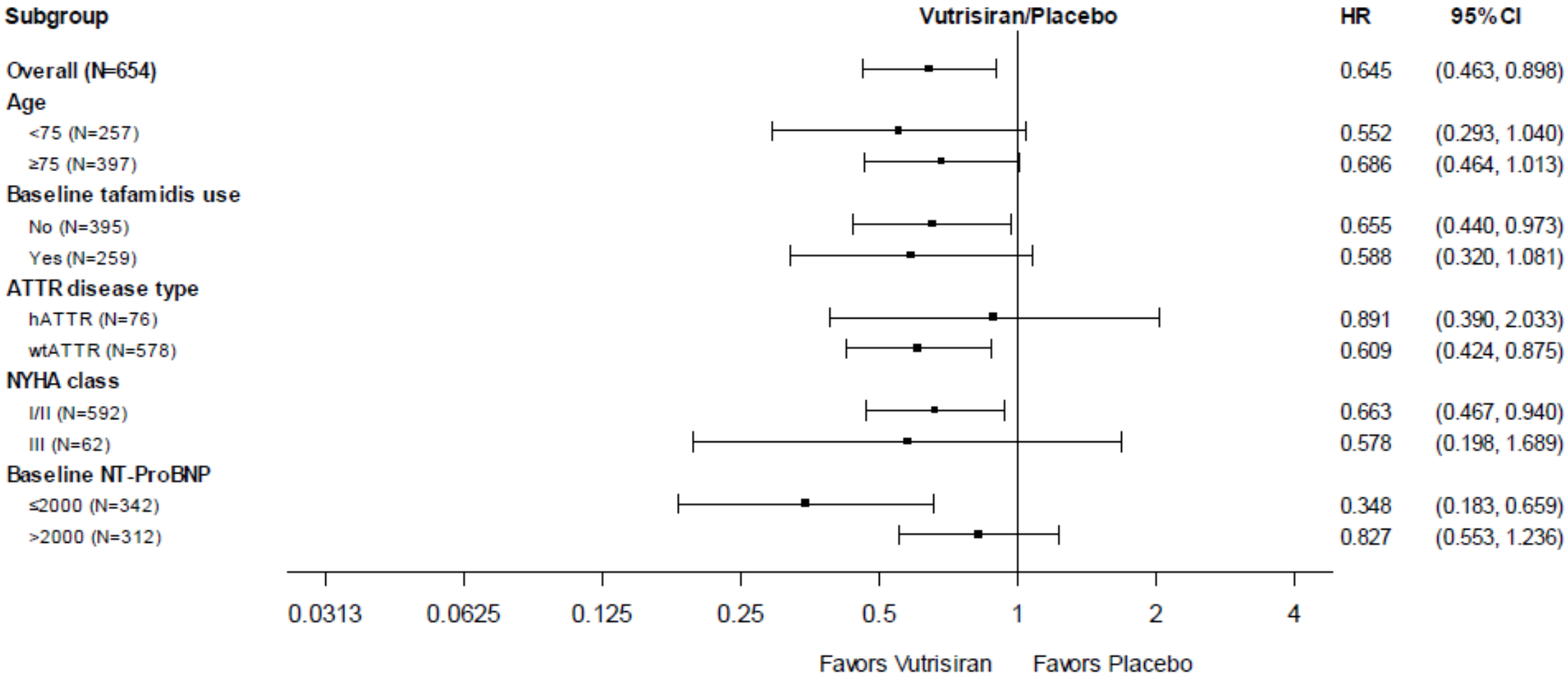
NYHA class	Criteria
1	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or shortness of breath.
2	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath, or chest pain.
3	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath, or chest pain.
4	Symptoms of heart failure at rest. Any physical activity causes further discomfort.

Abbreviations: FAP, Familial amyloid polyneuropathy; NYHA, New York Heart Association

HELIOS-B subgroup analyses (1/2)

Link to main slides

Forest plot: Subgroup analysis for ACM up to 42 months

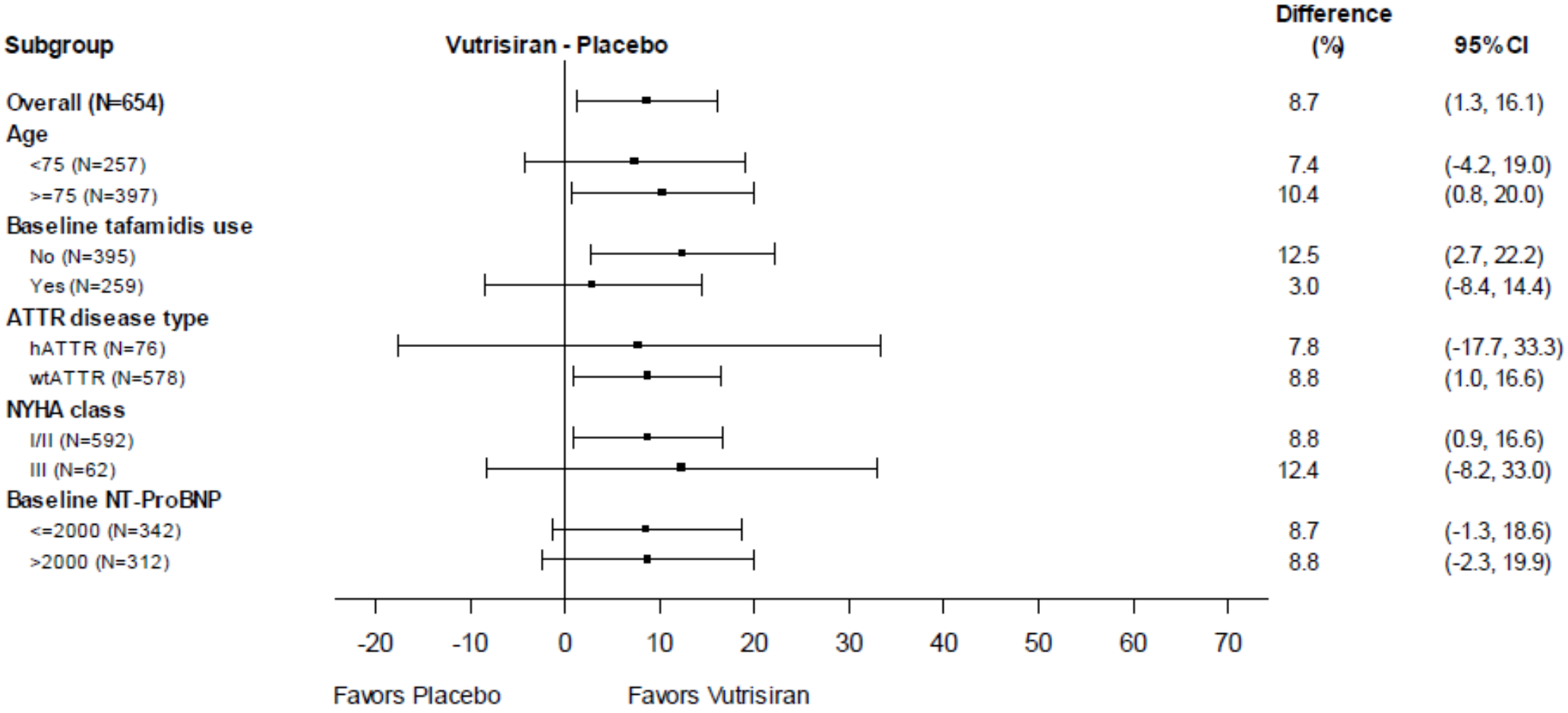


Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; NYHA, New York Heart Association

HELIOS-B subgroup analyses (2/2)

Link to main slides

Forest plot: Subgroup analysis for stable/improved NYHA class from baseline



Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; NYHA, New York Heart Association

Link to main slides

Comparison of hazard rates for parametric distributions fitted to survival

NYHA health state transition matrices (1/2)

Link to main slides

From NYHA class	To NYHA class health state											
	Vutrisiran monotherapy				Tafamidis monotherapy				BSC			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
Months 0–3 and 3–6 (Cycles 1 and 2)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 6–9 and 9–12 (Cycles 3 and 4)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 12–15 and 15–18 (Cycles 5 and 6)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											

Abbreviations: NYHA, New York Heart Association

NYHA health state transition matrices (2/2)

Link to main slides

From NYHA class	To NYHA class health state											
	Vutrisiran monotherapy				Tafamidis monotherapy				BSC			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
Months 18–21 and 21–24 (Cycles 7 and 8)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 24–27 and 27–30 (Cycles 9 and 10)*												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											
Months 30+ (base-case extrapolation phase, cycles 11+)												
I	[redacted]											
II	[redacted]											
III	[redacted]											
IV	[redacted]											

Abbreviations: NYHA, New York Heart Association