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

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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.

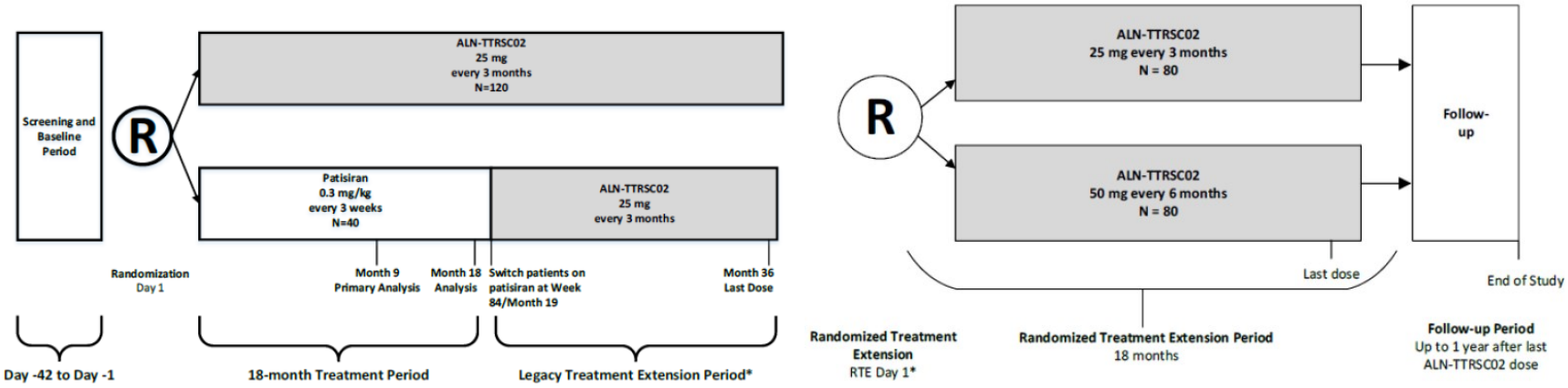
Eligibility criteria for HELIOS-A are shown in Table 10 of the CS, with baseline characteristics shown in Table 11 of the CS. The company states that demographic and baseline characteristics were widely overlapping and clinically comparable across treatment groups within study; the EAG broadly agrees 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:

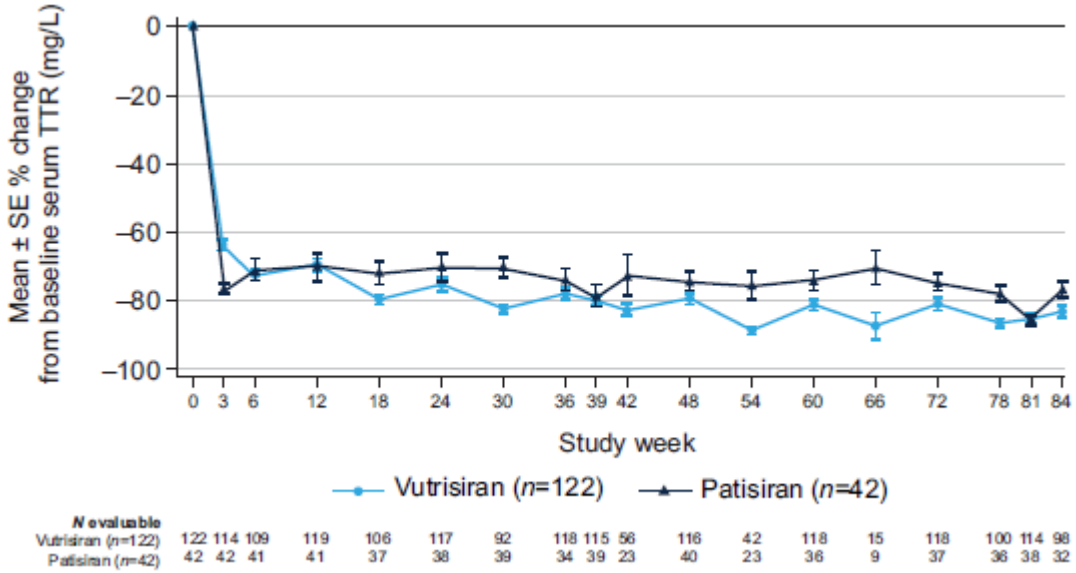
- Older (median age 63 vs 60)
- Had more advanced disease (Neuropathy Impairment Score ≥50; 54.6% vs 36.1%)[9]
- Had worse ambulatory function (Karnofsky Performance Status <=60; 28.6% vs 13.9% and 10MWT 0.79 m/s vs 1.01)
- Had higher cardiac involvement (51.9% had NYHA I or no heart failure and 46.8% 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.