NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Alnylam
2. **Clarification questions and company responses**
3. **Patient group, professional group, and NHS organisation submission** from:
   a. Cardiomyopathy UK
   b. UK ATTR Amyloidosis Patients' Association (UKATPA)
   c. National Amyloidosis Centre
   d. NHS England
4. **NICE medicines optimisation team (MOT) report**
5. **Expert responses to questions from the NICE technical team** from:
   a. Professor Marianna Fontana, Professor of Cardiology – clinical expert, nominated by Alnylam
   b. Professor Julian Gillmore, Centre Head and Research Lead - nominated by National Amyloidosis Centre
6. **External Assessment Report** prepared by PenTAG:
   a. Main report
   b. Appendix
7. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]

Document B

Company evidence submission

October 2022

File name	Version	Contains confidential information	Date
ID5074_Vutrisiran_Document B_[Redacted]	2	No	17 Oct 2022

Contents

List of tables

List of figures

List of abbreviations

Term	Definition
10-MWT	10-metre walk test
AE	adverse event
AIC	Akaike information criterion
ATTR amyloidosis	transthyretin-mediated amyloidosis
BIC	Bayesian information criterion
BL	baseline
BMI	body mass index
BSC	best supportive care
CEA	cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COMPASS-31	Composite Autonomic Symptom Score-31
CV	cardiovascular
EC	European Commission
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ERG	Evidence Review Group
ESC	enhanced stabilisation chemistry
EU	European Union
FAERS	FDA Adverse Events Reporting System
FAP	familial amyloid polyneuropathy
FDA	US Food and Drug Administration
GalNAc	N-acetylgalactosamine
GI	gastrointestinal
hATTR amyloidosis	hereditary transthyretin-mediated amyloidosis
HBV	hepatitis B virus
HCP	healthcare provider
HCRU	healthcare resource use
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HST	highly specialised technologies
HTA	health technology assessment
ICH	International Conference on Harmonisation
INR	international normalised ratio

Term	Definition
IRR	infusion-related reaction
ITC	indirect treatment comparison
IV	intravenous
KM	Kaplan-Meier
KPS	Karnofsky performance status
LNP	lipid nanoparticle
LS	least squares
mBMI	modified body mass index
MCID	minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
mNIS+7	modified Neuropathy Impairment Score+7
MoA	mechanism of action
mRNA	messenger RNA
NAC	National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score – Lower Limbs
NIS-W	Neuropathy Impairment Score – Weakness
NMA	network meta-analysis
Norfolk QOL-DN	Norfolk Quality of Life – Diabetic Neuropathy
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
ODD	Orphan Drug Designation
OR	odds ratio
OWSA	one-way sensitivity analysis
PBO	placebo
PBP	postural blood pressure
PD	pharmacodynamics
PK	pharmacokinetic
PNS	Peripheral Nerve Society
PND	polyneuropathy disability
Q3M	quarterly
Q3W	every 3 weeks
QALY	quality-adjusted life-year

Term	Definition
QOL	quality of life
QST	quantitative sensory testing
Q1W	once per week
RDI	relative dose intensity
R-ODS	Rasch-built Overall Disability Score
RNA	ribonucleic acid
RNAi	RNA interference
RR	risk ratio
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SEM	standard error of the mean
siRNA	small interfering RNA
SLR	systematic literature review
SmPC	Summary of Product Characteristics
THAOS	Transthyretin Amyloidosis Outcomes Survey
ToT	time on treatment
TTR	transthyretin
UK	United Kingdom
UPCR	urine protein creatinine ratio
ZBI	Zarit Burden Interview

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

B.1.1 Decision problem

The submission covers the full marketing authorisation of vutrisiran, namely, for the treatment of adults with hereditary transthyretin-mediated (hATTR) amyloidosis with stage 1 or stage 2 polyneuropathy.[1]

The submission covers the full population for the comparator, patisiran, as recommended by NICE in Highly Specialised Technology guidance (HST)10,[2] which is identical to the population indicated for treatment with vutrisiran.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hereditary transthyretin-related amyloidosis and stage 1 or stage 2 polyneuropathy.	hATTR amyloidosis in adult patients with FAP stage 1 or stage 2 polyneuropathy.	Equivalent to the NICE final scope. The population is defined according to the UK marketing authorisation for consistency.[1] This is identical to the population in the final recommendation in HST10 for the comparator, patisiran.[2]
Intervention	Vutrisiran	Vutrisiran	In line with NICE final scope
Comparator(s)	• Patisiran • Inotersen	Patisiran	[redacted] and [redacted], have informed Alnylam that they foresee vutrisiran supplanting patisiran as the standard of care considered as first-choice therapy for patients with hATTR amyloidosis with polyneuropathy in the UK. In view of its intended use and the body of evidence showing clinical efficacy similar to that of patisiran (with additional benefits related to SC administration), with the proposed PAS, vutrisiran is expected to provide similar or greater health benefits at similar or lower cost than those provided by patisiran in the identical patient population. Thus, vutrisiran is anticipated to displace patisiran in the current clinical pathway of care. Rationale for not including inotersen as a comparator includes: • Inotersen does not occupy the same clinical pathway position as patisiran. Patisiran is the standard of care and is considered as the first-choice therapy for patients. NAC

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			clinicians note that inotersen is rarely used in the UK due to limitations with its safety and efficacy profiles, as evidenced by their real-world clinical experience with inotersen.[3] • The limitations and subsequent rarity of use of inotersen are reflected in its market share. In the UK, the current market share of inotersen is [redacted] vs. [redacted] for patisiran, based on communication with NAC clinicians.[3] • Notably, the share of patisiran has [redacted] from [redacted] market share in January 2022 (estimated based on communications with NAC clinicians). This is despite the fact that inotersen and patisiran were both appraised by NICE in 2019 and inotersen was recommended by NICE 3 months prior to patisiran. The observation of a small market share which continues to decline highlights the plausibility that no (or only very few) patients in England will be receiving inotersen in the near future. Further explanation of the rationale behind exclusion of inotersen as a comparator is provided in B.1.3.5.3 Current therapies.
Outcomes	The outcome measures to be considered include: • Overall survival • Neurological impairment	The outcome measures addressed in this submission include: • Neurological impairment	**Overall survival** Assessment of potential treatment effects on overall survival was not an objective of the pivotal HELIOS-A trial for vutrisiran.[4] Accordingly, the study did not include an efficacy assessment of overall survival/mortality (deaths were recorded in safety monitoring).[4] Notably, the pivotal trial of patisiran, APOLLO—the primary data source for patisiran in HST10[2]—similarly did not

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Symptoms of polyneuropathy • Cardiac function • Autonomic function (including the effects on the gastrointestinal system and postural hypotension) • Weight loss • Effects of amyloid deposits in other organs and tissues (including the eye) • Serum TTR • Motor function • Adverse effects of treatment • HRQoL	• Symptoms of polyneuropathy • Autonomic function (including the effects on the gastrointestinal system and postural hypotension) • Weight loss • Serum TTR • Motor function • Adverse effects of treatment • HRQoL	include overall survival as an efficacy outcome,[5] and there were few observed deaths during the course of that study.[6,7] The HELIOS-A design was largely informed by the APOLLO study, and both studies were of commensurate size and duration. Therefore, Alnylam does not believe that overall survival is an appropriate or realistic outcome measure for this appraisal. However, safety information, including deaths, will be reported as part of the evidence submission. **Cardiac function** Consistent with the regulatory indication of vutrisiran as reflected in the UK and EU SmPCs,[1,8] Alnylam is seeking a NICE recommendation for vutrisiran in the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Alnylam believes that cardiac function should be excluded from this submission because a separate trial is ongoing to evaluate vutrisiran in patients with ATTR amyloidosis with cardiomyopathy,[9] and thus it would be premature and out of scope to consider cardiac outcomes within the present appraisal. **Effects of amyloid deposits in other organs and tissues (including the eye)** These outcomes were not addressed in HELIOS-A.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	A cost-comparison model has been developed for comparison of vutrisiran versus patisiran, which is the current standard of care for patients in the UK with hATTR amyloidosis with polyneuropathy.	NAC clinicians highlight vutrisiran will supplant patisiran as the standard of care for patients with hATTR amyloidosis with polyneuropathy in the UK. Therefore, Alnylam considers a cost-comparison evaluation appropriate for vutrisiran for treating hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, as vutrisiran is likely to provide similar or greater health benefits, at a similar or lower cost compared to patisiran in the same indication.[1,10,11] Vutrisiran and patisiran show a high degree of comparability in terms of treatment efficacy, in particular: • They demonstrate similar biological activity against TTR, the causative agent in hATTR amyloidosis with polyneuropathy, as demonstrated by the non-inferiority of vutrisiran versus patisiran in terms of reduction in serum TTR levels in a prespecified analysis in HELIOS-A.[4] • The EMA CHMP assessment report and the MHRA Orphan Drug Designation Assessment Report for vutrisiran both concluded comparable results in clinical endpoints between vutrisiran and patisiran in HELIOS-A[12,13] based on post hoc analyses which compared the two arms at Month 18 of the study. Vutrisiran and patisiran showed numerically comparable efficacy against clinical manifestations of hATTR amyloidosis with polyneuropathy. These post hoc findings are consistent with the observation of comparable reductions in serum TTR and can be explained by the shared mechanism of action and similar pharmacodynamic activity between patisiran and vutrisiran.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• Vutrisiran and patisiran showed comparable clinical efficacy in terms of morbidity and HRQoL, consistent with the demonstration of similar biologic activity in an NMA (B.3.9 Indirect and mixed treatment comparisons) that examined a comprehensive set of relevant data from clinical trials of vutrisiran and patisiran in patients with hATTR amyloidosis with polyneuropathy.[14] In addition to efficacy, vutrisiran and patisiran demonstrated comparable safety profiles in HELIOS-A;[4] however, IRRs associated with the IV infusion of patisiran represent an AE that is not associated with the use of vutrisiran. The cost-comparison analysis presented in this submission does not include AE-related costs despite the IRRs associated with patisiran administration, such that this analysis can be considered conservative. In addition to demonstrating comparable efficacy to patisiran, vutrisiran provides several additional advantages to patients with hATTR amyloidosis with polyneuropathy, their caregivers, HCPs, and NHS England, primarily due to the Q3M SC administration of vutrisiran versus the more frequent and burdensome Q3W IV administration of patisiran.[1,10] As the manufacturer of vutrisiran and patisiran, [redacted]. The cost-comparison analysis demonstrates the potential cost reductions that vutrisiran provides to the UK healthcare system, compared to patisiran. Alnylam has developed and presented this cost-comparison model without health states, as any health-state–associated costs

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			between vutrisiran and patisiran should be equal given their comparable clinical efficacy and comparable rates of discontinuation demonstrated (HELIOS-A).[4] For the submitted cost-comparison model, 5 years was selected as an adequate time horizon to demonstrate differences in the costs associated with vutrisiran and patisiran, in alignment with recently published NICE cost-comparison appraisals that used the same time horizon (TA734 and TA803).[15,16]

AE, adverse event; ATTR, transthyretin amyloidosis; CHMP, committee for Medicinal Products for Human Use; EMA, European Medicines Agency; EU, European Union; FAP, familial amyloid polyneuropathy; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; HCP, healthcare professional; HRQoL, health-related quality of life; HST, Highly Specialised Technology guidance; IRR, infusion-related reaction; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; NAC, National Amyloidosis Centre; NHS, National Health Service; NMA, network meta-analysis; PAS, Patient Access Scheme; Q3M, quarterly; Q3W, once every 3 weeks; SC, subcutaneous; SmPC, Summary of Product Characteristics; TTR, transthyretin; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

In appendix C include the Summary of Product Characteristics or information for use, and the UK public assessment report, scientific discussion or drafts.

Table 2: Technology being evaluated

UK approved name and brand name	Vutrisiran (AMVUTTRA™)
Mechanism of action	Vutrisiran is a chemically stabilised double-stranded siRNA that specifically targets variant and wild-type TTR mRNA and is covalently linked to a ligand containing three GalNAc residues to enable delivery of the siRNA to hepatocytes.[1] Through a natural process called RNAi, vutrisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in the reduction of variant and wild-type serum TTR protein levels.[1]
Marketing authorisation/CE mark status	EC marketing authorisation for vutrisiran was granted on 15 September 2022.[8] The CHMP posted a positive opinion for the market authorisation of vutrisiran on 21 July 2022.[17] MHRA approval of vutrisiran was granted 16 September 2022.[1]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	MHRA SmPC indication:[1] Vutrisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.
Method of administration and dosage	The recommended dose of vutrisiran is 25 mg administered via SC injection Q3M.[1]
Additional tests or investigations	None required
List price and average cost of a course of treatment	The pack price submitted to DHSC per pre-filled syringe of vutrisiran (25 mg in 0.5 mL solution for injection) is £95,862.36. Average yearly treatment with vutrisiran is estimated at £383,449.44.
Patient access scheme/commercial arrangement (if applicable)	A confidential PAS discount has been proposed for vutrisiran of [redacted]%, leading to a with-PAS price of £[redacted] per pack.

CHMP, Committee for Medicinal Products for Human Use; DHSC, Department of Health and Social Care; EC, European Commission; EU, European Union; GalNAc, *N*-acetylgalactosamine; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; MHRA, Medicines and Healthcare products Regulatory Agency; mRNA, messenger ribonucleic acid; PAS, Patient Access Scheme; Q3M, quarterly; RNAi, ribonucleic acid interference; SC, subcutaneous; siRNA, small interfering ribonucleic acid; TTR, transthyretin; UK; United Kingdom.

B.1.3 Health condition and position of the technology in the treatment

Hereditary transthyretin-mediated (hATTR) amyloidosis

- hATTR amyloidosis is a rare, inherited, rapidly progressive, debilitating, and fatal disease caused by misfolded transthyretin (TTR) that accumulates as amyloid deposits in multiple tissues including the nerves, heart, and gastrointestinal (GI) tract.[18-21]
- From disease onset, the multiple disease manifestations of hATTR amyloidosis impose a substantial burden on patients,[22,23] caregivers,[24,25] and healthcare resources.[24,26-28] This burden increases over time as the rapid progression of sensorimotor neuropathy symptoms leads to increasing disability, ultimately resulting in complete loss of ambulation and confinement to a wheelchair, and death.[22]
- The multiple disease manifestations (motor, sensory and autonomic) in hATTR amyloidosis with polyneuropathy are associated with a profound and rapid worsening of HRQoL, starting from the early stages of the disease.[20,23,29]
- hATTR amyloidosis with polyneuropathy has a considerable effect on patients' independence, dignity, and their ability to work, take part in family and social life, and carry out daily activities.[2]

Current treatment options and clinical pathway of care

- Patisiran is the current standard of care and is considered as the first-choice therapy for treatment-eligible patients with hATTR amyloidosis with polyneuropathy in England, with an estimated market share greater than [redacted]. The only other NICE-approved therapy, inotersen, is rarely used due to limitations with its safety and efficacy profiles, as evidenced by real-world clinical experience.[3]
- Amongst current NICE-recommended therapies for hATTR amyloidosis with polyneuropathy, patisiran is the only therapy that has been shown to halt polyneuropathy progression or improve polyneuropathy and HRQoL relative to patients' pre-treatment baseline in a substantial proportion of patients.[6,30,31] Nevertheless, there are still remaining unmet medical needs for patients who receive treatment with patisiran. Specifically, patisiran has limitations associated with its frequent dosing (every 3 weeks [Q3W]) and intravenous (IV) administration, which places added burden on patients, caregivers, healthcare providers (HCPs), and the NHS. IV administration of patisiran also carries the potential for IRRs and infusion-related complications, which can have serious implications for patients.
- A summary of the burden for patients, caregivers, HCPs, and the NHS regarding patisiran use is provided in B.1.3.5.4 Unmet need.

Unmet Need

- Additional treatment options are needed that:
    - Have efficacy comparable to that of patisiran in reducing TTR levels, halting or reversing polyneuropathy, and improving HRQoL.
    - Offer a favourable safety profile with no anticipated need for patient monitoring.

- Have the ability to reduce treatment burden and time requirements for patients, HCPs, and caregivers by offering administration that is minimally invasive, simplified, and less frequent, relative to the current standard of care.

Vutrisiran

- Vutrisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.[1]
- Vutrisiran has demonstrated a comparable efficacy profile to patisiran.
  - Compared to patisiran, vutrisiran demonstrated non-inferior reduction of serum TTR in HELIOS-A in a pre-specified statistical comparison.[4]
  - In agreement with the observation of similar pharmacodynamic activity in lowering serum TTR, which is the causative agent in the disease process of hATTR amyloidosis, a post hoc analysis of the vutrisiran and patisiran arms in HELIOS-A demonstrated comparable efficacy in clinical outcomes at Month 18. This analysis was noted by the CHMP in their assessment report which concluded that comparable efficacy was demonstrated.[12] The post hoc analysis was additionally noted to demonstrate comparable efficacy between patisiran and vutrisiran in the MHRA orphan drug report for vutrisiran.[13]
  - Similarly, a network meta-analysis (NMA) that compared vutrisiran and patisiran using data from both available pivotal clinical trials for these medicines (APOLLO and HELIOS-A) reaffirmed comparable clinical efficacy regarding ambulatory ability, polyneuropathy impairment, and HRQoL.[14]
- Compared to patisiran, which is administered via IV infusion Q3W, vutrisiran offers the benefit of less frequent dosing and less burdensome administration, through fixed-dose subcutaneous (SC) injection administered quarterly (Q3M).[1] The effects of this change in administration not only decrease the time-related burdens of treatment, but also increase safety for patients by obviating the risks associated with IV infusion including IRRs.

Anticipated place of vutrisiran in therapy

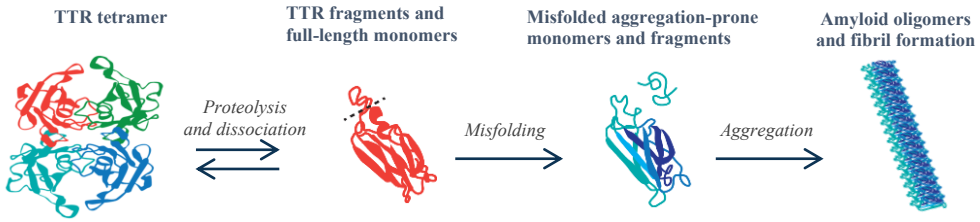
- Based on input from clinical experts and the advantages that vutrisiran provides versus patisiran, vutrisiran is expected to supplant patisiran as the standard of care and to be considered in all treatment-eligible patients with hATTR amyloidosis with polyneuropathy as the first-choice therapy.[3]
- In view of the intended use of vutrisiran by clinicians, the body of evidence showing clinical efficacy comparable to that of patisiran, the advantages of its subcutaneous dosing, and the proposed confidential patient access scheme (PAS), vutrisiran is likely to provide similar or greater health benefits at a similar or lower cost than those provided by patisiran in the identical patient population.

B.1.3.1 Disease overview

hATTR amyloidosis is an inherited, autosomal dominant, progressive, debilitating disease caused by the accumulation of amyloid fibrils consisting of both variant and wild-type TTR.[18,32] It is a multisystem disease with heterogeneous clinical presentation that includes sensory, motor, and autonomic (e.g., diarrhoea, sexual dysfunction, orthostatic intolerance) polyneuropathy and cardiomyopathy, with the potential involvement of other organ systems as well.[18,31-33]

Primarily produced in the liver, TTR functions as a transport protein for thyroxine and vitamin A.[18,34] TTR is a tetrameric protein composed of four monomers.[18] In the case of transthyretin-mediated (ATTR) amyloidosis, the tetrameric protein destabilises into unstable monomers and TTR fragments that can misfold and form amyloid fibril deposits in multiple organs, including the peripheral nervous system, heart, and GI tract, leading to cellular injury and organ dysfunction with corresponding clinical manifestations (Figure 1).[18,19,32,35]

Figure 1: Pathophysiology of hATTR amyloidosis



hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; TTR, transthyretin.
Source: Hawkins et al, 2015[18]; Kittleson et al, 2020[36]; Koike and Katsuno, 2019[37]

B.1.3.2 Clinical presentation and staging

The main clinical features of hATTR amyloidosis were presented to NICE in Section B of the company submission for HST10.[2] Table 3 provides an overview of two of the most widely used clinical staging systems in hATTR amyloidosis with polyneuropathy.[22] The familial amyloid polyneuropathy (FAP) staging system was originally developed to classify the disease based largely on the patient's ability to ambulate.[38] In the UK Summary of Product Characteristics (SmPC), vutrisiran is indicated for the treatment of adult patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy, as defined by FAP stage.[1] The polyneuropathy disability (PND) score is based on both sensory and motor impairment, and the associated impact on ambulation.[39] Higher scores on each of the staging systems are indicative of greater disease severity.[40]

Table 3: Clinical staging in hATTR amyloidosis

FAP stage*	PND score
Stage 0 – No symptoms **Stage 1** – Unimpaired ambulation **Stage 2** – Assistance with ambulation required **Stage 3** – Wheelchair-bound or bedridden	**Stage 0** – No symptoms **Stage I** – Sensory disturbances but preserved walking capability **Stage II** – Impaired walking capacity but ability to walk without a stick or crutches **Stage IIIA** – Walking with the help of one stick or crutch **Stage IIIB** – Walking with the help of two sticks or crutches **Stage IV** – Confined to a wheelchair or bedridden

*hATTR amyloidosis with peripheral neuropathy was historically referred to as FAP or TTR-FAP.[22]
FAP, familial amyloid polyneuropathy; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; PND, polyneuropathy disability.
Source: Coutinho et al, 1980[38]; Suhr et al, 1994[39]

B.1.3.3 Epidemiology of hATTR amyloidosis in the UK

Clinical experts from the NAC have informed Alnylam that they estimate there are [redacted] patients with hATTR amyloidosis with polyneuropathy in England.[3] In the Medicines and Healthcare products Regulatory Agency (MHRA) Orphan Drug Assessment Report for vutrisiran, an estimate of 235 patients with hATTR amyloidosis with polyneuropathy in Great Britain is suggested.[13]

B.1.3.4 Burden of disease

B.1.3.4.1 Clinical burden

In the absence of effective disease-modifying therapy, hATTR amyloidosis is a progressive, debilitating, and ultimately fatal disease.[41-43] hATTR amyloidosis imposes a substantial burden from the time of disease onset, with patients presenting with peripheral neuropathy (sensory and motor), autonomic neuropathy, GI impairment, cardiomyopathy, nephropathy, and/or ocular involvement.[22] Rapid progression of sensorimotor neuropathy symptoms leads to increased disability over time.[22] Progressive peripheral and autonomic neuropathy can also lead to inanition, causing infection or starvation.[16] Inanition is a leading cause of mortality in patients with hATTR amyloidosis with polyneuropathy.[44] Median survival from the time of diagnosis in hATTR amyloidosis with polyneuropathy has been found to be 4.7 years,[45] and survival from the time of symptom onset can range from 3 to 15 years.[46]

B.1.3.4.2 Patient burden: Health-related quality of life (HRQoL)

hATTR amyloidosis has a considerable effect on patients' independence, dignity, and their ability to work, take part in family and social life, and carry out daily activities.[2] Symptomatic patients have a reduced HRQoL at disease onset compared with the general, healthy population.[23] Significant impairments in HRQoL, measured using the Norfolk QoL – Diabetic Neuropathy (Norfolk QoL-DN) and EQ-5D assessment tools, have been observed in patients with hATTR amyloidosis compared to age-matched controls across a wide range of age groups (18 to 34 years, 35 to 49 years, 50 to 64 years, and 65 years and older).[23] HRQoL impairment worsens over time, as evidenced by a significant relationship between worsening scores on the Norfolk QoL-DN questionnaire and increasing duration of symptoms among symptomatic patients with hATTR amyloidosis.[29,47] The progressive worsening of HRQoL begins early in the disease course, with rapid deterioration in all five domains of the Norfolk QoL-DN score (activities of daily living, physical function/large fibre neuropathy, small-fibre neuropathy, symptoms, and autonomic neuropathy) observed over time for patients in FAP stages 1 and 2.[29] The initial worsening in Norfolk QoL-DN score is 9.12 points per year of symptom duration on average, until HRQoL impairment would be predicted to reach a maximum (i.e., worst possible level of impairment) after approximately 19 years.[47] In addition, the Rasch-built Overall Disability Score (R-ODS), which measures the degree of limitations on everyday activities and social participation, has also been shown to decrease in patients with hATTR amyloidosis.[4] Importantly, patisiran and vutrisiran have both been shown to maintain or improve HRQoL in patients with hATTR amyloidosis (B.3.6 Clinical effectiveness results).[4,6]

B.1.3.4.3 Caregiver burden

The polyneuropathy caused by hATTR amyloidosis progressively limits patients' autonomy, impairing their ability to perform activities of daily living, and impacts their HRQoL substantially.[22,23] As polyneuropathy progresses, patients may lose the ability to walk unaided and become wheelchair-bound or bedridden and increasingly dependent on others for care.[22] Caregiver burden (resulting from this dependence of patients on others for care) typically affects an older population that may be struggling with health issues of their own,

including age-related physical and cognitive declines, chronic illness, and some level of disability.[48]

In a cross-sectional online survey of caregivers (n=36) for patients with hATTR amyloidosis that included UK caregivers and was piloted and reviewed by the UK Amyloidosis Research Consortium (ARC), providing practical and emotional care was found to take an average 5.8 and 4.1 hours, respectively, per day.[49] Additionally, it was shown caregivers had significantly higher anxiety and depression compared to the matched general population.[49] The impact of hATTR amyloidosis on caregiver QoL has also been evaluated in a cross-sectional, noninterventional survey of adult patients (n=60) with hATTR amyloidosis and nonpaid caregivers (n=32) in Spain and the US.[25] The mean age for caregivers was 57.0 years in the US and 52.8 years in Spain, and the majority of caregivers in both countries were spouses or partners of affected patients.[25] On average, caregivers reported spending more than 45 hours per week caring for patients and had a mean Zarit Burden Interview (ZBI) score of 34.3, which is comparable to the caregiver burden reported in Alzheimer disease.[25] The survey reported particularly poor QoL among caregivers who also have the disease.[24,25]

These data suggest that caregivers for patients with hATTR amyloidosis in the UK face high levels of burden, and thus treatments that decrease this burden of care are needed.

B.1.3.4.4 Economic burden

Healthcare costs

In the NICE appraisal of patisiran (HST10), UK-specific healthcare resource utilisation (HCRU) costs for patients with hATTR amyloidosis according to PND score were estimated by a Delphi panel to be [redacted][2] These costs did not include the use of disease modifying therapies and were centred around polyneuropathy-related costs to the NHS and PSS.[2] The observation of comparable clinical effectiveness between vutrisiran and patisiran suggests a similar disease trajectory and, by extension, similar HCRU needs for managing disease manifestations (as reflected by different possible disease states) in patients receiving either therapy. However, it is important to note that patisiran, relative to vutrisiran, is associated with added costs due the requirement for more frequent administration, the need for complex IV administration, and required premedications.

B.1.3.5 Clinical pathway of care, unmet need and place of vutrisiran in therapy

B.1.3.5.1 Overview

Patisiran is the current standard of care and is considered the first-choice therapy for all treatment-eligible patients with hATTR amyloidosis with polyneuropathy in England. Patisiran is currently the only NICE recommended therapy in the UK that halts or reverses the progression of polyneuropathy relative to pre-treatment baseline in a substantial proportion of patients and significantly improves HRQoL from pre-treatment baseline in patients with hATTR amyloidosis with polyneuropathy.[6]

The only other NICE recommended therapy for patients with hATTR amyloidosis with polyneuropathy, inotersen, is rarely used in the UK, due to challenges encountered by clinicians in their real-world clinical experience with inotersen.[3] There are also safety issues associated with inotersen that include special warnings and contraindications on the UK product label.[50]

Although patisiran is currently the standard of care for hATTR amyloidosis with polyneuropathy, the administration profile of patisiran, which is weight-based and includes an IV infusion once every 3 weeks (Q3W), necessitates a time-consuming administration

procedure (approximately [redacted] hours), In addition, it requires premedication to reduce infusion related reactions (IRRs) and patient monitoring for IRRs by HCPs during and after treatment.[10] The IV infusion of patisiran also places a strain on the National Amyloidosis Centre (NAC), which is the setting for initial infusions, and NHS homecare delivery services for subsequent infusions.

Thus, there is a need for a treatment option with:

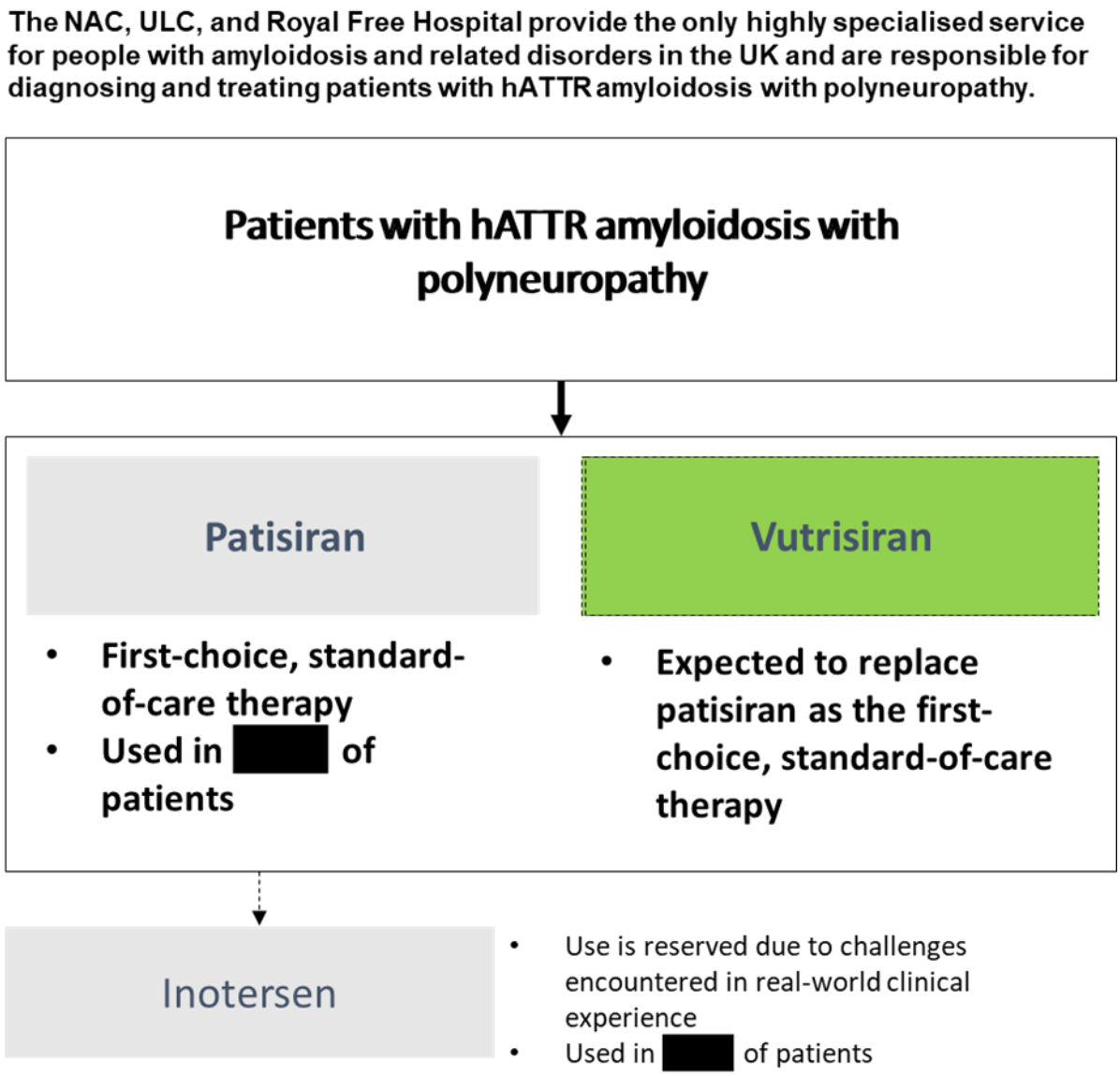
- Comparable efficacy as patisiran in halting or reversing polyneuropathy and improving HRQoL.
- A dosing scheme that is not weight-based to minimise dosing errors.
- A favourable safety profile (without IRRs) with no need anticipated for patient monitoring.
- No requirement for premedications.
- The ability to reduce treatment burden and time requirements for patients, HCPs, and caregivers.

Vutrisiran provides comparable efficacy to patisiran (described in B.3.6 Clinical effectiveness results and B.3.9 Indirect and mixed treatment comparisons) but offers a less burdensome administration profile through its Q3M SC dosing. Based on its clinical profile and the proposed confidential PAS for vutrisiran, vutrisiran is likely to provide similar or greater health benefits at similar or lower cost than those provided by patisiran. Thus, vutrisiran is expected by UK clinicians to supplant patisiran,[3] decreasing the aforementioned burdens associated with patisiran, which will benefit patients, caregivers, HCPs, and the NHS.

B.1.3.5.2 Clinical pathway of care

A representation of the clinical pathway of care for patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy in the UK is presented in Figure 2.

Figure 2: Clinical pathway of care for patients with hATTR amyloidosis with polyneuropathy in the UK



hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; NAC, National Amyloidosis Centre; ULC, University College London; UK, United Kingdom. Source: Figure generated from communications with key opinion leaders.[3]

B.1.3.5.3 Current therapies

A summary of the NICE-recommended therapies for patients with hATTR amyloidosis with polyneuropathy in the UK is provided in Table 4.

Table 4: Current therapies recommended in the UK for patients with hATTR amyloidosis with polyneuropathy

Approved therapies	**Patisiran (ONPATTRO)[11]**	**Inotersen (TEGSEDI)[50]**
Market authorisation holder	Alnylam Pharmaceuticals	Akcea Therapeutics
Marketing authorisation	hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy	Stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis
MoA	siRNA-mediated degradation of TTR mRNA in the liver	ASO-mediated degradation of TTR mRNA in the liver
Dose	0.3 mg/kg	284 mg
ROA	IV	SC
Frequency	Q3W	Q1W
Contraindications	• Hypersensitivity to active substance or any medication excipients	• Hypersensitivity to the active substance or any medication excipients • Platelet count <100 x 10^9/L prior to treatment • UPCR ≥113 mg/mmol (1 g/g) prior to treatment • eGFR <45 mL/min/1.73m^2 • Severe hepatic impairment
Monitoring requirements	Monitor infusion site during treatment	Platelet count • At least biweekly and potentially as often as once daily Hepatic function • Hepatic enzymes checked 4 months after starting treatment and then yearly Renal impairment • UPCR and eGFR should be monitored at least every 3 months
NICE appraisal	HST10[2] (14 August 2019) Recommended within its marketing authorisation	HST9[51] (22 May 2019) Recommended within its marketing authorisation
UK market share	[redacted]	[redacted]

ASO, antisense oligonucleotide; eGFR, estimated glomerular filtration rate; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; HST, highly specialised technology guidance; IV, intravenous; MoA, mechanism of action, ribonucleic acid interference; ROA, route of administration; siRNA, small interfering RNA; SC, subcutaneous; TTR, transthyretin; UK, United Kingdom; UPCR, urine protein to creatinine ratio. Note: inotersen is not considered an appropriate comparator due to the differences in contraindications, monitoring requirements, and market share, as outlined in the table.

Among current NICE-recommended products for hATTR amyloidosis with polyneuropathy, patisiran was shown to stabilise or improve patients' polyneuropathy (measured using modified Neuropathy Impairment Score [mNIS]+7) and HRQoL (measured using Norfolk QoL-DN) relative to their own pre-treatment baseline.[6] Notably, inotersen was shown to only slow worsening of polyneuropathy from pre-treatment baseline (i.e., patients continue to

experience neuropathy progression over time) on average and did not improve average HRQoL from pre-treatment baseline.[31,52]

In HST10 for patisiran, with regard to its efficacy profile, the NICE committee stated that:[2]

> "Clinical trial evidence shows that patisiran reduces disability and improves quality of life, by enabling patients to return to work, carry out daily activities, participate in a more active family and social life, and maintain their independence and dignity. There is also evidence suggesting that patisiran may provide long-term benefits by stopping the progression of amyloidosis and potentially reversing it."

In contrast, in HST9 for inotersen, the NICE committee stated that:[51]

> "Clinical trial evidence shows that inotersen slows progression of the disease considerably, although its long-term benefits are uncertain."

In addition, inotersen is approved in the UK and EU with certain special warnings and precautions for use, in addition to multiple contraindications (Table 4),[53] that are not present in the UK and EU product label for patisiran.[10,11]

The differences in the clinical pathway positions of patisiran and inotersen are reflected in their market share. Alnylam estimates that the patisiran market share is currently greater than [redacted], which represents [redacted] from a level of [redacted] market share in January 2022 (estimated based on communications with NAC clinicians).[3] This is especially notable considering that inotersen and patisiran were both appraised by NICE in 2019 and inotersen was recommended by NICE 3 months prior to patisiran.[2,51] The observation of a small and declining market share of inotersen suggests that it is plausible that no patients, or very few patients in the UK will be receiving inotersen in the near future.

B.1.3.5.4 Unmet need

Despite the status of patisiran as standard-of-care treatment in England for this condition, there continue to be unmet needs for patients with hATTR amyloidosis with polyneuropathy beyond the burdens for HCPs and the NHS in association with the use of patisiran.

Temporal burden

- A single treatment session with patisiran can take approximately [redacted] hours (not including travel),[3] consisting of premedication administration (60 minutes prior to infusion), infusion (80 minutes), and the need for HCP-monitoring post-infusion for IRRs.[10,11]
- IV infusion is required every 3 weeks.[10,11]
- Patients currently need to visit the NAC in London for initial treatments, potentially requiring significant travel for patients with hATTR amyloidosis. The SmPC states that patisiran can be considered for delivery via homecare after at least three well-tolerated infusions in a clinic.[10,11] Currently, all patients in the UK are moved to homecare for patisiran administration following treatment initiation at the NAC.
- Loss of time due to administration and/or travel requirements is inherently burdensome and may also result in productivity losses for working patients, as well as for caregivers accompanying patients at treatment sessions.

Health-related burden and requirement for premedication

- IV administration of patisiran carries the potential for IRRs and IV infusion-related complications at the site of the peripheral IV catheter, such as extravasation or phlebitis.

- In clinical studies with patisiran as of July 12, 2022, [redacted][54]
- To minimise the risk of IRRs, a premedication regimen is required every treatment session.
    - The premedication regimen includes an IV corticosteroid (dexamethasone 10 mg or equivalent), H1 blocker (diphenhydramine 50 mg, or equivalent [in clinical practice chlorphenamine 10 mg is used]), H2 blocker (ranitidine 50 mg, or equivalent [in clinical practice oral famotidine 20mg is used][3]), and oral paracetamol.[10,11]
    - In the event of a shortage of any component of premedication, treatment would be severely compromised for patients with hATTR amyloidosis.
    - In addition, the premedication regimen itself carries its own risk of adverse effects. For example, fatigue or drowsiness from premedication can last up to 2 days.
- The weight-based dosing scheme for patisiran may also introduce a risk of medication errors. According to the FDA Adverse Events Reporting System (FAERS), [redacted].
- In current conditions in which SARS-CoV-2 transmission risk may be heightened in healthcare environments, dosing of patisiran every 3 weeks may carry additional risks associated with healthcare interactions.
- Patients receiving patisiran can also be fragile and elderly, amplifying the potential burden of IRRs, other infusion-related complications, AEs associated with premedication, and increased exposure to healthcare settings.

Burden to HCPs and the NHS

After initial treatments, patients on patisiran are reliant on a robust homecare delivery service requiring the availability of HCPs trained to provide IV infusions. Alnylam notes that homecare delivery services in the UK are experiencing chronic long-term staff shortages, potentially jeopardising the administration of patisiran to patients in accordance with their ongoing Q3W treatment schedule, in view of the associated HCP time requirements. The European Medicines Agency (EMA) Committee for Orphan Drug Medicinal Products (COMP) and the MHRA Orphan Drug Designation Assessment Report for vutrisiran concluded that for treatment with patisiran, up to 10 hours of active HCP time is required per patient with hATTR amyloidosis per year.[13,55]

Similarly, the NAC has limited infusion capacity for patients with hATTR amyloidosis. In addition, the ability of the NAC to maintain infusion capacity is reliant on adequate HCP staffing. Alnylam notes chronic nurse staffing challenges in the UK NHS particularly as a result of the COVID pandemic;[56] thus, should there be a failure of homecare delivery in the UK, it is unlikely that the NAC could accommodate patisiran infusions for all patients affected.

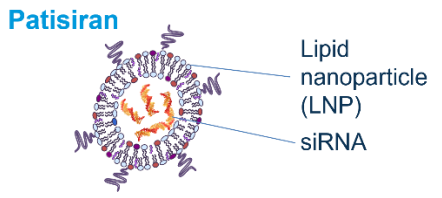
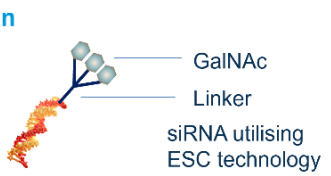
Given the burden associated with patisiran treatment as described herein, there is need for a treatment for hATTR amyloidosis with polyneuropathy that provides comparable clinical benefit to patisiran, but with a less burdensome administration profile for patients and the UK healthcare system.

B.1.3.5.5 Vutrisiran

Vutrisiran is an siRNA therapeutic comprising a synthetic, chemically modified, double-stranded siRNA covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues.[57] Employing the same mechanism of action as patisiran, vutrisiran is an siRNA molecule designed to promote the catalytic degradation of both variant and wild-type TTR mRNA, which, in turn, decreases the production of both variant and wild-type TTR protein.[57-59] This activity results in reduced serum TTR protein levels and reduced TTR protein deposits in tissues.[57,59,60] Such reductions are crucial to halting polyneuropathy of hATTR amyloidosis, as shown in the APOLLO trial of patisiran.[6,10] Therefore, like patisiran, treatment with vutrisiran is disease modifying as it targets and improves the underlying disease and its clinical manifestations.[10,61]

While the biological activity and clinical efficacy of vutrisiran are comparable to those of patisiran (detailed fully in B.3.6 Clinical effectiveness results and B.3.9 Indirect and mixed treatment comparisons), its novel delivery mechanism represents an advance within the broader treatment landscape. In particular, vutrisiran makes use of enhanced stabilisation chemistry (ESC), a term that refers to chemical modifications designed to increase the metabolic stability of the medicinal substance, which allows for infrequent (Q3M) dosing (Table 5).[61] In addition, covalent linkage of the medicinal substance to a ligand containing three GalNAc residues allows rapid and specific delivery of vutrisiran to hepatocytes. While patisiran employs lipid-nanoparticle technology to target liver tissue, the use of ESC-GalNAc technology by vutrisiran enables targeting of liver tissue and comparable biological effects on TTR reduction, while also being administered SC and less frequently.

Table 5: ESC-GalNAc platform versus lipid nanoparticles

	Lipid nanoparticles	ESC-GalNAc platform
		
Stability enhancement (protection of siRNA from nucleases)	siRNA encapsulation in LNPs	Chemical modifications of the siRNA
Delivery to liver	Natural pathway involving association of LNP with hepatocytes whereby LNP is taken up by endocytosis and siRNA released into the cytoplasm	Natural pathway involving the siRNA GalNAc ligand binding to the ASGPR on hepatocytes for subsequent endocytosis
Administration	Q3W dosing via IV infusion	Q3M dosing via SC injection

ASGPR, asialoglycoprotein receptor; ESC, enhanced stabilisation chemistry; GalNAc, N-acetylgalactosamine; IV, intravenous; LNP, lipid nanoparticle; Q3M, quarterly; Q3W, every 3 weeks; RNA, ribonucleic acid; SC, subcutaneous; siRNA, small interfering RNA.
Source: Cullis and Hope, 2017[62]; Brown et al, 2020[63]; Springer and Dowdy, 2018[64]

The benefits resulting from the ESC-GalNAc platform utilised by vutrisiran versus the lipid nanoparticle technology utilised by patisiran, for patients, caregivers, HCPs, and the healthcare system, are described in Table 6.

Table 6: Benefits of vutrisiran over patisiran

Characteristic	Patisiran	Vutrisiran
Dosing frequency	• Q3W • Dosed 17–18 times per year • More frequent dosing, more difficult to manage than vutrisiran	• Q3M • Dosed 4 times per year • Less frequent dosing, easier to manage than patisiran
Route of administration	• IV • Requires a hospital or homecare visit lasting several hours • Limited to settings with infusion capabilities • Imposes burden on patients and caregivers	• SC • Usually takes less than 5 mins and can be administered in a variety of potential outpatient settings • Less burdensome than patisiran
Dosage	• Weight-based dose	• Fixed dose, which can help reduce dosing errors and ensures ease of administration
Potential for IRRs	• Yes	• No
Premedication regimen to reduce risk of IRRs	• IV corticosteroid (dexamethasone 10 mg or equivalent) • IV H1 blocker (diphenhydramine 50 mg, or equivalent [in clinical practice IV chlorphenamine 10 mg is used][3]) • IV H2 blocker (ranitidine 50 mg, or equivalent [in clinical practice oral famotidine 20 mg is used][3]) • Oral paracetamol 500 mg	• Not applicable
Monitoring for IRRs	• Yes	• Not applicable
Potential for AE to premedication regimen	• Yes	• Not applicable
Burden to healthcare system due to administration	• Higher relative to vutrisiran in terms of infusion chair time, homecare, and healthcare professional time, due to IV administration • Higher relative to vutrisiran in terms of monitoring and treatment for IRRs and other AEs, due to premedication requirements and IV administration	• Lower relative to patisiran due to SC administration; reduces HCRU requirements and saves healthcare professional time • Eliminates the potential for AEs related to IV infusion or arising from the components of premedication
Burden for patients and caregivers due to administration	• Higher relative to vutrisiran in terms of loss of time/productivity (IV administration process takes [redacted] hours)	• Lower relative to patisiran
Potential impact on other conditions requiring IV	• Reduces infusion capacity available for other patients	• Frees IV infusion capacity for other patients

Characteristic	Patisiran	Vutrisiran
infusion treatments		
Risk related to COVID/ iatrogenic disease	• Requires substantial duration of exposure to healthcare settings for vulnerable older age patients	• Minimizes duration of exposure to healthcare settings for vulnerable older age patients (e.g., by reducing the number and duration of hospital/homecare visits)

AE, adverse event; HCRU, healthcare resource use; IRR, infusion-related reaction; IV, intravenous; Q3W, every 3 weeks; Q3M, every 3 months; SC, subcutaneous.
Source: ONPATTRO (patisiran) Summary of Product Characteristics[11]; AMVUTTRA (vutrisiran) Summary of Product Characteristics[1]

Figure 3 compares the time burden associated with a single treatment with patisiran or vutrisiran, including the duration of travel time to the NAC and the length of time for which a patient may be impacted by treatment fatigue or AEs from premedication.

Figure 3: Comparison of time requirements for treatment with vutrisiran and patisiran

IRR, infusion related reaction; IV, intravenous; NAC, National Amyloidosis Centre; SC, subcutaneous. Source: Figure generated from communications with key opinion leaders.[3]

The benefits that the vutrisiran administration profile provides compared to patisiran have been noted by the EMA COMP and the MHRA Orphan Drug Designation Assessment Report for vutrisiran.[13,55] Recognition of this benefit was based in large part on the observation of strong positive feedback from patients with hATTR amyloidosis treated with vutrisiran compared with patients treated with patisiran during the 18-month randomised treatment period of the pivotal phase 3 trial of vutrisiran, HELIOS-A, as well as highly positive feedback about vutrisiran from patients who switched from patisiran to vutrisiran during the extension phase of the HELIOS-A trial.[55]

Overall, the aforementioned advantages of vutrisiran over patisiran are expected to reduce the burdens of treatment previously presented by patisiran, for patients and caregivers, in addition to HCPs and the NHS:

Decreased temporal burdens

- Vutrisiran significantly decreases the frequency of treatment.
- The total time required for treatment with vutrisiran (<5 minutes) is significantly less than for treatment with patisiran (approximately [redacted] hours).

Decreased health-related burdens

- SC vutrisiran administration obviates the risk of IRRs.
- There is no premedication requirement for vutrisiran, which removes the risk of premedication-associated fatigue or drowsiness, potentially lasting up to 2 days with patisiran. Elimination of premedication requirements also removes the risk that components of premedication regimens would not be available, as required for appropriate patient care with patisiran, due to shortages caused or exacerbated by future COVID waves.
- The fixed dosing of vutrisiran eliminates the need to calculate and administer an appropriate dose for each patient on the basis of body weight, a potential source of medication errors in the administration of patisiran.
- By minimising the amount of time patients spend in healthcare settings to receive treatment, vutrisiran would support efforts to ensure minimal COVID/iatrogenic disease transmission in a highly vulnerable population.

Decreased burdens to HCPs and the NHS

- Healthcare systems would systematically benefit as vutrisiran would reduce/eliminate the burden and cost associated with IV delivery of care (e.g., infusion chair time, nurse time, and homecare). The reduced burden would also contribute to alleviating system staffing pressures.
- Vutrisiran would free up capacity for IV infusion services that could be provided to other patients.
- Vutrisiran decreases the time requirements for HCPs due to its less frequent administration and shorter time required to perform a single administration.

B.1.4 Equality considerations

The use of vutrisiran in the UK is not expected to raise any issues related to equality given its clinical comparability with patisiran and the committee's note on equality considerations with patisiran in HST10. In HST10, the following was stated regarding equality:[2]

> "The committee noted the potential equality issue raised by clinical experts and the company, and recognised that specific mutations were more common in some ethnic groups in the UK. It also considered whether the age of onset of the condition raised particular issues of equality. The committee concluded that its recommendations apply equally, regardless of age or ethnicity, so a difference in disease prevalence in different age and ethnic groups does not in itself represent an equality issue."

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Patisiran, the comparator in the company evidence submission, was recommended by NICE in HST10 as a treatment for the population specified in the decision problem for this appraisal.[2]

In HST10, the committee concluded that the outcomes measured in patisiran's pivotal trial, APOLLO, likely captured most of the aspects of the condition important to people with hATTR amyloidosis. The committee considered APOLLO endpoints beyond those directly incorporated in the cost-effectiveness model, including mNIS+7, Norfolk QoL-DN, and serum TTR levels, when concluding that the evidence showed that patisiran offers considerable benefit for patients and that in addition to stopping disease progression, patisiran has the potential to reverse it.[2] Table 7 provides a summary of the relevant clinical outcomes included in the NICE appraisal of patisiran.

Table 7: Clinical outcomes and measures appraised in published NICE guidance for patisiran

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
Patisiran (NICE HST10)	Neurological Impairment	PND score (6 separate scores [0, 1, 2, 3A, 3B, and 4])	Yes. Used to define health states.	Yes. Worsening PND scores were associated with increased health-state costs and decreased QALYs.	Approach was reviewed and accepted by the committee.	PND score may not capture all aspects of the condition.
Patisiran (NICE HST10)	Neurological Impairment (including autonomic and motor function)	mNIS+7	No	Not applicable	The committee accepted the company's position of not using the mNIS+7, but instead using change in PND score as the basis for health states in the company's model.	None.
Patisiran (NICE HST10)	HRQoL	Norfolk QoL-DN	No	Not applicable	Norfolk QoL-DN was not used to define health states or as a basis for inputs in the company model for patisiran. The EQ-5D-5L utility values collected in APOLLO were mapped to EQ-5D-3L to capture HRQoL in the model. The committee accepted this approach.	None.
Patisiran (NICE HST10)	HRQoL	EQ-5D-5L	Yes	Yes. Utilities assigned to PND	The company used EQ-5D-5L data collected from the APOLLO pivotal trial to	The committee requested refinements to the duration of predicted treatment-

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
				scores affected QALYs.	inform a regression model that estimated utilities for patients in the economic analysis. The committee acknowledged the use of EQ-5D-5L as a measure of quality of life and accepted the company's implementation of EQ-5D-5L data in the regression model, after adoption of certain refinements to the model (to cap the duration of predicted treatment-related utility gains or losses).	related utility gains or losses.
Patisiran (NICE HST10)	Survival	Mortality	Yes	Yes. Mortality affected LYs and QALYs.	The committee accepted the company's position on modelling survival using published data from natural history studies.	Mortality estimates in the model initially incorporated cardiac and PND score hazard ratios from published data. After committee considerations, only PND score was incorporated into mortality estimates in the company's model.
Patisiran (NICE HST10)	Cardiac function	NT-proBNP level. A threshold of 3000 pg/mL was used for	Yes. Used to define health states and for	Yes. Greater proportions of patients above or at the threshold increased model	The committee accepted the company's approach in incorporating NT-proBNP in the model.	NT-proBNP level (combined with PND score) may not capture all aspects of the condition.

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
		binary assessment.	modelling mortality.	health-state costs and decreased QALYs.		

EQ-5D-3L, EuroQol-5 dimension 3-level; EQ-5D-5L, EuroQol-5 dimension 5-level; HST, highly specialised technology; ICER, incremental cost-effectiveness ratio; LY, life year; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PND, polyneuropathy disability; QALY, quality-adjusted life year.

B.2.1.1 Stopping and starting of patisiran

The CEA included treatment discontinuation for patients who entered PND stage IV, in addition to incorporating a time-on-treatment (ToT) discontinuation curve (Kaplan–Meier curve) from APOLLO data, meaning patients had some probability of stopping treatment at any time based on the ToT curve. The committee suggested that including both stopping rules simultaneously could overestimate stoppage of patisiran.[2] However, after recognising that treatment discontinuation rates in APOLLO were very low and subsequently had minimal impact on the treatment discontinuation in the model, resulting in minimal effects on the incremental cost-effectiveness ratio (ICER), the committee accepted the company's approach to modelling treatment discontinuation.[2]

B.2.2 Resource use assumptions

For the CEA for patisiran appraised in HST10, a Delphi panel approach was used to determine the resource use by the NHS and Personal Social Services Research Unit (PSSRU) for UK patients with hATTR amyloidosis. This investigation stratified resource use and associated per-cycle costs by PND score and NT-proBNP levels. The NICE appraisal committee concluded that there were some uncertainties in these resource use assumptions which would be incorporated into decision making.[2]

The key economic drivers of the patisiran CEA in HST10 were:

- Patisiran list price
- Annual cost of patisiran
    - Estimated using cost per dose of patisiran and relative dose intensity (RDI), which provided a measure of actual doses taken in practice. The RDI was calculated to be 0.97 based on the number of doses administered as a proportion of scheduled doses in APOLLO.
- Administration costs
    - Administration of patisiran was considered comparable with complex chemotherapy IV infusion and was accordingly estimated to cost £301 per treatment (NHS Reference Costs [2016/2017]).[65]
    - The eligibility for patients to undergo homecare infusions was unknown at the time of the appraisal. Therefore, the model assumed all infusions were administered at the NAC.
- Health-state costs
    - Per-cycle costs were assigned for each health state defined by the combination of PND score and NT-proBNP category (less than 3000 pg/mL or equal to or greater than 3000 pg/mL). The costs were based on generic drug use, and use of NHS and PSSRU resources. One-off costs were also assigned for patients transiting into each PND score category.
- AE costs
- Miscellaneous costs
- End-of-life costs

B.2.2.1 Relevance to the decision problem for vutrisiran

In terms of relevance to the decision problem for vutrisiran, the observation of comparable clinical effectiveness between vutrisiran and patisiran as shown by comparable reductions in

serum TTR levels to patisiran through Month 18 in HELIOS-A (Figure 4),[4] the within trial post hoc analysis from HELIOS-A (Table 16), and the NMA (B.3.9 Indirect and mixed treatment comparisons) suggests a similar disease trajectory and, by extension, similar HCRU needs for managing disease manifestations (as reflected by different possible disease states) in patients receiving either therapy. Given the expectation of similarity in terms of such costs, the current economic analysis submission is a cost-comparison model without health states—this submission does not include health-state-specific HCRU and associated costs.

Therefore, state-specific HCRU estimates and associated costs from the patisiran submission (HST10) are not relevant for this submission. The only HCRU differences expected between vutrisiran and patisiran are from their different routes of administration and the need for premedication with patisiran, which are conservatively accounted for in this cost-comparison model. For this reason, AE, miscellaneous, and end-of-life costs were not included in the current submission for vutrisiran.

B.3 Clinical effectiveness

The comparable clinical efficacy of vutrisiran and patisiran supports a cost-comparison analysis for the appraisal of vutrisiran.

Trials that assessed vutrisiran and patisiran

- Pivotal phase 3 studies have assessed the safety and efficacy of vutrisiran (technology being evaluated) and patisiran (comparator technology) in hATTR amyloidosis with polyneuropathy. HELIOS-A assessed the efficacy and safety of vutrisiran, and APOLLO assessed the efficacy and safety of patisiran.
    - The vutrisiran-HELIOS-A evidence base included important outcomes also considered in the previous patisiran-APOLLO evidence base, including the primary outcome, change from baseline in mNIS+7, the key secondary outcome, change from baseline in Norfolk QoL-DN score, reduction of serum TTR levels, and other important exploratory outcomes.[4,6]
    - HELIOS-A randomised patients with hATTR amyloidosis with polyneuropathy to receive vutrisiran or patisiran (reference arm). Pre-specified primary and secondary endpoint analyses, excluding the analysis of serum TTR reduction, compared vutrisiran to the APOLLO placebo group as an external control. A pre-specified non-inferiority analysis compared percent serum TTR reduction between the vutrisiran and patisiran arms.[4]
    - APOLLO randomised patients with hATTR amyloidosis with polyneuropathy to receive patisiran or placebo. Primary and secondary endpoint analyses involved comparison of the patisiran and placebo arms.[6]

Vutrisiran and patisiran provide comparable clinical efficacy

- Vutrisiran was shown to achieve comparable reductions in serum TTR levels to patisiran through Month 18 in HELIOS-A, as demonstrated by a prespecified statistical noninferiority analysis.[4]
- Post hoc analyses (Table 16) compared the HELIOS-A vutrisiran and patisiran arms on multiple outcomes at Month 18 of the study. In these analyses, vutrisiran and patisiran showed numerically comparable efficacy against clinical manifestations of hATTR amyloidosis with polyneuropathy, as noted by the EMA CHMP in their assessment report for vutrisiran,[12] and in the MHRA Orphan Drug Designation Assessment Report for vutrisiran.[13] These post hoc findings are consistent with the observation of comparable reductions in serum TTR and can be explained by the shared mechanism of action between patisiran and vutrisiran.
- An NMA (B.3.9 Indirect and mixed treatment comparisons) of vutrisiran and patisiran using data from both available pivotal clinical trials for these medicines (HELIOS-A and APOLLO) demonstrated their comparable efficacy in all three measures evaluated:[14]
    - Likelihood of maintenance or improvement from baseline to Month 18 in PND score, a clinical outcome assessing both sensory as well as motor impairment and the associated impact on ambulation (which was used to define health states in the CEA model submitted for patisiran [HST10][2]), indicating comparable benefit in terms of halting or reversing worsening of functional disability in patients with hATTR amyloidosis.

- Change from baseline to Month 18 in the primary outcome of both pivotal studies, mNIS+7, which measures the totality of the sensorimotor and autonomic polyneuropathy (postural blood pressure [PBP]) in hATTR amyloidosis, indicating comparable benefits in terms of polyneuropathy impairment in patients with hATTR amyloidosis.
- Change from baseline to Month 18 in the key secondary outcome of both pivotal studies, Norfolk QoL-DN, indicating comparable benefits in HRQoL in patients with hATTR amyloidosis.

B.3.1 Identification and selection of relevant studies

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

- Systematic literature reviews (SLRs) of relevant clinical and non-clinical evidence pertaining to predefined interventions for the treatment of adults with hATTR amyloidosis to support upcoming Health Technology Assessment (HTA) submissions for vutrisiran were conducted (searches were initially run in October 2021 and an update was executed in July 2022).
- A total of 1,697 unique records (+570 records in the update) were identified in the clinical and non-clinical SLRs combined, of which 273 (+92) full-text publications were screened using predefined PICOS criteria, resulting in:
    - 133 records for inclusion in the clinical SLR, representing 32 unique studies
    - Seven records for inclusion in the non-clinical SLR, representing four unique studies/analyses
    - No CCAs were identified in the non-clinical SLR

B.3.2 List of relevant clinical effectiveness evidence

A summary of the pivotal study (HELIOS-A) that demonstrated the clinical effectiveness of vutrisiran is provided in Table 8. In HELIOS-A, patients were randomised 3:1 to receive vutrisiran or patisiran.[4] In this pivotal trial, the clinical efficacy of vutrisiran was compared against an external placebo group from the APOLLO trial of patisiran in patients with hATTR amyloidosis with polyneuropathy.[6] A patisiran arm was included in HELIOS-A as a benchmark for comparing reductions in serum TTR between vutrisiran and patisiran. This within-study patisiran arm also allowed post hoc efficacy and safety comparisons between vutrisiran and patisiran, as well as validation of the use of the external control group from APOLLO for pre-specified efficacy comparisons in HELIOS-A (discussed further in B.3.3.1.2 Patisiran reference comparator arm).

The APOLLO study was reviewed by NICE in the appraisal of patisiran (HST10).[2] It is summarised in appendix D.

Table 8: Clinical effectiveness evidence; pivotal vutrisiran trial

Study	HELIOS-A (NCT03759379)[4,66]
Study design	Treatment arms: • Vutrisiran

	• Patisiran APOLLO (NCT01960348)[6,67] treatment arm (external comparator for primary and secondary endpoint analyses, excluding analysis of serum TTR reduction): • Placebo
Population	Male and female patients 18 to 85 years of age with a diagnosis of hATTR amyloidosis with polyneuropathy with a documented *TTR* variant (N=164).
Intervention(s)	Vutrisiran (25 mg) administered SC Q3M
Comparator(s)	Patisiran (0.3 mg/kg) administered IV Q3W (Reference arm): Comparator for vutrisiran in noninferiority analysis of serum TTR reduction[4] Placebo (external control group from the APOLLO trial): Comparator for vutrisiran for all primary and secondary endpoints, excluding serum TTR reduction[4]
Indicate if study supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	• Neurological impairment: mNIS+7, PND score • Symptoms of polyneuropathy: Norfolk QoL-DN • Serum TTR • Motor function: PND, 10-MWT • Weight loss: mBMI • Autonomic function (including the effects on the gastrointestinal system and postural hypotension): mBMI and mNIS+7 • Adverse effects of treatment • HRQoL: Norfolk QoL-DN, R-ODS

10-MWT, 10-metre walk test; hATTR, hereditary transthyretin-mediated amyloidosis; HRQoL, health-related quality of life; IV, intravenous; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Q3M, quarterly; Q3W, once every 3 weeks; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Score; SC, subcutaneous; TTR, transthyretin.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the clinical methodologies used to assess vutrisiran is provided in Table 9.

Table 9: Comparative summary of trial methodology

Trial number (acronym)	HELIOS-A (NCT03759379)[4,66]	APOLLO* (NCT01960348)[6,67]

Location and settings where data were collected	HELIOS-A was carried out at 57 sites in 22 countries (United States, Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Greece, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, and the United Kingdom).	APOLLO was carried out at 52 sites in 21 countries (United States, Argentina, Australia, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, Turkey, and the United Kingdom).
Trial design	Phase 3, global, randomised, open-label, 18-month study to evaluate the efficacy and safety of vutrisiran in patients with hATTR amyloidosis. Patients were randomised 3:1 to receive vutrisiran or patisiran. **The placebo arm of the APOLLO study was used as an external comparison for vutrisiran in analyses of primary and secondary efficacy endpoints, excluding serum TTR reduction, in the HELIOS-A study.**[4]	Phase 3, global, randomised, double-blind, placebo-controlled, 18-month study to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis.
Eligibility criteria for participants	Eligibility criteria for the HELIOS-A study are provided in Table 10. Eligibility criteria for the APOLLO study are provided in appendix D. Key criteria for inclusion in both studies: • Male or female 18 to 85 years of age • Diagnosis of hATTR amyloidosis with documented *TTR* variant (for APOLLO, diagnosis of FAP† with documented *TTR* variant) • NIS of 5 to 130 • KPS ≥60%	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and**	Trial arms: • Vutrisiran 25 mg SC Q3M (n=122) • Patisiran 0.3 mg/kg IV Q3W (n=42) (Reference arm) Concomitant medications • Summarised in Table 10	Trial arms: • Patisiran 0.3 mg/kg IV Q3W (n=148) • Placebo IV Q3W (n=77) (Comparator arm) Concomitant medications • Summary of concomitant medications for patients in the APOLLO trial are included in Appendix D.

comparator(s) (n=[x]) **Permitted and disallowed concomitant medication**		
Primary outcomes (including scoring methods and timings of assessments)	Outcome measures of the study are described in further detail inB.3.3.1.4 Assessments. Primary (vs. external placebo arm from APOLLO at Month 18): • Change from BL in mNIS+7 Secondary (vs. external placebo arm from APOLLO at Month 18): • Norfolk QoL-DN (key secondary outcome) • 10-MWT • mBMI • R-ODS Secondary (vs. within-trial patisiran arm from HELIOS-A at Month 18): • Percentage reduction from BL in serum TTR levels (noninferiority analysis) Select exploratory analyses • PND score change from baseline to Month 18	For the primary and secondary outcome measures, patisiran was assessed vs. within-trial placebo arm from APOLLO at Month 18. Primary: • Change from BL in mNIS+7 Secondary: • Norfolk QoL-DN (key secondary outcome) • NIS-W score • 10-MWT • mBMI • R-ODS • COMPASS-31 Select exploratory analyses • PND score change from baseline to Month 18

10-MWT, 10-metre walk test; BL, baseline; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated amyloidosis; HST, Highly Specialised Technology guidance; HRQoL, health-related quality of life; IV, intravenous; KPS, Karnofsky Performance Scale; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, neuropathy impairment score; NIS-W, Neurological impairment score-weakness; Q3M, quarterly; Q3W, once every 3 weeks; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score; SC, subcutaneous; TTR, transthyretin.*APOLLO trial data was included in an NMA of vutrisiran and patisiran (B.3.9 Indirect and mixed treatment comparisons).†The term 'FAP' has historically been used to describe hATTR amyloidosis with polyneuropathy.[68,69] Thus, the patient populations in APOLLO and HELIOS-A had the identical hereditary condition, namely hATTR amyloidosis with polyneuropathy.

B.3.3.1 HELIOS-A study design

HELIOS-A was a phase 3, randomised, open-label, multicentre, global study to evaluate the efficacy and safety of vutrisiran over 18 months in patients with hATTR amyloidosis with polyneuropathy.[70] The study had two arms: a vutrisiran treatment arm and a patisiran treatment arm (reference arm).[70] Patients in HELIOS-A were randomised 3:1 to receive vutrisiran 25 mg SC Q3M or patisiran 0.3 mg/kg IV infusion Q3W for 18 months.[70] Randomisation was stratified by *TTR* genotype (V30M versus non-V30M) and baseline NIS score (<50 versus ≥50).[70]

B.3.3.1.1 External placebo control arm

The placebo arm of the APOLLO study (NCT01960348), a phase 3 study that evaluated the efficacy and safety of patisiran in patients with hATTR amyloidosis, was used as an external control for the HELIOS-A study.[70] Specifically, the APOLLO placebo arm served as the pre-specified comparator group for all primary and secondary endpoint analyses, excluding the analysis of serum TTR reduction. APOLLO enrolled a similar patient population to HELIOS-A and incorporated similar endpoints.[6]

Based on International Conference on Harmonisation (ICH), EMA, and FDA guidelines, an external comparison is an appropriate clinical study design for diseases occurring in small populations, when the natural history of the disease course is well understood.[71-73] The natural history of hATTR amyloidosis has been well-characterised in several large randomised controlled clinical trials (RCTs), including the APOLLO study, as well as observational natural history studies.[6,20,30,74]

Importantly, these studies all demonstrate similar rates of disease progression, despite having been conducted at substantially different points in time and in patients with varying disease characteristics across a range of geographies. Therefore, whilst the HELIOS-A and APOLLO trial populations were largely similar (as the inclusion criteria were very similar for both studies), any differences in baseline characteristics between the HELIOS-A and APOLLO populations do not invalidate the approach of using the placebo arm of APOLLO as the external control for vutrisiran in HELIOS-A. In view of the available data, there is no basis to expect that a different trend in mNIS+7 would have been observed in a placebo group in HELIOS-A, had one been included, and the placebo arm of the APOLLO study was therefore deemed an appropriate external control for the HELIOS-A study.

Use of an external placebo comparator in HELIOS-A was necessary due to ethical considerations preventing the inclusion of a within-trial placebo arm. According to the scientific recommendations of the EMA and the ICH, a study design involving a within-study placebo group would be unethical in a context where there are other therapeutic alternatives available that are known to prevent irreversible morbidity. In fact, as of mid 2022, no product in development for hATTR amyloidosis is being studied in a placebo-controlled trial (www.ClinicalTrials.gov). This includes the study of eplontersen in patients with hATTR amyloidosis with polyneuropathy by Ionis Pharmaceuticals, which is a phase 3, open-label trial,[75] as well as the ATTRibute-PN clinical trial (NCT04418024, NCT04882735) of acoramidis (AG10) in patients with ATTR amyloidosis with polyneuropathy, which was recently withdrawn by the sponsor.[76,77] The ATTRibute-PN trial was originally designed as a placebo-controlled trial but that design was withdrawn because “after a careful review of the currently available treatments worldwide for patients with ATTR-polyneuropathy, Eidos has made the decision to halt the current study design.” The ATTRibute-PN trial was then redesigned as a single-arm study.[76,77] In February 2022, the ATTRibute-PN trial was cancelled altogether.[76,77] This decision highlights the practical and ethical issues with conducting placebo-controlled trials in hATTR amyloidosis.

B.3.3.1.2 Patisiran reference comparator arm

The patisiran reference arm in the HELIOS-A study served as a benchmark for assessing whether TTR reduction with vutrisiran is noninferior to that seen with patisiran.[70] The sample size for the patisiran arm also provided >90% power to establish noninferiority of vutrisiran compared to patisiran with respect to TTR reduction at Month 18, assuming that both interventions have a similar effect on TTR reduction. As previously noted, this analysis was specified as a secondary endpoint.[70] At the request of the EMA and to support health technology assessment submissions, the patisiran reference comparator arm was also used for post hoc comparisons of mNIS+7, Norfolk QoL-DN, and 10-metre walk test (MWT) between vutrisiran and patisiran,[70] and data from the patisiran reference arm of HELIOS-A Company evidence submission template for Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074].

were also included in an NMA of patisiran, vutrisiran, and placebo.[14] The patisiran reference arm also provided a within-study comparison of safety outcomes for patisiran and vutrisiran. Finally, inclusion of a patisiran reference arm helped to validate use of the external control group from APOLLO for efficacy comparisons in HELIOS-A (by allowing assessment of the similarity of response to patisiran treatment between the HELIOS-A and APOLLO populations, as an indicator of comparability between these two populations).

It was not possible to perform a formal within-trial analysis for noninferiority of mNIS+7 results with vutrisiran versus patisiran in HELIOS-A because the trial could not be powered for this endpoint. An adequately powered, formal, direct noninferiority comparison between vutrisiran and patisiran based on mNIS+7 would require a study with a sample size of approximately 400 patients; recruiting a study population of such size would have been neither viable nor ethical in this rare, orphan disease where the estimated European prevalence is approximately 1/100,000.[55]

For APOLLO, the full trial population of 225 patients were enrolled in the study from December 2013 to January 2016. The APOLLO trial experience indicates that the time required to recruit a larger cohort of approximately 400 patients, to power a noninferiority comparison of mNIS+7 results between vutrisiran and patisiran, would have been infeasibly long. This issue would have been further exacerbated by the potentially reduced pool of eligible clinical trial participants after the APOLLO and NEURO-TTR trials had been completed, and by the increasing availability of patisiran and inotersen in clinical practice in various countries (thereby reducing the attractiveness of participating in trials of investigational therapies) at the time of enrolment for the HELIOS-A trial.

B.3.3.1.3 Patient selection criteria

Eligibility criteria of the HELIOS-A study are presented in Table 10. The eligibility criteria for APOLLO are provided in appendix D.

Table 10: HELIOS-A: Eligibility criteria

Inclusion criteria	
• 18 to 85 years of age • hATTR amyloidosis with documented TTR variant • NIS of 5 to 130	• PND score ≤IIIb • KPS ≥60% • Willing and able to comply with the study requirements and provide written informed consent
Exclusion criteria	
• Prior liver transplant or likely to undergo liver transplant during study treatment period • Known other (non-hATTR) forms of amyloidosis • Clinical evidence of leptomeningeal amyloidosis • NYHA Class >II • ALT and/or AST >1.5× ULN reference range • Total bilirubin >ULN (>1.5 ULN in	• Major surgery within the preceding 3 months or planned during study treatment period • Active infection requiring systemic antiviral, antiparasitic, or antimicrobial therapy that will not be completed prior to study drug dosing • Malignancy within the past 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been

patients with Gilbert syndrome) • INR >1.2 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed) • Platelet count <50,000/μL • ANC <1500 cells/mm3 • eGFR ≤30 mL/min/1.73m2 (using MDRD formula) • Vitamin B12 <LLN • HBV, HCV, or HIV infection • Prior TTR-lowering treatment or gene therapy for hATTR amyloidosis • Current treatment with tafamidis, doxycycline, tauroursodeoxycholic acid, or diflunisal • Other known causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, monoclonal gammopathy) that the treating physician believes to be contributing to the patient's neuropathy • Acute coronary syndrome within the preceding 3 months • Uncontrolled cardiac arrhythmia or unstable angina • T1DM or T2DM for ≥5 years • Untreated hypo- or hyperthyroidism	successfully treated • Anticipated survival <2 years • History of multiple drug allergies, history of allergic reaction to an oligonucleotide or GalNAc, or had a prior severe reaction to a liposomal product or any component of patisiran • Unable to take the required premedications • Intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability • Any condition making the patient unsuitable for dosing or which could interfere with study compliance, patient safety and/or patient participation through the Month 18 study visit • Unwilling to comply with the contraceptive requirements of the trial • Pregnant or breastfeeding • Unwilling or unable to limit alcohol consumption throughout the course of the study • History of alcohol abuse within the past 12 months

ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate aminotransaminase; eGFR, estimated glomerular filtration rate; GalNAc, N-acetylgalactosamine; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalised ratio; KPS, Karnofsky performance status; LLN, lower limit of normal; MDRD, Modification of Diet in Renal Disease; NIS, Neuropathy Impairment Score; NYHA, New York Heart Association; PND, polyneuropathy disability; SC, subcutaneous; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTR, transthyretin; ULN, upper limit of normal.
Sources: Alnylam Data on File. HELIOS-A 18-Month Clinical Study Report, 2022[78]; Adams et al, 2022[4]

Key demographic and baseline characteristics for patients enrolled in the HELIOS-A trial and patients in the placebo arm of the APOLLO trial are presented in Table 11. Demographic and baseline characteristics were widely overlapping and clinically comparable across treatment groups.

Table 11: HELIOS-A: Key demographic and baseline characteristics (safety and efficacy population)

Characteristic	Vutrisiran (HELIOS-A) (n=122)	Patisiran (HELIOS-A) (n=42)	Placebo (APOLLO) (n=77)
Age at screening (yrs), median (range)	60 (26, 85)	60 (31, 81)	63 (34, 80)
Male, n (%)	79 (65)	27 (64)	58 (75)
Race, n (%)			
Asian	21 (17)	8 (19)	25 (33)
Black	4 (3)	4 (10)	1 (1)
White	86 (71)	29 (69)	50 (65)
Other	10 (8)	1 (2)	0
More than 1 race	1 (1)	0	0
Unknown	0	0	1 (1)
Region*, n (%)			
North America	27 (22)	8 (19)	10 (13)
Western Europe	43 (35)	20 (48)	36 (47)
Rest of world	52 (43)	14 (33)	31 (40)
Years since diagnosis with hATTR amyloidosis, median (range)	1.9 (0.0, 15.3)	2.4 (0.1, 12.5)	1.4 (0.0, 16.5)
TTR genotype, n (%)			
V30M	54 (44)	20 (48)	40 (52)
non-V30M	68 (56)	22 (52)	37 (48)
Previous tetramer stabiliser use, n (%)	75 (62)	33 (79)	41 (53)
FAP stage, n (%)			
1	85 (70)	31 (74)	37 (48)
2	37 (30)	11 (26)	39 (51)
3	0	0	1 (1)
PND score, n (%)			
I	44 (36)	15 (36)	20 (26)
II	50 (41)	17 (41)	23 (30)
IIIA	16 (13)	7 (17)	22 (29)
IIIB	12 (10)	3 (7)	11 (14)
IV	0	0	1 (1)
NYHA Class†, n (%)			
No heart failure	68 (56)	21 (50)	–
Class I	11 (9)	5 (12)	40 (52†)
Class II	43 (35)	16 (38)	36 (47)
Missing data	0	0	1 (1)

hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; FAP, familial amyloid polyneuropathy; NYHA, New York Heart Association; PND, polyneuropathy disability; TTR, transthyretin; V30M, valine-to-methionine at position 30. *North America: USA, Canada; Western Europe: Belgium, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom; Rest of world: Argentina, Australia, Brazil, Bulgaria, Cyprus, Japan, Korea, Malaysia, Mexico, Taiwan, Turkey.†In the APOLLO study, NYHA class was classified as I through IV, without the option to

categorise patients as having "no heart failure"; thus, patients classified as NYHA class I in APOLLO included both those without heart failure and those with heart failure who had no symptoms during ordinary physical activity.
Source: Alnylam Data on File. HELIOS-A 18-Month Clinical Study Report, 2022[78]; Adams et al, 2022[4]; APOLLO Clinical Study Report.[79]

B.3.3.1.4 Assessments

The primary endpoint of the HELIOS-A study is based on mNIS+7, which assesses the progression of the motor and the sensory aspects of polyneuropathy, as well as some autonomic manifestations, such as postural hypotension, and correlates with both FAP and PND scores.[20] The mNIS+7 assessment scale ranges from 0 to 304 points. A score of zero equates to absence of polyneuropathy and the upper bound represents a maximally affected individual. Therefore, a negative change versus a patient's own baseline represents neurologic improvement.[5,58,74]

A consensus report of the international Peripheral Nerve Society (PNS) defined a 2-point change as the minimal clinically important difference (MCID) for scores on the original NIS assessment (from which the mNIS+7 assessment is derived).[80] At present, MCID has not been defined for the mNIS+7 assessment used in APOLLO and HELIOS-A; however, given the rationale in the PNS consensus report and precedents in trials using NIS-LL and NIS+7 (i.e., other assessments derived from the NIS) as endpoints, a similar threshold of 2 points could be reasonably applied to mNIS+7.

In addition to mNIS+7, Norfolk QoL-DN was used in the HELIOS-A study to measure HRQoL,[5] R-ODS was used to measure the degree of limitations on everyday activities and social participation,[5] 10-MWT was used to measure gait speed,[70] and mBMI was used to measure nutritional status and wasting as an indicator of autonomic neuropathy.[70] All were secondary endpoints, with Norfolk-QoL-DN serving as the key secondary endpoint. Table 12 provides a summary of the assessments included in post hoc comparisons of patisiran and vutrisiran in HELIOS-A, including the directionality of measure and the MCID (results of post hoc analysis are provided in Table 16).

Table 12: Summary of assessments in HELIOS-A used for pos hoc comparison of patisiran and vutrisiran

Outcome Measure	Directionality of Measure	MCID
mNIS+7	Lower scores are more favourable	2 points[80]
Norfolk QOL-DN	Lower scores are more favourable	8.8 points[81]
10-MWT (m/s)	Higher scores are more favourable	0.10 m/s[82]
R-ODS	Higher scores are more favourable	No MCID reported
mBMI	Higher scores are more favourable	No MCID reported

10-MWT, 10-metre walk test; mBMI, modified body mass index; MCID, minimal clinically important difference; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score.

- The Norfolk QoL-DN score assesses 35 measures of symptoms and functional impairment related to nerve function, with higher scores indicating worse HRQoL.[5] An MCID of 8.8 points has recently been reported in the literature for Norfolk QoL-DN.[81] Norfolk QoL-DN has also been demonstrated to correlate with FAP stages.[47]
- The R-ODS is a 24-item scale used to assess the ability to perform everyday activities, with a lower score indicating worsening disability.[5] The MCID of the R-ODS has not yet been reported in the literature. However, an analysis of data from APOLLO and the phase 2 patisiran OLE study indicated that the R-ODS is a reliable and valid measure of activity and social participation limitations in patients with hATTR amyloidosis.[83]

- The 10-MWT measures the time taken to walk 10 metres without assistance from another person (although ambulatory aids such as canes as walkers are permitted).[70] The numerical output of the test is the patient's walking speed in metres per second. At each time point, the test is performed on two separate occasions approximately 24 hours apart but not more than 7 days apart, with positive change values corresponding to improvement.[58,70] Among older adults, including those with mobility disabilities and subacute stroke survivors, a mean increase of 0.05 m/s represents a small meaningful change in gait speed while an increase of 0.10 m/s represents a substantial clinically meaningful change, based on distribution and anchor-based approaches.[82]
- mBMI is calculated as the product of BMI (weight in kilograms divided by the square of height in metres) and serum albumin (g/L).[70] mBMI is a measure of inanition/wasting, which is a leading cause of death in patients with hATTR amyloidosis.[44] While no MCID for mBMI has been established in hATTR amyloidosis, decreases in mBMI are associated with the presence of autonomic neuropathy and resulting malnutrition, which when severe, is a predictor of mortality.[84]

Quantification of serum TTR reduction in the HELIOS-A trial served as a secondary endpoint to compare the activity of patisiran and vutrisiran in a pre-specified non-inferiority analysis. PND score change from baseline was also evaluated in the trial as an exploratory endpoint, to assess polyneuropathy impairment and ambulation.

- Reductions in serum TTR are indicative of clinical efficacy, as TTR accumulation in tissues and organ systems leads to clinical manifestations of the disease.
- An improvement in PND score is indicative of improved ambulatory function. A finding of "no change" in PND score reflects preservation of ambulatory function and therefore a halting of advancing disease impairment, which is also a highly clinically meaningful outcome in this progressively disabling disease.

B.3.3.1.5 Blinding

As the HELIOS-A trial was an open-label study, data integrity was maintained by measures and strategies, including data access restrictions, designed to prevent or minimise potential unintentional biases during the conduct of the study.[78] These measures and strategies included the following:[78]

- Personnel performing mNIS+7 component assessments did not reference any previous assessments in order to minimise the potential for knowledge of prior assessments to influence subsequent assessments.
- Norfolk QOL-DN questionnaires were completed by the patients themselves without any assistance, to minimise potential for study personnel to influence interpretation of and responses to questionnaire items. Study personnel reviewed general instructions with patients and checked questionnaires for completeness only.
- mNIS+7 results were evaluated by certified, qualified personnel, who did not have access to the patients' treatment assignments.
- Primary clinical research representatives and clinical operations staff did not have access to any mNIS+7 or Norfolk QoL-DN data in the electronic data capture system before the Month 9 primary analysis (Month 9 assessment served as the primary endpoint for the United States Food and Drug Administration and select other regulatory bodies; the EMA and MHRA retained Month 18 as the primary endpoint for analysis).

- Primary clinical research and clinical operations study team representatives and study sites did not have access to pharmacodynamic (PD) or pharmacokinetic (PK) data or analyses based on actual treatment groups before the Month 9 primary analysis.

All other data, including treatment assignment, remained otherwise unrestricted to study members, given the open-label design and differences between study treatment administration methods.[78]

B.3.3.1.6 Endpoints

Efficacy outcomes for HELIOS-A are summarised in Table 9.

The safety and tolerability of vutrisiran in patients with hATTR amyloidosis with polyneuropathy were assessed through the surveillance and recording of AEs including serious adverse events (SAEs), recording of concomitant medication, physical examination, electrocardiogram (ECG) findings, laboratory tests, and measurements of vital signs, weight, and height.[70]

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 HELIOS-A overview

The modified intent-to-treat (mITT) population of the HELIOS-A study was defined as all randomised patients who received any amount of study drug.[70] The safety population was defined as all randomised patients who received any amount of study drug, grouped according to the treatment actually received.[70] For efficacy analyses, patients were analysed according to the treatment to which they were randomised.[58] The TTR per-protocol (PP) population was defined as the set of mITT population patients with a non-missing serum TTR assessment at baseline and ≥1 trough serum TTR assessment associated with adequate treatment compliance between Month 6 and Month 18.

HELIOS-A used the placebo group from the APOLLO study as an external control for efficacy analyses. Patient-level data from HELIOS-A were compared with patient-level data from APOLLO for these analyses. Analysis models compared vutrisiran (HELIOS-A) and the placebo group from APOLLO.[78,85]

A mixed-effects model for repeated measures (MMRM) was the default analysis for most continuous efficacy endpoints at Month 18 unless otherwise specified.[78] Maximum percentage reduction and mean percentage reduction from baseline in serum TTR over 18 months, and mean percentage reduction from baseline in serum TTR at steady state between Month 6 and Month 18 were summarised using descriptive statistics.[78]

B.3.4.2 HELIOS-A sample size determination

Enrolment of approximately 160 patients was planned for the HELIOS-A study.[86] The sample size was chosen to enable an adequate characterisation of the long-term safety profile, as well as the efficacy of vutrisiran in this patient population.

This sample size was chosen based on power analyses using data from the APOLLO trial. Specifically, for mNIS+7 change from baseline at 9 months, the observed mean (±standard deviation [SD]) was 15 ± 17 points for the placebo group from the APOLLO study. A mean change of 0 points from baseline was assumed for the vutrisiran group, resulting in >90% power to establish superiority over placebo at the target sample size using a 2-sided t-test

with a significance level of 0.05. For the Norfolk QoL-DN total score change from baseline at 9 months, the observed mean (±SD) was 11.5 ± 19.2 points for the placebo group from the APOLLO study. By assuming a mean change of -4 points for the vutrisiran group, it was determined that the target sample size resulted in >90% power to establish superiority over placebo using a 2-sided t-test with a significance level of 0.05. The sample size chosen also provided >90% power to establish noninferiority of vutrisiran compared to patisiran in terms of percent reduction in serum TTR, assuming that vutrisiran and patisiran have a similar effect on TTR reduction.

For safety, a sample size of >100 patients on vutrisiran was considered to be able to provide reasonable assurance that the true cumulative 1-year incidence of an adverse drug event is no greater than 3% when that event is not observed during the trial.

B.3.4.3 HELIOS-A study hypotheses

For most inferentially-evaluated efficacy endpoints, the null hypothesis for the superiority comparison of vutrisiran vs placebo was defined as follows:

- H_0: No difference between vutrisiran and placebo (APOLLO): difference (vutrisiran – placebo) = 0

For the TTR percent reduction endpoint, the null hypothesis for the noninferiority comparison of vutrisiran vs patisiran was defined as follows:

- H_0: Vutrisiran is inferior to patisiran: difference in median TTR reduction (vutrisiran – patisiran) ≤ -10%

B.3.4.4 HELIOS-A statistical analyses

Statistical analyses used to evaluate outcomes in the HELIOS-A trial are summarised in Table 13.

Table 13: Analysis of primary and secondary endpoints in HELIOS-A

Primary endpoint	Statistical method	Analysis population
mNIS+7 change from BL at Month 18	MMRM	mITT
Secondary endpoint		
Norfolk QoL-DN change from BL at Month 18	MMRM	mITT
10-MWT change from BL at Month 18	MMRM	mITT
mBMI change from BL at Month 18	MMRM	mITT
R-ODS change from BL at Month 18	MMRM	mITT
TTR percent reduction through Month 18	Stratified Hodges-Lehmann	TTR PP

10-MWT, 10-metre walk test; BL, baseline; mBMI, modified body mass index; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score; TTR, transthyretin; TTR PP, TTR per-protocol.

See appendix D for details of participant numbers and participant flow in HELIOS-A.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

Results from the HELIOS-A trial are presented in this submission to demonstrate the clinical effectiveness of vutrisiran for patients with hATTR amyloidosis. These data were published in a peer-reviewed scientific journal in July 2022.[4] Table 14 presents quality assessment results for HELIOS-A. A similar table is provided for APOLLO in appendix D.

Table 14: Quality assessment results for HELIOS-A

Trial	HELIOS-A
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Not applicable
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Appendix D provides a detailed quality assessment for the HELIOS-A trial.

B.3.6 Clinical effectiveness results

Demonstration of the comparable efficacy of vutrisiran and patisiran to support a cost-comparison analysis

- Vutrisiran was shown to reduce serum TTR levels with pharmacodynamic activity similar to that of patisiran through Month 18 in HELIOS-A, as demonstrated by a prespecified statistical noninferiority analysis.[4]
- In a post hoc analysis (Table 16) of primary and secondary endpoints assessed at Month 18, comparable outcomes with regard to clinical manifestations of hATTR amyloidosis with polyneuropathy were observed between the patisiran and vutrisiran arms in HELIOS-A, as expected based on the finding of similar pharmacodynamic activity between these two therapies. This was noted to demonstrate comparable clinical efficacy between patisiran and vutrisiran in the CHMP assessment report of vutrisiran,[12] which was also noted in the MHRA Orphan Drug Designation Assessment Report for vutrisiran.[13]
- Similarly, an NMA that compared vutrisiran and patisiran using data from both pivotal clinical trials for these medicines (APOLLO and HELIOS-A) reaffirmed comparable clinical efficacy regarding ambulatory ability, polyneuropathy impairment, and HRQoL (B.3.9 Indirect and mixed treatment comparisons).[14]

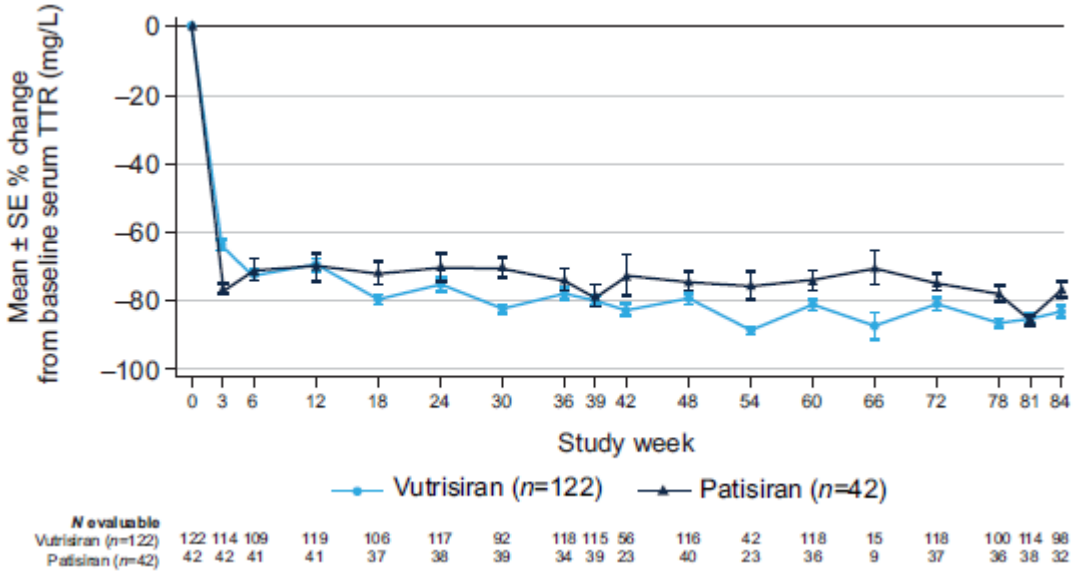
Clinical efficacy of vutrisiran versus external placebo

- Vutrisiran significantly improved neuropathy versus external placebo and halted the progression of polyneuropathy (as measured by mNIS+7) relative to pre-treatment baseline through 18 months of treatment.[4]
- Vutrisiran significantly improved HRQoL compared with external placebo at Month 18 and halted the worsening of HRQoL (as measured by Norfolk-QoL-DN) relative to pre-treatment baseline through 18 months of treatment.[4]
- A significantly greater proportion of patients treated with vutrisiran experienced reversal in neuropathy impairment (mNIS+7) and improvement in HRQoL (Norfolk QoL-DN) from baseline through Month 18 compared with those treated with placebo.[78]
- Clinically and statistically significant benefits were observed for vutrisiran versus external placebo through 18 months of treatment for all other secondary endpoints, including 10-MWT, R-ODS, and mBMI,[4] indicating treatment benefits in terms of ambulatory ability, ability to perform activities of daily living, and nutritional status.

B.3.6.1 Change in serum TTR levels through Month 18

Vutrisiran demonstrated noninferiority compared to within-study patisiran in terms of PD activity, as the median treatment difference in TTR percent reduction from baseline (vutrisiran – patisiran) was 5.28% (95% CI, 1.17 to 9.25), the lower limit of which was above the prespecified noninferiority margin of -10%.[4,78] The time-averaged trough TTR percent reduction from baseline through Month 18 was 84.7% for vutrisiran and 80.6% for patisiran. Patients in the vutrisiran arm achieved sustained reduction in serum TTR levels comparable to patients in the patisiran arm.[4,78] The mean (SD) steady-state serum TTR reduction from baseline through Month 18 (Week 81) was 88% (16%) for the vutrisiran arm and 86% (10%) for the patisiran arm.[4,78]

Figure 4: HELIOS-A secondary endpoint: change in serum TTR levels through Month 18



SE, standard error; TTR, transthyretin.
Source: Adams et al, 2022[4]

B.3.6.2 Main clinical endpoint included in the cost-effectiveness analysis of patisiran (HST10): change in PND score from baseline to Month 18

At Month 18 in HELIOS-A, change in PND score from baseline (improved, no change, or worsened) was assessed (Table 15).[85] Similar trends in maintenance or improvement in PND score are evident for patisiran and vutrisiran. The comparable efficacy of vutrisiran and patisiran regarding PND score change from baseline has also been demonstrated via NMA (B.3.9 Indirect and mixed treatment comparisons).

Table 15: Change in PND score for patisiran and vutrisiran

		HELIOS-A	
		Vutrisiran (N=122) n (%)	Patisiran (N=42) n (%)
Change from baseline to Month 18	Improved	[redacted]	[redacted]
	No change	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]
	Missing	[redacted]	[redacted]

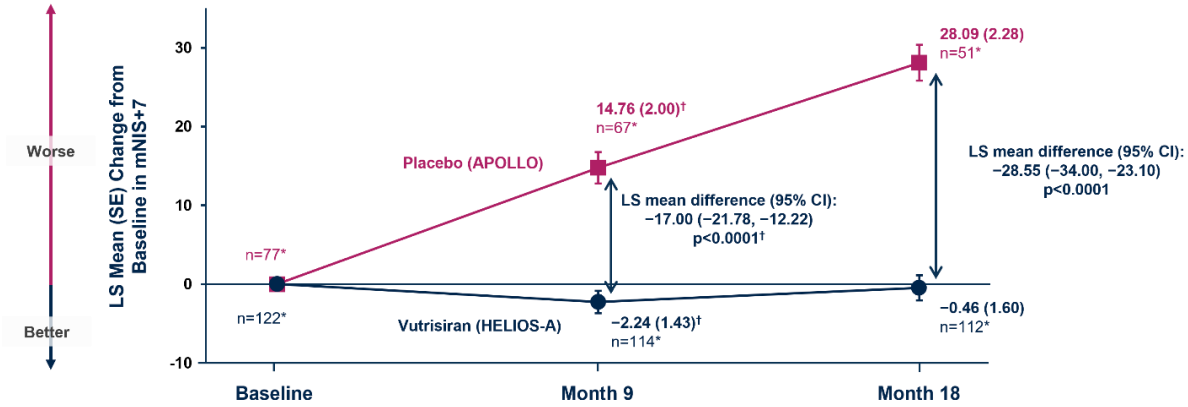
Source: HELIOS-A Clinical Study Report[79,85]

B.3.6.3 HELIOS-A primary endpoint: change in mNIS+7 from baseline at Month 18

At Month 18, the LS mean change from baseline in mNIS+7 was significantly more favourable for the vutrisiran arm compared with the APOLLO placebo arm, with a treatment difference of −28.55 (p<0.0001; Figure 5).[4] The LS mean change from baseline at Month 18 was −0.46 for the vutrisiran arm, where a negative value indicates overall improvement compared to baseline, while the LS mean change from baseline at Month 18 was 28.09 for the placebo arm, where a positive value indicates overall worsening compared to baseline.[4] In APOLLO, patisiran also demonstrated significant benefit versus placebo when considering LS mean change from baseline in mNIS+7.[6] The comparable efficacy of vutrisiran and

patisiran regarding mNIS+7 change from baseline has been demonstrated via post hoc analyses of data from HELIOS-A (Table 16) and via NMA (B.3.9 Indirect and mixed treatment comparisons).

Figure 5: HELIOS-A primary endpoint: mNIS+7 change from baseline at Month 18



*Number of evaluable patients. †Data presented at Month 9 obtained from the completed Month 9 primary analysis. CI, confidence interval; LS, least squares; mNIS+7, modified Neuropathy Impairment Score+7; SE, standard error. Source: Adams et al, 2022[4]

Vutrisiran also demonstrated statistically significant benefit compared to placebo for all secondary endpoints in HELIOS-A. These are presented in appendix J.

B.3.6.4 Post hoc within-study comparison of patisiran and vutrisiran in HELIOS-A

A post hoc analysis of key efficacy endpoints at Month 18 was conducted using MMRM to compare treatment outcomes between the vutrisiran and patisiran groups within the HELIOS-A trial.[12] Overall, the vutrisiran arm showed similar results to the within-study patisiran arm of the HELIOS-A trial (Table 16).[12] From baseline to Month 18, the LS mean difference between the vutrisiran and patisiran arms of the HELIOS-A trial was −1.46 (95% CI −7.36, 4.43) for change in mNIS+7, −1.6 (95% CI −8.6, 5.4) for change in Norfolk QOL-DN, 0.034 (95% CI −0.064, 0.132) for change in 10-MWT, 14.2 (95% CI −21.9, 50.3) for mBMI, and 0.1 (95% CI −2.0, 2.2) for change in R-ODS.[12]

Table 16: Post hoc within-study comparison of the vutrisiran and patisiran arms of the HELIOS-A trial at Month 18

	Baseline		Month 18		
	n	Mean (SD)	n	LS mean change (SEM)	LS mean difference (95% CI)
mNIS+7					
Vutrisiran (n=122)	122	60.57 (35.99)	112	0.06 (1.48)	−1.46 (−7.36, 4.43)
Patisiran (n=42)	42	57.68 (33.71)	36	1.53 (2.59)	
Norfolk QOL-DN					
Vutrisiran (n=122)	121	47.1 (26.3)	111	−2.5 (1.8)	−1.6 (−8.6, 5.4)
Patisiran (n=42)	42	47.3 (29.9)	38	−0.8 (3.0)	
10-MWT (m/s)					
Vutrisiran (n=122)	122	1.006 (0.393)	112	−0.019 (0.025)	0.034 (−0.064, 0.132)
Patisiran (n=42)	42	1.011 (0.400)	38	−0.053 (0.043)	
mBMI					
Vutrisiran (n=122)	122	1057.4 (233.8)	113	21.8 (9.2)	14.2 (−21.9, 50.3)
Patisiran (n=42)	42	1058.1 (228.8)	38	7.6 (15.8)	
R-ODS					
Vutrisiran (n=122)	122	34.1 (11.0)	113	−1.2 (0.5)	0.1 (−2.0, 2.2)
Patisiran (n=42)	42	34.0 (10.4)	38	−1.3 (0.9)	

10-MWT, 10-metre walk test; CI, confidence interval; LS, least squares; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score+7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score; SD, standard deviation; SEM, standard error of the mean.
Source: CHMP Assessment Report[12]

These differences between vutrisiran and patisiran were neither statistically nor clinically significant. In terms of clinical significance, the mean difference between vutrisiran and patisiran was well below the MCID that has been reported in the literature for all measures where such a threshold has been established (mNIS+7: 2 points; Norfolk-QoL-DN, 8.8 points; 10-MWT, 0.10 m/s).

B.3.7 Subgroup analysis

Subgroup analyses are not presented as vutrisiran provides clinical benefits comparable to those of patisiran in the full indicated population, which is identical to the population indicated for patisiran in HST10.[2]

B.3.8 Meta-analysis

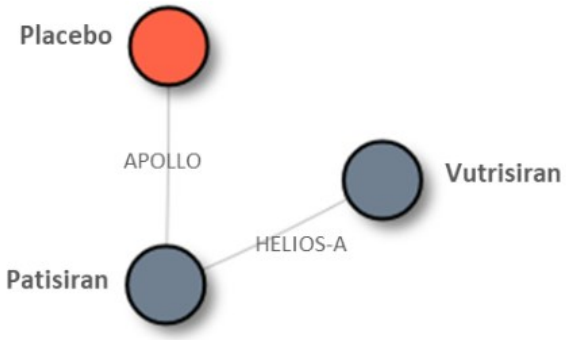
As no further phase 3 RCTs studying the efficacy and safety of vutrisiran for patients with hATTR amyloidosis with polyneuropathy were found, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

In appendix D, full details of the methodology for the NMA are included. A copy of the NMA report is included with the submission.

To further assess the relative efficacy of vutrisiran and patisiran using a comprehensive set of data from pivotal trials, an NMA was conducted that included the two arms from HELIOS-A (vutrisiran and patisiran) and the 2 arms from APOLLO (patisiran and placebo), as depicted in Figure 6.[14] The NMA assessed the efficacy of vutrisiran and patisiran across three key outcomes of hATTR amyloidosis with polyneuropathy, in line with the anticipated indication for vutrisiran: PND score, mNIS+7, and Norfolk QoL-DN score.

Figure 6: Diagram of evidence network assessing vutrisiran and patisiran



Overall, the NMA found that the estimated likelihood of achieving improvement or no change in PND score from baseline to Month 18 was comparable for vutrisiran and patisiran. Improving or stabilizing PND score (i.e., avoiding worsening of PND score) is of clear clinical value, as the normal natural history of polyneuropathy of hATTR amyloidosis is marked by progressive disability, and each change in PND score category represents a concrete, marked change in ambulatory status. Therefore, the results of the NMA provide further evidence of similar clinical efficacy for vutrisiran and patisiran on the outcome of ambulatory ability. This finding was consistent between an analysis involving imputation of missing data (Table 17 and Table 18) and an analysis considering observed data only (Table 19 and Table 20). The analysis method involving imputation assumes missing patient data to be indicative of worsening in PND score, while the method using observed data does not consider missing data as part of the analysis.

Estimated differences between patisiran and vutrisiran in terms of the magnitude of their effect on mNIS+7 score change from baseline were also not clinically meaningful (Table 21), based on an MCID threshold of 2 points. This finding substantiates the similar efficacy of

vutrisiran and patisiran in treating polyneuropathy in patients with hATTR amyloidosis. The estimated median difference in Norfolk QoL-DN score change between patisiran and vutrisiran was also small and not clinically meaningful based on an 8.8-point MCID threshold,[81] indicating that vutrisiran and patisiran have comparable efficacy on the outcome of HRQoL in patients with hATTR amyloidosis (Table 22).

In summary, the results of this NMA across all outcomes analysed demonstrate comparable clinical efficacy for patisiran and vutrisiran when considering key outcome measures used to assess patients with hATTR amyloidosis with polyneuropathy.

Table 17: Pairwise risk ratios between treatments* for achieving the binary outcome of improvement or no change (vs. worsening) in PND score using imputed data

RR (95% CrI)	Placebo	Patisiran	Vutrisiran
Placebo	[redacted]	[redacted]	[redacted]
Patisiran		[redacted]	[redacted]
Vutrisiran			[redacted]

*Treatment arm listed in column represents reference group for each pairwise comparison.
CrI, credible interval; RR, risk ratio.

Table 18: Pairwise odds ratios between treatments* for achieving the binary outcome of improvement or no change (vs. worsening) in PND score using imputed data

OR (95% CrI)	Placebo	Patisiran	Vutrisiran
Placebo	[redacted]	[redacted]	[redacted]
Patisiran		[redacted]	[redacted]
Vutrisiran			[redacted]

*Treatment arm listed in column represents reference group for each pairwise comparison.
CrI, credible interval; OR, odds ratio.

Table 19: Pairwise risk ratios between treatments* for achieving the binary outcome of improvement or no change (vs. worsening) in PND score using observed data

RR (95% CrI)	Placebo	Patisiran	Vutrisiran
Placebo	[redacted]	[redacted]	[redacted]
Patisiran		[redacted]	[redacted]
Vutrisiran			[redacted]

*Treatment arm listed in column represents reference group for each pairwise comparison.
CrI, credible interval; RR, risk ratio

Table 20: Pairwise odds ratios between treatments* for achieving the binary outcome of improvement or no change (vs. worsening) in PND score using observed data

OR (95% CrI)	Placebo	Patisiran	Vutrisiran
Placebo			
Patisiran			
Vutrisiran			

*Treatment arm listed in column represents reference group for each pairwise comparison.
CrI, credible interval; OR, odds ratio.

Table 21: Pairwise comparison between treatments* on mNIS+7 score

Difference (95% CrI)	Placebo	Patisiran	Vutrisiran
Placebo			
Patisiran			
Vutrisiran			

*Treatment arm listed in column represents reference group for each pairwise comparison.
CrI, credible interval; mNIS+7, modified Neuropathy Impairment Score +7.

Table 22: Pairwise comparison between treatments* on Norfolk QoL-DN score

Difference (95% CrI)	Placebo	Patisiran	Vutrisiran
Placebo			
Patisiran			
Vutrisiran			

*Treatment arm listed in column represents reference group for each pairwise comparison.
CrI, credible interval; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy.

Uncertainties in the indirect and mixed treatment comparisons

This NMA benefits from high-quality data from RCTs that have comparable study populations and use identical outcome measures. Notably, HELIOS-A and APOLLO had the same inclusion/exclusion criteria. In addition, the binary outcome of improvement or no change in PND score and the continuous outcome of mNIS+7 and Norfolk QOL-DN score were assessed in the two trials based on the same definitions and assessment timeframe. The overall comparability across the two RCTs served as the foundation for assessing comparative efficacy via this NMA.

The results of this study should be considered in light of its limitations. First, the evidence network was sparse (i.e., only one trial per link), which did not allow reliable estimation of the potential between-study variance using a random-effects model. Second, a non-trivial proportion of patients in HELIOS-A and APOLLO had missing PND score, mNIS+7, and/or Norfolk QOL-DN scores.

To assess the robustness of the NMA results to the potential impact of missing data, two sets of analyses were conducted to estimate the proportion of patients with improvement or

no change in PND scores by treatment arm: a non-responder imputation (NRI) analysis and analysis considering only observed data, without any imputation. The NRI method results in conservative estimates of the percentage of patients with improvement or no change in PND score in all treatment arms in the evidence network, since it imputes all missing data as a worsening of PND score. In contrast, the approach using observed data only assumes a random pattern of missing data and results in less conservative estimates of the percentage of patients achieving the outcome of interest in all treatment arms in the evidence network.

The treatment efficacy of vutrisiran and patisiran, respectively, relative to placebo on the binary outcome of achieving improvement or no change in PND score was estimated to be slightly stronger when using an NRI approach, due to higher rates of missingness observed in the placebo arm than in the vutrisiran and patisiran arms. Nonetheless, irrespective of the approach used to handle missing data, the estimated likelihood of achieving improvement or no change in PND score was highly similar for vutrisiran vs. patisiran (risk ratio [95% CI]: NRI, [redacted]; observed data, [redacted]. The robustness of this finding to different assumptions about missing data, together with the known correlation of both mNIS+7 and Norfolk-QoL-DN scores with ambulatory status in hATTR amyloidosis, suggests that uncertainties related to the impact of missing data do not alter the conclusion that vutrisiran and patisiran provide comparable efficacy on the outcomes of ambulatory ability, polyneuropathy impairment, and HRQoL in hATTR amyloidosis with polyneuropathy.

B.3.10 Adverse reactions

- At 18 months, vutrisiran was well tolerated, with no safety signals relating to laboratory values, low discontinuation rates, and no serious safety concerns.[78]
- Vutrisiran and patisiran have comparable safety and tolerability in patients with hATTR amyloidosis; however, there is a risk of IRRs associated with the IV infusion of patisiran, which is obviated by the SC administration of vutrisiran.

Through 18 months of treatment in HELIOS-A, vutrisiran was well tolerated and the majority of AEs were mild or moderate in severity, comparable to safety outcomes for patisiran assessed in HELIOS-A and APOLLO.[78,79] In HELIOS-A, there were no treatment-related discontinuations or deaths with either vutrisiran or patisiran.[78] AEs were consistent with the underlying disease pathology, informed by observations of the APOLLO placebo arm.[78] No safety signals in laboratory values were identified, and no hepatic safety concerns were observed.[78] Summaries of the safety results and most common AEs from HELIOS-A and APOLLO are provided in Table 23 and Table 24.

Table 23: Summary of safety results at Month 18 for patisiran and vutrisiran from HELIOS-A

	Vutrisiran (HELIOS-A) (n=122)	Patisiran (HELIOS-A) (n=42)	Placebo* (APOLLO) (n=77)
AEs, n (%)	119 (98)	41 (98)	75 (97)
SAEs, n (%)	32 (26)	18 (43)	31 (40)
Severe AEs, n (%)	19 (16)	16 (38)	28 (36)
Treatment discontinuations due to AEs, n (%)	3 (3)	3 (7)	11 (14)
Study withdrawals due to AEs, n (%)	3 (3)	2 (5)	9 (12)
Deaths, n (%)	2 (2)	3 (7)	6 (8)

AE, adverse event; SAE, serious adverse event. *External placebo group was from the APOLLO trial. Source: Adams et al, 2022[4]

Table 24: AEs (≥10%) in any treatment group at Month 18: HELIOS-A

Preferred term, n (%)	Patisiran (HELIOS-A) (n=42)	Vutrisiran (HELIOS-A) (n=122)	Placebo (APOLLO) (n=77)
Diarrhoea	7 (16.7)	17 (13.9)	29 (37.7)
Fall	6 (14.3)	22 (18.0)	22 (28.6)
Oedema, peripheral	4 (9.5)	16 (13.1)	17 (22.1)
Nausea	4 (9.5)	12 (9.8)	16 (20.8)
UTI	8 (19.0)	16 (13.1)	14 (18.2)
Constipation	5 (11.9)	5 (4.1)	13 (16.9)
Dizziness	0	13 (10.7)	11 (14.3)
Muscular weakness	0	6 (4.9)	11 (14.3)
Asthenia	0	5 (4.1)	9 (11.7)
Cough	1 (2.4)	9 (7.4)	9 (11.7)
Headache	5 (11.9)	11 (9.0)	9 (11.7)
Anaemia	2 (4.8)	1 (0.8)	8 (10.4)
Fatigue	1 (2.4)	5 (4.1)	8 (10.4)
Pain in extremity	3 (7.1)	18 (14.8)	8 (10.4)
Syncope	1 (2.4)	12 (9.8)	8 (10.4)
Vomiting	4 (9.5)	9 (7.4)	8 (10.4)
IRR	10 (23.8)	0	7 (9.1)
Arthralgia	4 (9.5)	13 (10.7)	0

AE, adverse event; IRR, infusion-related reaction; UTI, urinary tract infection. *External placebo group was from the APOLLO trial. Source: Adams et al, 2022[4]; Alnylam Data on File. HELIOS-A 18-Month Clinical Study Report, 2022[78]

Based on the collective data from APOLLO and HELIOS-A, it can be seen that both patisiran and vutrisiran provide comparable and acceptable safety and tolerability profiles for patients with hATTR amyloidosis with polyneuropathy. AEs observed with both agents were consistent with the underlying disease pathology, informed by observations of the APOLLO placebo arm.[78] A standout grouping of AEs that should be noted are IRRs in patisiran-treated patients. In contrast to patisiran, which is administered via IV infusion, Vutrisiran is administered via the SC route, and therefore, the potential for IRRs is obviated, as observed in the HELIOS-A trial.

B.3.11 Conclusions about comparable health benefits and safety

- Vutrisiran has shown a comparable efficacy and safety profile to patisiran in patients with hATTR amyloidosis with polyneuropathy.
- Vutrisiran was shown to reduce serum TTR levels with pharmacodynamic activity similar to that of patisiran through Month 18 in HELIOS-A, as demonstrated by a prespecified statistical noninferiority analysis.[4]

- In a post hoc analysis (Table 16) of primary and secondary endpoints assessed at Month 18, comparable outcomes with regard to clinical manifestations of hATTR amyloidosis with polyneuropathy were observed between the patisiran and vutrisiran arms in HELIOS-A, as expected based on the finding of similar pharmacodynamic activity between these two therapies. This analysis was noted to demonstrate comparable clinical efficacy between patisiran and vutrisiran in the CHMP assessment report of vutrisiran,12 which was also noted in the MHRA Orphan Drug Designation Assessment Report.[13]
- Similarly, an NMA that compared vutrisiran and patisiran using data from both pivotal clinical trials for these medicines (APOLLO and HELIOS-A) reaffirmed comparable clinical efficacy regarding ambulatory ability, polyneuropathy impairment, and HRQoL.[14]

In the HELIOS-A trial, vutrisiran was shown to be an efficacious treatment for patients with hATTR amyloidosis with polyneuropathy, with demonstrated benefits over external placebo in terms of all primary and secondary endpoints, covering the full range of clinical and humanistic impacts of this disease.[4]

A prespecified within-study noninferiority analysis of serum TTR reduction for vutrisiran and patisiran in HELIOS-A demonstrated that vutrisiran and patisiran had similar pharmacodynamic activity as measured by reduction of serum TTR levels over 18 months.[4] This finding provides a biological basis for the comparable clinical benefits of these siRNA therapeutics, as reductions in serum TTR decrease TTR deposition in tissues and organs, which is responsible for the clinical manifestations of hATTR amyloidosis.[18,19,32,35] As expected in view of their similar pharmacodynamic activity, a post hoc analysis of key efficacy parameters using MMRM for the within-study comparison of the vutrisiran and patisiran arms of the HELIOS-A study showed similar results for these two siRNA therapies in terms of change in polyneuropathy involvement (mNIS+7), quality of life (Norfolk QoL-DN), gait speed/ambulatory ability (10-MWT), nutritional status (mBMI), and disability (R-ODS). These analyses have supported conclusions made in the CHMP Assessment Report and the MHRA Orphan Drug Designation Assessment Report for vutrisiran that patisiran and vutrisiran had comparable results in clinical endpoints in HELIOS-A.[12,13]

Furthermore, a comparison of vutrisiran and patisiran via an NMA that considered data from both pivotal clinical trials for these therapies, HELIOS-A and APOLLO, further supports their comparable clinical effectiveness. The NMA, which assessed key outcomes of hATTR amyloidosis with polyneuropathy (change in PND score, mNIS+7 and Norfolk-QoL-DN), was developed in line with NICE methods for assessing comparative effectiveness through indirect comparisons. These outcomes were all assessed in HST10 for patisiran.[2]

PND score change from baseline in APOLLO was the main outcome measure that informed the patisiran cost-effectiveness model in HST10.[2] NMA of this endpoint, which reflects a change in ambulatory function and thereby a broader change in disease status, across HELIOS-A and APOLLO showed similar outcomes between vutrisiran and patisiran in terms of the likelihood of maintenance or improvement of PND score.[14] This indicates that vutrisiran is comparable to patisiran when considering the primary clinical outcome that was included in the CEA used to assess patisiran.

NMA of mNIS+7 and Norfolk QOL-DN, which are reflective of polyneuropathy impairment and HRQoL respectively, across HELIOS-A and APOLLO once again showed similar treatment effects between vutrisiran and patisiran, further establishing the comparable clinical effectiveness of these siRNA therapies.

Both vutrisiran and patisiran showed acceptable safety profiles for patients with hATTR amyloidosis with polyneuropathy. Additionally, due to its SC administration, vutrisiran

eliminates the risk of IRRs associated with the IV route of administration required for patisiran.

In addition to providing similar efficacy and acceptable safety, vutrisiran offers advantages over patisiran in terms of less frequent dosing and less burdensome administration, through fixed-dose SC injection every 3 months with no requirement for drug monitoring. In contrast, patisiran is administered more frequently (Q3W), dosing is weight-based, and administration involves IV infusion, which requires premedication to reduce the risk of IRRs as well as monitoring of patients for IRRs.[10] The advantages of vutrisiran are be expected to yield benefits over patisiran, including avoidance of the risk of IV administration-related AEs or weight-based dosing errors, reduced travel and time demands for patients and caregivers, reduced HCRU, and lower burden to the NHS. Consistent with these expectations, the EMA COMP has recognised that vutrisiran offers meaningful benefit to patients in terms of reduced treatment burden, based on survey data from the HELIOS-A trial demonstrating patients' preference for treatment with vutrisiran over patisiran.[55] The patient preference for vutrisiran over patisiran based on the HELIOS-A survey was also noted in the MHRA Orphan Drug Designation Assessment Report for vutrisiran.[13]

Vutrisiran is expected to represent a step-change in the management of hATTR amyloidosis with polyneuropathy in the UK. Specifically, NAC clinicians [redacted] and [redacted], have informed Alnylam that they foresee vutrisiran supplanting patisiran as the standard of care for patients with hATTR amyloidosis with polyneuropathy in the UK. This view was echoed by NAC expert feedback received during the scoping of the present appraisal.

In view of its intended use and the body of evidence showing clinical efficacy similar to that of patisiran (with further advantages related to SC administration), the benefits of vutrisiran are demonstrated in a cost-comparison analysis presented in B.4 Cost-comparison analysis.

B.3.12 Ongoing studies

The open-label extension study of HELIOS-A is currently ongoing. However, Alnylam does not anticipate that data from this study will provide additional evidence for vutrisiran in the next 12 months for the condition being appraised.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

B.4.1.1 Place of administration

The NAC provides the only highly specialised service for patients with amyloidosis in England and all patients with hATTR amyloidosis with polyneuropathy will have treatment initiated by clinicians at the NAC.

Vutrisiran is administered SC Q3M. The first dose of vutrisiran is expected to be administered by an HCP at the NAC, with subsequent doses expected to be administered by a nurse practitioner in a home-care setting, every three months.[1,3]

Patisiran, the comparator in the company submission, is administered IV Q3W. The SmPC for patisiran states that patients can be considered for home administration of patisiran after at least 3 well-tolerated infusions at the clinic.[10,11] Following treatment initiation, all patisiran patients in England receive subsequent doses via Lloyds clinical homecare by a nurse practitioner in a home-care setting, every three weeks.

Assumptions and inputs regarding the administration of patisiran or vutrisiran at home or in clinical settings in the cost-comparison analysis (CCA), based on current practices and expectations regarding place of administration, are summarised in B.4.2.1 Features of the CCA, and associated costs to NHS are summarised in B.4.2.2 Costs in the CCA.

B.4.1.2 Administration-related resource use

Vutrisiran is administered via SC injection and is supplied in a pre-filled syringe.[1] Patisiran is supplied in a vial and is intended for IV infusion.[10,11] The time and cost requirements for IV administration versus SC administration are significant. Infusion with patisiran takes approximately 80 minutes, which includes two separate stages of infusion: an initial slow-rate 15-minute infusion followed by infusion at an increased rate for the remainder of the session.[10,11]

Due to the differences in route of administration, there are additional healthcare resource requirements associated with patisiran. Specifically, due to the risk of IRRs from the IV administration of patisiran, a premedication regimen administered 60 minutes prior to patisiran infusion is required.[10,11] This is associated with additional costs and time requirements for HCPs. Due to the risks of IRRs with patisiran, there is also a need for HCPs to monitor patients during and after patisiran infusion.[10,11]

Altogether, the time requirements for HCPs for the administration of patisiran are understood to exceed [redacted] hours,[3] whereas total administration time for vutrisiran is estimated to be less than 5 minutes.

B.4.1.3 Posology

Vutrisiran

The recommended dose of vutrisiran is 25 mg administered via SC injection once every 3 months.[1]

Patisiran

The recommended dose of patisiran is 0.3 mg per kg body weight administered via IV infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg.[11]

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the CCA

The objective of the CCA was to evaluate the costs associated with using vutrisiran or patisiran to treat patients with hATTR amyloidosis with polyneuropathy from a UK NHS perspective.

To perform this comparison, a CCA model was developed in Microsoft Excel®. The model compares the costs associated with the use of vutrisiran or patisiran for treating patients with hATTR amyloidosis with polyneuropathy in the UK over a 5-year period. The model incorporates acquisition costs, posology, administration frequency and type, premedication requirements, and treatment discontinuation rates. The general features of the CCA are summarised in Table 25.

Table 25: Features of the CCA model for vutrisiran vs. patisiran

Component	Approach
Population	Adult patients (≥18 years of age) with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy
Intervention	Vutrisiran 25 mg Q3M SC
Comparator	Patisiran 0.3 mg/kg Q3W IV
Outcome	Total treatment cost per patient
Perspective	UK NHS healthcare perspective
Time horizon	5 years
Discounting	Costs were not discounted

CCA, cost-comparison analysis; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; IV, intravenous; Q3M, quarterly; Q3W, once every 3 weeks; SC, subcutaneous.

B.4.2.1.1 Time horizon

The base-case time horizon used in the CCA is 5 years. Five years was selected as an adequate time horizon to demonstrate differences in the costs associated with patisiran and vutrisiran, in alignment with recently published NICE cost-comparison appraisals that used the same time horizon (TA734 and TA803),[15,16] and given that key aspects of treatment administration that may impact cost are either time-invariant (e.g., monitoring requirements, dose frequency) or are likely to reach a “steady state” (e.g., site of administration) as early as the second dose of treatment. Time horizons of 2 and 10 years are additionally provided as scenario analyses in the CCA.

B.4.2.1.2 Patient characteristics and posology

Based on the HELIOS-A trial and the prescribing label for vutrisiran,[1] this CCA assumes one unit (25 mg) as the required dose of vutrisiran per administration, with administration required four times annually.

The mean number of patisiran vials used per patient per administration in the CCA was based on historical UK-specific data on administration of patisiran from Lloyds Pharmacy Clinical Homecare.[87] The vast majority of UK patients are represented in this estimation since, as noted in B.4.1.1 Place of administration, almost all UK patients receive patisiran via

Lloyds Clinical Homecare following treatment initiation at the NAC. Alnylam understands the estimation from Lloyds is based on deliveries made for the purpose of a nurse visit to perform drug infusion and thus is representative of infused vials. [redacted]. This figure is therefore included in the CCA as the mean number of vials of patisiran used per administration.

Alnylam believes that this is the most robust estimate available for patisiran vial utilisation in the UK, since it reflects an independently generated estimate of current real-world utilisation in the UK population, with the vast majority of UK patients captured.

An additional scenario analysis is included where estimated mean patisiran vials used per administration is based on the bodyweight distribution observed in patients in HELIOS-A.

B.4.2.1.3 Drug administration

Different drug administration profiles are used in the CCA for vutrisiran and patisiran. Based on clinician input, the initial SC administration for vutrisiran in the CCA is assumed to be at the NAC, with all subsequent administrations occurring at home.[3] Vutrisiran is assigned an administration frequency of four times per year, based on its Q3M dosing regimen.

Based on the patisiran SmPC, it is assumed that patients receive three initial IV infusions of patisiran at the NAC, while all subsequent infusions are administered via homecare.[10,11] Patisiran is administered Q3W;[10,11] accordingly, in the model, it is assigned an administration frequency of 17.39 times per year.

B.4.2.1.4 Premedication

The extra costs associated with the premedication regimen required for patisiran must also be considered in the CCA. As described in B.4.1.2 Administration-related resource use, a premedication regimen is required prior to IV infusion of patisiran to reduce the risk of IRRs.[10,11] The SC administration profile of vutrisiran obviates requirement for premedication to minimise IRR risk.[1] The cost of premedication is incorporated for every infusion of patisiran.

B.4.2.1.5 Time on treatment

In the CCA, time on treatment (ToT) represents time to discontinuation of treatment from all causes excluding death. ToT was assumed to be equivalent for both vutrisiran and patisiran based on the rate of patient discontinuation in HELIOS-A and on input from clinical experts at the NAC.[3]

To compare extrapolations of ToT in HELIOS-A for vutrisiran and patisiran, Kaplan–Meier (KM) treatment discontinuation curves were generated from observed data in the HELIOS-A trial from baseline to Month 18. Based on these curves, parametric models were generated to extrapolate ToT across the 5-year time horizon. Akaike information criterion (AIC) and Bayesian information criterion (BIC) estimators were used to evaluate the relative quality (i.e., fit) of the parametric models considered, namely Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, and Gamma. Based on AIC and BIC estimators, the Exponential parametric function was selected to model ToT for both patisiran and vutrisiran in the CCA. After 5 years, estimates for the proportion of patients on treatment are very similar across treatment arms (91.98% for vutrisiran and 91.94% for patisiran). Therefore, ToT for patisiran was set as equal to ToT for vutrisiran in the base-case analysis.

A scenario analysis is included in the CCA where patisiran ToT is extrapolated from patisiran discontinuation data in HELIOS-A. Further details regarding the determination of ToT in the CCA are provided in appendix K.

B.4.2.1.6 Discount rate

In the NICE user guide for submitting single technology cost-comparison assessments, it is stated that discounting of costs is not normally required for cost comparison. Accordingly, the discount rate is set to zero in the base-case scenario.

B.4.2.2 Costs in the CCA

Costs in the CCA include drug acquisition costs and costs for healthcare resource utilisation. Healthcare resource utilisation costs include costs for administration and the required premedication regimen for patisiran. Drug acquisition costs reflect a proposed simple discount PAS for vutrisiran and the approved simple discount PAS for patisiran.

B.4.2.2.1 Intervention and comparators' acquisition costs

A summary of the acquisition costs for vutrisiran and patisiran is provided in Table 26.

Table 26: Acquisition costs of the intervention and comparator technologies per patient

	Vutrisiran	Patisiran
Pharmaceutical formulation	25-mg solution for injection in pre-filled syringe (total volume 0.5 mL)	2 mg/mL concentrate solution for infusion (total 10 mg patisiran formulated as lipid nanoparticles)
Acquisition cost (excluding VAT)	£[redacted] (one pre-filled syringe)	£[redacted] (one vial)
Average cost of a course of treatment (acquisition costs only)	£[redacted] annually* assuming 1 pre-filled syringe per administration and four administrations per year.	£[redacted] annually† assuming [redacted] vials per administration and 17.39 administrations per year.

VAT, value-added tax. *Acquisition costs do not incorporate time on treatment.
*£[redacted] is the cumulative cost of acquisition of vutrisiran over 5 years.
†£[redacted] is the cumulative cost of acquisition of patisiran over 5 years.

B.4.2.2.2 Intervention and comparators' healthcare resource use and associated costs

The costs associated with HCRU for vutrisiran and patisiran in the CCA are summarised in Table 27. These include costs for home and in-clinic (NAC) SC administration for vutrisiran and home and in-clinic (NAC) IV administration and premedication for patisiran. The cost of IV administration of patisiran at home in the CCA is assumed to be equal to administration cost at the NAC. A scenario analysis that includes home administration costs equal to 125% and 150% of the cost of administration at the NAC is also provided, as added costs for homecare are estimated to be incurred in real-world practice.

In appendix G, a description of how relevant cost and HCRU data for England were identified is provided.

Table 27: Summary of healthcare resource use and costs

	Vutrisiran	Patisiran
Complex IV infusion at the NAC		
Unit cost	N/A	£470.81 (administration cost)
Price year	N/A	2020/2021
Source reference	N/A	NHS reference costs (2020/2021)[88]
Rationale for source	N/A	Cost was based on the delivery of complex IV infusion of chemotherapy (Deliver more complex parenteral chemotherapy at first attendance, day case and regular day/night [HRG code: SB13Z]). This was the same code used for IV infusion costs for patisiran in HST10.[2]
Yearly cost	N/A	£1,415.43 (first year only, as only the first three IV infusions are administered at the NAC)
Cost over the 5-year time horizon*	N/A	£1,415.43 (first three IV infusions are administered at the NAC)
Complex IV infusion at home		
Unit cost	N/A	£470.81
Price year	N/A	2020/2021
Source reference	N/A	The price is assumed to be equal to the price of complex IV infusion at the clinic. NHS England funds patisiran homecare in the UK and while Alnylam estimates IV infusion in a homecare setting can incur additional costs to the NHS versus IV infusion at the NAC, Alnylam is unable to fully estimate these costs. Thus, a conservative approach of assuming equal costs between IV infusion at the NAC and homecare has been used.
Rationale for source	N/A	
Yearly cost	N/A	£6,773.30 in the first year (all but initial three IV infusions are administered at home). £8,187.39 for all subsequent years
Cost over the 5-year time horizon*	N/A	£39,523.22
Subcutaneous administration at the NAC		
Unit cost	£90.49 (administration cost)	N/A

	Vutrisiran	Patisiran
Price year	2021	N/A
Source reference	NHS reference costs (2020/2021)[89]	N/A
Rationale for source	Cost was based on the cost associated with specialist nursing (cancer related, adult, face to face [HRG code: N10AF])	N/A
Yearly cost	£90.49 (first year only, as only the first SC administration is performed at the NAC)	N/A
Cost over the 5-year time horizon	£90.49	N/A
Subcutaneous administration at home		
Unit cost	£33.00 (for 1 hour of community-based nurse wage)	N/A
Price year	2021	N/A
Source reference	PSSRU Unit Costs of Health and Social Care[90]	N/A
Rationale for source	In the source reference, the hourly wage for a community-based nurse (band 4) was listed at the specified rate of £33.00 per hour. Administration is not expected to take longer than one hour.	N/A
Yearly cost	£99.00 (first year, as the first administration is performed at the NAC and the second, third, and fourth SC administrations are performed at the patient's home) £132.00 (subsequent years)	N/A
Cost over the 5-year time horizon*	£627.00	N/A
Premedication		
Unit cost	N/A	£9.91 (acquisition cost) See Table 28 for individual unit costs.
Price year	N/A	2022
Source reference	N/A	Dexamethasone: MIMS database[91] Paracetamol: MIMS database[92] Chlorphenamine: MIMS database[93] Famotidine: MIMS database[94]
Rationale for source	N/A	MIMS is an up-to-date prescribing reference for HCPs in the UK.

	Vutrisiran	Patisiran
Yearly cost	N/A	£172.34
Cost over the 5-year time horizon*	N/A	£861.67

HCP, healthcare professional; HRG, Healthcare Resource Group; IV, intravenous; MIMS, Monthly Index of Medical Specialties; NAC, National Amyloidosis Centre; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SC, subcutaneous; UK, United Kingdom. *Resource costs for the full time horizon (5 years) do not incorporate time on treatment.

Premedication dosage and associated costs for a single administration of patisiran (as used to inform the total unit cost of premedication listed in Table 27) are presented in Table 28.

Table 28: Patisiran premedication costs

Premedication	Dose per administration (mg)	Marketed packs	mg per unit	Units per pack	Pack price (£)	Cost per administration (£)
Dexamethasone	10	Injection	6.6	10	25.85	5.17
Paracetamol	500	Tablets	500	100	2.34	0.02
Chlorphenamine	10	Injection	10	5	22.50	4.50
Famotidine	20	Tablets	20	28	6.02	0.22
Total						9.91

B.4.2.3 Adverse reaction unit costs and resource use

AEs observed in the HELIOS-A trial for patisiran and vutrisiran were generally similar,[4] and were therefore not incorporated into the CCA as a simplifying assumption to facilitate decision-making. It is noted that IV administration of patisiran, but not SC administration of vutrisiran, is associated with the risk of IRRs, so this assumption of similar safety profiles for both therapies could be regarded as conservative. As explained above, costs associated with the premedication regimen required for patisiran to reduce the risk of IRRs are incorporated into the CCA.

B.4.2.4 Miscellaneous unit costs and resource use

All costs related to the CCA have been described.

B.4.2.5 Clinical expert validation

In 2022, Alnylam Pharmaceuticals solicited expert opinion to validate the current clinical pathway for hATTR amyloidosis with polyneuropathy, how vutrisiran would be positioned in the current clinical pathway of care, and key modelling approaches, inputs, and assumptions from a clinical perspective for the economic analysis of vutrisiran. The criteria for selecting clinical experts consisted of ensuring clinicians:

- Were members of the amyloidosis highly specialised service at the NAC at the Royal Free Hospital, London.
- Were responsible for the treating patients with hATTR amyloidosis with polyneuropathy with existing NICE recommended therapies, patisiran and inotersen.
- Had been investigators in the HELIOS-A study programme, to obtain their insights into how vutrisiran would be utilised in the current clinical pathway based on their hands-on experience using vutrisiran in HELIOS-A.

Two UK-based clinical experts meeting all of these criteria were approached to participate in web-based interviews: [redacted] and [redacted]. Both clinical experts agreed to these interviews.

In total, three interviews (17th March, 12th September and 20th September) were conducted, lasting between 30–60 mins each and both clinical experts attended all three interviews.

Both clinicians are investigators on ongoing studies for Alnylam and other competitor manufacturers and products. They have served as congress speakers for Alnylam as well as competitor manufacturer and products

The information provided by Alnylam and verbalised during interviews as background for discussion consisted of:

- An overview of the HELIOS-A study and its results.
- Alnylam's estimation of the time and burden associated with IV administration of patisiran, where clinical expert validation was sought.
- Alnylam's estimation of the benefits offered by vutrisiran relative to patisiran, where clinical expert validation was sought.

Feedback on key model inputs and assumptions as discussed in these interviews are summarised in Table 29.

Table 29: Clinical validation

Aspect for clinical validation	Details
Numbers of patients with hATTR amyloidosis with polyneuropathy in England	[redacted] These assumptions were used in the company submitted budget impact assessment.
Current clinical pathway of care	The clinical experts explained, that patisiran was the standard-of-care and considered as first-choice therapy for patients with hATTR amyloidosis with polyneuropathy in the UK. They noted that more than [redacted] of their patients with hATTR amyloidosis with polyneuropathy, treated with a NICE recommended therapy, were currently receiving patisiran. The clinical experts noted inotersen did not occupy the same position in the clinical pathway of care as patisiran. Inotersen is rarely used in the UK due to challenges encountered in the clinicians' real-world clinical experience with inotersen treatment. Clinicians highlighted that consequent to these real-world challenges, since launch, the number of patients treated with inotersen has [redacted]. They also reported [redacted] in usage between interview 1 and interview 3. Currently fewer than [redacted] of patients with hATTR amyloidosis with polyneuropathy, treated with a NICE recommended therapy, are receiving inotersen. This clinical expert feedback was used to generate Figure 2 in B.1.3.5.2 Clinical pathway of care.

Aspect for clinical validation	Details
Treatment setting for patisiran	The clinical experts stated that patients from England treated with patisiran were initiated on patisiran treatment at the NAC and, following initiation, 100% of these patients transitioned to receive patisiran treatment via homecare. (Alnylam notes the patisiran SmPC states that patisiran can be considered for administration via homecare after at least 3 well-tolerated infusions in a clinic). This feedback was used to inform the cost of administering patisiran in the submitted cost-comparison analysis and budget impact assessment.
Treatment burden associated with IV infusion of patisiran	The clinical experts reviewed and validated the administration time required at the NAC and in the homecare setting and the associated patient, carer, and clinical burden as described in B.1.3.5 Clinical pathway of care, unmet need and place of vutrisiran in therapy and Figure 3. Notably the clinicians highlighted that fatigue or drowsiness from premedication could last for up to 2 days following the day of administration of patisiran.
The similarity of clinical efficacy between vutrisiran and patisiran	The clinical experts reflected on their experience of treating patients with hATTR amyloidosis with polyneuropathy with patisiran in the APOLLO and HELIOS-A studies and in real-world practice and their experience of treating patients with vutrisiran in HELIOS-A. The clinical experts held, that based on their clinical experiences with both treatments, vutrisiran offered comparable clinical effectiveness relative to patisiran, with benefits for patients, carers, and HCPs due to the SC Q3M dosing associated with vutrisiran versus the IV Q3W dosing associated with patisiran.
Benefits of vutrisiran versus patisiran	The clinical experts validated the benefits of vutrisiran for patients, carers and HCPs as described in B.1.3.5.5 Vutrisiran in Figure 6.
Position of vutrisiran in the clinical care pathway	The clinical experts highlighted vutrisiran would supplant patisiran in the current clinical pathway of care, as the standard-of-care, and be considered the first-choice therapy for patients with hATTR amyloidosis with polyneuropathy. This clinical expert feedback was used to generate Figure 2 in B.1.3.5.2 Clinical pathway of care.

Aspect for clinical validation	Details
Switching patients currently receiving patisiran to vutrisiran	The clinical experts stated their intention to switch all patients with hATTR amyloidosis with polyneuropathy currently receiving patisiran to vutrisiran within 6 to 12 months from when vutrisiran is available. This feedback was used to inform the company submitted budget impact assessment.
Treatment setting for vutrisiran	The clinical experts highlighted their intention to provide the initial administration of vutrisiran at the NAC and then transition 100% of patients to continue vutrisiran treatment via homecare. This feedback was used to inform the administration costs of vutrisiran in the company submitted cost-comparison and budget impact assessment.
Time on treatment and mortality	The clinical experts considered it a reasonable assumption, based on their experience with patisiran and vutrisiran (as noted in the row labelled 'The similarity of clinical efficacy between vutrisiran and patisiran' in this table) that patients' time-on-treatment and mortality outcomes would be similar were patients treated with either vutrisiran or patisiran. This feedback was used to inform modelling of time-on-treatment and mortality in the company submitted cost-comparison, and in the budget impact assessment.

hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; HCP, healthcare professional; IV, intravenous; NAC, National Amyloidosis Centre; SC, subcutaneous; SmPC, Summary of Product Characteristics; Q3M, quarterly; Q3W, once every 3 weeks; UK, United Kingdom.

B.4.2.6 Uncertainties in the inputs and assumptions

The CCA is aligned with the approved UK and EU product labels for patisiran and the expected product label for vutrisiran in terms of administration practices.[1,10,11] Modelling choices and assumptions made in the CCA are presented in Table 30.

Table 30: Assumptions in the CCA

Modelling choices and assumptions	Rationale and caveats
First three IV infusions of patisiran are administered at the NAC	• The patisiran SmPC states that three well-tolerated infusions must occur prior to receiving patisiran at home.[10,11]
First SC injection of vutrisiran is administered at the NAC	• Clinicians have provided validation to Alnylam that patients will receive their first administration of vutrisiran at the NAC prior to transitioning to homecare administration.[3]
Cost of patisiran IV infusion is the same	• The cost of IV infusion is based on NHS cost for chemotherapy administration in clinical settings.[88] As a simplifying

Modelling choices and assumptions	Rationale and caveats
at home and at the NAC	assumption, the model uses the same cost estimate for IV infusion whether it is performed in a clinical setting (i.e., at NAC) or at home. • Despite this simplifying assumption, there is potential for costs associated with IV infusion to be elevated in homecare. Therefore, a scenario analysis addressing this has been included in the CCA.
Cost of SC administration of vutrisiran at home	• Assigned cost is one hour's wage of a community-based nurse.[90] • SC administration of vutrisiran is estimated to take less than 5 minutes. Therefore, this costing approach could overestimate the cost of administering vutrisiran at home.
ToT for patisiran is equal to that of vutrisiran	• The ToT extrapolations for vutrisiran and patisiran from HELIOS-A patient discontinuation data were very similar after 5 years (91.98% for vutrisiran and 91.94% for patisiran) and NAC clinicians have confirmed that discontinuation rates of patisiran and vutrisiran are similar in clinical practice.[3] • A scenario analysis that estimates ToT for patisiran using discontinuation data from the patisiran arm of HELIOS-A has been included.
Mortality	• Assessment of potential treatment effects on mortality was not an objective of the HELIOS-A study, informed by the observation that there were few deaths in the patisiran APOLLO study (a study of comparable size and identical duration to HELIOS-A). • The few observed deaths in both the vutrisiran HELIOS-A and patisiran APOLLO studies makes it difficult to appropriately or adequately assess the effect of these medicines on mortality. • [redacted] • Therefore, Alnylam does not believe it is appropriate to model potential effects on mortality in the context of this cost-comparison analysis.
[redacted] vials of patisiran used per patient per administration	• Usage is estimated from real-world clinical use of patisiran in the UK.[87] • A scenario analysis is presented where the estimated number of patisiran vials per administration is set at [redacted], based on weight distribution of the entire HELIOS-A patient population.
Vitamin A supplementation	• Supplementation with vitamin A is specified in the SmPCs of both patisiran and vutrisiran,[1,11] and is therefore assumed to be the same for both medications. The cost has not been included in the CCA.

IV, intravenous; NAC, National Amyloidosis Centre; NHS, National Health Service; SC, subcutaneous; ToT, time on treatment UK, United Kingdom.

B.4.3 Base-case results

Results from base-case analysis from the CCA are presented in Table 31. The total costs for 5 years of treatment in England, including drug acquisition costs, drug administration costs, and patisiran premedication costs, with ToT incorporated, are £[redacted] for vutrisiran and £[redacted] for patisiran. A cost differential of £[redacted] between the two treatments shows vutrisiran to be a cost-saving option for the treatment of patients with hATTR amyloidosis with polyneuropathy.

Table 31: Results from base-case analysis

Technologies	Acquisition costs	Administration costs	Premedication costs	Total costs
Vutrisiran	£[redacted]	£690	£0	£[redacted]
Patisiran	£[redacted]	£39,279	£827	£[redacted]
Vutrisiran vs. patisiran	£[redacted]	£-38,589	£-827	£[redacted]

B.4.4 Sensitivity and scenario analyses

B.4.4.1 One-way sensitivity analyses

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses (OWSA) were performed where key model parameters were varied one at a time around their base-case values. The 95% CI was approximated by setting high and low values as the base case ± 1.96 times the standard error (SE). When the SE was not available, 10% of base-case value was used to approximate the SE. High and low values used in the OWSA are presented in Table 32.

Table 32: Values used in OWSA

Parameter	Base case	Lower value	Higher value
Complex IV infusion cost at home	£470.81	£378.53	£563.09
Complex IV infusion cost at the NAC	£470.81	£378.53	£563.09
SC administration cost at the NAC	£90.49	£72.75	£108.23
SC administration cost at home	£33.00	£26.53	£39.47
Proportion of patients receiving vutrisiran at home (after initial administration at the NAC)*	100.00%	80%	same as base case
Proportion of patients receiving patisiran at home (after three administrations at the NAC)*	100.00%	80%	same as base case
Premedication cost per patisiran administration	£9.91	£7.97	£11.85

IV, Intravenous; OWSA, one-way sensitivity analysis; SC, subcutaneous. *Patients not receiving vutrisiran or patisiran at home are assumed to continue at the NAC.

Changes in incremental costs with changes in each parameter are ranked and summarised in Table 33 and depicted in Figure 7. As can be seen, the model was most sensitive to changes in the cost of IV infusion of patisiran in homecare settings. In contrast, if the cost of SC administration of vutrisiran is modified in the CCA, the outcome on total cost is significantly less impacted.

Table 33: Ranked OWSA incremental cost variations

Parameter	Lower value incremental costs	Upper value incremental costs	Variation
Complex IV infusion cost at home (patisiran)	[redacted]	[redacted]	[redacted]
Complex IV infusion cost at the NAC (patisiran)	[redacted]	[redacted]	[redacted]
Premedication cost per patisiran administration	[redacted]	[redacted]	[redacted]
SC administration cost at home (vutrisiran)	[redacted]	[redacted]	[redacted]
Proportion of patients receiving vutrisiran at home (after initial administration at the NAC*)	[redacted]	[redacted]	[redacted]
SC administration cost at the NAC (vutrisiran)	[redacted]	[redacted]	[redacted]
Proportion of patients receiving patisiran at home (after three administrations at the NAC)*	[redacted]	[redacted]	[redacted]

IV, intravenous; OWSA, one-way sensitivity analysis; SC, subcutaneous. *Patients not receiving vutrisiran or patisiran at home are assumed to continue at the NAC.

Figure 7: OWSA tornado plot

IV, intravenous; OWSA, one-way sensitivity analysis; SC, subcutaneous. *Patients not receiving vutrisiran at home are assumed to continue at the NAC.

B.4.4.2 Scenario analyses

Scenario analyses have been included to provide additional information beyond what is presented in the base-case analysis. These include scenarios modelling variations from the base case with respect to mean patisiran vial usage per administration, ToT for patisiran, costs associated with IV infusion of patisiran at home, and time horizon.

Patisiran vial usage

A separate analysis for patisiran vial usage is included, where the average required number of vials per administered dose is estimated at [redacted], based on the weight distribution of the total patient population of HELIOS-A.

Patisiran ToT

In the base-case analysis, patisiran ToT is assumed to be equal to vutrisiran ToT, which was estimated based on extrapolation from data on patient discontinuation of vutrisiran in HELIOS-A.[78] A separate scenario analysis was conducted where patisiran ToT was estimated based on extrapolation from data on patisiran discontinuation in HELIOS-A.[78] In addition, a scenario analysis where ToT is not included for either patisiran or vutrisiran is included. Summaries of ToT extrapolations for patisiran and vutrisiran from HELIOS-A data are provided in appendix J.

Cost of IV administration at home

The cost for IV administration of patisiran is assumed to be the same irrespective of being administered at the NAC or in a homecare setting. Nonetheless, performing IV infusions in a homecare setting can incur additional costs to the NHS, and these costs can vary regionally. Additionally, the model currently accounts only for the IV infusion cost (£470.81) and no other auxiliary costs associated with IV infusion treatment. For example, the costs to supply and maintain infusion pumps for patisiran is a significant cost that is not included in the model. In the absence of accessible micro costing data on these auxiliary services, scenarios are modelled to account for these additional costs by adjusting the base-case infusion cost structure by +25% and +50% in two scenario analyses.

Additional time-horizons

Scenarios modelling the cost comparison of vutrisiran versus patisiran over time horizons of 2 and 10 years are provided. A 2-year time horizon (to present cost outcomes over a time

period similar to that of the HELIOS-A trial follow-up) and a 10-year time horizon (to estimate longer term cost outcomes) were modelled in scenario analyses.

Results of scenario analyses

Results of the scenario analyses are presented in Table 34.

Table 34: Vutrisiran CCA model scenario analysis results

	Acquisition cost (£)	Administration cost (£)	Premedication cost (£)	Total cost (£)
Mean patisiran vial use per administration of [redacted]				
Vutrisiran	[redacted]	690	0	[redacted]
Patisiran	[redacted]	39,279	827	[redacted]
Difference	[redacted]	-38,589	-827	[redacted]
Patisiran ToT extrapolated from patisiran discontinuation in HELIOS-A				
Vutrisiran	[redacted]	690	0	[redacted]
Patisiran	[redacted]	39,271	826	[redacted]
Difference	[redacted]	-38,581	-826	[redacted]
ToT not included for patisiran or vutrisiran				
Vutrisiran	[redacted]	717	0	[redacted]
Patisiran	[redacted]	40,944	862	[redacted]
Difference	[redacted]	-40,226	-862	[redacted]
IV infusion of patisiran costs 25% more at home compared to the NAC				
Vutrisiran	[redacted]	690	0	[redacted]
Patisiran	[redacted]	48,748	827	[redacted]
Difference	[redacted]	-48,058	-827	[redacted]
IV infusion of patisiran costs 50% more at home compared to the NAC				
Vutrisiran	[redacted]	690	0	[redacted]
Patisiran	[redacted]	58,218	827	[redacted]
Difference	[redacted]	-57,528	-827	[redacted]
2-year time horizon				
Vutrisiran	[redacted]	317	0	[redacted]
Patisiran	[redacted]	16,107	339	[redacted]
Difference	[redacted]	-15,790	-339	[redacted]
10-year time horizon				
Vutrisiran	[redacted]	1,273	0	[redacted]
Patisiran	[redacted]	75,405	1,587	[redacted]
Difference	[redacted]	-74,133	-1,587	[redacted]

IV, intravenous; NAC, National Amyloidosis Centre; ToT, time on treatment.

B.4.5 Subgroup analysis

Subgroup analyses were not included in the CCA.

B.4.6 Interpretation and conclusions of economic evidence

As evidenced in B.3 Clinical effectiveness, the clinical efficacy of vutrisiran is comparable to that of patisiran for the treatment of patients with hATTR amyloidosis with polyneuropathy. However, due to vutrisiran's SC Q3M administration versus patisiran's IV Q3W administration, vutrisiran offers benefits for patients, caregivers, and the NHS.

Given the comparable efficacy and in keeping with NICE guidance for evaluating technologies using a CCA, a CCA has been conducted that simulated the treatment and treatment-administration costs of vutrisiran and patisiran over a 5-year time horizon in the base case. This analysis was conducted from a UK NHS perspective with all model inputs representing and comparing current clinical practice for patisiran and expected clinical practice for vutrisiran. Results from the base-case analysis over 5 years of treatment with vutrisiran demonstrate cumulative cost-savings of £[redacted] compared to treatment with patisiran. These cost savings are attributable to the reduced cost for administration for vutrisiran (£38,589) and the lack of premedication costs (£827). Notably, the less frequent and less burdensome SC administration profile of vutrisiran is associated with an estimated £39,416 reduction in non–acquisition-related costs per patient compared to patisiran. Results from the OWSA showed that variability in model parameters had effects on the estimated difference in costs between vutrisiran and patisiran, but none resulted (on either end of range) in total costs that favour the use of patisiran

In the additional scenario analyses presented, vutrisiran was consistently found to demonstrate cost-savings compared to patisiran, including when vial consumption estimates for patisiran from HELIOS-A were used.

Considering that vutrisiran is expected to supplant patisiran, resulting in reduced costs and treatment burden while maintaining comparable clinical efficacy, vutrisiran should be regarded as a preferable substitute for patisiran for the treatment of patients with hATTR amyloidosis with polyneuropathy in England. The introduction of vutrisiran represents a step-change in the clinical management of hATTR amyloidosis with polyneuropathy, imparting positive impacts on patients, HCPs, and caregivers, while also reducing financial costs and burdens currently borne by the NHS.

B.5 References

1. Medicines and Healthcare products Regulatory Agency (MHRA). AMVUTTRA (vutrisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; Date 16 September 2022.
2. National Institute for Health and Care Excellence (NICE). Patisiran for treating hereditary transthyretin amyloidosis (HST10).2019.
3. Alnylam Pharmaceuticals. Data on File. National Amyloidosis Centre (NAC) key opinon leader input.
4. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2022:1-9.
5. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. *BMC Neurol.* 2017;17(1):181.
6. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):11-21.
7. Adams D, Polydefkis M, González-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol.* 2021;20(1):49-59.
8. European Medicines Agency (EMA). AMVUTTRA (vutrisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; Date TBD.
9. Clinicaltrials.gov. HELIOS-B: a study to evaluate vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy (NCT04153149). 2022; https://clinicaltrials.gov/ct2/show/NCT04153149. Accessed February 17 2022.
10. European Medicines Agency (EMA). ONPATTRO (patisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; 19 January 2022.
11. Medicines and Healthcare products Regulatory Agency (MHRA). ONPATTRO (patisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; 01 January 2021.
12. Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report. Amvuttra.2022.
13. Medicines and Healthcare products Regulatory Agency (MHRA). [Draft] Orphan Drug Designation Assessment Report (vutrisiran).2022.
14. Alnylam Pharmaceuticals. Data on File. Network meta-analysis of vutrisiran and patisiran in the treatment of hereditary transthyretin-mediated amyloidosis 2022.
15. National Institute for Health and Care Excellence (NICE). Secukinumab for treating moderate to severe plaque psoriasis in children and young people (TA734). 2021; https://www.nice.org.uk/guidance/ta734.
16. National Institute for Health and Care Excellence (NICE). Risankizumab for treating active psoriatic arthritis after inadequate response to DMARDs (TA803). 2022; https://www.nice.org.uk/guidance/ta803.
17. European Medicines Agency (EMA). Summary of opinion (initial authorisation): AMVUTTRA. 2022; https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-amvuttra_en.pdf. Accessed 05 Aug 2022.
18. Hawkins PN, Ando Y, Dispenzeri A, et al. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med.* 2015;47(8):625-638.
19. Hanna M. Novel drugs targeting transthyretin amyloidosis. *Curr Heart Fail Rep.* 2014;11(1):50-57.
20. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: A multinational natural history study. *Neurology.* 2015;85(8):675-682.

21. Mohty D, Damy T, Cosnay P, et al. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis.* 2013;106(10):528-540.
22. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8:31.
23. Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin.* 2013;29(1):63-76.
24. Stewart M, Loftus J, Lenderking WR, et al. Characterizing Disease Burden in an Ultra-Rare Disease in the United States: Transthyretin (TTR) Amyloidosis Patients & Caregivers. *Value in Health.* 2013;16(7):A386.
25. Stewart M, Shaffer S, Murphy B, et al. Characterizing the high disease burden of transthyretin amyloidosis for patients and caregivers. *Neurol Ther.* 2018;7(2):349-364.
26. Berk J, Lin H, Agarwal S, et al. Impact of hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy on daily living and work productivity: baseline results from APOLLO. Presented at the The XVIth International Symposium on Amyloidosis, Kumamoto, Japan, Mar 26-29,, 2018.
27. Schmidt H, Lin H, Agarwal S, et al. Impact of hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy on use of health care services: an analysis of the APOLLO study. Presented at the The XVIth International Symposium on Amyloidosis, Kumamoto, Japan, Mar 26-29,, 2018.
28. Wixner J, Mazzeo A, Nienhuis H, et al. Impact of ATTRv amyloidosis in daily life from the HELIOS-A study: evaluating patients' ability to work, disability status, and need for caregiver assistance. Presented at the 3rd European ATTR Amyloidosis meeting for Patients and Doctors (EU-ATTR), Virtual, September 6-8, 2021.
29. Coelho T, Vinik A, Vinik EJ, et al. Clinical measures in transthyretin familial amyloid polyneuropathy. *Muscle Nerve.* 2017;55(3):323-332.
30. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology.* 2012;79(8):785-792.
31. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):22-31.
32. Conceicao I, Gonzalez-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst.* 2016;21(1):5-9.
33. Damy T, Judge DP, Kristen AV, et al. Cardiac findings and events observed in an open-label clinical trial of tafamidis in patients with non-Val30Met and non-Val122Ile hereditary transthyretin amyloidosis. *J Cardiovasc Transl Res.* 2015;8(2):117-127.
34. Eisele YS, Monteiro C, Fearns C, et al. Targeting protein aggregation for the treatment of degenerative diseases. *Nat Rev Drug Discov.* 2015;14(11):759-780.
35. Niemietz C, Chandhok G, Schmidt H. Therapeutic oligonucleotides targeting liver disease: TTR amyloidosis. *Molecules.* 2015;20(10):17944-17975.
36. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. *Circulation.* 2020;142(1):e7-e22.
37. Koike H, Katsuno M. Ultrastructure in transthyretin amyloidosis: from pathophysiology to therapeutic insights. *Biomedicines.* 2019;7(1):11.
38. Coutinho P, da Silva A, Lopes J, Resende A. Forty years of experience with Type I amyloid neuropathy: review of 483 cases. Chapter in Glenner GG, e Costa PP, de Freitas AF, eds. *Amyloid and Amyloidosis.* Amsterdam: Excerpta Medica; 1980:88-98.
39. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med.* 1994;235(5):479-485.

40. Magrinelli F, Fabrizi GM, Santoro L, et al. Pharmacological treatment for familial amyloid neuropathy. *Cochrane Database of Systematic Reviews.* 2016;10:Art. No.: CD012395.
41. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol.* 2021;268(6):2109-2122.
42. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *American Journal of Managed Care.* 2017;23(7 Suppl):S107-S112.
43. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. *Curr Opin Neurol.* 2016;29 (Suppl 1):S3-S13.
44. Gertz MA, Kyle RA, Thibodeau SN. Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. *Mayo Clin Proc.* 1992;67(5):428-440.
45. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid.* 2015;22(2):123-131.
46. National Institute for Health and Care Research (NIHR). Vutrisiran for treating hereditary transthyretin amyloidosis.2022.
47. Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst.* 2014;19(2):104-114.
48. Arriagada P. The experiences and needs of older caregivers in Canada. 2020; https://www150.statcan.gc.ca/n1/pub/75-006-x/2020001/article/00007-eng.htm. Accessed 08 August 2022.
49. Acaster S, Lo SH, Nester-Parr S. Hereditary transthyretin amyloidosis caregiver burden study [Presented at ISPOR 2019, New Orleans, USA, 18–22 May 2019]. *Value Health.* 2019;22:S347.
50. Medicines and Healthcare products Regulatory Agency (MHRA). TEGSEDI (inotersen) Summary of Product Characteristics. Akcea Therapeutics Ireland Ltd.; Dublin, Ireland; 01-Jan-2021.
51. National Institute for Health and Care Excellence (NICE). Inotersen for treating hereditary transthyretin amyloidosis (HST9).2019.
52. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. *Eur J Neurol.* 2020;27(8):1374-1381.
53. European Medicines Agency (EMA). TEGSEDI (inotersen) Summary of Product Characteristics. Akcea Therapeutics Ireland Ltd.; Dublin, Ireland; 17 August 2021.
54. Alnylam Pharmaceuticals. Data on File.
55. European Medicines Agency: Committee for Orphan Medicinal Products. EMA/COMP position on review of criteria for orphan designation. 25 July 2022 2022.
56. Wood E, King R, Senek M, et al. UK advanced practice nurses' experiences of the COVID-19 pandemic: a mixed-methods cross-sectional study. *BMJ Open.* 2021;11(3):e044139.
57. Habtemariam BA, Karsten V, Attarwala H, 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):372-382.
58. Adams D, Tournev IL, Taylor MS, et al. HELIOS-A: 9-month results from the phase 3 study of vutrisiran in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy. Presented at the Peripheral Nerve Society (PNS) Annual Meeting, Virtual, June 12-13 and 25-27,, 2021.

59. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med.* 2013;369(9):819-829.
60. Adams D, Tournev IL, Taylor MS, et al. HELIOS-A: study of vutrisiran in patients with hATTR amyloidosis. Presented at the 26th edition of the Journées de la Société Francophone du Nerf Périphérique (SFNP), Virtual, January 21-22, 2022.
61. AMVUTTRA (vutrisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; February 2022.
62. Cullis PR, Hope MJ. Lipid Nanoparticle Systems for Enabling Gene Therapies. *Mol Ther.* 2017;25(7):1467-1475.
63. Brown CR, Gupta S, Qin J, et al. Investigating the pharmacodynamic durability of GalNAc-siRNA conjugates. *Nucleic Acids Res.* 2020;48(21):11827-11844.
64. Springer AD, Dowdy SF. GalNAc-siRNA Conjugates: Leading the Way for Delivery of RNAi Therapeutics. *Nucleic Acid Ther.* 2018;28(3):109-118.
65. National Health Service. NHS Reference Costs (2016/2017); deliver more complex parenteral chemotherapy at first attendance, day case and regular day/night (SB13Z).
66. Clinicaltrials.gov. HELIOS-A: A study of vutrisiran (ALN-TTRSC02) in patients with hereditary transthyretin amyloidosis (hATTR amyloidosis) (NCT03759379). 2021; https://clinicaltrials.gov/ct2/show/NCT03759379. Accessed June 18 2021.
67. Clinicaltrials.gov. APOLLO-B: a study to evaluate patisiran in participants with transthyretin amyloidosis with cardiomyopathy (ATTR amyloidosis with cardiomyopathy) (NCT03997383). 2021; https://clinicaltrials.gov/ct2/show/NCT03997383. Accessed August 4 2021.
68. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol.* 2011;10(12):1086-1097.
69. Luigetti M, Romano A, Di Paolantonio A, et al. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. *Ther Clin Risk Manag.* 2020;16:109-123.
70. Alnylam Pharmaceuticals. Data on File. HELIOS-A Clinical Study Protocol. Cambridge, MA:2021.
71. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use: Guideline on Clinical Trials in Small Populations.2006.
72. Food and Drug Administration (FDA). Proposed FDA Work Plan for 21st Century Cures Act Innovation Account Activities.2016.
73. International Conference on Harmonization (ICH). Choice of Control Group and Related Issues in Clinical Trials-E10.2000.
74. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *Jama.* 2013;310(24):2658-2667.
75. Clinicaltrials.gov. A phase 3 global, open-label, randomized study to evaluate the efficacy and safety of ION-682884 in patients with hereditary transthyretin-mediated amyloid polyneuropathy (NCT04136184). 2022; https://clinicaltrials.gov/ct2/show/NCT04136184. Accessed June 12 2022.
76. Clinicaltrials.gov. A phase 3, open-label, multicenter, single-arm study to evaluate the efficacy and safety of acoramidis in subjects with symptomatic transthyretin amyloid polyneuropathy (ATTRibute-PN Study) (NCT04882735). 2022; https://clinicaltrials.gov/ct2/show/NCT04882735. Accessed April 25 2022.
77. Clinicaltrials.gov. A phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of AG10 in subjects with symptomatic transthyretin amyloid polyneuropathy (ATTRibute-PN Study) (NCT04418024). 2022; https://clinicaltrials.gov/ct2/show/NCT04418024. Accessed April 25 2022.
78. Alnylam Pharmaceuticals. Data on File. HELIOS-A 18-Month Clinical Study Report. Cambridge, MA:2022.
79. Alnylam Pharmaceuticals. Data on File. APOLLO Clinical Study Report. Cambridge, MA:2017.

80. Peripheral Nerve Society. Diabetic polyneuropathy in controlled clinical trials: Consensus Report of the Peripheral Nerve Society. *Ann Neurol.* 1995;38(3):478-482.
81. Yarlas A, Lovley A, Brown D, et al. Responder analysis for neuropathic impairment and quality-of-life assessment in patients with hereditary transthyretin amyloidosis with polyneuropathy in the NEURO-TTR study. *J Neurol.* 2022;269(1):323-335.
82. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc.* 2006;54(5):743-749.
83. Regnault A, Denoncourt RN, Strahs A, et al. 22nd International Abstracts Book: Measurement properties of the Rasch-Built Overall Disability Scale in patients with hereditary ATTR amyloidosis with polyneuropathy. *Value Health.* 2017;20(5):A330.
84. Suhr OB, Conceicao IM, Karayal ON, et al. Post hoc analysis of nutritional status in patients with transthyretin familial amyloid polyneuropathy: impact of tafamidis. *Neurol Ther.* 2014;3(2):101-112.
85. Alnylam Pharmaceuticals. Data on File. HELIOS-A Clinical Study Report. Cambridge, MA:2021.
86. Alnylam Pharmaceuticals. Data on File. HELIOS-A Statistical Analysis Plan. Cambridge, MA:2021.
87. LloydsPharmacy. Clinical homecare patisiran usage (September 2021 to August 2022).
88. National Health Service. NHS Reference Costs (2020/2021); deliver more complex parenteral chemotherapy at first attendance, daycase and regular day/night (SB13Z).
89. National Health Service. NHS Reference Costs (2020/2021); specialist nursing, cancer related, adult, face to face (N10AF).
90. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care. PSSRU;2021.
91. Monthly Index of Medical Specialities (MIMS). MIMS database: dexamethasone. https://www.mims.co.uk/drugs/endocrine/inflammatory-disorders/dexamethasone. Accessed 29 September 2022.
92. Monthly Index of Medical Specialities (MIMS). MIMS database: paracetamol. https://www.mims.co.uk/drugs/pain/pain-fever/paracetamol. Accessed 29 September 2022.
93. Monthly Index of Medical Specialities (MIMS). MIMS database: chlorphenamine. https://www.mims.co.uk/drugs/allergic-disorders/allergic-rhinitis-urticaria-other-allergies/chlorphenamine-injection. Accessed 30 September 2022.
94. Monthly Index of Medical Specialities (MIMS). MIMS database: famotidine. https://www.mims.co.uk/drugs/gastrointestinal-tract/peptic-ulcer-z-e-syndrome/famotidine. Accessed 30 September 2022.
95. Centre for Reviews and Dissemination (CRD). Systematic Reviews: Guidance for Undertaking Reviews in Health Care. York, UK:2009.
96. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual [Internet]. NICE;2014.
97. Cooper C, Dawson S, Peters J, et al. Revisiting the need for a literature search narrative: A brief methodological note. *Res Synth Methods.* 2018;9(3):361-365.
98. Dias S, Welton JW, Sutton JS, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London:2014.
99. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health.* 2011;14(4):429-437.

B.6 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

C1.1 SmPC

The MHRA SmPC is included with the submission in the references package.

C1.2 UK public assessment report

The UK public assessment report is included with the submission in the references package.

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

Accompanying this submission is the SLR report.

The overall objective of the SLRs is to support HTA submissions for vutrisiran in the treatment of hATTR amyloidosis with polyneuropathy. They have been designed to identify all relevant clinical and non-clinical evidence (e.g., economic evaluations, HCRU, costs, and utilities) for the use of vutrisiran, patisiran, inotersen, or tafamidis in the treatment of adult patients with hATTR amyloidosis. The searches have been designed to be sensitive to the overall condition and to identify all relevant hATTR amyloidosis literature.

The clinical SLR identified clinical trials, including RCTs, open-label extensions of RCTs, and single-arm clinical trials, as well as observational studies that assessed and reported the clinical efficacy of relevant hATTR amyloidosis treatments. Safety data from included studies was also captured.

The non-clinical SLR identified published economic analyses (including CEAs, CCAs, etc), as well as studies that reported healthcare cost or resource utilisation estimates and/or utilities pertinent to hATTR amyloidosis and its treatments.

The process of study identification was divided into searches of bibliographic databases, to identify published studies, and non-database search methods, to identify in-process, unpublished, or grey literature. The searches were conducted systematically and transparently in accordance with international standards, including the CRD and NICE guidance.[95,96] Taking into account that publications could include populations with diverse hATTR phenotypes (polyneuropathy, cardiomyopathy, and mixed), a broad search and screening strategy was used to capture all relevant evidence. For vutrisiran HTA submissions, the focus is on hATTR amyloidosis with polyneuropathy.

The original SLRs searched for evidence to October 2021. An update was executed in July 2022.

Electronic database searches

Bibliographic databases were searched from database inception using predefined search strategies. Two search strategies were employed: one focused on retrieving clinical evidence and another designed to capture economic and HRQoL evidence. A search narrative for each SLR, describing the rationale behind the search terms and filters used, is reported in the appendix.[97] The basic search strategy structure was:

- **Clinical:** ((search terms for familial amyloidosis) AND (search terms for inotersen OR tafamidis OR patisiran OR vutrisiran) AND (search filters for interventional study designs)
- **Non-clinical:** ((search terms for familial amyloidosis) AND (search terms for inotersen OR tafamidis OR patisiran OR vutrisiran) AND (search terms for resource use (economics or costs) OR search terms for HRQoL or utilities))

The following bibliographic databases were searched separately for each SLR:

- MEDLINE®, 1946–present (OVID)
- MEDLINE In-Process & Other Non-Indexed Citations (OVID)
- MEDLINE Epub Ahead of Print (OVID)

- Embase, 1980–present (OVID)
- PsycINFO, 1806–present (OVID)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- PubMed (NLM) – e-publications only
- International Network of Agencies for Health Technology Assessment Database (INAHTA)

In addition to those set out above, the following bibliographic databases and web-based resources were also searched for the non-clinical SLR:

- Econlit, 1886–present (EBSCOHost)
- CEA Registry (CEVR)
- EconPapers within Research Papers in Economics (RePEc)
- EuroQol website
- NHS Economic Evaluation Database (EED)
- ScHARR Health Utilities Database (HUD)

Manual searches

In addition to bibliographic databases, several non-database sources were also searched.

Conference data

Abstract books from the following conferences were hand-searched from 2019 to 2022 to identify relevant data for both SLRs:

- European ATTR (EU ATTR) Amyloidosis Meeting
- International Symposium on Amyloidosis – International Society of Amyloidosis (ISA)
- Peripheral Nerve Society (PNS) Annual Meeting

To supplement the hand-searching for relevant conference data, conference abstracts were further identified through searches of:

- Embase, 1980–present (OVID)
- Conference Proceedings Citation Index-Science (CPCI-S), 1990–present (Web of Science, Clarivate Analytics)
- International Society for Pharmacoeconomic and Outcomes Research (ISPOR) Presentation Database (non-clinical search only)

Bibliographic searches for conference data from these databases were date limited from 2019 to the date of the searches (original: October 2021; update: July 2022) to align with the inclusion criteria for hand-searched conference data.

HTA organizations

The following websites were hand-searched to identify any relevant guidelines/technology appraisals and any nested economic evaluations:

- The National Institute for Health and Care Excellence (NICE)
- Scottish Medicine Consortium (SMC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)

Guidelines or technology appraisals meeting inclusion criteria were checked to identify any potentially relevant studies.

Trial registries

The following trials registries and platforms were searched to identify studies for the clinical SLR:

- ClinicalTrials.gov
- EU Clinical Trials Register
- International Clinical Trials Registry Platform (ICTRP)

Manual bibliography review

Bibliographies of relevant systematic reviews or meta-analyses were hand-searched for applicable primary publications. No relevant studies were identified that were not already captured by the other searches.

Study selection

Two levels of screening (title–abstract and full-text screening) using predefined Population, Intervention, Comparator, Outcome, and Study design (PICOS) criteria were performed during study selection. PICOS criteria for the clinical and non-clinical SLRs are listed in Table 35 and Table 36, respectively.

Title–abstract screening was conducted independently by two researchers using Covidence systematic review software. At the onset of the screening phase, both researchers pilot-tested the inclusion criteria on a subset of records to ensure consistency between researchers and reliability of study selection. The Covidence software offers the option of "yes/no/maybe" for article inclusion. Records that are designated as "Maybe" at the title–abstract screening stage are advanced to full-text screening. Records were advanced to full-text screening in case of doubt by either researcher. No records were excluded at title–abstract screening due to insufficient information.

The full-text publications of records that progressed through title–abstract screening were retrieved for further review. As with title–abstract screening, screening of full-text publications was conducted by two independent researchers using Covidence systematic review software. The same inclusion and exclusion criteria used in title–abstract screening were applied during full-text screening.

Disagreements between both researchers were resolved through discussion or, if necessary, by consulting a third researcher. Studies were excluded if they did not meet the inclusion criteria; if they presented preliminary results in abstract form only; or if they were duplicate publications, narrative reviews, editorials, or letters. The study selection results are presented in a PRISMA flow chart (Figure 8).

Table 35. Study selection (PICOS) criteria for the clinical SLR

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with hATTR amyloidosis	• Children (<18 years) • Mixed populations (e.g., adults and children) excluded if data for the population of interest are not reported separately

Criteria	Inclusion criteria	Exclusion criteria
Intervention	• Inotersen • Patisiran • Tafamidis • Vutrisiran	• Other therapies
Comparators	• Placebo • Established clinical management without inotersen/patisiran/tafamidis • Active intervention (i.e., head-to-head trials) • No comparator	• Non-pharmacologic therapies (e.g., physiotherapy)
Outcomes	**Efficacy** • mNIS+7 score (including mNIS+7$_{Ionis}$) • Norfolk QOL-DN questionnaire • NIS • NIS-LL • PND score • FAP stage • 10-MWT • Percent reduction in serum TTR levels • R-ODS • mBMI • NT-proBNP levels • KPS **Safety** • All AEs • Treatment-emergent AEs • All SAEs	• Pharmacodynamic (aside from TTR reduction) and/or pharmacokinetic outcomes • Other non-clinical outcomes (e.g., gene or protein expression outcomes)

Criteria	Inclusion criteria	Exclusion criteria
	• Mortality • Treatment-related mortality • Discontinuation due to AEs	
Study design	• RCTs (phases I–IV) • Randomized crossover trials • Randomized cluster trials • Head-to-head comparisons • Long-term follow-up studies (e.g., open-label follow-up studies) • Single-arm trials • Observational studies (retrospective and prospective)	• Small sample size (≤10 patients) • Studies reporting pooled data from >1 trial • Preclinical studies • Animal studies • Prognostic studies • Case reports • Commentaries and letters • Consensus reports • Systematic and non-systematic reviews*
Limits	• No date limits applied for non-conference clinical data • Conference data published from January 1, 2019 to search dates (original SLR: October 2021; updated SLR: July 2022)	• Conference data published before January 1, 2019

10-MWT, 10-metre walk test; AE, adverse event; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated amyloidosis; KPS, Karnofsky Performance Status; mBMI, modified Body Mass Index; mNIS+7, modified Neuropathy Impairment Score+7; NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score–Lower Limb; Norfolk QOL-DN, Norfolk Quality of Life–Diabetic Neuropathy; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PND, polyneuropathy disability; RCT, randomized, controlled trial; R-ODS, Rasch-built Overall Disability Score; SAE, serious adverse event; SLR, systematic literature review; TTR, transthyretin.
*Relevant systematic reviews were searched for unique studies but not included.

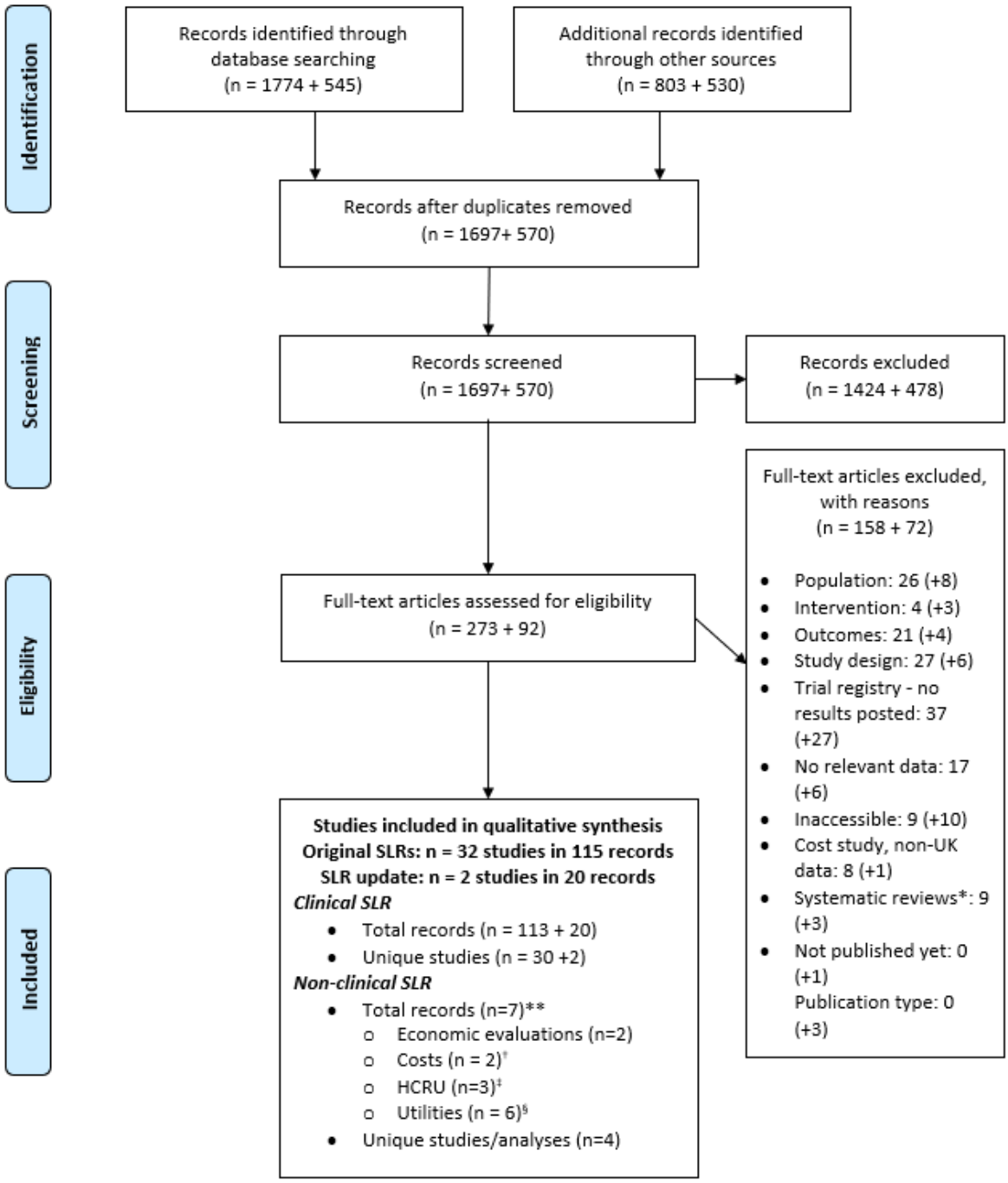
Table 36. Study selection (PICOS) criteria for the non-clinical SLR

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with hATTR amyloidosis	• Children (<18 years) • Mixed populations (e.g., adults and children) excluded if data for population of interest are not reported separately
Interventions	• Inotersen • Patisiran • Tafamidis • Vutrisiran	• Other therapies
Comparators	• Any comparator or no comparator	• No exclusion criteria
Outcomes	• Economic evaluation outcomes ICERs QALYs LYs DALYs	• No exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
	• Direct costs: Medication costs Outpatient visits & costs Hospitalization costs (emergency room or hospital visits) Laboratory costs Diagnostic costs (e.g., MRI, x-rays) Resource-use estimates Cost per treatment success, per remission, or per QALY/LY gained • Indirect costs: Productivity loss costs (wages lost because of travel or absences from work) Out-of-pocket expenses Travel costs for patients and caregivers WPAI • Utilities (including but not limited to): EQ-5D HUI	
Study design	• Economic analyses (cost-effectiveness, cost-utility, cost-benefit, cost-minimization, cost-comparison analyses) • Prospective or retrospective studies reporting costs, resource utilization, or utilities	• Commentaries and letters • Consensus reports • Systematic and non-systematic reviews • Articles reporting cost estimates that are not based on data (e.g., publications making general reference to cost burden)
Limits	• Publication after January 1, 1999 (non-conference records) • Conference data published on or after January 1, 2019 • For cost/HCRU data: Publications reporting any relevant UK data within the date limits noted above*	• Publication prior to December 31, 1998 (non-conference records) • Conference data published before January 1, 2019 • For cost/HCRU data: Publications not reporting any UK data*

DALY, disability-adjusted life year; hATTR, hereditary transthyretin-mediated amyloidosis; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; LY, life year; MRI, magnetic resonance imaging; QALY, quality-adjusted life year; SLR, systematic literature review; WPAI, Work Productivity and Activity Index.
*The SLR searches identified HCRU and cost evidence regardless of region. At the screening stage, studies with no UK data were excluded with a reason (i.e., non-UK data).

Figure 8: PRISMA diagram



HCRU, healthcare resource use; SLR, systematic literature review.
*Systematic reviews were hand-searched for relevant studies but were not included in the SLRs.
**Five of the seven records were also included in the clinical SLR.
†Costs were only reported in the two economic evaluations identified for inclusion.
‡Two of the three records reporting HCRU were the two economic evaluations identified for inclusion.
§Two of the six records reporting utilities were the two economic evaluations identified for inclusion.

Complete reference lists of included and excluded studies are provided in the SLR report.

Summary of trials used for indirect or mixed treatment comparisons

Table 37 provides a summary of the trials used for NMA of patisiran and vutrisiran.

Table 37: Summary of the trials used to carry out the NMA of patisiran and vutrisiran

	Vutrisiran	Patisiran	Placebo
HELIOS-A	Yes	Yes	No
APOLLO	No	Yes	Yes

Methods and outcomes of studies included in indirect or mixed treatment comparisons

The trials included in the NMA of patisiran and vutrisiran included similar populations which are presented in Table 11 for HELIOS-A and appendix D1.4 for APOLLO. The outcomes for both trials were identical and are provided in Table 8 for HELIOS-A and appendix D1.4 for APOLLO. Outcomes for comparison were based on the clinical outcomes used to assess patisiran, the comparator, in HST10,[2] in addition to the primary and key secondary outcomes of both studies, mNIS+7 and Norfolk QoL-DN, which assess polyneuropathy and HRQoL in patients with hATTR amyloidosis.

Methods of analysis of studies included in the indirect or mixed treatment comparison

Methodology for the NMA is provided in appendix D1.5.

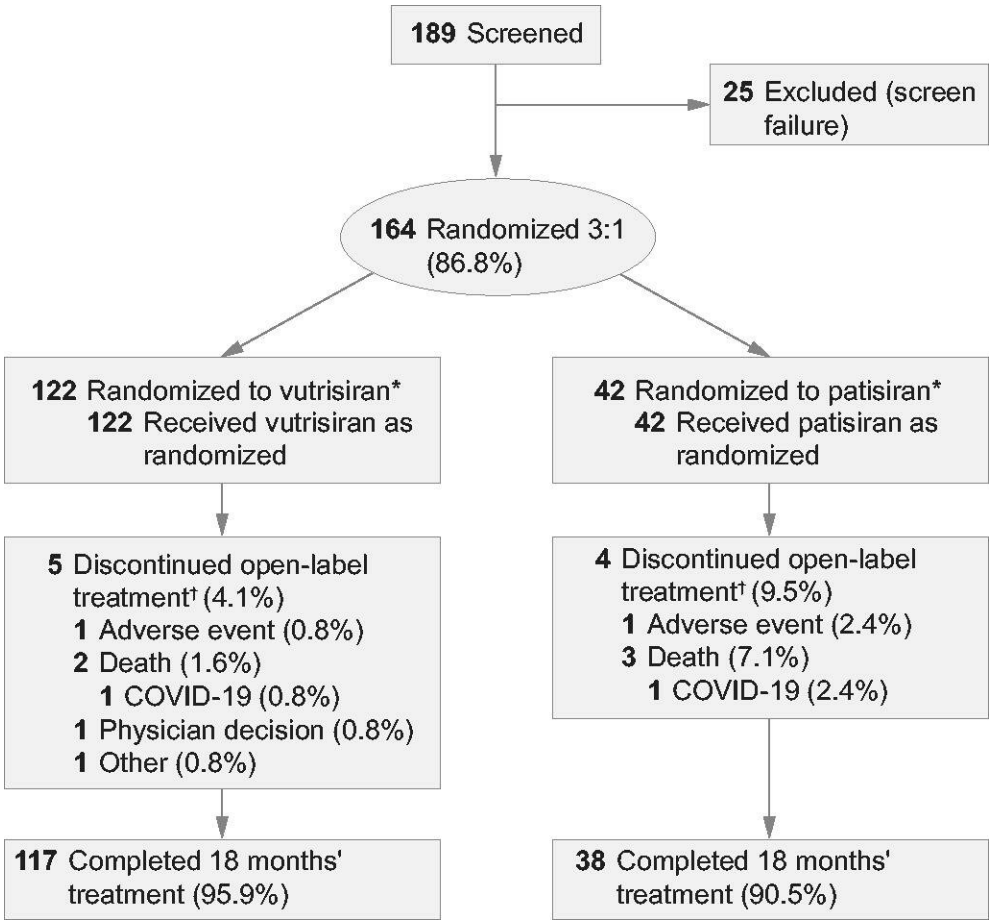
Risk of bias of studies included in indirect or mixed treatment comparisons

Quality assessments for HELIOS-A and APOLLO are provided in appendix D1.3.

D1.2 Participant flow in the relevant randomised controlled trials

A total of 164 patients were enrolled and randomised to receive vutrisiran (n=122) or patisiran (n=42); 77 patients were included in the external placebo arm from APOLLO.[58] At Month 18, a total of 5 (4.1%) patients in the vutrisiran arm had discontinued study drug (1 due to an unrelated AE, 2 due to death of the patient unrelated to study treatment, 1 due to physician decision for a patient who did not comply with study visits and was considered lost to follow-up, and 1 due to withdrawal of consent to treatment by the patient).[78] In the patisiran arm, 4 (9.5%) patients had discontinued study drug at Month 18 (1 due to an unrelated AE and 3 due to the death of the patient unrelated to study treatment).[78]

Figure 9: Consort diagram of patient flow in HELIOS-A



Patient flow in HELIOS-A trial. Modified intent-to-treat population (mITT): all patients who were randomised and received at least one dose of the study drug. †Total number of patient discontinuations at the end of 18 months. In both the patisiran and vutrisiran groups, 1 patient discontinued due to suspected or confirmed diagnosis of COVID-19 or due to the impact of the global COVID-19 pandemic, reported in addition to the primary reason for treatment discontinuation. There were two deaths due to COVID-19, one in each treatment arm. Taken from Adams et al, 2022[4]

D1.3 Quality assessment for each trial

Table 38: Quality assessment of HELIOS-A trial

Trial	HELIOS-A
Was randomisation carried out appropriately?	Yes. For the two treatment arms, patients were randomised 3:1 to receive vutrisiran 25 mg SC Q3M or patisiran 0.3 mg/kg IV infusion Q3W for 18 months.[70] Randomisation was stratified by *TTR* genotype (V30M versus non-V30M) and baseline NIS score (<50 versus ≥50).[70] HELIOS-A investigators used an IRS to randomise patients to each arm.[4] Greater numbers of patients were included in the vutrisiran group to provide adequate data for categorising adverse drug events.[86] Patient number in the patisiran group was selected for adequate power for noninferiority analysis of serum TTR level reduction between vutrisiran and patisiran.[86]
Was the concealment of treatment allocation	Not applicable. This was an open-label study.

adequate?	
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Yes. Key demographic and baseline characteristics for patients enrolled in the HELIOS-A trial and patients in the placebo arm of the APOLLO trial are presented in Table 11. Demographic and baseline characteristics were widely overlapping and clinically comparable across treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. HELIOS-A was an open-label study. Data integrity was maintained by different measures and strategies, including data access restrictions, designed to prevent or minimise potential and unintentional biases during the conduct of the study.[78] A full summary of these strategies is provided in B.3.3.1.5 Blinding.
Were there any unexpected imbalances in drop-outs between groups?	No. By Month 18 of the HELIOS-A trial, 5 (4.1%) patients receiving vutrisiran had discontinued the study drug, while for patisiran, this number was 4 (9.5%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. The primary and secondary outcomes that were proposed for the HELIOS-A trial match data that were reported.[70,78]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. HELIOS-A included a mITT group defined as all randomised patients who received any amount of study drug. All efficacy data collected during the study, regardless of whether before or after treatment discontinuation, were included for analyses, with the exception of mNIS+7 and Norfolk QoL-DN collected post local standard treatment for hATTR amyloidosis, and mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS on or after the onset of a serious COVID-19 AE.

10-MWT, 10-metre walk test; AE, adverse event; hATTR, hereditary transthyretin-mediated amyloidosis; IRS, Interactive Response System; IV, intravenous; mITT, modified intent-to-treat; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Q3M, quarterly; Q3W, once every 3 weeks; NIS, neuropathy impairment score; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score; SC, subcutaneous; TTR, transthyretin.

Table 39: Quality assessment of APOLLO trial

Was randomisation carried out appropriately?	Yes Conducted using an IRS.
Was the concealment of treatment allocation adequate?	Yes Conducted using an IRS.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes Demographics and clinical characteristics were generally balanced between the patisiran and placebo treatment arms.

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes Patients and study personnel who monitored patients during infusions and performed clinical assessments were blinded to the study treatment. Unblinded personnel and pharmacists prepared the drug for administration but were not involved in patient management or safety or efficacy assessments. Details of patients who discontinued study drug at 9 months due to rapid disease progression remained blinded throughout the study.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes, for overall study A larger proportion of patients withdrew in the placebo group. Data not specifically presented for cardiomyopathy subgroup. No adjustment was made.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No Outcomes reported as stated a priori, clearly stated exploratory subgroup analysis performed on cardiac subgroup.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes ITT method used and appropriate. Missing data imputed using pre-specified algorithm where appropriate.

IRS, interactive response system; ITT, intention to treat.

D1.4 APOLLO trial relevant information

The eligibility criteria for APOLLO are provided in Table 40.

Table 40: APOLLO eligibility criteria

Inclusion criteria
• Adults aged 18-85 years with diagnosis of FAP with documented TTR mutation • NIS of 5-130 and a PND score of ≤IIIB (met at baseline screening visit) • NCS sum of SNAP, tibial CMAP, ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points • KPS requirements ≥60% • ANC ≥1500 cells/mm^3 and platelet count ≥50,000 cells/mm^3 • AST and ALT ≤2.5 ULN, total bilirubin within normal limits, INR ≤2.0 (patients on anticoagulant therapy up to INR ≤3.5 and those with total bilirubin ≤2 ULN were eligible if the elevation was secondary to documented Gilbert's syndrome and the patient had ALT and AST levels within normal ranges) • Serum creatinine of ≤2 ULN • No active hepatitis B or hepatitis C by serology • Negative pregnancy test as appropriate and cannot be breastfeeding

- Birth control: Female and male patients of child-bearing age or with partners of such age agreed to use 2 methods of birth control during the study and for 75 days after the last dose
- Willingness to comply with protocol schedule; written informed consent

Exclusion criteria

- Prior liver transplant or planned to undergo liver transplant during the study period
- Known cause of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, monoclonal gammopathy, etc.) not related to hATTR amyloidosis
- Primary amyloidosis or leptomeningeal amyloidosis
- Type I diabetes
- Type II diabetes for ≥5 years
- Vitamin B12 below LLN
- Untreated hypo- or hyperthyroidism
- Major surgery within the past 3 months or major surgery planned during any point of the study period
- Active Hepatitis B or C, or HIV infection
- Active infection requiring systemic antiviral or antimicrobial therapy that was not completed prior to first dose of study drug administration
- Malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
- NYHA heart failure classification of >2
- Acute coronary syndrome within the past 3 months
- Uncontrolled cardiac arrhythmia or unstable angina
- Known history of alcohol abuse or daily, heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer])
- Investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the investigational drug, whichever was longer
- Participated in a clinical study with antisense oligonucleotide (3-month washout period prior to start of APOLLO study drug administration)
- Currently taking tafamidis, doxycycline, or TUDAC (14-day washout period prior to start of APOLLO study drug administration)
- Currently taking diflunisal (3-day washout period prior to start of APOLLO study drug administration)
- Prior severe reaction to liposomal product or a known hypersensitivity to oligonucleotides or any component of patisiran
- Unable to take required premedications
- Anticipated survival <2 years (opinion of investigator)
- Considered unfit
- Under legal protection

Concomitant medications

- Any investigational agent other than patisiran
- Tafamidis
- Diflunisal
- Doxycycline/TUDCA
- Corticosteroids other than those administered as premedications prior to the dose of patisiran, those used to treat an infusion reaction, or topical or inhaled corticosteroids. However, for patients with chronic inflammatory disorders (eg, asthma, rheumatoid arthritis, etc.), systemically administered steroids were permitted provided that: 1) the dose was <20 mg/day prednisone or equivalent if administered chronically, or 2) for doses ≥20 mg/day, administration was limited to no more than 5 consecutive days. Additionally, an intra-articular injection of a corticosteroid was also permitted.

Abbreviations: ALT: alanine transaminase; ANC: absolute neutrophil count; AST: aspartate transaminase; CMAP: compound muscle action potential; FAP: familial amyloidotic polyneuropathy; HIV: human immunodeficiency virus; INR: international; KPS: Karnofsky performance status; LLN: lower limit of normal; NCS: nerve conduction study; NIS: Neuropathy Impairment Score; NYHA: New York Heart Association; PND: Polyneuropathy Disability Score; SNAP: sensory nerve action potential; TTR: transthyretin; ULN: upper limit of normal. Source: APOLLO Clinical Study Report[79], Adams et al. 2018[6]

Table 41: Clinical effectiveness evidence; pivotal patisiran trial

Study	APOLLO (NCT01960348)[6,67]
Study design	Treatment arms: • Patisiran • Placebo
Population	Male and female patients 18 to 85 years of age with a diagnosis of hATTR amyloidosis with polyneuropathy with a documented *TTR* variant (N=225).
Intervention(s)	Patisiran (0.3 mg/kg) administered IV Q3W
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation (yes/no)	Yes (approved for commercial use in the UK in 2018 by the MHRA).
Reported outcomes specified in the decision problem	• Neurological impairment: mNIS+7, PND • Symptoms of polyneuropathy: mNIS+7, Norfolk QOL-DN • Serum TTR • Motor function: PND score, 10-MWT • Weight loss: mBMI • Autonomic function (including the effects on the gastrointestinal system and postural hypotension): mBMI, mNIS+7, COMPASS 31. • Adverse effects of treatment • HRQoL: Norfolk QoL-DN, R-ODS

10-MWT, 10-metre walk test; hATTR, hereditary transthyretin-mediated amyloidosis; HRQoL, health-related quality of life; IV, intravenous; mBMI, modified body mass index; MHRA, Medicines and Healthcare products Regulatory Agency; mNIS+7, modified Neuropathy Impairment Score +7; Q3M, quarterly; Q3W, once every 3 weeks; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score; SC, subcutaneous; TTR, transthyretin.

D1.5 NMA methodology

A fixed-effects Bayesian NMA was conducted to estimate the relative efficacy of different treatments according to the guidance from the Decision Support Unite (DSU) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Indirect Treatment Comparisons Good Research Practices Task Force.[98,99] Given a sparse evidence network that consists of a very limited number of studies relative to the number of treatments, e.g., only one trial per link as for the NMA considered here, a fixed-effect model is preferred. The reason for this preference is that the between-study variance in a random-effect model cannot be appropriately estimated when there is only one study per link, such that the results (i.e., posterior distributions) generated via random-effects modelling are unreliable.[99] Therefore, a fixed-effects model was used in this analysis.

The Bayesian NMA was conducted using the Markov chain Monte Carlo (MCMC) method with non-informative priors for parameters of interest. The probabilities of achieving improvement or no change in PND score were modelled as a binary outcome using logit link. The mean changes from baseline in mNIS+7 and Norfolk QoL-DN scores were modelled as

continuous variables. The models were run with three chains and 50,000 iterations per chain (with 5,000 adaptation and 50,000 burn-in iterations). Five thousand posterior samples per chain were generated using a thinning factor of 10 and were used to estimate posterior statistics.

For the binary outcome of improvement or no change vs. worsening in PND score, treatment effects were estimated as risk ratio (RR) and odds ratio (OR) for achieving improvement or no change with a given treatment relative to placebo. For mNIS+7 and Norfolk QoL-DN scores, treatment effects were estimated as differences between a given treatment and placebo in terms of mean change from baseline to study endpoints. As applicable, median RRs, ORs, and treatment differences versus placebo (drawn from posterior distributions) and the corresponding 95% credible intervals (CrI) were reported.

This NMA was performed to assess the comparative efficacy of vutrisiran and patisiran. Two RCTs, HELIOS-A and APOLLO, were included in the network. Specifically, two randomised treatment arms from APOLLO (patisiran and placebo) and two randomised treatment arms from the HELIOS-A trial (vutrisiran and patisiran) were included in this NMA. In the primary analysis of the HELIOS-A trial, a prespecified external placebo control from the APOLLO trial was used to establish the efficacy of vutrisiran relative to placebo in primary and secondary efficacy analyses. The use of an external placebo control (rather than including a within-trial placebo control arm) for the HELIOS-A trial is deemed necessary to assess the benefit of vutrisiran vs. placebo (i.e., supportive care measures) in this rare disease area due to the ethical concern for ensuring that patients not receiving the investigational therapy were on a proven active treatment (i.e., patisiran in this case) for hATTR amyloidosis. However, the inclusion of the direct link between vutrisiran and the external placebo arm (APOLLO) in the NMA network would result in a duplication of the placebo arm of APOLLO in the network (as this arm is already included via linkage to patisiran in APOLLO), which would inflate the sample size and lead to artificially increased precision of the treatment effect estimates. Therefore, the external placebo arm used in the HELIOS-A study was not included in this NMA. The effect of vutrisiran relative to placebo is established via the indirect link through patisiran within the NMA.

All analyses were implemented using the statistical software R and Just Another Gibbs Sampler (also known as JAGS).

Appendix E: Subgroup analysis

Subgroup analyses are not presented.

Appendix F: Adverse reactions

There are no additional data to present regarding AEs outside of what is presented in B.3.10 Adverse reactions.

Appendix G: Cost and healthcare resource identification

The non-clinical SLR identified published economic analyses, as well as studies that reported healthcare cost or resource utilisation estimates. HST10 was identified in this search.

Healthcare resource costs were identified by searching relevant UK clinical databases. For administration costs, the 2020/2021 NHS national tariff workbook was used to identify the cost associated with complex chemotherapy (HRG code: SB13Z), which was assumed to be a relevant cost for the complex IV administration of patisiran at the NAC. This was also conservatively estimated to be the cost of IV administration of patisiran at home. This same NHS code was used to account for the cost of infusion of patisiran in HST10.[2] The cost of SC administration of vutrisiran at the NAC was based on 2020/2021 NHS national tariff workbook costs for specialist nursing (HRG code: N10AF).[89] The cost of SC administration of vutrisiran at home was estimated to be represented by the cost of the hourly wage (1 hour) of a community based nurse, identified via PSSRU-published costs.[90] The acquisition costs for the premedication components required for patisiran were sourced from the MIMS database.[91-94]

Appendix H: Price details of treatments included in the submission

H1.1 Price of intervention

Table 42: Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	PAS price
Vutrisiran	SC	25 mg	25 mg	£95,862.36		£[redacted]

SC, subcutaneous.

H1.2 Price of comparators and subsequent treatments

Table 43: Details of comparators and subsequent treatment costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	PAS price
Patisiran	IV	0.3 mg/kg bodyweight	10 mg per vial	£[redacted]		£[redacted]

IV, intravenous.

Appendix I: Checklist of confidential information

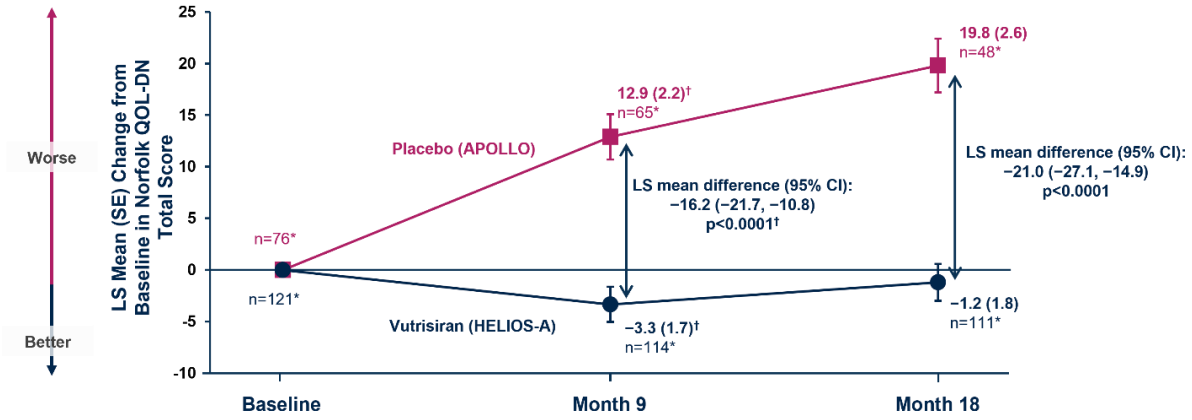
Included with the submission is the Checklist of confidential information.

Appendix J: Comparison of vutrisiran versus placebo in HELIOS-A across all secondary endpoints

J1.1 HELIOS-A key secondary endpoint: change in Norfolk QoL-DN from baseline at Month 18

At Month 18, the LS mean change from baseline in Norfolk QoL-DN was −1.2 for the vutrisiran arm, indicating patients maintained their baseline level of HRQoL, while the LS mean change from baseline for the placebo arm was 19.8, indicating overall worsening compared to baseline, for a treatment difference of −21.0 (p<0.0001; Figure 10).[4]

Figure 10: HELIOS-A key secondary endpoint: Norfolk QoL-DN change from baseline at Month 18



*Number of evaluable patients. †Data presented at Month 9 obtained from the completed Month 9 primary analysis. CI, confidence interval; LS, least squares; Norfolk QoL-DN, Quality of Life-Diabetic Neuropathy; SE, standard error. Source: Adams et al, 2022[4]

J1.2 Key secondary endpoints at Month 18

Significant treatment effects were observed in the vutrisiran arm relative to the APOLLO external placebo arm for all other secondary endpoints at Month 18, demonstrating durable and clinically significant improvement across a range of measures that assess changes in how patients feel or function (R-ODS [level of disability in performing activities of daily living/social participation], 10-MWT [ambulatory ability/gait speed], and mBMI [nutritional status]) (Table 44).[4]

Table 44: HELIOS-A: Month 18 efficacy results

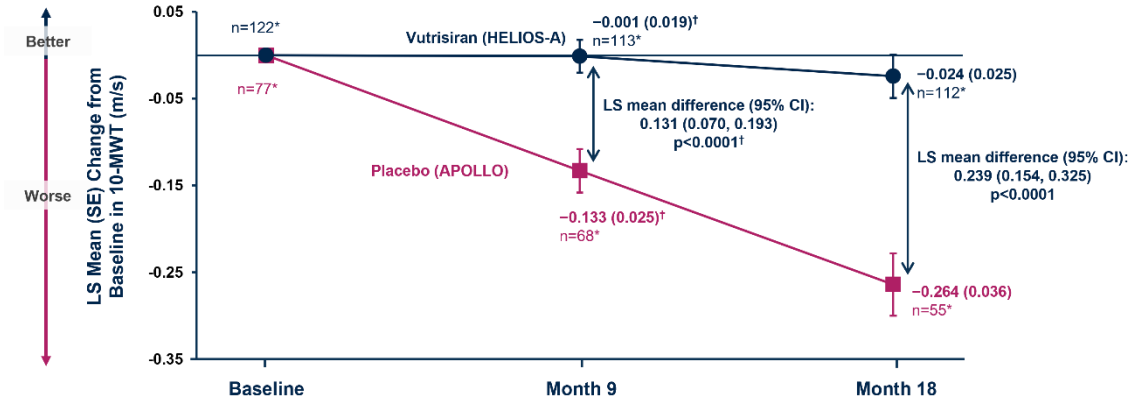
	LS mean change from BL to 18 months (±SE)		Treatment difference vs. placebo (95% CI)	p value
	Placebo (APOLLO) (95% CI) (n=77)	Vutrisiran (HELIOS-A) (95% CI) (n=122)		
10-MWT (m/s)	−0.264±0.036 (−0.334, −0.194)	−0.024±0.025 (−0.075, 0.026)	0.239±0.043 (0.154, 0.325)	p<0.0001
R-ODS	−9.9±0.8 (−11.5, −8.3)	−1.5±0.6 (−2.6, −0.3)	8.4±1.0 (6.5, 10.4)	p<0.0001
mBMI	−115.7±13.4 (−142.2, −89.1)	25.0±9.5 (6.3, 43.8)	140.7±16.4 (108.4, 172.9)	p<0.0001

10-MWT, 10-metre walk test; BL, baseline; CI, confidence interval; LS, least squares; m/s, metres/second; mBMI, modified body mass index; R-ODS, Rasch-built Overall Disability Score; SE, standard error.
Source: Adams et al, 2022[4] Note: For 10-MWT, R-ODS, and mBMI, a numerical increase represents a favourable outcome.

J1.2.1 Change in 10-MWT from baseline at Month 18

Ambulatory ability, as assessed by 10-MWT, was stable compared to baseline for the vutrisiran arm, with a LS mean change from baseline to Month 18 of −0.024 m/s. In the placebo arm, the LS mean change from baseline to Month 18 was −0.264 m/s, where a negative value indicates overall worsening compared to baseline, for a treatment difference of 0.239 (p<0.0001) (Figure 11).[4]

Figure 11: HELIOS-A secondary endpoint: 10-MWT change from baseline at Month 18



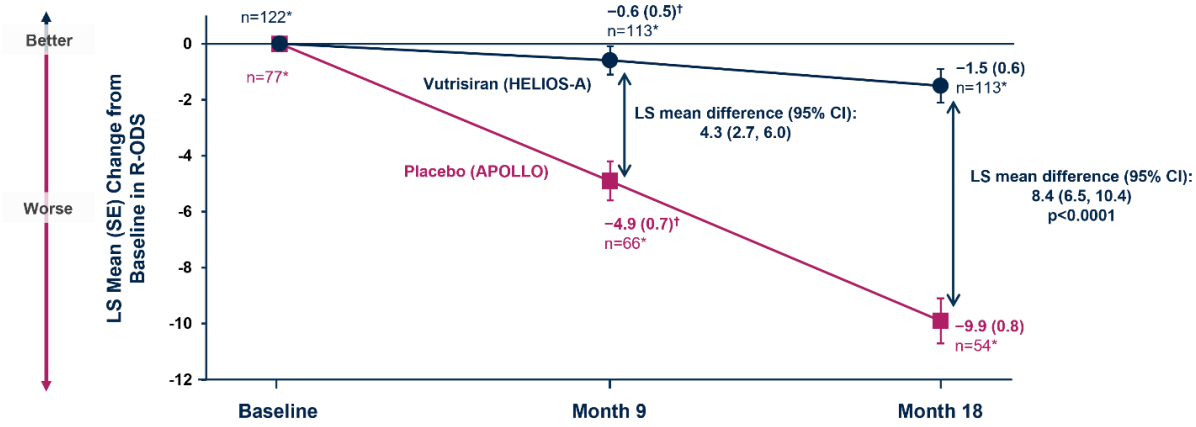
*Number of evaluable patients. †Data presented at Month 9 obtained from the completed Month 9 primary analysis.
10-MWT; 10-metre walk test; CI, confidence interval; LS, least squares; SE, standard error.
Source: Adams et al, 2022[4]

J1.2.2 Change in R-ODS from baseline at Month 18

Ability to perform daily activities and participate in social activities, as assessed by R-ODS, was stable compared to baseline for the vutrisiran arm, with a LS mean change from baseline to Month 18 of −1.5. In the placebo arm, the LS mean change from baseline to

Month 18 was −9.9, indicating overall worsening compared to baseline, for a treatment difference of 8.4 (p<0.0001) (Figure 12).[4]

Figure 12: HELIOS-A secondary endpoint: R-ODS change from baseline at Month 18

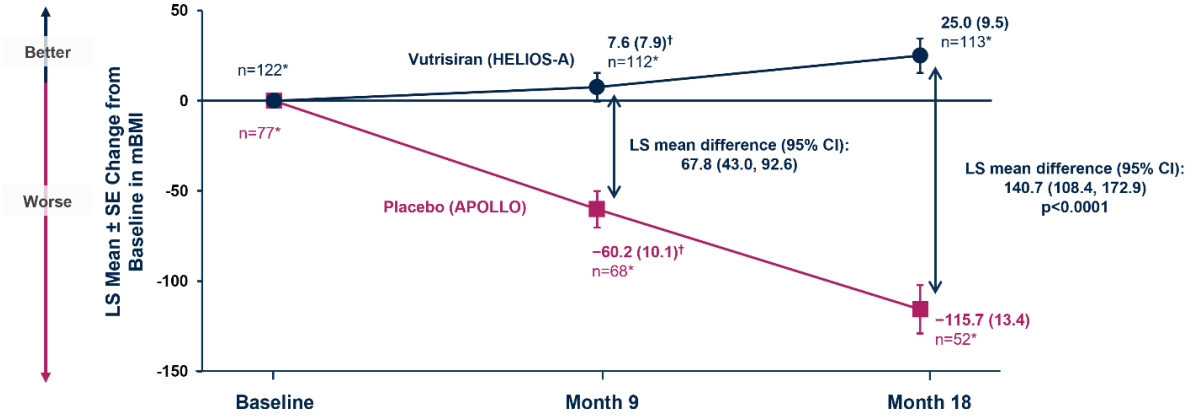


*Number of evaluable patients. †Data presented at Month 9 obtained from the completed Month 9 primary analysis.
CI, confidence interval; LS, least squares; R-ODS, Rasch-built Overall Disability Score; SE, standard error.
Source: Adams et al, 2022[4]

J1.2.3 Change in mBMI from baseline at Month 18

At Month 18, the LS mean change from baseline in nutritional status, as assessed by mBMI, was 25.0 for the vutrisiran arm, indicating improvement compared to baseline, while the LS mean change from baseline for the placebo arm was −115.7, indicating overall worsening compared to baseline, for a treatment difference of 140.7 (p<0.0001) (Figure 13).[4]

Figure 13: HELIOS-A secondary endpoint: mBMI change from baseline at Month 18



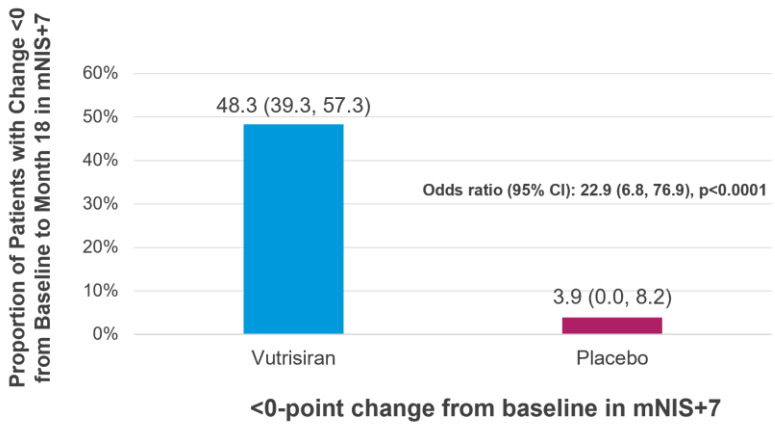
*Number of evaluable patients. †Data presented at Month 9 obtained from the completed Month 9 primary analysis.
CI, confidence interval; LS, least squares; mBMI, modified body mass index; SE, standard error.
Source: Adams et al, 2022[4]

J1.3 Binary analysis: mNIS+7 and Norfolk QoL-DN at Month 18

A binary outcomes analysis was conducted to compare the proportion of patients with a change of <0 points from baseline to Month 18 in mNIS+7 (i.e., improvement in neuropathy)

between the vutrisiran arm and the APOLLO placebo arm.[78] In the vutrisiran arm, 48.3% of patients showed an improvement in neuropathy (change from baseline in mNIS+7 <0) at Month 18 compared to 3.9% of patients in the APOLLO placebo arm (OR 22.9 [95% CI 6.8, 76.9], p<0.0001) (Figure 14).[78]

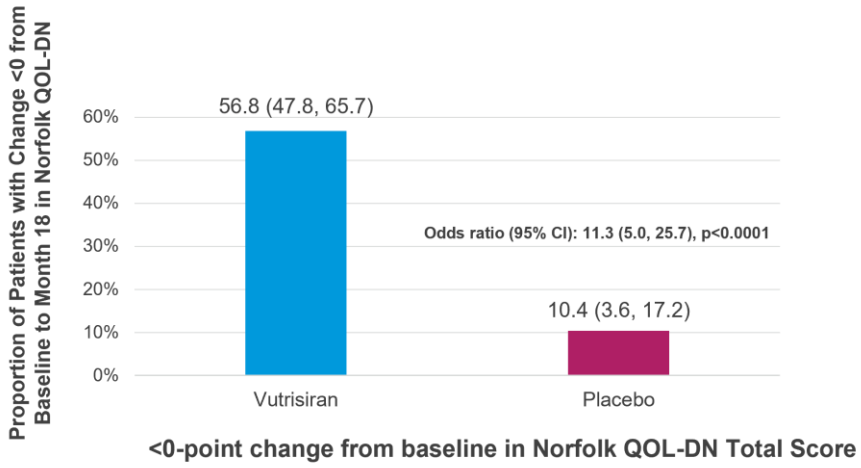
Figure 14: HELIOS-A binary analysis: Reversal in neuropathy impairment from baseline at 18 months*†



*HELIOS-A patients with missing post-baseline values due to COVID-19 (including values on or after onset of a serious COVID-19 AE) were excluded from the analysis. Assessments after initiation of local standard treatment for hATTR amyloidosis were treated as missing. †Patients included in analysis: vutrisiran (n=118) and placebo (APOLLO) (n=77).
CI, confidence interval; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; mNIS+7, modified Neuropathy Impairment Score+7.
Source: Alnylam Pharmaceuticals. Data on File. HELIOS-A 18-Month Clinical Study Report, 2022[78]

A binary analysis was also conducted to compare the proportion of patients with a change of <0 points from baseline to Month 18 in Norfolk QoL-DN (i.e., improvement in HRQoL) between the vutrisiran arm and the APOLLO placebo arm.[78] In the vutrisiran arm, 56.8% of patients showed an improvement in HRQoL (change from baseline in Norfolk QoL-DN <0) at Month 18 compared to 10.4% of patients in the APOLLO placebo arm (OR 11.3 [95% CI 5.0, 25.7], p<0.0001) (Figure 15).[78]

Figure 15: HELIOS-A binary analysis: Improvement in Norfolk QoL-DN from baseline at 18 months*†



*HELIOS-A patients with missing postbaseline values due to COVID-19 (including values on or after onset of a serious COVID-19 AE) were excluded from the analysis. Assessments after initiation of local standard treatment for hATTR amyloidosis were treated as missing. †Patients included in analysis: vutrisiran (n=118) and placebo (APOLLO) (n=77). CI, confidence interval; hATTR amyloidosis, hereditary transthyretin-mediated amyloidosis; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy; QoL, quality of life. Source: Alnylam Pharmaceuticals. Data on File. HELIOS-A 18-Month Clinical Study Report, 2022[78]

Appendix K: Time on treatment in the CCA

Table 45: Fit statistics of parametric models to patisiran and vutrisiran time-on-treatment data

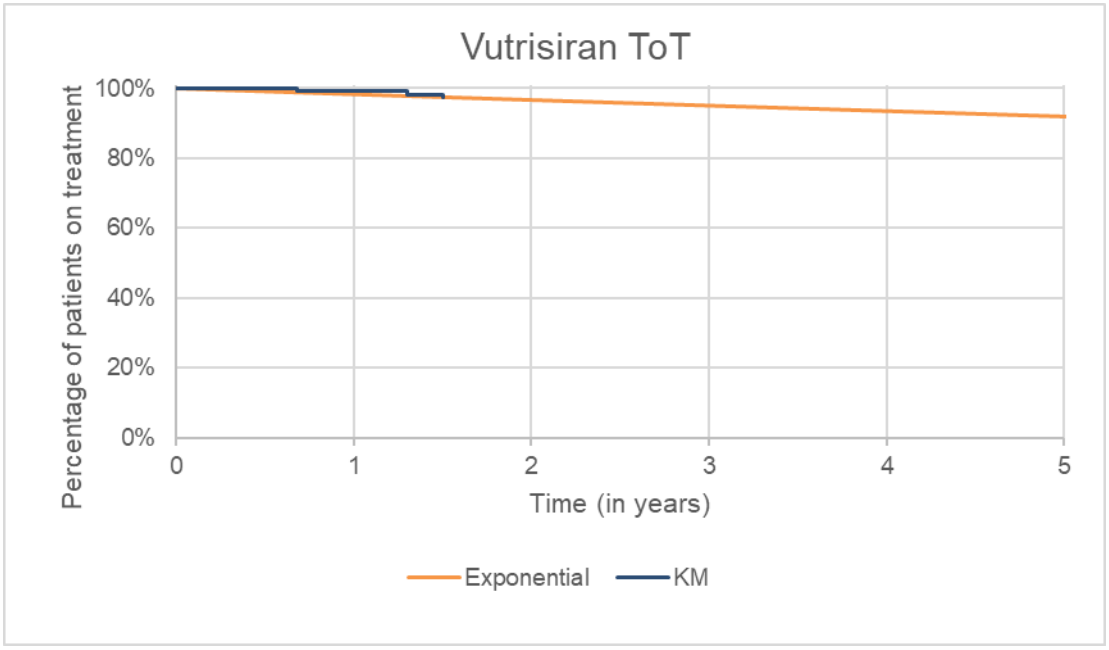
Vutrisiran						
Fitting Statistic	Exponential	Weibull	Log-Logistic	Log-Normal	Gompertz	Gamma
AIC	31.969	31.037	31.048	31.161	49.500	33.027
BIC	34.773	36.646	36.656	36.769	55.100	41.439
Sum AIC + BIC	66.742	67.683	67.704	67.930	104.600	74.466
Patisiran						
Fitting Statistic	Exponential	Weibull	Log-Logistic	Log-Normal	Gompertz	Gamma
AIC	12.051	13.182	13.175	13.045	19.100	14.900
BIC	13.788	16.657	16.650	16.521	22.600	20.113
Sum AIC + BIC	25.839	29.839	29.825	29.566	41.700	35.013

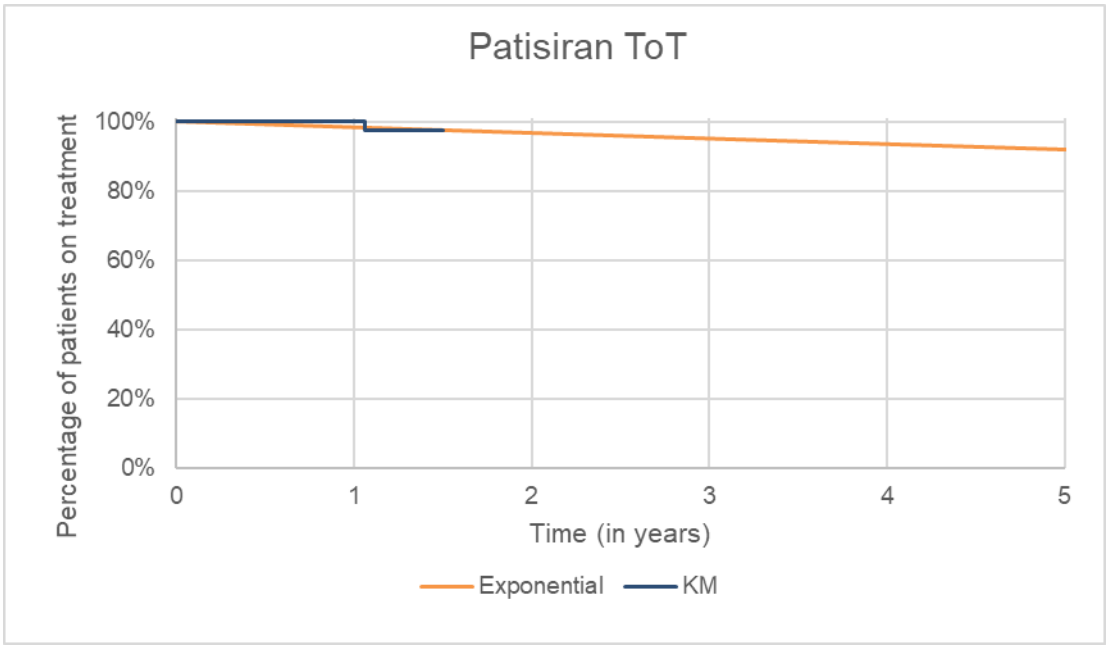
AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 46: Model parameters for parametric functions to extrapolate patisiran and vutrisiran time on treatment curves

Vutrisiran						
Parameter	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Gamma
Intercept	6.5754	4.0251	4.0172	4.5737	6.5757	3.9563
Scale		0.3085	0.3072	0.8575	-10.0020	0.1546
Patisiran						
Parameter	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Gamma
Intercept	6.5707	4.1270	4.1099	4.4647	6.5711	4.4985
Scale		0.3384	0.3352	0.8097	-10.0021	1.4467

Figure 16: Vutrisiran and patisiran time on treatment





KM, Kaplan–Meier; ToT, time on treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

[ID5074] Vutrisiran for treating hereditary transthyretin-related amyloidosis

Company response to clarification questions

October 2022

File name	Version	Contains confidential information	Date
ID5074 Vutrisiran Alnylam response to clarification questions Redacted	1	Yes	21 October 2022

This document contains confidential information.

Preamble

Alnylam would like to express our sincere appreciation for the prompt review by the External Assessment Group (EAG) of our cost-comparison submission for vutrisiran for treating hereditary transthyretin-related (hATTR) amyloidosis. We have addressed each of the questions to the best of our abilities in the time available, and would be pleased to provide any additional information that may be required. We wish to note that some of our responses contain commercial-in-confidence information that has been marked accordingly.

Response to clarification questions

1. Please provide the full reference for the information received from Lloyds Pharmacy Clinical Homecare regarding the mean number of vials used per patient per administration for patisiran. In particular:

- *The information in the exact format supplied by Lloyds*

Response: The base-case estimate of [redacted] patisiran vials per patient in the company submission (CS) was a mean value calculated directly by LloydsPharmacy Clinical Homecare, and provided to Alnylam in a confidential email in September 2022. Although LloydsPharmacy also provided detailed data to Alnylam, these data are not at the level of individual patients, but rather at the level of patisiran vials delivered. To address the EAG's request to the best of our ability, we are providing the detailed data in an Excel file accompanying this response (*ID5074 LloydsPharmacy patisiran data CIC.xlsx*). We request that the contents of this file be treated as commercial in confidence.

The Excel file contains two worksheets:

- Sheet1: raw data for delivered vials
- Sheet2: summary counts

We are forwarding this Excel file as supplied by LloydsPharmacy with only the following changes by Alnylam:

- Revising the filename for clarity
- Addition of confidentiality messages
- Deletion of two columns from Sheet1 (*Document No.* and *Location Code*) to avoid the inclusion of any identifying information (e.g., about location of vial delivery) that could break patient confidentiality

In the Excel file, vial quantities that are negative values represent patisiran vials shipped out for delivery; these deliveries are made for the purpose of a nurse visit to infuse the patient and thus are equivalent to infused vials. Vial quantities that are positive values represent vial returns (for unknown reasons).

In Sheet1, the *Posting Date* column gives the month and year of delivery made for the purpose of a nurse visit and patient infusion. Other column headings are self-explanatory.

- *The number of patients and administrations of drug that are contained within the records*

Response: As explained above, the data provided to Alnylam by LloydsPharmacy preclude identifying individual patients, so cannot be used to estimate the number of patients. However, Alnylam understands that each row in Sheet1 with a negative value in the *Quantity* column represents a single delivery made for the purpose of a nurse visit to infuse a single patient, which is equivalent to an administration. Thus, these records contain 1996 administrations.

- *The standard deviation around the mean number of vials*

Response: Because the records do not identify individual patients, it is not possible to calculate mean or standard deviation (SD) number of vials per patient. Instead, we are submitting another version of the LloydsPharmacy dataset showing our calculation of mean (SD) vials across administrations (*ID5074 LloydsPharmacy patisiran data Alnylam calculations CIC.xlsx*), as explained in our response to the following question.

- *How the mean number of vials (and standard deviation) varied within the time period covered (Sept 2021 to Aug 2022); preferably as a monthly breakdown*

Response: We have provided the requested monthly breakdown in Sheet2 of the Excel file *ID5074 LloydsPharmacy patisiran data Alnylam calculations CIC.xlsx* so that the EAG can directly assess how these values varied over time. Note that the calculation of numbers in columns A–H of this worksheet was performed by LloydsPharmacy, while the numbers in columns K–M were calculated by Alnylam. Column A (*Row Labels*) indicates the month and year within the overall time period covered by the LloydsPharmacy data. Across the full time period covered, the mean (SD) number of vials per administration was estimated at [redacted] ([redacted]).

2. Please provide full details of the calculation for the average number of vials required per patient for patisiran based on the HELIOS-A weight distribution including a list (preferably in Excel) of the individual patient weights from the trial.

Response: As presented in Section B.4.4.2 of the CS, a scenario analysis for patisiran vial usage is included in the submitted cost-comparison analysis whereby the average required number of patisiran vials per administered dose is set at [redacted], estimated from the bodyweight distribution of the total patient population of HELIOS-A (i.e., patients in both treatment arms).

The estimated average of [redacted] patisiran vials was calculated as follows:

1. For each patient, we retrieved the bodyweight at baseline from the HELIOS-A database.

2. We calculated vial usage for different bodyweight categories using the number of required vials for patients within each category according to the posology instructions in the product label,[1] as shown in Table 1.

Table 1: Patisiran vial requirements by bodyweight category

Bodyweight (kg)	Number of vials per dose (10 mg per vial)	Number of vials per year
33.5–66.9	2	34
>66.9–99.9	3	51
≥100	3	51

Source: ONPATTRO Summary of Product Characteristics[1]

3. We defined five categories of bodyweight and calculated the number and percentage of patients in HELIOS-A within each category, as shown in Table 2.
4. We derived the weighted average vial consumption by calculating the sum-product of the percentage of patients and vials required, yielding [redacted] vials as shown in Table 2.

Table 2: Bodyweight distribution of all patients in HELIOS-A and estimated average patisiran vial consumption for scenario analysis

Bodyweight (kg)	Patients		Number of vials required	Weighted average vials*
	n	%		
33.5–66.9	[redacted]	[redacted]	2	[redacted]
>66.9–99.9	[redacted]	[redacted]	3	[redacted]
≥100†	[redacted]	[redacted]	3	[redacted]
Total	**164**	**100.00**		[redacted]

*Value within each bodyweight category is calculated as the percentage of patients multiplied by the number of vials required; total is the sum of these products.
†Per the ONPATTRO Summary of Product Characteristics[1]

In the timeframe available for this response, we were unable to verify whether we are permitted to provide NICE with a list of the individual patient weights from HELIOS-A without violating patient confidentiality and the terms of the participants' informed-consent agreements. Given these privacy concerns, we hope that the details of the calculations provided above will adequately address the EAG's question.

3. Please provide the RIS file for the Endnote library references.

Response: We provided the RIS file of references in the EndNote library for the CS on Wednesday 19 October 2022.

4. Please provide additional details for the calculation of differences in serum TTR levels.

Response: The following sections provide detailed explanations of the calculations of (A) between–treatment-arm differences in reduction of serum transthyretin (TTR) trough levels, and (B) within-arm reduction from baseline in steady-state peak TTR levels.

A. Noninferiority analysis of median treatment difference in TTR percent reduction (trough) from baseline (vutrisiran – patisiran)

As explained in Section B.3 of the CS, the HELIOS-A trial included as a secondary endpoint a pre-specified noninferiority analysis to compare the activity of patisiran and vutrisiran on serum TTR reduction. Calculations were pre-defined in HELIOS-A per the trial's statistical analysis plan (SAP).

Time-averaged trough TTR percent reduction through Month 18 was defined as the average trough TTR percent reduction (i.e., percent reduction based on TTR levels measured before study-drug dose administration on the day of a post-baseline visit) relative to baseline during the Month 6–18 interval (the steady-state period for both vutrisiran and patisiran). Note that the term "trough reduction" in this context refers to the least extent of pharmacodynamic activity/TTR reduction from baseline (i.e., TTR reduction that is furthest from complete) during the interval between doses.

The analysis population for this endpoint was the TTR per-protocol population, defined as all patients in the modified intent-to-treat (mITT) population who had a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment between Month 6 (Week 24) and Month 18 (Week 72) that met the following criteria (which were required for inclusion of a post-baseline TTR assessment in the analysis):

- At the study visit at which the TTR assessment took place, the assessment had to have been performed before administration of study drug.
- The assessment must not have been performed after initiation of local standard treatment for hATTR amyloidosis (as was allowed, per investigator judgment, for patients who remained in the HELIOS-A study after discontinuing study drug).
- The patient had to have received their complete, planned study-drug administration at the treatment visit approximately 12 weeks before the study visit at which the TTR assessment took place (*for patients in the vutrisiran arm, in alignment with the vutrisiran dosing schedule*) or at the treatment visit approximately 3 weeks before the study visit at which the TTR assessment took place (*for patients in the patisiran arm, in alignment with the patisiran dosing schedule*).
- *For patients in the vutrisiran arm:* The patient had to have received their complete, planned study-drug administration at 2 consecutive planned treatment visits before the study visit at which the TTR assessment took place, to ensure steady state pharmacodynamics.

The treatment difference between vutrisiran and patisiran in TTR percent reduction from baseline was calculated per the following three-step process:

- Step 1: Time-averaged trough TTR percent reduction from baseline was calculated as follows for each patient:
  - The patient's baseline TTR level was defined as the average serum TTR level across all TTR measurements performed on study (i.e., after enrolment) for that patient, including those from any unscheduled visits, before the date and time of the patient's first dose of study treatment.
  - The patient's TTR percent reduction from baseline was calculated by determining the percentage reduction from baseline for each trough TTR assessment (i.e., TTR assessment before study-drug dose administration on the day of a study visit) performed for the patient between Months 6 and 18, and then calculating the average percentage reduction from baseline across all of these assessments;

for the purposes of this calculation, only trough TTR assessments that met the criteria for inclusion in the analysis, as described above, were considered.

- Step 2: Group median time-averaged trough TTR percent reduction from baseline was calculated for each treatment arm using the Hodges-Lehmann method[2] for estimation of a 1-sample median (pseudomedian):
  – Inputs used were individual-patient–level estimates of time-averaged trough TTR percent reduction from baseline (calculated as described above) for the treatment arm of interest.
  – The outputs from this step were the time-averaged trough TTR percent reduction results of 84.7% from baseline for vutrisiran and 80.6% from baseline for patisiran, as reported in Section B.3.6.1 of the CS.

- Step 3: Median difference between treatment arms in terms of time-averaged trough TTR percent reduction from baseline was calculated using the Hodges-Lehmann method[2] for estimation of a 2-sample median difference:
  – Inputs used were individual-patient–level estimates of time-averaged trough TTR percent reduction from baseline (calculated as described above) for each treatment arm.
  – The analysis was stratified by previous TTR stabiliser use (yes vs. no); values within each stratum were first aligned by the within-stratum 1-sample Hodges-Lehmann median, and the 95% confidence interval (CI) for the median difference between the vutrisiran and patisiran groups was then calculated.
  – The output from this step was the median treatment difference (vutrisiran – patisiran) of 5.28% (95% CI, 1.17 to 9.25) in TTR percent reduction from baseline, as reported in Section B.3.6.1 of the CS.

As pre-specified in the HELIOS-A SAP and stated in the primary publication for the study (Adams et al. 2022[3]), noninferiority of vutrisiran vs. patisiran was to be declared if the lower limit of the 95% CI for the median difference in TTR percent reduction between treatment arms (vutrisiran – patisiran) was greater than –10%. Note that the

convention used for reporting analysis results was that reductions from baseline were assigned a positive value (e.g., an 80% reduction from baseline would be indicated by an analysis output of "80%", while a 20% increase from baseline would be indicated by an analysis output of "–20%"); thus, the pre-specified noninferiority margin of –10% reflects a scenario in which the percent TTR reduction from baseline was less pronounced (by 10 percentage points) in the vutrisiran arm vs. the patisiran arm. Therefore, the lower limit of the 95% CI for the median treatment difference, (+)1.17, was above the prespecified noninferiority margin of –10%.[3]

B. Descriptive analysis of steady-state peak TTR percent reduction from baseline through Month 18

In addition to the noninferiority analysis of *trough* TTR percent reduction described above, our CS and the primary publication[3] report results of a descriptive analysis of *steady-state peak* TTR percent reduction from baseline through Month 18. The latter analysis provides an estimate of the TTR percent reduction seen when the pharmacodynamic effects of the treatment of interest have reached their maximum level within the dosing interval, for a dosing interval during the steady-state phase of treatment. Note that the term "peak reduction" in this context refers to the greatest extent of pharmacodynamic activity/TTR reduction from baseline (i.e., reduction that is closest to complete) during the interval between doses.

The analysis population for steady-state peak TTR percent reduction was the mITT population, defined as all randomised patients who received any amount of study drug; patients were analysed according to the treatment to which they were randomised.

The within-treatment steady-state peak TTR percent reduction from baseline was calculated per the following two-step process:

- Step 1: Steady-state peak TTR percent reduction from baseline was calculated for each patient, as follows:
  - The patient's baseline TTR level was defined as the average serum TTR level across all TTR measurements performed on study for that patient, including

those from any unscheduled visits, before the date and time of the patient's first dose of study treatment.
  - In the vutrisiran arm, each patient's peak TTR percent reduction was calculated by determining the percentage reduction from baseline to TTR assessment at study week 66.
  - In the patisiran arm, each patient's peak TTR percent reduction was calculated by determining the percentage reduction from baseline to TTR assessment at study month 18.

- Step 2: Descriptive statistics on steady-state peak TTR percent reduction from baseline through Month 18 were calculated by treatment arm, as follows:
  - Per-patient results as calculated above were used as inputs to calculate the mean (SD) of peak TTR percent reduction from baseline across all patients in the treatment arm of interest.
  - The outputs from this step were the mean (SD) steady-state peak serum TTR reduction results of 88% (16%) from baseline for the vutrisiran arm and 86% (10%) from baseline for the patisiran arm, as reported in the CS and by Adams et al. 2022 (see Supplementary Table S4 in the publication).[3]

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). ONPATTRO (patisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; 01 January 2021.
2. Hodges JL, Jr., Lehmann EL. Rank methods for combination of indepdendent experiments in analysis of variance. *Annals of Mathematical Statistics.* 1962;33(2):482-497.
3. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2022:1-9.

NICE National Institute for Health and Care Excellence

Streamlined Cost Comparison Appraisal
Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Cardiomyopathy UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cardiomyopathy UK is the national charity for people affected by cardiomyopathy. The charity provides a range of support and information services, provides clinical education opportunities, raises awareness of the condition among the general public, facilitates research and advocates for improved access to quality treatment. The charity's database contains 18,000 individuals and there are around 150 active volunteers who facilitate support groups, provide peers support, advocate for improvements in health services, undertake fundraising activities and take on a range of other roles. The charity's trustees, the majority of whom have personal experience of the condition, are ultimately responsible for the charity and are supported by a professional staff team. The charity is funded by community fundraising (33%), donations and legacies (24%) charitable trusts and companies (29%) and the pharmaceutical industry (14%). Total income from the year January 2021-December 2021 was £945K
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment	The charity received £10,000 from Alnylam in 2021 towards the costs of our online clinical education programme, around 1% of total income for that year. No funding has been received from Alnylam in 2022.

companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In 2021, the charity also received funding from; Novartis, £23,800 towards a national awareness campaign for cardiomyopathy Pfizer, £21,100 towards regional advocacy project Sanofi, £5,000 towards online medical education AstraZeneca, £10,000 towards online medical education BMS, £62,000 towards online medical education, awareness and educational activity
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The main source of data comes from the charity's national user survey 2022 **(n.536)** and the partners, carers and loved ones of people with all forms of cardiomyopathy **(n.62)** The charity, and the clinical community, are increasingly recognising the connection between Amyloidosis and Cardiomyopathy, especially in relation to restrictive cardiomyopathy. This submission highlights views of people with restrictive cardiomyopathy but we have also included feedback from the wider cardiomyopathy community as we feel that these suitably reflect those of individuals with Amyloidosis Cardiomyopathy.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Most people with restrictive cardiomyopathy (the form of cardiomyopathy most associated with amyloidosis) told us that their condition has a significant impact on them day to day. All respondents reported that their condition had impacted their mental health and had made it hard to cope over the last six months. Respondents found that the condition especially affected their confidence, social networks and personal relationships and left them feeling isolated. The majority had also sought advice on finances and benefits. The wider cardiomyopathy community also reported that the condition had an impact on their mental health although fewer (50%) said that they had found it hard to cope over the last six month.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The main difficulties that people with cardiomyopathy report in relation to their care and treatment on the NHS tend to be around receiving an initial diagnosis. 52% of respondents were initially diagnosed with another condition, most commonly asthma or anxiety.
8. Is there an unmet need for patients with this condition?	Although there are existing treatments for amyloidosis with neuropathy, there current treatments for cardiomyopathy are heart failure medication to manage symptoms, ICD's and other devices, surgical intervention (ablation and myectomy) or transplantation. There is a need to develop and make accessible new medication that addresses the specific needs of people with cardiomyopathy.

9. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	N/A
10. Is it appropriate to compare this technology to [add the comparator]?	Our understanding is that the delivery of Vutrisiran is less onerous on patients as it requires fewer and less invasive injections than Patisiran

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	•

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Streamlined Cost Comparison Appraisal

Viridian for treating hereditary transthyretin-related amyloidosis [ID5074]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	UK ATTR Amyloidosis Patients' Association (UKATPA) Registered Charity Number: 1183624
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a charity set-up to represent and support patients and their families living with ATTR Amyloidosis. We also collaborate with doctors, nurses, and the pharma companies in support of patients, We are funded in several ways: Donations, fund raising and grants from pharma companies. The charity is Trustee based and they are all patients. Due to this have members. We do have a databased of friends of the charity. There are currently 6 Trustees and 80 friends of the charity on the database.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Not in the last 12 months. UKATPA has received grants in the past for specific project from the company and from the manufacturer of the comparator drug.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Talking to the members of our patient association, attending patient's and doctor's meetings and surveying patients with hATTR neuropathy.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a life limiting condition, currently with no cure, hTTR Amyloidosis changes your life and the lives of your family. As the disease progresses you are unable to do simple day to day things without support. It causes debilitating cardiovascular, neurological, and renal issues. Individuals with hATTR frequently have difficulty walking, experience severe fatigue and breathlessness all of which limit the activities in which they can participate. Dizziness when changing position, diarrhoea and other gut symptoms are also common among patients. Loss of sensation in the feet and hands in particular relating to heat, cold, and fine motor skills such as buttoning up clothes and opening packets, wallets etc. further increase the challenges of daily life. Taken as a whole these symptoms can significantly reduce an individual's quality of life, rendering them unable to do things they used to enjoy, increase their need for care and reducing their ability to participate fully in their own lives, including their ability to maintain employment. TTR Amyloidosis causes a heavy burden on families and carers. The symptoms mentioned above make it difficult to live independently so can have a major impact on them. They experience a loss of a loved one, not only because that person can no longer support the family but also that they become a different person as they are having to deal with constant pain and discomfort. This can result in them being more distant and 'living in their own bubble' of the disease. Carers are often required to leave or change their jobs to accommodate their loved one and their disease. Closeness between a couple where Amyloidosis affects one of them can be reduced. Patience and love are often tested, and the relationship can become hugely different from the one they had prior to amyloidosis hitting. Physically carers often take over the tasks that their loved one with ATTR can no longer do, in addition to taking on the physically demanding role of carer. The financial implications for families can also be significant, reducing hours, leaving work all together or taking early retirement are common adaptations among those with hATTR. The individuals acting as carers also frequently reduce their paid employment to allow them to care, this reduction of income often co-insides with the need for more expenditure on services and adaptations to support the individual with hATTR. It is important to note that hATTR has a significant impact not only on physical health but also on the mental health of individuals and their carers. As this is a genetic condition, families can, and often do, have multiple members who are living with or who have died as a result of hATTR. This is distressing and stressful for all involved. As hATTR is a rare condition families can also feel socially isolated and unsupported.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Care and treatment on the NHS are currently very inconsistent, in particular the need for better genetic counselling and psychological support are issue frequently faced by patients and their families/carers. Late diagnosis is a significant problem for those with hATTR, in the past lack of available treatment has been cited as one reason why some doctors have not been interested in diagnosing the disease. As more treatments become available the patient community is optimistic this will begin to change. Two treatments are available to patients with hATTR neuropathy in the UK (patisiran and inotersen). These treatments have completely changed the quality of life and the outlook of patients and carers. Having Vutrisiran available would be another huge step ahead for patients.
8. Is there an unmet need for patients with this condition?	Patients with hATTR neuropathy do have access to treatment however due to the administration of these treatments via infusion they are time consuming for patients to receive. Vutisiran administration is less frequent and less time consuming for the patient than Patisiran.

9. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have a sensitivity to existing drugs or the pre-medication given with them (paracetamol. Steroids, ranitidine, or famotidine, chlorphenamine). Or who develop side effects.
10. Is it appropriate to compare this technology to [add the comparator]?	Yes, it is appropriate to compare this technology to patisiran.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	NO

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Patisiran and Inoteresen have had a massive positive impact in the quality of live and outlook of patients with hATTR, relatives and carers. • Having Vutrisiran available would be another huge step ahead from the point of view of the patients and carers. • At present, Patisiran is home delivered to most patients every three weeks. It takes a nurse most of the day to travel to the patient's home, give the premedication and then administer the infusion. The cost of administration would be less with Vutrisiran • It would be much better for the patients to have Vutrisiran, so they do not need the pre-medication drugs (which cause more side-effects than the drug) and it would be much more convenient and economical for the patient. • Vutrisiran would decrease the risk of complications (failure to cannulate, phlebitis, extravasation injury)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Streamlined Cost Comparison Appraisal
Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]
NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

NICE National Institute for Health and Care Excellence

About you

Your name	
Name of your organisation	National Amyloidosis Centre
Please indicate your position in the organisation	Department of Health and Social Care or Welsh Government in general? • Commissioning services for the Department of Health and Social Care or Welsh Government specific to the condition for which NICE is considering this technology? • Responsible for quality of service delivery in the ICB (e.g. medical director, public health director, director of nursing)? • A specialist in the treatment of people with the condition for which NICE is considering this technology? • A specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)? • Other (please specify):
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	None

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion	The condition is treated with patisiran, a similar RNAi therapeutic which has to be given with a pre-medication and by intravenous infusion every 3 week (lifelong). It is prescribed via National Amyloidosis Centre throughout England & NI and separately in Scotland. Efficacy is not in question. The only current alternative is inotersen which is associated with significant toxicity and is rarely prescribed.

between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?	
To what extent and in which population(s) is the technology being used in your local health economy? **Is there variation in how it is being used in your local health economy?** **Is it always used within its licensed indications? If not, under what circumstances does this occur?** **What is the impact of the current use of the technology on resources?** **What is the outcome of any evaluations or audits of the use of the technology?** **What is your opinion on the appropriate use of the technology?**	Patisiran is being used only in patients with hereditary ATTR amyloidosis with polyneuropathy (i.e., the licensed indication). It is only ever prescribed within the licensed indication. Vutrisiran would simply replace the use of patisiran in the same cohort of patients. There is little variation – the first patisiran infusion is routinely administered at NAC and subsequent infusions are administered via Lloyds Homecare team to patients in their homes. The treatment is unequivocally resulting in marked clinical benefit and arresting progression of this hitherto relentlessly progressive and ultimately fatal disease which is associated with a huge disease burden for patients and their families.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	It would markedly improve their quality of life and unequivocally prolong their life
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	Specialist clinics only. Initially via National Amyloidosis Centre only and subsequently via a UK Amyloidosis Network (once this is in existence)
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	Equivalent impact to patisiran although great reduction in nursing costs due to preferential route and frequency of administration without a need for pre-medications.
Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin	Yes, it would free up homecare nursing time, no need for IV infusion sets, no need for pre-medications

pumps, or the loss of funds to other programmes)?	
Would there be any need for education and training of NHS staff?	No additional training necessary

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	There would be no disadvantages in relation to any of the patient groups/populations highlighted.
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	Helios-A trial, APOLLO trial

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	Vutrisiran is a 'straight swap' for patisiran which is currently used in the identical population but has the inconvenience of being administered every 3 weeks by slow IV infusion and requires administration of pre-medications. This is a lifelong therapy which currently results in patients being 'out of action' for at least one day every 3 weeks and is associated with complications (infusion-related reactions, extravasation, steroid pre-med associated adverse effects), all of which would be removed by vutrisiran.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Streamlined Cost Comparison Appraisal

Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	This drug, if approved by NICE, would be within the clinical amyloidosis pathway
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a single centre that manages the care of patients with amyloidosis and there are shared care arrangements in place
8. What impact would the technology have on the current pathway of care?	This technology would provide another clinical option for this condition. It would reduce the treatment burden on patients as the drug is administered at three monthly intervals via subcut injections. The other treatments are administered • Inotersen, weekly sub cut injections • Patisiran infusion every three weeks

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	This drug is not currently commissioned. 122 patients were treated with inotersen and patisiran in 2021/22

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be administered by sub cut injection which is a method already used in this clinical care pathway
10a. How does healthcare resource use differ between the technology and current care?	The clinical service will be the same. The treatment burden on the patient will reduce as will the cost of homecare for drug delivery
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology should only be prescribed by the national specialist centre for amyloidosis or a centre with whom it has established shared care or as part of a clinical network.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for staff, patients and the g-home care company in relation to this treatment is required. This is usually provided by the drug company.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	I am not aware of any informal or formal rules outside of the clinical pathway.
11. What is the outcome of any evaluations or audits of the use of the technology?	NA

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are no potential equality issues associated with this treatment. The significant reduction in the number of times that the drug has to be taken would be welcomed by patient
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]

NICE medicines optimisation team briefing

November 2022

Advice

A full single technology appraisal of vutrisiran for hereditary transthyretin-related amyloidosis is unlikely to add value. A fast-track appraisal with a cost comparison comparing vutrisiran to patisiran and inotersen is likely to be appropriate. However, differences in safety profiles and service delivery also need to be considered.

Rationale

Vutrisiran shows similar clinical efficacy and safety to patisiran based on limited phase 3 clinical trial evidence. Patisiran has the same mechanism of action as vutrisiran, is used in the same patient population, and at the same point in the treatment pathway. Patisiran has already been recommended for treating hereditary transthyretin amyloidosis in HST10 (August 2019).

Inotersen, which has a slightly different mechanism of action, is also recommended in HST9 (May 2019). However, there are differences in safety profiles, service delivery and acquisition costs between vutrisiran, patisiran and inotersen; as well as factors that affect people's choice of treatment, such as route and frequency of administration, time and travel required for treatment, and monitoring requirements.

Technology overview

Vutrisiran (Amvuttra) is a gene-silencing treatment licensed in the UK for hereditary transthyretin-mediated amyloidosis in adults with stage 1 or stage 2 polyneuropathy. It is a solution for injection containing 25 mg vutrisiran in a single-use, pre-filled syringe for subcutaneous injection (SPC for vutrisiran).

Context

Hereditary transthyretin (hATTR) amyloidosis is an ultra-rare condition caused by inherited mutations in the transthyretin (TTR) gene. This causes the liver to produce abnormal TTR protein, which accumulates as deposits in body tissues (amyloidosis). These deposits can disrupt the structure and damage the function of affected tissues. People may mainly have symptoms of polyneuropathy or cardiomyopathy, but most patients seen in the NHS will have symptoms of both over the course of the condition (HST9).

NICE has published highly specialised technology guidance on inotersen (HST9) and patisiran (HST10) for treating hereditary transthyretin amyloidosis in adults with stage 1 or stage 2 polyneuropathy.

Table 1: Characteristics of vutrisiran compared with patisiran and inotersen

	Vutrisiran	Patisiran	Inotersen
Indication	Treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy (Amvuttra SPC)	Treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy (Onpattro SPC)	Treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy (Tegsedi SPC)
Dosage and route of administration	25 mg by subcutaneous injection every 3 months	300 micrograms/kg by intravenous infusion every 3 weeks. Dosage based on actual body weight	284 mg by subcutaneous injection once a week. Dosage adjusted If platelet count is reduced (see SPC for details)

Mechanism of action	Small interfering ribonucleic acid (siRNA) that causes the breakdown of TTR messenger RNA in the liver which reduces serum TTR protein	siRNA that causes the breakdown of TTR messenger RNA in the liver which reduces serum TTR protein	2′-O-2-methoxyethyl phosphorothioate antisense oligonucleotide inhibitor of TTR production. By selectively binding to TTR messenger RNA, it prevents the synthesis of TTR in the liver, which reduces serum TTR protein
Resource impact	Subcutaneous treatment: given by healthcare professional (not self-administered), clinic costs, health professional time in clinic or at home, travel to specialist clinic if not given at home, less frequent administration. Service delivery costs may be lower	Intravenous treatment: clinic costs, health professional time in clinic or at home, travel to specialist clinic if not given at home, more frequent administration	Subcutaneous treatment: self-administered at home after training, more frequent administration, frequent monitoring requirements

Current practice

The prevalence of hATTR amyloidosis is estimated to be less than 1 in 100,000 people in the general European population. In the UK there are thought to be around 150 people with the disease (Final scope for vutrisiran technology appraisal [ID5074]).

Diagnostic services for amyloidosis, and the gene-silencing treatments, inotersen and patisiran, are commissioned by NHS England in line with NICE guidance. NICE recommends inotersen (HST9) and patisiran (HST10) as options for treating hATTR amyloidosis in adults with stage 1 and stage 2 polyneuropathy.

The National Amyloidosis Centre in London provides the only highly specialised service for people with amyloidosis and related disorders in the UK. People with hATTR amyloidosis are assessed and followed up every 6 months at the centre, and treatment is started there.

Vutrisiran will likely fit into the pathway as another gene-silencing treatment option for hATTR amyloidosis in adults with polyneuropathy, with individual patient factors and acquisition cost affecting choice. Subcutaneous dosing, less frequent administration and less monitoring requirements could be more convenient for people and may reduce service delivery costs in terms of clinical costs and healthcare professional's time.

Factors for decision making

Effectiveness

One multicentre, open-label, phase 3 randomised controlled trial (n=164) has reported on the effectiveness and safety of vutrisiran in adults with hATTR amyloidosis with polyneuropathy (Adams et al. 2022). The study population had a median of 2.22 years (IQR 4.15 years) since diagnosis of hATTR amyloidosis, a median age of 60, 65% were male and 70% were white. Participants were randomised 3:1 to treatment with vutrisiran 25 mg subcutaneously every 3 months (n=122) or patisiran 300 micrograms/kg intravenously every 3 weeks (n=42).

The primary outcome of the study, change from baseline in the modified neuropathy impairment score +7 (mNIS+7, a 304 point measure), and most of the secondary outcomes compared vutrisiran with an external placebo group from a phase 3 study of patisiran (Adams et al. 2018). After 9 months of treatment, there was a statistically significant improvement in mNIS+7 with vutrisiran (least squares mean difference -17.00 [95% confidence interval -21.78 to -12.22], $p=3.54 \times 10^{-12}$) compared with placebo. There was also a statistically significant

improvement compared with placebo after 18 months treatment. Outcomes on quality of life, nutritional status, disability measures and gait speed also showed statistically significant improvements compared with placebo.

There was no statistical analysis between vutrisiran and patisiran for any clinical patient orientated outcomes. However, the European public assessment report (EPAR) on vutrisiran (Amvuttra) concluded that comparable results in clinical endpoints were seen in the trial. Vutrisiran was statistically non-inferior to patisiran for TTR serum level percentage reduction over 18 months treatment.

Safety

In Adams et al. (2022), over 18 months treatment, adverse events were reported in approximately 97% of participants in all 3 groups. Serious adverse advents were reported in 26.2%, 42.9% and 40.3% of participants in the vutrisiran, patisiran and external placebo groups, respectively. Adverse events led to stopping treatment in 2.5%, 7.1% and 14.3% of participants in the vutrisiran, patisiran and external placebo groups, respectively. Two participants (1.6%) in the vutrisiran group had serious adverse events (dyslipidaemia and urinary tract infection) considered related to vutrisiran. There were 2 deaths (1.6%) in the vutrisiran group, 3 (7.1%) in the patisiran group and 6 (7.8%) in the placebo group, none of which were considered related to the study drug. Mild and transient injection site reactions occurred in 4.1% of participants in the vutrisiran group. Infusion-related reactions occurred in 23.8% of participants in the patisiran group. No statistical analyses were conducted for any of the safety outcomes.

The SPC on vutrisiran lists common adverse reactions as arthralgia, pain in extremities, dyspnoea, injection site reactions and increase in blood alkaline phosphatase.

Vutrisiran, patisiran and inotersen reduce vitamin A levels, and daily oral vitamin A supplementation is needed to reduce the potential risk of ocular symptoms. Pregnancy prevention measures are also needed with all 3 gene-silencing treatments because low or high vitamin A levels may be associated with an increased risk of fetal malformation.

Patient centred factors

Vutrisiran is given as a subcutaneous injection every 3 months, and the SPC states that the injection should be given by a healthcare professional. Treatment with patisiran or inotersen involves more frequent treatment, longer administration time or additional monitoring compared to vutrisiran.

Patisiran is given as an intravenous infusion every 3 weeks. It is given over approximately 80 minutes and, because of infusion-related reactions, needs intravenous premedication given at least 60 minutes before the start of every infusion. Home infusions given by a healthcare professional can be considered after at least 3 doses of patisiran have been well tolerated in the clinic (patisiran SPC), but this can be challenging to implement locally. Before this point, travel to the specialist centre in London would likely be needed.

Inotersen is given as a subcutaneous injection every week, and can be self-administered at home after training. Because inotersen is associated with reductions in platelet count, blood tests are needed every 2 weeks, with more frequent blood tests and dosage adjustments if the platelet count is reduced (inotersen SPC).

Health inequalities

Hereditary transthyretin amyloidosis is a very rare condition and a delay of 4 years from the first symptoms appearing to getting a diagnosis is typical (HST10). There is only 1 specialist centre in the UK (in London) for the assessment, follow-up and initiation of treatment for people with

hATTR amyloidosis. This could lead to health inequalities in term of accessibility for people living in more remote areas of the UK, people who would need to travel long distances or people who may have difficulties travelling due to co-morbidities or disabilities.

There are over 120 reported TTR genetic mutations associated with hATTR amyloidosis (EPAR on vutrisiran [Amvuttra]), and specific mutations are more common in some ethnic groups in the UK (HST10).

Limitations of the evidence

Adams et al. (2022) compared vutrisiran with an external placebo for the primary outcome and most of the secondary outcomes. Vutrisiran was compared with patisiran for the disease orientated outcome of TTR serum levels, but there is no direct comparison for any patient orientated outcome. There are no efficacy or safety data comparing vutrisiran with inotersen.

The placebo group was taken from an earlier phase 3 study of patisiran, so was a different study population. The EPAR on vutrisiran [Amvuttra] reports that this placebo population appeared to have more severe disease. This could lead to overestimation of the vutrisiran treatment effect. Adams et al. (2022) was also open label, which increases the risk of bias.

The primary outcome was the modified neuropathy impairment score +7. The EPAR reports that it is a disease specific, sensitive and reproducible composite measure of neuropathy progression, which has been used in many clinical studies in hATTR amyloidosis.

There is a lack of longer-term efficacy and safety data for vutrisiran. An extension phase to Adams et al. (2022) where all participants receive vutrisiran is ongoing (NCT03759379).

NICE National Institute for Health and Care Excellence

ID5074 Vutrisiran for treating hereditary transthyretin-related amyloidosis

Questions for clinical experts

The following questions relate to people with hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy

1. Does the mean weight of people with hATTR amyloidosis differ to that of the general population, and if so, why?

   MF: I do not believe this is significant. However, with advanced hATTR amyloidosis lose weight.

2. Is the mean weight in HELIOS-A [redacted] reflective of the mean patient weight in the UK?

   MF: I think so.

3. Which mean weight is most plausible for this population? [redacted] or [redacted]

   MF The average weight in our population is ~ 75 kg.

4. Are vials shared between people with hATTR amyloidosis?

   MF: No, vials are not shared.

5. Is it more plausible that [redacted] or [redacted] vials are used per patient per dosing session for patisiran?

   MF: Most patients have 3 vials.

6. The manufacturer currently estimates a level of wastage of around [redacted] for patisiran. Does this figure seem realistic? If not, what percentage of wastage would be more realistic?

   MF: I think [redacted] is the maximum.

7. When considering administration of patisiran via homecare, is it more likely to take [redacted] or 2 hours 20 minutes?

   MF: [redacted].

ID5074 Vutrisiran for treating hereditary transthyretin-related amyloidosis

Questions for clinical experts

The following questions relate to people with hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy

1. Does the mean weight of people with hATTR amyloidosis differ to that of the general population, and if so, why? Not appreciably (however, patients in the advanced stages of hATTR amyloidosis do lose weight).

2. Is the mean weight in HELIOS-A ([redacted]) reflective of the mean patient weight in the UK? Yes, just about. The mean in patients generally may be slightly higher.

3. Which mean weight is most plausible for this population? [redacted] or [redacted] Average weight is about 75 kg.

4. Are vials shared between people with hATTR amyloidosis? No

5. Is it more plausible that [redacted] or [redacted] vials are used per patient per dosing session for patisiran? Not quite sure what you mean. Most patients have 3 vials because they are over 60kg.

6. The manufacturer currently estimates a level of wastage of around [redacted] for patisiran. Does this figure seem realistic? If not, what percentage of wastage would be more realistic? Yes, realistic.

7. When considering administration of patisiran via homecare, is it more likely to take [redacted] or 2 hours 20 minutes? Including the pre-medications and set up time, [redacted]

[ID5074]: Vutrisiran for treating hereditary transthyretin-related amyloidosis

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
Authors	**Dawn Lee,** Associate Professor[1] **G.J. Melendez-Torres,** Professor[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
Correspondence to	Dawn Lee 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; D.Lee7@exeter.ac.uk
Date completed	31/10/2022
Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135752.
Declared competing interests of the authors	Authors have no competing interests to declare.
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows	Lee D, Melendez-Torres GJ. [ID5074]: Vutrisiran for treating hereditary transthyretin-related amyloidosis. Peninsula Technology Assessment Group (PenTAG), 2022.
Copyright	© 2022, PenTAG, University of Exeter. Copyright is retained by Alnylam Pharmaceuticals for tables and figures copied and/or adapted from the company submission and other submitted company documents.

Author Contributions:	
Dawn Lee	Project lead, lead for EAG's critical appraisal of the economic evidence, writing and editorial input
G.J. Melendez-Torres	Lead for EAG's critical appraisal of the clinical evidence. Guarantor of the report

Template Date	July 2017

Table of Contents

List of tables

List of Figures

Abbreviations

Abbreviation	Definition
10MWT	10-metre walk test
ADR	adverse drug reaction
AE	adverse event
ATTR amyloidosis	transthyretin-mediated amyloidosis
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CS	company submission
CSR	clinical study report
DHSC	Department of Health and Social Care
EAG	Evidence Assessment Group
eMIT	electronic marketing information tool
hATTR amyloidosis	hereditary transthyretin-mediated amyloidosis
HRQL	health-related quality of life
HST	highly specialised technologies
HTA	health technology assessment
IRR	infusion-related reaction
IV	intravenous
LS	least squares
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
mRNA	messenger RNA
NAC	National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIS	Neuropathy Impairment Score
NMA	network meta-analysis
Norfolk QOL-DN	Norfolk Quality of Life – Diabetic Neuropathy
NRI	non-responder imputation

Abbreviation	**Definition**
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
PAS	patient access scheme
PATT	Proportionate Approach to Technology Appraisals
PND	polyneuropathy disability
Q3M	quarterly
Q3W	every 3 weeks
R-ODS	Rasch-built Overall Disability Score
RTE Period	Randomized Treatment Extension Period
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SLR	systematic literature review
SmPC	Summary of Product Characteristics
TTR	transthyretin
UK	United Kingdom
V30M	Val30Met mutation

1. SUMMARY OF THE EAG'S VIEW OF THE COMPANY'S COST COMPARISON CASE

The company (Alnylam) has made a case that vutrisiran is cost-effective compared with patisiran using a cost comparison approach as a pilot under the Proportionate Approach to Technology Appraisals (PATT) process.

The company's case is based on three key points:

1. Patisiran is the only relevant comparator;
2. Vutrisiran has been demonstrated to have similar effectiveness and safety to patisiran both within the HELIOS-A trial and within an indirect comparison which includes alternate methods to impute missing data and the placebo arm from the APOLLO trial; and
3. Vutrisiran has been priced similarly to patisiran over the course of a year for drug costs based on the company's estimate of the number of vials required per patient. Therefore, savings in administration and per-medication costs lead to an expected cost saving.

The EAG is content that points one and two are accurate. Thus, the EAG supports the company's case that vutrisiran provides similar or greater benefits. The EAG is less clear that point 3 is supported, driven primarily by uncertainty around the assumptions presented for the number of vials needed for each administration of patisiran and the cost of administration for patisiran via the homecare service. Note that the uncertainty around vial requirements does not apply to vutrisiran as vutrisiran is administered at a fixed dose.

The cost comparison presented [redacted] Savings are made on both administration and pre-medication costs ([redacted] and [redacted] difference respectively using the company's preferred cost codes).

The cost comparison bases the vial numbers required for weight-basing dosing of patisiran on historical UK-specific data on administration of patisiran from Lloyds Pharmacy Clinical Homecare, which provides home care for the majority of patients. [redacted] When compared to the mean weight in HELIOS-A, this represents a high level of wastage (~[redacted]). The company

provided an additional scenario using HELIOS-A data which led to an estimate of an average of [redacted] vials. An estimate which unfortunately cannot be fully verified.

Issues were also identified within the costs assumed for administration (which would appear to be inflated for patisiran) and pre-medication which did not use the recommended source for drug cost data (eMIT).

Four scenario analyses are presented by the EAG in Table 1 along with a preferred base case.

[redacted]

Table 1: EAG scenario analyses and preferred base case

Scenario	Incremental costs over 5 years vutrisiran vs patisiran	
	Vial numbers from Lloyd's data	Vial numbers from trial data
Company base case	[redacted]	[redacted]
1. Reduce inpatient administration costs for patisiran in line with HST10	[redacted]	[redacted]
2. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed [redacted] hours in line with company submission)	[redacted]	[redacted]
3. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed 2 hours 20 minutes in line with the patisiran SmPC)	[redacted]	[redacted]
4. Use eMIT for pre-medication costs	[redacted]	[redacted]
EAG preferred base case (Scenarios 1, 2 and 4)	[redacted]	[redacted]

The company, the National Amyloidosis Centre and the UK ATTR Amyloidosis Patients' Association all raise potential benefits to patients and carers not considered within the cost comparison analysis, specifically: benefits to patients from a less frequent, shorter and more convenient mode of administration, a decreased risk of potential complications with patisiran such as dosing error, infusion-related reactions, failure to cannulate, phlebitis, extravasation injury and side-effects from pre-medication drugs.

2. CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

Discussions between NICE, the company and the EAG facilitated this appraisal being undertaken as a pilot under the PATT process.

The company's decision problem broadly meets the final NICE scope. The EAG's considerations in respect of population, intervention, comparators, and outcomes assessed are provided below.

2.1. Population

The population in the decision problem is adults with hereditary transthyretin-mediated (hATTR) amyloidosis with stage 1 or stage 2 polyneuropathy. This is the full licensed population for both vutrisiran and its comparator patisiran.

2.2. Intervention

The intervention is vutrisiran, which is administered subcutaneously (SC) at a fixed dose of 25mg 4 times per year. Vutrisiran must be administered by a healthcare professional, thus it is not suitable for self-administration.[1,2] According to the manufacturer submission, the first dose of vutrisiran is expected to be administered by a healthcare provider at the National Amyloidosis Centre, with subsequent doses expected to be administered by a nurse practitioner in a home-care setting.

The pack price submitted to the Department of Health and Social Care (DHSC) per pre-filled syringe of vutrisiran (25 mg in 0.5 mL solution for injection) is [redacted]. A confidential patient access scheme (PAS) discount has been proposed for vutrisiran of [redacted] leading to a with-PAS price of [redacted] per pack. The yearly treatment cost is [redacted] for 4 administrations per year.

2.3. Comparators

The comparators defined in the scope are patisiran (recommended in HST10) and inotersen (recommended in HST9). The company limit comparison to patisiran, which is also marketed by Alnylam, with the justification being that patisiran is considered the standard of care first-line choice for patients and that inotersen is rarely used due to its safety and efficacy profile. This aligns with input from the National Amyloidosis Centre, the single centre involved in prescription

of treatment for hATTR who consider that the majority of patients are treated with patisiran as inotersen 'is associated with significant toxicity'. They consider that 'vutrisiran would simply replace the use of patisiran in the same cohort of patients'.

Vutrisiran is a similar agent to patisiran with the same mechanism of action (targeting the production of transthyretin (TTR) synthesis in the liver by acting on mRNA) and very similar pharmacodynamic effect (%TTR reduction, with misfolded TTR being the main pathological aetiology for hATTR).[1] The patent expiry dates for patisiran and vutrisiran are 29 Aug 2028 and 16 Sept 2032 respectively.[3]

Patisiran is administered intravenously (IV) at a weight-based dose of 0.3mg/kg every 3 weeks. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg. The SmPC for patisiran states that patients can be considered for home administration of patisiran after at least 3 well-tolerated infusions at the clinic.[2] According to the manufacturer submission, following treatment initiation, all patisiran patients in England receive subsequent doses via Lloyds Clinical Homecare by a nurse practitioner in a home-care setting, every three weeks. Infusion with patisiran takes approximately 80 minutes and a premedication regimen is required to be administered 60 minutes prior to patisiran infusion to reduce the risk of infusion-related reactions (IRRs).

The pack price submitted to DHSC per vial of patisiran 10mg formulated as lipid nanoparticles) is [redacted]. The yearly treatment cost is [redacted] annually assuming [redacted] vials per administration for 17.36 administrations per year. The number of vials required per year is an area of uncertainty (see Section 4.1.1).

2.4. Outcomes

The outcomes presented largely align with the final scope with the exception of the exclusion of overall survival, cardiac function and effects of amyloid deposits in other organs and tissues (including the eye).

The justification for exclusion of overall survival is that few events were observed in either HELIOS-A (pivotal trial of vutrisiran) or APOLLO (pivotal trial of patisiran) and that it was considered as a safety, rather than an efficacy, endpoint in both trials. This is considered justified by the EAG as the number of events observed per arm is indeed low; 2 (2%) vs 3 (7%) for vutrisiran vs patisiran in HELIOS-A (Table 23, CS Document B).

The justification for exclusion of cardiac function provided is that Alnylam believes that cardiac function should be excluded from this submission because a separate trial is ongoing to evaluate vutrisiran in patients with ATTR amyloidosis with cardiomyopathy and therefore inclusion in this submission is premature. This is not consistent with HST10 where cardiac function (based on N-terminal prohormone B-type natriuretic peptide [NT-proBMP]) was considered a key outcome (and included in the economic model) for the same population as considered within the scope here,[4] this is acknowledged by the company in CS Table 7. However, the Committee for Medicinal Products for Human Use (CHMP) report is reassuring as they conclude based upon an adjusted geometric mean ratio of 0.49 for vutrisiran / placebo vs 0.45 for patisiran / placebo that 'despite the redefinition of the cardiac subpopulation in HELIOS-A and the baseline differences between HELIOS-A and APOLLO, the magnitude of effect of vutrisiran on NT-proBNP is considered similar to that of patisiran obtained in APOLLO'.[1] The CHMP also consider that the results are comparable based upon echocardiographic parameters. Issues were raised around the cardiac safety data presented; however, the CHMP conclusion is that the findings of imbalance in treatment-emergent adverse events in cardiac arrhythmia within the HELIOS-A study as well as the higher incidence of syncope in the cardiac subpopulation could be chance findings due to the low subject numbers.

Effects of amyloid deposits in other organs and tissues (including the eye) were not included as they were not addressed in HELIOS-A.

3. CLINICAL EFFECTIVENESS

3.1. Summary: EAG's critique of the clinical effectiveness evidence submitted

The CHMP and Medicines and Healthcare products Regulatory Agency (MHRA) have given positive opinions relating to the similarity of effectiveness between vutrisiran and patisiran based upon similar mechanism of action, the achievement of non-inferiority for serum TTR reductions at Month 18 which is considered a surrogate for favourable clinical outcomes in TTR, post-hoc within trial analyses from HELIOS-A demonstrating similar clinical outcomes and an indirect comparison using data from the APOLLO study.[1,5]

The MHRA concludes that 'it appears efficacy of vutrisiran is at least non inferior to patisiran'.[5] The CHMP also concluded that: 'the overview of safety (including the incidence of ADRs, severe AEs, SAEs, AEs leading to treatment discontinuation and to stopping study participation, respectively as well as the incidence of death cases) in the HELIOS-A vutrisiran group compared relatively favourably to the HELIOS-A patisiran group'.[1]

3.1.1. Clinical evidence submitted by the company

The company reports the details of two studies: HELIOS-A which assessed the efficacy and safety of vutrisiran, and APOLLO which assessed the efficacy and safety of patisiran and is used within indirect comparison.[6,7]

3.1.2. HELIOS-A overview

HELIOS-A is a Phase III global randomised open-label study evaluating the efficacy and safety of vutrisiran over 18 months in patients with hATTR amyloidosis with polyneuropathy.[8] The study had two arms: a vutrisiran treatment arm and a patisiran treatment arm (reference arm).

3.1.2.1. HELIOS-A study design

The study design is shown in Figure 1. Patients in HELIOS-A were randomised 3:1 to receive vutrisiran 25 mg SC Q3M or patisiran 0.3 mg/kg IV infusion Q3W for 18 months. Randomisation was stratified by *TTR* genotype (V30M versus non-V30M) and baseline Neuropathy Impairment Score (NIS) (<50 versus ≥50). HELIOS-A trial was designed as an open-label study due to the differences between study treatment administration methods. Data integrity was maintained by

various strategies including evaluation of mNIS+7 by personnel who did not have access to treatment assignment data and other data access restrictions.

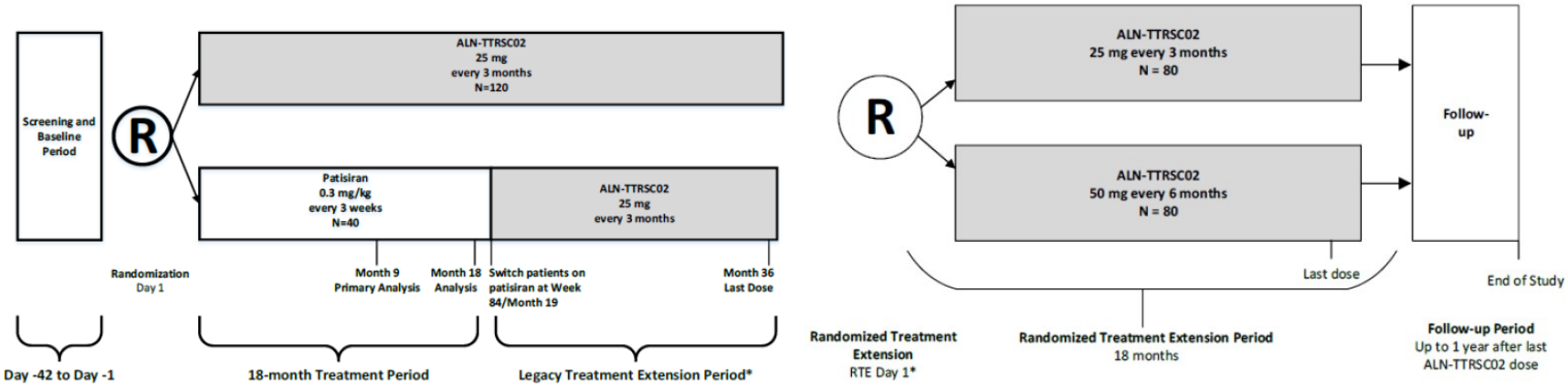
Eligibility criteria for HELIOS-A are shown in Table 10 of the CS, with baseline characteristics shown in Table 11 of the CS. The company states that demographic and baseline characteristics were widely overlapping and clinically comparable across treatment groups within study; the EAG broadly agrees with this with the exception of previous tetramer stabiliser use which was observed in 79% of patients receiving patisiran versus 62% receiving vutrisiran and region where slightly more patients were treated in Western Europe in the patisiran arm (48% vs 35%). Given the small patient numbers involved these differences are not considered likely to be material.

The company state that efficacy analysis was performed on the modified intent-to-treat (mITT) population defined as all randomised patients who received any amount of study drug. The main analysis, however, excluded patients with missing data. Presentation of the “true” mITT population for Month 18 data required re-analyses to be requested by the CHMP using appropriate missing data handling strategies.[1] Analyses including alternative methods for imputation of missing data are presented within the network meta-analysis (NMA).

The primary endpoint of the HELIOS-A study is change from baseline in the mNIS+7 compared to the placebo arm of the APOLLO study at Month 18. The mNIS+7 assesses the progression of the motor and the sensory aspects of polyneuropathy, as well as some autonomic manifestations, such as postural hypotension and is assessed on a scale from 0 to 304 points with a negative change representing neurologic improvement. A full list of the included primary and secondary endpoints is provided in Table 13 of the CS. A formal non-inferiority comparison to patisiran was performed only for serum TTR reduction at Month 18. Other comparisons between the two within-trial arms were conducted post-hoc. A full list of efficacy outcomes is reported in Table 9 of the CS.

The open-label extension study of HELIOS-A is currently ongoing with the final clinical study report (CSR) due to be produced in 2025.[1] Outcomes are only reported for the 18-month treatment period and not the treatment extension period within the CS although data are available up to data cut-off date of 26 August 2021 within the second CSR and CHMP assessment report. Based on the CHMP assessment report the data presented is for safety only and did not show any new signals.[1]

Figure 1: The study design for HELIOS-A from (HELIOS-A CSR2)



Abbreviations: ALN-TTRSC02=vutrisiran; RTE=Randomized Treatment Extension.

* Previously referred to as the 18-month Treatment Extension Period (per protocol Amendment 3 and earlier); the Legacy Treatment Extension Period, as of Amendment 4, was replaced with the RTE Period. Patients transition into the RTE Period either after completion of the 18-month Treatment Period or at their next vutrisiran dosing visit in the Legacy Treatment Extension Period, depending on the timing of amendment approval and completion of the Month 18 efficacy visit. Patients complete the RTE Period in lieu of the Legacy Treatment Extension Period.

*RTE Day 1 in lieu of the Legacy Treatment Extension Period Study Week 84 visit, or later.

3.1.2.2. HELIOS-A analysis strategy

The analysis strategy for HELIOS-A was primarily based on mixed-effects models for repeated measures (MMRM), using the mITT population, comparing baseline with month 18 measures on all outcomes except for TTR percent reduction. This was linked with a corresponding set of null hypotheses relating to non-inferiority equating the difference between the two arms to 0.

Analysis for TTR percent reduction through month 18 used a different method, which the EAG queried at clarification. In response to clarification question 4, the company commented that analysis for TTR percent reduction first derived an eligible sample of measurements within each person, focusing on those measurements between month 6 and month 18 post-baseline in which the TTR measurement was undertaken a) immediately before administration of the study drug (thus a 'trough' measurement) and b) following a previous complete administration of the drug. The subsequent analysis estimated a person-level average of trough TTR percent reductions (where reductions were benchmarked against baseline to estimate a percent); compared medians between groups, accounting for a stratifier by previous TTR stabiliser use; and used the Hodges-Lehmann procedure to estimate a confidence interval. The null hypothesis for this outcome was thus that the difference in median TTR reductions indicated vutrisiran was inferior to patisiran, with a worse TTR reduction by 10%.

3.1.2.3. HELIOS-A critical appraisal

The company's critical appraisal for HELIOS-A is presented in CS document B Table 14, as well as in CS Appendix D. The EAG agrees that the company's appraisal of HELIOS-A is broadly reasonable. Key areas where risk of bias could emerge primarily relate to the open-label nature of the trial, which meant that patients and providers were not blinded to treatment assignment. The EAG also noted some imbalances in treatment arms (see 3.1.2.1) but did not believe that these posed a threat to the study's validity. However, one area where the company's appraisal is limited is their consideration of missing data (as opposed to dropouts). As is acknowledged in the report of the network meta-analysis, individual outcomes may have higher levels of missingness than the number of people who have dropped out. This generates an unclear risk of bias.

3.1.3. Comparison to placebo within APOLLO

APOLLO is a completed, Phase 3, multicenter, multinational, randomized, double-bind, placebo-controlled study comparing patisiran to placebo. Whilst the company states that demographic

and baseline characteristics were widely overlapping and clinically comparable across treatment groups, the CHMP considered that the disease characteristics of the patients are worse in the placebo group of the APOLLO study compared to HELIOS-A. The EAG agrees with CHMP's assessment. In particular,[1] the population was:

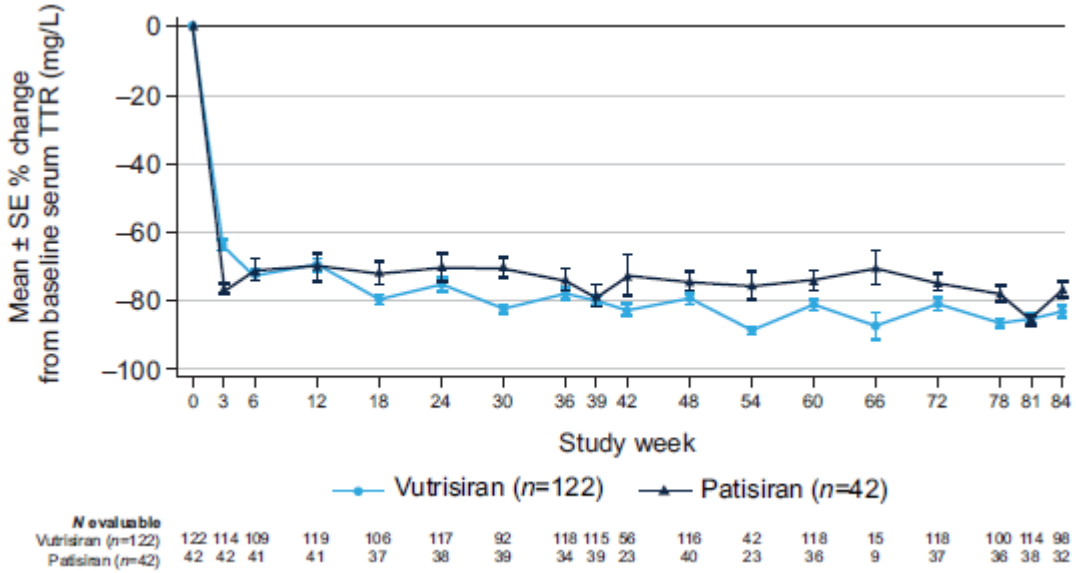
- Older (median age 63 vs 60)
- Had more advanced disease (Neuropathy Impairment Score ≥50; 54.6% vs 36.1%)[9]
- Had worse ambulatory function (Karnofsky Performance Status <=60; 28.6% vs 13.9% and 10MWT 0.79 m/s vs 1.01)
- Had higher cardiac involvement (51.9% had NYHA I or no heart failure and 46.8% had NYHA II vs 55.7%, 9.0% and 35.2% of patients had no heart failure, NYHA I and NYHA II)
- Had worse HRQL (Norfolk Quality of Life – Diabetic Neuropathy [Norfolk QoL-DN] scale 55.5 vs 47.1)

MMRM is the default analysis for most continuous efficacy endpoints comparing vutrisiran in HELIOS-A to placebo in APOLLO.

3.1.4. HELIOS-A clinical effectiveness results

In a within-trial comparison, vutrisiran demonstrated non-inferiority compared to patisiran in terms of pharmacodynamics activity, as the median treatment difference in TTR percent reduction from baseline (vutrisiran – patisiran) was 5.28% (95% CI, 1.17 to 9.25), the lower limit of which was above the prespecified noninferiority margin of a 10% worsening (i.e. -10%; see Figure 2).

Figure 2: HELIOS-A secondary endpoint: change in serum TTR levels



SE, standard error; TTR, transthyretin.

Source: Adams et al, 2022[7]; Figure 4, CS document B

Table 16 of the CS presents the results of the post-hoc within study comparison of vutrisiran and patisiran and is adapted here in Table 2. In all cases the LS mean different point estimate favours vutrisiran and differences were neither statistically nor clinically significant.

Table 2: Post hoc within-study comparison of vutrisiran and patisiran at Month 18

	Baseline		Month 18			Direction of change that favours vutrisiran
	n	Mean (SD)	n	LS mean change (SEM)	LS mean difference (95% CI)	
mNIS+7						
Vutrisiran (n=122)	122	60.57 (35.99)	112	0.06 (1.48)	**−1.46 (−7.36, 4.43)**	Negative
Patisiran (n=42)	42	57.68 (33.71)	36	1.53 (2.59)		
Norfolk QOL-DN						
Vutrisiran (n=122)	121	47.1 (26.3)	111	−2.5 (1.8)	**−1.6 (−8.6, 5.4)**	Negative
Patisiran (n=42)	42	47.3 (29.9)	38	−0.8 (3.0)		
10-MWT (m/s)						
Vutrisiran (n=122)	122	1.006 (0.393)	112	−0.019 (0.025)	**0.034 (−0.064, 0.132)**	Positive
Patisiran (n=42)	42	1.011 (0.400)	38	−0.053 (0.043)		
mBMI						

	Baseline		Month 18			Direction of change that favours vutrisiran
	n	Mean (SD)	n	LS mean change (SEM)	LS mean difference (95% CI)	
Vutrisiran (n=122)	122	1057.4 (233.8)	113	21.8 (9.2)	**14.2 (−21.9, 50.3)**	Positive
Patisiran (n=42)	42	1058.1 (228.8)	38	7.6 (15.8)		
R-ODS						
Vutrisiran (n=122)	122	34.1 (11.0)	113	−1.2 (0.5)	**0.1 (−2.0, 2.2)**	Positive
Patisiran (n=42)	42	34.0 (10.4)	38	−1.3 (0.9)		

10-MWT, 10-metre walk test; CI, confidence interval; LS, least squares; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score+7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Score; SD, standard deviation; SEM, standard error of the mean.

Source: CHMP Assessment Report[1]

Bold text indicates point estimate for LS mean difference favours vutrisiran

Finally, in a naïve comparison using APOLLO data, clinically and statistically significant benefits were observed for vutrisiran versus external placebo through 18 months of treatment for the primary endpoint and all secondary endpoints.

3.1.4.1. Network meta-analysis

In addition to the pre-specified and post-hoc analysis of HELIOS-A the manufacturer presented a fixed-effects Bayesian NMA comparing vutrisiran and patisiran for polyneuropathy disability (PND) score, mNIS+7, and Norfolk QoL-DN score based on the HELIOS-A and APOLLO trials. No justification is provided as to why these 3 endpoints have been selected beyond these representing “key outcomes”.

The NMA adds little additional value beyond the inclusion of more robust methods for imputation of missing data as the common comparator within the network is the comparator of interest to this submission (patisiran). This is mostly because there are no trials comparing vutrisiran against placebo. However, the impact of imputation of missing data is highly relevant to explore as the manufacturer notes in the CS that “a non-trivial proportion of patients in HELIOS-A and APOLLO had missing PND score, mNIS+7, and/or Norfolk QOL-DN scores.” 5-10% of patients had missing data at either month 9 or 18. A non-responder imputation (NRI) analysis is presented where patients with missing information to determine endpoint status are considered as treatment failures which the company considers to be conservative. The EAG notes that whether this method is conservative depends on the distribution of missingness; if greater in one arm, then that arm may have a lower estimate of effectiveness than the ‘true’ value.

Table 3 presents a comparison of the NMA results with those observed within the trial where some missing data was excluded rather than imputed based on Tables 16 – 22 of the CS. The impact of alternative methods for imputing missing data differs in the direction and magnitude of impact across endpoints. In all cases, however, the point estimate remains in favour of vutrisiran and substantiates the similar efficacy of vutrisiran and patisiran; qualitative conclusions in respect of non-inferiority are not different.

Table 3: Comparison of NMA and observed within trial results

	Excluding missing data Mean (95% CrI / CI)	Imputing missing data Mean (95% CrI)	Direction that favours vutrisiran
Improvement or no change (vs. worsening) in PND score			
Risk ratio	[redacted]	[redacted]	Positive
Odds ratio	[redacted]	[redacted]	Positive
mNIS+7 (difference)	[redacted]	[redacted]	Negative
Norfolk QOL-DN (difference)	[redacted]	[redacted]	Negative

CI, confidence interval; CrI, credible interval; mNIS+7, modified Neuropathy Impairment Score+7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability

Notes: observed data where missing data were excluded are taken from Table 16 in the CS, here the 95% confidence interval (rather than credible interval) is presented

3.1.4.2. Safety

In HELIOS-A, there were no treatment-related discontinuations or deaths with either vutrisiran or patisiran and the majority of adverse events (AEs) were mild or moderate in severity. The safety summaries provided in Tables 23 and Table 24 of the CS demonstrate that vutrisiran and patisiran have comparable safety and tolerability; however, there is a risk of IRRs associated with the IV infusion of patisiran (23.8% in HELIOS-A and 9.1% in APOLLO), which is obviated by the SC administration of vutrisiran.

4. COST-COMPARISON

The cost comparison presented [redacted] Savings are made on both administration and pre-medication costs ([redacted] and [redacted] difference respectively using the company's preferred cost codes).

4.1. Drug acquisition costs

4.1.1. Number of vials per administration

The cost comparison bases the vial numbers required for weight-basing dosing of patisiran on historical UK-specific data on administration of patisiran from Lloyds Pharmacy Clinical Homecare which provides homecare for the majority of patients. [redacted] The data used within the calculation was provided to the EAG in response to clarification questions. The analysis relies on the assumption that each row represents a single delivery made for the purpose of a nurse visit to infuse a single patient, which is equivalent to one administration. Based upon this assumption the records contain [redacted] administrations, or administrations for approximately [redacted] patients based on the patisiran dosing schedule. This is consistent with the NHSE submission which states that there were 122 patients treated with inotersen and patisiran in 2021/22. Little variation is seen in the mean number of vials required per month. There is some uncertainty in the data as there are a few records which indicate a dose of 60mg was received by an individual which is not possible according to the SmPC. However, this is unlikely to have a large impact on results.

[redacted] equates to a mean weight per patient of approximately [redacted] This is high compared to the average weight in the general population in England (85.4kg for men and 72.1kg for women in 2019).[10] Assuming that roughly two-thirds of the patient population are male in line with the clinical trials this would equate to wastage of over [redacted] When compared to the mean weight in HELIOS-A and the placebo arm of APOLLO ([redacted] and [redacted] respectively; Table 14.1.2.1 of the 18 month CSR) the wastage assumed is even higher (over [redacted]).

An additional scenario analysis is included in the CS where the mean patisiran vials used per administration is estimated based on the bodyweight distribution observed in patients in

HELIOS-A in the economic model with an average of [redacted] quoted. In response to clarification questions the company provide the calculations used to produce the weighted average number of vials required (Table 4). The calculations appear correct based on the data provided; however, they could not be cross-checked against the CSR. Unfortunately, within the timeframe available for their response, the company were unable to verify whether they were permitted to provide NICE with a list of the individual patient weights from HELIOS-A.

Table 4: Bodyweight distribution of all patients in HELIOS-A and estimated average patisiran vial consumption for scenario analysis

Bodyweight (kg)	Patients		Number of vials required	Weighted average vials*
	n	%		
33.5–66.9	[redacted]	[redacted]	2	[redacted]
>66.9–99.9	[redacted]	[redacted]	3	[redacted]
≥100†	[redacted]	[redacted]	3	[redacted]
Total	**164**	**100.00**		[redacted]

*Value within each bodyweight category is calculated as the percentage of patients multiplied by the number of vials required; total is the sum of these products.
†Per the ONPATTRO Summary of Product Characteristics

4.1.2. Time on treatment

The company assume that time on treatment is the same for vutrisiran and patisiran in line with the assumption of equal effectiveness. Functionality is also incorporated within the model to explore the use of differential time on treatment based upon extrapolation of HELIOS-A data. The data presented excludes discontinuation due to death which is not recommended; regardless of this issue, there is little benefit to using these data as few discontinuations were seen in either arm during the trial. Of the 122 patients in the vutrisiran group, [redacted] patients discontinued study drug during the treatment period, for patisiran [redacted] patients discontinued during the treatment period.

4.2. Other costs

Other than drug acquisition costs the model also includes:

- Drug administration costs
    - Patisiran: based upon the cost code delivery of complex IV infusion of chemotherapy (Deliver more complex parenteral chemotherapy at first attendance, day case and regular day/night [HRG code: SB13Z]) which has increased from £310 in HST10 to

£470.81. This is assumed to be the same for homecare as well as administration within the National Amyloidosis Centre (NAC). The original HST10 submission did not include the cost of homecare. The company argue that using the cost code for in-hospital delivery is appropriate due to the need to purchase equipment (infusion IV pumps) to deliver patisiran at home. This would not appear to be appropriate as portable pumps are relatively inexpensive (£250 - £1,500 based upon a quick search) and are able to be used for a number of years once purchased for a patient.

  - Vutisiran: £90.49 at first visit based upon a face to face appointment with a specialist nurse and £33.00 at home based on 1 hour of community-based nurse time

  - For both medications 100% of patients are assumed to receive treatment at home after the initial round of administrations required by the SmPC. This aligns with the NAC's submission in respect to administration of patisiran

- Pre-medication: £9.91 per administration for patisiran. This is an over-estimate as MIMS costs are used rather than eMIT. Using eMIT costs this reduces to £2.51 per administration.[11]

The model does not include the impact of IRRs, non-inclusion of which would be assumed to result in a small cost difference in favour of patisiran as most IRRs will be treated by slowing or interrupting the infusion.[2]

5. EAG COMMENTARY ON ROBUSTNESS OF EVIDENCE SUBMITTED

Based on the evidence supplied by the company the EAG is satisfied that vutrisiran is the relevant comparator and that vutrisiran and patisiran have similar effectiveness and safety. The EAG are not satisfied that the cost comparison presented supports vutrisiran having a lower cost, driven primarily by uncertainty around the assumptions presented for the number of vials needed for each administration of patisiran.

5.1. EAG scenario analyses

Four scenario analyses are presented by the EAG in [redacted]

Table 5 along with a preferred base case.

5.1.1. Reduce inpatient administration costs for patisiran in line with HST10

As noted in Section 4.2 the administration cost used for patisiran represents a considerable increase in the absolute cost within HST10 (£310 vs £470.81) and is based upon chemotherapy costs rather than being specific to hATTR. This scenario therefore reduces the cost to that used within HST10.

5.1.2. Reduce home administration costs for patisiran assuming a specialist nurse delivers both patisiran and vutrisiran

As noted in Section 4.2 the CS assumes that the cost of delivering patisiran at home is the same as the cost for administration within the NAC. This would not appear to hold face validity. As it would be expected that the same homecare service is used for vutrisiran as has already been set up for patisiran, the EAG analysis assumes that patisiran, like vutrisiran, is delivered by a specialist nurse.

Two scenarios are presented, one where delivery is assumed to take [redacted] in line with the CS and one where the infusion time is assumed to be 2 hours 20 minutes in line with the patisiran SmPC.{Medicines, #65} A delivery time of [redacted] is applied within the EAG base case rather than the more pessimistic scenario using infusion times from the SmPC as it is acknowledged that the cost of infusion IV pumps is not included within the analysis currently.

5.1.3. Use eMIT for pre-medication costs

This scenario uses eMIT costs rather than costs from MIMs as per NICE guidelines.[12] Using eMIT reduces pre-medication costs to £2.51 per administration from £9.91.[11]

5.1.4. EAG scenario analysis results

[redacted]

Table 5: EAG scenario analyses and preferred base case

Scenario	Incremental costs over 5 years vutrisiran vs patisiran	
	Vial numbers from Lloyd's data	Vial numbers from trial data
Company base case	[redacted]	[redacted]
1. Reduce inpatient administration costs for patisiran in line with HST10	[redacted]	[redacted]
2. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed [redacted] hours in line with company submission)	[redacted]	[redacted]
3. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed 2 hours 20 minutes in line with the patisiran SmPC)	[redacted]	[redacted]
4. Use eMIT for pre-medication costs	[redacted]	[redacted]
EAG preferred base case (Scenarios 1, 2 and 4)	[redacted]	[redacted]

The company, the National Amyloidosis Centre and the UK ATTR Amyloidosis Patients' Association all raise potential benefits to patients and carers not considered within the cost comparison analysis. Specifically: benefits to patients from a less frequent, shorter and more convenient mode of administration, a decreased risk of potential complications with patisiran

such as dosing error, infusion-related reactions, failure to cannulate, phlebitis, extravasation injury and side-effects from pre-medication drugs.

References

1. Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report. Amvuttra. Available at: https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf (last accessed 25 October 2022). 2022.

2. European Medicines Agency. AMVUTTRA (vutrisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V. Date of revision of the text: 16 September 2022. Last updated on emc: 23 September 2022. Available at: https://www.medicines.org.uk/emc/product/14060/smpc (last accessed 25 October 2022). 2022.

3. Medicines and Healthcare products Regulatory Agency (MHRA). Decision Orphan Register. Updated 17 October 2022 Available at: https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register (last accessed: 25 October 2022). 2022.

4. National Institute for Health and Care Excellence (NICE). HST 10: Patisiran for treating hereditary transthyretin amyloidosis. Published: 14 August 2019. Available at: https://www.nice.org.uk/guidance/hst10 (last accessed: 25 October 2022). 2019.

5. Medicines and Healthcare products Regulatory Agency (MHRA). [Draft] Orphan Drug Designation Assessment Report (vutrisiran). 2022.

6. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):11-21.

7. Adams D, Tournev IL, Taylor MS, Coelho T, Plante-Bordeneuve V, Berk JL, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. 2022:1-9.

8. Alnylam Pharmaceuticals. Clinical Study Protocol ALN-TTRSC02-002. HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis). NCT03759379. Original protocol: 11 October 2018. Document date: 19 February 2021.

Available at: https://clinicaltrials.gov/ProvidedDocs/79/NCT03759379/Prot_000.pdf (last accessed 25 October 2022). Cambridge, MA; 2021.

9. Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report. Amvuttra. [Table 10] Available at: https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf (last accessed 25 October 2022). 2022.

10. National Statistics. Health Survey for England 2019: Overweight and obesity in adults and children. Available at: https://files.digital.nhs.uk/9D/4195D5/HSE19-Overweight-obesity-rep.pdf (last accessed: 25 October 2022). 2020.

11. Department of Health and Social Care. Guidance: Drugs and pharmaceutical electronic market information tool (eMIT) Published 16 March 2011. Last updated 28 September 2021. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (last accessed: 25 October 2022). 2011.

12. National Institute for Health Care Excellence (NICE). NICE health technology evaluations: the manual. Published: 31 January 2022. Available at: https://www.nice.org.uk/process/pmg36 (last accessed: 25 October 2022). 2022.

[ID5074]: Vutrisiran for treating hereditary transthyretin-related amyloidosis, Appendix

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
Authors	**Dawn Lee,** Associate Professor[1] **G.J. Melendez-Torres,** Professor[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
Correspondence to	Dawn Lee 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; D.Lee7@exeter.ac.uk
Date completed	22/11/2022
Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135752.
Declared competing interests of the authors	Authors have no competing interests to declare.
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows	Lee D, Melendez-Torres GJ. [ID5074]: Vutrisiran for treating hereditary transthyretin-related amyloidosis, Appendix. Peninsula Technology Assessment Group (PenTAG), 2022.
Copyright	© 2022, PenTAG, University of Exeter. Copyright is retained by Alnylam Pharmaceuticals for tables and figures copied and/or adapted from the company submission and other submitted company documents.

Author Contributions:	
Dawn Lee	Project lead, lead for EAG's critical appraisal of the economic evidence, writing and editorial input
G.J. Melendez-Torres	Lead for EAG's critical appraisal of the clinical evidence. Guarantor of the report

Template Date	July 2017

IMPACT OF WASTAGE ON THE COST COMPARISON

This Appendix presents extreme scenario testing around the impact of wastage on the cost comparison case vutrisiran in hATTR. As noted in the main EAG report company's case is based on three key points:

1. Patisiran is the only relevant comparator;
2. Vutrisiran has been demonstrated to have similar effectiveness and safety to patisiran both within the HELIOS-A trial and within an indirect comparison which includes alternate methods to impute missing data and the placebo arm from the APOLLO trial; and
3. Vutrisiran has been priced similarly to patisiran over the course of a year for drug costs based on the company's estimate of the number of vials required per patient. Therefore, savings in administration and per-medication costs lead to an expected cost saving.

The EAG is content that points one and two are accurate. Thus, the EAG supports the company's case that vutrisiran provides similar or greater benefits. The EAG is less clear that point 3 is supported, driven primarily by uncertainty around the assumptions presented for the number of vials needed for each administration of patisiran and the cost of administration for patisiran via the homecare service. The uncertainty around vial requirements does not apply to vutrisiran as vutrisiran is administered at a fixed dose.

The cost comparison bases the vial numbers required for weight-basing dosing of patisiran on historical UK-specific data on administration of patisiran from Lloyds Pharmacy Clinical Homecare, which provides home care for the majority of patients. [redacted] When compared to the mean weight in HELIOS-A, this represents a high level of wastage (~[redacted]). The company provided an additional scenario using HELIOS-A data which led to an estimate of an average of [redacted] An estimate which unfortunately cannot be fully verified.

Four scenario analyses were originally presented by the EAG in Table 1 along with a preferred base case. [redacted]

.

This Appendix provides an additional two scenarios which should be viewed as extreme scenario testing. The first scenario assumes that there is no wastage (i.e. vials are shared) and that the mean patient weight is the same as reported within the 18 month CSR for HELIOS-A ([redacted]); the second again assumes that vials can be shared but in this scenario the mean patient weight is assumed equivalent to the general population in England (85.4kg for men and 72.1kg for women in 2019) with 65% of patients assumed to be male in line with HELIOS-A.[1] Both scenarios are applied in addition to the changes within the EAG base case and in both scenarios a dose of 0.3mg/kg is applied to all patients. This makes these scenarios an overestimate as patients weighing more than 100kg should receive a flat dose of 30mg. Table 2 presents the number of vials required under each assumption.

In both scenarios vutrisiran is [redacted] with incremental costs increasing to over [redacted] and [redacted] demonstrating the large impact of even small changes in the number of vials required per administration for patisiran within the current analysis.

Table 1: EAG scenario analyses and preferred base case

Scenario	Incremental costs over 5 years vutrisiran vs patisiran	
	Vial numbers from Lloyd's data	Vial numbers from trial data
Company base case	[redacted]	[redacted]
1. Reduce inpatient administration costs for patisiran in line with HST10	[redacted]	[redacted]
2. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed [redacted] hours in line with company submission)	[redacted]	[redacted]
3. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed 2 hours 20 minutes in line with SmPC)	[redacted]	[redacted]
4. Use eMIT for pre-medication costs	[redacted]	[redacted]
EAG preferred base case (Scenarios 1, 2 and 4)	[redacted]	[redacted]
Additional scenario 1: EAG base case + no wastage for patisiran; patient mean weight assumed the same as HELIOS-A ([redacted])	[redacted]	
Additional scenario 2: EAG base case + no wastage for patisiran; patient mean weight assumed the same as UK general population (80.7kg)	[redacted]	

Table 2: Vials required for patisiran

Scenario	Mean vials required per administration
Lloyd's data	[redacted]
Company's analysis based on trial data	[redacted]
Assuming no wastage for patisiran; patient mean weight assumed the same as HELIOS-A ([redacted])	[redacted]
Assuming no wastage for patisiran; patient mean weight assumed the same as UK general population (80.7kg)	[redacted]

References

1. National Statistics. Health Survey for England 2019: Overweight and obesity in adults and children. Available at: https://files.digital.nhs.uk/9D/4195D5/HSE19-Overweight-obesity-rep.pdf (last accessed: 25 October 2022). 2020.

Single Technology Appraisal

Vutrisiran for treating hereditary transthyretin-related amyloidosis [ID5074]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 22 November** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Clarification of sign (i.e., direction) of difference in costs between vutrisiran and patisiran

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1, page 7: "Savings are made on both administration and pre-medication costs [redacted] and [redacted] difference respectively using the company's preferred cost codes)." Section 4, page 20: identical sentence. In both instances, some readers may misinterpret the cost differences as positive for the calculation vutrisiran – patisiran.	In the quoted sentence on both page 7 and page 20, Alnylam recommends either changing "difference" to "savings" or adding minus signs before both costs.	Either of the suggested edits will avoid any potential for confusion regarding the direction of the difference in costs between vutrisiran and patisiran.	This is not a factual inaccuracy. The first word of the sentence is savings making it clear that these are cost savings with the introduction of vutrisiran.

Issue 2 Clarification of source of home administration time estimate in EAG Scenario 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1, Table 1, page 8: "3. Reduce home administration costs for	In both Table 1 and Table 5, Alnylam recommends revising the text for Scenario 3 as follows:	The suggested edit will avoid any potential for confusion regarding the source the EAG	Thank you for raising this, we have made this amendment.

patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed 2 hours 20 minutes in line with SmPC)" Section 5.1.4, Table 5, page 24: identical text for Scenario 3. In both tables, the grammatical structure of the scenario description may lead the reader to assume the source is the vutrisiran SmPC rather than the patisiran SmPC.	"3. Reduce home administration costs for patisiran to use the same assumptions as vutrisiran (£33 per hour, assumed 2 hours 20 minutes in line with the patisiran SmPC)"	used for their assumption of home administration time.	

Issue 3 Clarification of price, yearly cost, and vial consumption for patisiran

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, page 10: "The pack price submitted to DHSC per pre-filled syringe of vutrisiran (10mg formulated as lipid nanoparticles) is [redacted] The yearly treatment	Alnylam recommends correcting the quoted text as follows: "The pack price submitted to DHSC per vial of patisiran (10mg formulated as lipid nanoparticles) is [redacted] The yearly treatment cost is [redacted] annually	The suggested edit will correct the misidentification of the drug to which these price, yearly cost, and vial consumption numbers apply.	Thank you for raising this, we have made this amendment.

cost is [redacted] annually assuming [redacted] vials per administration for 17.36 administrations per year." The price, yearly cost, and vial consumption numbers all refer to patisiran, not vutrisiran. Also, patisiran is supplied in vials, not pre-filled syringes as indicated in the first sentence.	assuming [redacted] vials per administration for 17.36 administrations per year."		

Issue 4 Clarification of methods for analysing TTR reduction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1.2.2, page 15: "The subsequent analysis estimated a person-level average of trough TTR percent reductions (where reductions were benchmarked against baseline to estimate a percent); compared medians between groups, accounting for a stratifier by previous TTR stabiliser use; and used	Alnylam recommends expanding the quoted text as follows: "The subsequent analysis estimated a person-level average of trough TTR percent reductions (benchmarked against baseline); used the Hodges-Lehmann method to estimate the median trough TTR percent reduction among patients in each treatment arm; and used the Hodges-Lehmann method to estimate the median difference (with associated 95%	The suggested edits will more accurately describe the method by which these statistics were estimated.	This is not a factual inaccuracy. The description is appropriate as a summary.

the Hodges-Lehmann procedure to estimate a confidence interval." The quoted sentence does not comprehensively report the statistics for which the Hodges-Lehmann was used.	confidence interval) between treatment arms in terms of trough TTR percent reduction, accounting for a stratifier by previous TTR stabiliser use."		

Issue 5 Clarification of baseline characteristics in the APOLLO-placebo vs HELIOS-A-vutrisiran treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1.3, page 16: "Had worse ambulatory function (Karnofsky Performance Status <=60; 28.6% vs 13.9% and 10MWT 1.01 vs 0.79 m/s)" "Had worse HRQL (Norfolk Quality of Life – Diabetic Neuropathy [Norfolk QoL-DN] scale 47.1 vs 55.5)" The quoted bullets swap the order of 10MWT and Norfolk QoL-DN scores at baseline for the APOLLO placebo group and the	Alnylam recommends revising the quoted bullets as follows: "Had worse ambulatory function (Karnofsky Performance Status <=60; 28.6% vs 13.9% and 10MWT 0.79 vs 1.01 m/s)" "Had worse HRQL (Norfolk Quality of Life – Diabetic Neuropathy [Norfolk QoL-DN] scale 55.5 vs 47.1)"	The suggested edits will correct the order of reporting of 10MWT and Norfolk QoL-DN for APOLLO-placebo vs HELIOS-A-vutrisiran.	Thank you for raising this, we have made this amendment.

HELIOS-A vutrisiran group, compared with the other variables in this bulleted list and compared with the order expected given the grammatical structure of the preceding paragraph, in which APOLLO comes before HELIOS-A.			

Issue 6 Characterisation of impact on model results of not including the impact of infusion-related reactions (IRRs)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2, page 22: "The model does not include the impact of IRRs, non-inclusion of which would be assumed to result in a small cost difference in favour of patisiran as most IRRs will be treated by slowing or interrupting the infusion.[2]" The explicit conclusion that excluding IRRs would only reduce costs in the patisiran arm by a small	Alnylam recommends revision of the quoted sentence as follows: "The model does not include the impact of IRRs, non-inclusion of which can be considered a conservative modeling approach, favouring patisiran, since IRRs would increase costs associated with patisiran treatment and thereby increase potential cost savings with vutrisiran treatment."	The suggested edit would avoid drawing a conclusion about the magnitude of the cost difference in favour of patisiran that may not be factually correct because: • Slowing the infusion would increase HCP time needed to complete the infusion, increasing costs in the patisiran arm; • Interrupting the infusion could require a repeat visit, increasing HCP time and	This is not a factual inaccuracy. The time required for infusion in the company's submission which comes the NAC would be expected to already include the time needed when infusions have to be slowed. Infusion interruptions due to are rare. In the HELIOS-A CSR [redacted] interruptions are

amount is speculative and may not be factually correct.		costs, as well as potentially resulting in more vial wastage, again increasing costs in the patisiran arm; • More complicated IRRs may require additional management, incurring additional resources and associated costs [redacted]	reported for patisiran across [redacted] patients compared to [redacted] interruptions for vutrisiran. Patients on patisiran would be expected to have received [redacted] doses based on the reported patient exposure years of [redacted] patient years. Wastage from interrupted visits would be expected to be included within the information provided by Lloyds. The company have not provided the denominator relevant to the [redacted] The number of infusions that occurred in all studies of patisiran as of July 2022 would be expected to be high enough that this represents a small

			proportion. Based on APOLLO alone the OLE contains a cumulative drug exposure of [redacted] person-years which equates to over [redacted] infusions (OLE CSR Section 2.3).

Issue 7 Correction of minor typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Abbreviations list, page 5: "amyloidosis" is misspelled in the abbreviations "ATTR amyloidoisis" and "hATTR amyloidoisis".	Alnylam recommends that the quoted abbreviations be corrected as follows: "ATTR amyloidosis" "hATTR amyloidosis	Correction of typographic error.	Thank you for raising this, we have made this amendment.
Section 3.1.3, page 16: unmatched parenthesis at end of bullet "Had more advanced disease (Neuropathy Impairment Score ≥50; 54.6% vs 36.1%)[9])"	Alnylam recommends that the unmatched parenthesis be deleted so the bullet reads as follows: "Had more advanced disease (Neuropathy Impairment Score ≥50; 54.6% vs 36.1%)[9]"	Correction of typographic error.	Thank you for raising this, we have made this amendment.

Location of incorrect marking	Description of incorrect marking	Amended marking	
ID5074 vutrisiran EAG report 31102022CM [ACIC, company cPAS].docx			
Section 3.1.4.1, Table 3, page 19	Numeric results of the network meta-analysis redacted as CiC in the Company Submission (Document B, Tables 17–22) are presented in the EAG report without CiC highlighting. Alnylam requests that CiC markup be added as shown at right.	[redacted]	Thank you for raising this, we have made this amendment.
Section 4.1.1, page 20	CiC markup should be added to the numbers in the following sentence because these were based on confidential data provided under license to	"Based upon this assumption the records contain [redacted] administrations, or administrations for approximately [redacted] patients based on the patisiran dosing schedule."	Thank you for raising this, we have made this amendment.

	Alnylam from Lloyds Pharmacy: “Based upon this assumption the records contain 1996 administrations, or administrations for approximately 115 patients based on the patisiran dosing schedule.”		