NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Eplontersen for treating hereditary transthyretin-related amyloidosis [ID6337]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Eplontersen for treating hereditary transthyretin-related amyloidosis [ID6337]

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 AstraZeneca:
   a. Full submission
   b. Submission addendum
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group and professional group submissions** from:
   a. Amyloidosis UK
   b. Association of British Neurologists Neuromuscular Advisory Group

4. **External Assessment Report** prepared by BMJ Technology Assessment Group

5. **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

Eplontersen for treating hereditary transthyretin-related amyloidosis [ID 6337]

Document B

Company evidence submission

February 2024

File name	Version	Contains confidential information	Date
ID6337_Eplontersen_NICE_Document B [CON]	Final	Yes	26th February 2024

Contents

Tables and Figures

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

B.1.1 Decision problem

Eplontersen is anticipated to be indicated for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv-PN).

The population considered within this appraisal is adults with Stage 1 and Stage 2 ATTRv-PN, which is aligned with the study population in the pivotal trial for eplontersen (NEURO-TTRansform). This population is also aligned with that for vutrisiran in the published NICE technology appraisal guidance (TA868); vutrisiran is considered to be the only relevant comparator for eplontersen since it is the only treatment for ATTRv-PN that is both established and used substantially in clinical practice.[1]

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 with Stage 1 or Stage 2 polyneuropathy.	Adults with hereditary transthyretin-related amyloidosis with Stage 1 or Stage 2 polyneuropathy.	N/A
Intervention	Eplontersen	Eplontersen	N/A
Comparator(s)	• Vutrisiran • Patisiran • Inotersen	Vutrisiran	NICE guidance states that the chosen comparator for a cost-comparison submission must be established, and have substantial use, in clinical practice in England.[1] Based on these requirements, vutrisiran is considered to be the only relevant comparator for patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) in England. This is demonstrated by prescribing data from the NAC where [redacted] of [redacted] of patients with ATTRv-PN receive vutrisiran, compared to [redacted] ([redacted]) receiving patisiran and [redacted] [redacted] receiving inotersen. These data are aligned with UK prescribing data from Blueteq, which show that [redacted] patients commenced treatment with vutrisiran in Q2 and Q3 of 2023, and [redacted] initiated treatment on patisiran or inotersen.[2] Consequently, patisiran and inotersen do not meet the criteria for relevant comparators, as defined by NICE. In line with this, NICE has confirmed that vutrisiran is the key comparator to eplontersen, with patisiran and inotersen only included in the list of comparators for

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			completeness, given that both are recommended by NICE.[3]
Outcomes	The outcome measures addressed in this submission include: • Overall survival • Neurological impairment • 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	The outcome measures addressed in this submission include: • Neurological impairment • Symptoms of polyneuropathy • Autonomic function (including the effects on the gastrointestinal system and postural hypotension) • Weight loss (nutritional status) • Serum TTR • Motor function • Adverse effects of treatment • HRQoL	• Overall survival, cardiac function and the effects of amyloid deposits in other organs such as the eye were not measured in NEURO-TTRansform • Cardiac function was not measured in NEURO-TTRansform and is not a relevant outcome for this patient population
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 • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published	• A cost-comparison model has been developed for comparison of eplontersen versus vutrisiran, which is the current standard of care for patients in the UK with ATTRv-PN • Costs are considered	N/A – A cost-comparison model has been conducted in line with the NICE reference case

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	from an NHS and PSS perspective	

Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; HRQoL: health-related quality of life; NAC: National Amyloidosis Centre; NHS: National Healthcare System; PSS: personal social services; TTR: transthyretin; UK: United Kingdom.

B.1.2 Description of the technology being evaluated

The draft summary of product characteristics (SmPC) for eplontersen that covers the indication of relevance to this submission (adults with hereditary transthyretin amyloidosis with Stage 1 or Stage 2 polyneuropathy) is provided in Appendix C. Details of the technology being evaluated, including the method of administration, dosing and related costs, are provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Eplontersen (Brand name to be decided)
Mechanism of action	Eplontersen is an ASO with liver-specific targeting, providing consistent and sustained reduction of TTR at its source (the liver).[4, 5] Eplontersen uses LICA technology to provide targeted delivery of the ASO to liver hepatocytes, which are the primary source of systemic TTR production.[4] Within hepatocytes, eplontersen binds to *TTR* mRNA (including the mRNA of all *TTR* variants tested to date), and induces ribonuclease H1-mediated cleavage of *TTR* mRNA, thereby preventing TTR protein production.[4]
Marketing authorisation/CE mark status	Marketing authorisation for eplontersen in this indication is anticipated to be granted by the MHRA in [redacted], subject to no procedural delays.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Eplontersen is anticipated to be indicated for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv-PN).
Method of administration and dosage	45 mg solution for SC injection in a pre-filled pen (referred to as an auto-injector throughout), allowing for self-administration.
Additional tests or investigations	No additional tests are required prior to the administration of eplontersen.
List price and average cost of a course of treatment	The list price of eplontersen is anticipated to be [redacted] for a 45 mg vial.[a] The yearly cost of treatment with eplontersen, based on 12 injections per year, is [redacted].
Patient access scheme/commercial arrangement (if applicable)	A confidential PAS discount has been proposed for eplontersen of [redacted]% leading to a with-PAS price of [redacted] per pack and [redacted] per year.

Footnote: [a]At the time of submission, a submission has not yet been made to the Department of Health and Social Care for approval to list eplontersen at this price, however an application will be made, and the list price will be confirmed prior to publication of papers by NICE.
Abbreviations: ASO: antisense oligonucleotide silencer; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; LICA; ligand-conjugated antisense; MHRA: Medicines and Healthcare Products Regulatory Agency; mRNA: messenger ribonucleic acid; PAS: patient access scheme; SC: subcutaneous; SmPC: summary of product characteristics; TTR: transthyretin.

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

ATTRv-PN

- Hereditary transthyretin amyloidosis (ATTRv) is an ultra-rare, systemic, and fatal genetic disease, resulting from inherited mutations in the *TTR* gene.[6, 7] ATTRv-PN (PN for polyneuropathy) is a form of the condition which is characterised by peripheral nerve damage; TTR amyloid fibrils predominantly accumulate in peripheral nerves, resulting in damage to sensory, motor and autonomic nerves.[8-11] This progressive, irreversible condition leads to life-threatening multisystem impairment[6, 7] and ATTRv-PN patients face a median overall survival of 4.7 years following diagnosis.[12]
- There is a significant health-related quality of life impairment associated with ATTRv-PN due to the range of progressively worsening, debilitating symptoms that patients experience. Individuals with ATTRv-PN are at greater risk of experiencing psychological distress and mental health problems compared with the general population.[13-15] The disease also places a significant burden on the emotional wellbeing of patients' families and caregivers.[9, 16]
- ATTRv-PN is associated with substantial economic burden, including high resource use and costs for hospitalisation, home care and special housing. This is exacerbated by the cost and resource use involved in treatment administration since existing ATTRv-PN treatments involve administration by healthcare professionals (HCPs) and some treatments require regular side-effect monitoring.[12, 17] Additionally, ATTRv-PN exerts a substantial impact on productivity since the symptoms of ATTRv-PN reduce the ability of patients to gain and keep employment.

Current Management

- Silencers are the only reimbursed treatment for ATTRv-PN.[12, 18, 19] The National Amyloidosis Centre (NAC) is the only service commissioned by the NHS's National Specialised Services and funded by the Department of Health for the management of ATTRv-PN patients in the UK.
- Vutrisiran (TA868) is the current standard of care treatment, with a clinical expert from the NAC confirming that [redacted] of [redacted] patients with ATTRv-PN at the NAC are treated with vutrisiran, and all newly diagnosed patients are initiated on vutrisiran.[12, 20] However, vutrisiran is associated with administration limitations; it requires administration by an HCP every three months, necessitating HCPs to travel to patients' homes after the first dose is administered.[12] This is particularly significant given that approximately 30–40% of patients are of working age.[20]
- Other NICE recommended therapies including patisiran and inotersen are no longer routinely used in clinical practice due to their burdensome administration and monitoring requirements (patisiran) and limitations with safety and efficacy (inotersen).[2, 12, 20]
- Vutrisiran offers benefits compared to other treatments such as inotersen and patisiran, yet it does not fully meet the needs of patients.[12] There remains a need for additional treatment options associated with fewer administration challenges, to reduce the burden on the NHS and provide patients with greater autonomy.

Proposed Positioning of Eplontersen

- Eplontersen is an antisense oligonucleotide (ASO) silencer which uses ligand-conjugated-antisense (LICA) technology to provide targeted delivery of the ASO to liver hepatocytes, providing consistent and sustained reduction of TTR at its source.[4, 5]
- The proposed positioning for eplontersen is as a treatment for patients with Stage 1 or Stage 2 ATTRv-PN, offering a therapeutic option for slowing or halting progression of ATTRv-PN.
- As demonstrated in an indirect treatment comparison, vutrisiran and eplontersen have similar treatment effects for the treatment of ATTRv-PN. However, eplontersen does not require HCP administration which would reduce the administration and economic burden. As a result, eplontersen is anticipated to decrease administration-related costs associated with regular administration of vutrisiran by HCPs.

B.1.3.1 ATTRv-PN overview

Amyloidosis is a group of diseases characterised by the accumulation of amyloid fibrils (insoluble, degradation-resistant protein fibres) in tissues and organs. Transthyretin amyloidosis (ATTR) is a rare, systemic, progressively debilitating and fatal disease.[9, 21]

ATTR is classified into two distinct forms – hereditary ATTR (ATTRv; v for "variant") amyloidosis and wild-type ATTR (ATTRwt). ATTRv is the genetic form of the disease, resulting from inherited autosomal-dominant mutations in the *TTR* gene encoding transthyretin (TTR).[6, 7] In contrast, ATTRwt amyloidosis refers to ATTR amyloidosis that is caused by age-related deposition of misfolded TTR amyloid fibrils, occurring without an identified *TTR* mutation.[22]

ATTRv is heterogenous and systemic, meaning patients can experience a wide range of symptoms affecting organs and tissues such as the heart, eyes, nerves and gastrointestinal (GI) tract. Disease progression manifests as worsening symptoms, involving an increasing number of organs and eventually resulting in death.[23]

ATTRv is further categorised into two forms, depending on the predominant clinical presentations:[22]

- ATTRv with polyneuropathy (ATTRv-PN) – a condition characterised by damage to the peripheral nerves[22]
- ATTRv with cardiomyopathy (ATTRv-CM) – a condition characterised by amyloid fibril infiltration of the heart[22]

The majority of *TTR* mutations give rise to a mixed clinical phenotype, whereby patients experience both neurological and cardiac impairment and, in clinical practice, a wide range of overlapping phenotypes are observed.[22]

In ATTRv-PN, TTR amyloid fibrils predominantly accumulate in peripheral nerves, resulting in progressive, irreversible polyneuropathy (PN) that leads to life-threatening multisystem impairment.[6, 7] TTR is primarily synthesised and secreted by the liver and functions as a serum transport protein for thyroxine and retinol throughout the body and brain.[24] In healthy individuals, TTR circulates in the plasma and cerebrospinal fluid as a tetramer.[24] However, in patients with ATTRv-PN, the structure of this protein complex is destabilised due to mutations in the *TTR* gene, resulting in dissociation of the tetramer. The dissociated mutant TTR monomers subsequently misfold and aggregate to form amyloid fibrils, which are associated with cytotoxicity and cell degeneration.[24] The amyloid fibrils are deposited in multiple organs, leading to a range of clinical manifestations.[24] Disruption at the blood-nerve barrier (the physical boundary between the peripheral nerve axons and blood stream) can also occur, further contributing to the development of neuropathy.[25]

Several classification systems have been developed in ATTRv-PN to categorise the disease into defined stages (see Table 3). The Coutinho scale and familial amyloidotic polyneuropathy (FAP) stage are based on ambulation and neuropathy, while the polyneuropathy disability (PND) score is based on ambulation only.[26] The FAP and PND scores are used in clinical practice as proxies for disease progression – it is anticipated that scores will worsen to reflect the rapid neuropathic progression and dysfunction caused by progressive ATTRv-PN.[27]

Eplontersen is anticipated to be indicated for the treatment of adult patients with Stage 1 or 2 ATTRv-PN.

Table 3. Classification systems in ATTRv-PN

Coutinho		FAP[a,b]		PND[b]	
0	No symptoms	**0**	Asymptomatic	**0**	No symptoms
1	• Does not require assistance with ambulation • Disease is limited to lower limbs; slight weakness of the extensors of the big toes	**1**	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs	**I**	Sensory disturbances but preserved walking capability
				II	Impaired walking capacity but able to walk without a stick or crutches
2	• Required assistance with ambulation • Motor signs progress in lower limbs with steppage gait and distal amyotrophies; the muscles of the hands begin to be wasted and weak	**2**	Assistance with ambulation required; mostly moderate impairment, progression to the lower limbs, upper limbs, and trunk	**IIIa**	Walking with the help of one stick of crutch
				IIIb	Walking with the help of two sticks or crutches
3	• Confined to a wheelchair or bedridden • Generalised weakness and areflexia	**3**	Bedridden or confined to a wheelchair; severe sensory, motor, and autonomic involvement of all limbs	**IV**	Confined to a wheelchair or bedridden

Footnotes: Ambulation is the ability to walk and move about. Amyotrophy is progressive wasting of muscle tissues. Areflexia is a condition in which muscles are unresponsive to stimuli. [a]Adams et al. (2015) classified patients with FAP Stage II as PND Stage IIIa or IIIb, and FAP Stage III as PND Stage IV.[27] [b]Based on the classification system described by Coutinho et al (1980).[28]
Source: Table adapted from CADTH, 2020[26] and Hawkins 2015[22]
Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; FAP: familial amyloidotic polyneuropathy; PND: polyneuropathy disability.

B.1.3.2 Disease burden

Clinical Burden

ATTRv-PN is a life-threatening condition associated with increased mortality compared with the general population. Patients face a median survival of 4.7 years following diagnosis (depending on the specific *TTR* mutation), which ranges from 3–15 years following symptom onset.[12] Survival is heterogenous among patients, and is influenced by several factors, including age at disease onset, the specific *TTR* variant and disease phenotype.[22, 23]

Patients with ATTRv-PN can present with early- or late-onset disease (symptoms presenting at ≤50 and >50 years of age, respectively).[23] ATTRv-PN affects the somatic and autonomic divisions of the peripheral nervous system (PNS); the somatic division is responsible for transmitting motor and sensory information whereas the autonomic division regulates involuntary

processes such as heart rate and digestion.[6, 8, 10] Ultimately, this means ATTRv-PN affects multiple organ systems and imposes a substantial clinical burden on patients.[8-11]

Initial symptoms vary, but can include sensory symptoms, such as pain, paraesthesia and numbness in the hands and feet, which can lead to secondary symptoms including plantar ulcers.[29] Other manifestations include cardiac dysfunction, kidney manifestations, ocular disorders, central nervous system (CNS) dysfunction,[23] and sleep disorders.[13] Autonomic neuropathy symptoms include sexual dysfunction, as well as orthostatic hypotension which may result in fainting, serious injury and ultimately hospitalisation.[9, 11, 18, 23] Gastrointestinal disturbances, including constipation, diarrhoea and faecal incontinence which can result in severe malnutrition and be so severe that patients may avoid leaving home.[30]

Progressive disease is characterised by sensory loss, loss of reflexes, reduced motor skills, and muscle weaknesses.[23] Support with walking is required within 3–5 years of symptom onset, with patients becoming dependent on support from a wheelchair within 5–10 years of symptom onset.[31]

Health-Related Quality of Life Burden

There is a significant health-related quality of life (HRQoL) impairment associated with the wide range of progressively worsening, debilitating symptoms of ATTRv-PN. Patients are at greater risk of experiencing psychological distress and mental health problems compared with the general population, and depression and anxiety occur with a greater incidence in patients with more advanced ATTRv-PN.[13-15]

A 2019 cross-sectional study found that HRQoL (measured using the 36-Item Short Form [SF-36]) was significantly worse in patients with ATTRv amyloidosis (n=172) than in the general population (n=4,040; $p<0.05$ across all SF-36 domains), with the greatest deficits observed in physical functioning.[15] Additionally, in a study investigating 11 rare diseases, one of the lowest utilities was reported for patients with ATTRv-PN (EQ-5D-3L: 0.51).[17]

Additionally, diagnosis of ATTRv-PN in the UK can take up to 4 years.[12, 18] The impact of diagnostic delay, combined with the uncertainty of prognosis, also exacerbates the physical and mental health burden.[32]

Caregiver Burden

Disease progression is accompanied by a decline in patients' independence, severely impacting the daily lives of their families and caregivers. A cross-sectional study reported that each patient required an average of 45.9 hours of caregiver time per week, for both practical care and emotional support.[16, 33] The rapid, irreversible impairment associated with ATTRv-PN places a significant burden on the emotional wellbeing and everyday lives of patients' families and caregivers.[9] In particular, families report feelings of loss associated with the negative impact of ATTRv-PN on patients' functional ability, and are significantly more likely to experience sleep problems and stress than caregivers of those with chronic conditions.[16, 33] Caregivers experience impairments in physical and mental health, with the burden estimated to be comparable to that of caregivers of people with Alzheimer's disease.[27, 33] These detrimental impacts were demonstrated in a cross-sectional study which reported lower EQ-5D-3L utility scores for caregivers when compared with matched controls, with low scores predominantly driven by the anxiety/depression domain.[16]

Economic Burden

ATTRv-PN is associated with substantial economic burden due to high resource use costs associated with hospitalisation, home care, special housing, psychologists, assistant nursing, orthotics and parenteral nutrition.[34] High resource use costs are exacerbated by administration and monitoring costs; ATTRv-PN treatments involve administration by healthcare professionals (HCPs) and some treatments also require regular side-effect monitoring.[35] Additionally, the cost of diagnosis, and systemic nature of ATTRv-PN which requires multidisciplinary care, further contributes to the high disease costs.[29, 36] The costs of ATTRv-PN increase as the disease progresses; a Delphi panel of seven UK ATTRv amyloidosis experts found that the average cost of PN-related resources ranged from £223 at PND 0 to £14,114 at PND IV (costs per patient/ six months).[37] Indirect costs are also incurred from treatment administration burden, out-of-pocket costs and travelling to receive treatment.[12, 35]

In addition to the high healthcare system costs, ATTRv-PN exerts a substantial impact on productivity since the symptoms of ATTRv-PN reduce the ability of patients to work. A 2020 global patient survey (n=38) found that only 38% of patients were employed full-time and 23% of patients were unable to work.[38] Time spent caring for patients also limits the employment opportunities of caregivers. A UK 2021 cross-sectional survey (n=36) found that roughly half of caregivers for patients with ATTRv in England indicated they had either changed jobs for flexibility (6%), reduced their work hours (22%) or stopped work completely (22%).[16]

B.1.3.3 Epidemiology

ATTRv-PN is endemic (localised to a specific area) in some countries. A clinical expert from the National Amyloidosis Centre (NAC) advised that the current diagnosed prevalence of Stage 1 and Stage 2 ATTRv-PN is [redacted] patients in England, Northern Ireland and Wales, while the total prevalence is estimated to be around double[redacted].[20] The distribution of ATTRv genotypes varies geographically and ethnically. Globally, the V50M mutation (previously known as V30M) is most common, followed by V22I and E89Q.[39] In the UK, the most common *TTR* mutation is T80A (previously known as T60A), which is often found in people of Irish ancestry.[11]

B.1.3.4 Diagnosis

In the UK, people with ATTRv-PN symptoms present to their primary care physician who will refer them to secondary care after approximately 6–8 months. Patients will eventually be referred to the NAC for confirmation of diagnosis.[18, 19] The NAC is the only service commissioned by the National Health Service's (NHS) National Specialised Services and funded by the Department of Health for the management of ATTRv-PN patients in the UK. They are responsible for diagnosing and treating all patients with ATTRv-PN.[20]

Timely initiation of treatment is crucial in ATTRv-PN, given the rapid and irreversible disease course.[40, 41] Despite this, ATTRv-PN is an under-recognised condition, with referral to the NAC taking up to 4 years from symptom onset.[12, 18] Several factors contribute to this delay, such as the low prevalence and lack of awareness of ATTRv-PN, heterogeneity among phenotypes and the high incidence of co-morbidities and/or non-specific symptoms.[23] ATTRv-PN typically occurs in middle-aged and older people, with the mean age of symptom onset being 61.5 years.[42] In line with this, the majority of patients included in the NEURO-TTRansform study were less than 65 years old.[43] As such, it can be difficult to distinguish between common symptoms of ATTRv-PN and features of the normal aging process such as pain and fatigue.[9]

Diagnosis of ATTRv-PN relies on the combination of clinical history, blood tests, nerve conduction studies (NCS), histopathological evidence genetic testing and imaging, as each approach in isolation presents a risk of a false-positive or false-negative result. For patients in whom there is clinical suspicion of ATTRv-PN, tissue biopsies are used to identify amyloid deposits and confirm the detected precursor protein as TTR, then DNA sequencing is used to identify the causal *TTR* gene mutation.[11, 44] To determine the type of amyloidosis, amyloid typing by light microscopy immunohistochemistry or immunoelectron microscopy is conducted.[44]

B.1.3.5 Current Management

Current Recommended Therapies

Silencers (inotersen, patisiran, vutrisiran) are the only NICE recommended treatment for ATTRv-PN, blocking TTR mRNA synthesis and limiting the production of wild-type and mutant TTR protein. All silencer therapies are indicated for the treatment of Stage 1 or Stage 2 ATTRv-PN, and are initiated at the NAC.

Inotersen was the first silencer recommended by NICE (May 2019) for the treatment of Stage 1 or Stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis (HST9)[19] but the therapy is associated with numerous real-world challenges (Table 4) and consequently, is rarely used in clinical practice. UK clinical expert opinion from the NAC, provided as part of the vutrisiran appraisal, confirmed that inotersen is associated with significant toxicity and is rarely prescribed.[12] For example, treatment with inotersen requires regular monitoring for numerous side effects, with monitoring of platelet counts required as frequently as every day due to the association of inotersen with thrombocytopaenia.[45]

Patisiran was recommended by NICE for treating hereditary transthyretin-mediated amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy in August 2019 (HST10).[18] As outlined by clinician input in TA868, patisiran, at the time, became the standard of care for all eligible patients with ATTRv-PN in England.[12] Whilst patisiran offered clinical benefits, it requires time-consuming intravenous (IV) administration and, due to the risk of infusion-related reactions (IRRs), constant monitoring during infusion by HCPs.[12]

In 2023, vutrisiran received a positive recommendation from NICE for the treatment of hereditary transthyretin-related amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy (TA868).[12] Vutrisiran has replaced patisiran as the standard of care, with a clinical expert at the NAC indicating that [redacted] of patients receive vutrisiran, [redacted] receive patisiran, and [redacted] receive inotersen.[20] Both clinicians confirmed that all new patients would be initiated on vutrisiran.[20] Furthermore, the clinician input is aligned with UK prescribing data from Blueteq, which show that [redacted] patients in England commenced treatment with vutrisiran in Q2 and Q3 of 2023, with [redacted] initiating on patisiran or inotersen.[2]

Vutrisiran offers similar treatment effects to patisiran but is associated with lower costs due to its subcutaneous (SC) mode of administration, which removes the potential for IRRs and therefore does not require patients to receive premedication to reduce the risk of such complications. Additionally, vutrisiran only requires administration every three months, compared to every three weeks for patisiran. However, vutrisiran still requires administration by an HCP every three months, necessitating HCPs to travel to patients' homes after the first dose is administered at the NAC. The pivotal trial for vutrisiran was designed for HCP administration and, as such, the specific requirements in the SmPC for vutrisiran require HCP administration.[12, 46]

A summary of the recommended silencer therapies is presented in Table 4.

Table 4. Current therapeutics recommended by NICE in the UK for the treatment of ATTRv-PN

Recommended therapy	Inotersen (Tegsedi)[45]	Patisiran (Onpattro)[47]	Vutrisiran (Amvuttrra)[48]
Marketing authorisation holder	Akcea Therapeutics	Alnylam Pharmaceuticals	Alnylam Pharmaceuticals
Marketing authorisation	Treatment of ATTRv-PN in adult patients with Stage 1 or Stage 2 polyneuropathy	Treatment of ATTRv-PN in adult patients with Stage 1 or Stage 2 polyneuropathy	Treatment of ATTRv-PN in adult patients with Stage 1 or Stage 2 polyneuropathy
Mechanism of action	ASO-mediated degradation of TTR	TTR-specific siRNA; mediates TTR mRNA degradation	TTR-specific siRNA; mediates TTR mRNA degradation
Dosing schedule	284 mg QW; SC	0.3 g/kg IV Q3W; pre-medication required to reduce risk of IRRs	25 mg Q3M; SC
Contraindications	• Hypersensitivity to the active substance, or medication excipients • Platelet count <100 x 109/L prior to treatment • UPCR ≥113 mg/mmol (1g/g) prior to treatment • EGFR <45 ml/min/1.73m^2 • Severe hepatic impairment	Severe hypersensitivity to the active substance or medication excipients	Severe hypersensitivity to the active substance or medication excipients
Monitoring requirements	Platelet count: • During entire treatment course (from daily to biweekly) • 8 weeks following treatment discontinuation UPCR and EGFR: • At least every 3 months • 8 weeks following treatment discontinuation Liver function: • Hepatic enzymes monitored 4 months after	Patients must be monitored during infusion and, if clinically indicated, after infusion	None required

Recommended therapy	Inotersen (Tegsedi)[45]	Patisiran (Onpattro)[47]	Vutrisiran (Amvuttrra)[48]
	treatment initiation; annually thereafter		
NICE appraisal	HST9[19]	HST10[18]	TA868[12]
Market share[a], 2, 20	[redacted]	[redacted]	[redacted]

Footnote: [a]Market share data is based on exact number of patients receiving each treatment from the NAC in England, Northern Ireland and Wales.
Abbreviations: ASO: antisense oligonucleotide; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; EGFR: estimated glomerular filtration rate; IRR: infusion-related reactions; IV: intravenous; QW: every week; NAC: National Amyloidosis Centre; Q3M: every 3 months; Q3W: every 3 weeks; SC: subcutaneous; siRNA: small interfering ribonucleic acid; TTR: transthyretin; UPCR: urine protein to creatine ratio.

Unmet Need

As described above, current treatments do not fully meet the needs of patients, with earlier treatments being associated with burdensome administration (patisiran) and safety monitoring procedures (inotersen). Since the introduction of vutrisiran, patients are able to access an improved disease-modifying treatment option. However, vutrisiran is administered subcutaneously by HCPs, requiring HCPs to visit the patient's home every three months. Over a 5-year time horizon, these visits accumulate an estimated total cost of £627.00 per patient, as reported in TA868.[12] Crucially, this cost does not consider the burden of regular home visits on patients' daily lives and therefore undermines the true impact associated with vutrisiran administration.

Consequently, there is a need for a new therapeutic option for patients with ATTRv-PN, that can delay disease progression whilst offering greater patient autonomy and reducing the burden of treatment on patients, their caregivers and the healthcare system. Vutrisiran, the current standard of care for ATTRv-PN, is associated with administration limitations and consequently, there is a need for a treatment that provides more autonomy and that can be self-administered at home.[4, 12]

B.1.3.6 Proposed positioning of eplontersen in the treatment pathway for patients with ATTRv-PN with Stage 1 or Stage 2 polyneuropathy

Mode of Action

Eplontersen is an antisense oligonucleotide (ASO) silencer which uses ligand-conjugated-antisense (LICA) technology to provide targeted delivery of the ASO to liver hepatocytes, the primary source of systemic TTR production. This leads to high potency and a consistent and sustained reduction of TTR at its source, thereby minimising off-target effects and allowing for reduced dosing compared to silencers without LICA technology.[4, 5]

Within hepatocytes, eplontersen binds to both mutant and wild-type *TTR* mRNA (including the mRNA of all *TTR* variants tested to date), and induces ribonuclease H1-mediated cleavage of *TTR* mRNA, thereby triggering the degradation of mRNA and limiting the production of wild-type and mutant TTR protein.[4]

The pivotal trial for eplontersen in ATTRv-PN is NEURO-TTRansform (NCT04136184), a phase III, multicentre, open-label randomised controlled trial (RCT).[4] Stage 1 and 2 patients were randomised to either receive eplontersen from trial initiation, or inotersen-eplontersen switch whereby patients received inotersen for 34 weeks before switching to eplontersen at Week 37. The trial was designed for self-administration of eplontersen. Due to the rarity and speed of progression of ATTRv-PN, and multiple available treatments for the condition, inclusion of a randomised placebo arm in the trial was considered to be unethical. Therefore, the eplontersen treatment arms in NEURO-TTRansform was compared to an external, historical placebo arm (NEURO-TTR trial).[4] The NEURO-TTRansform trial is described in more detail in Section B.3.

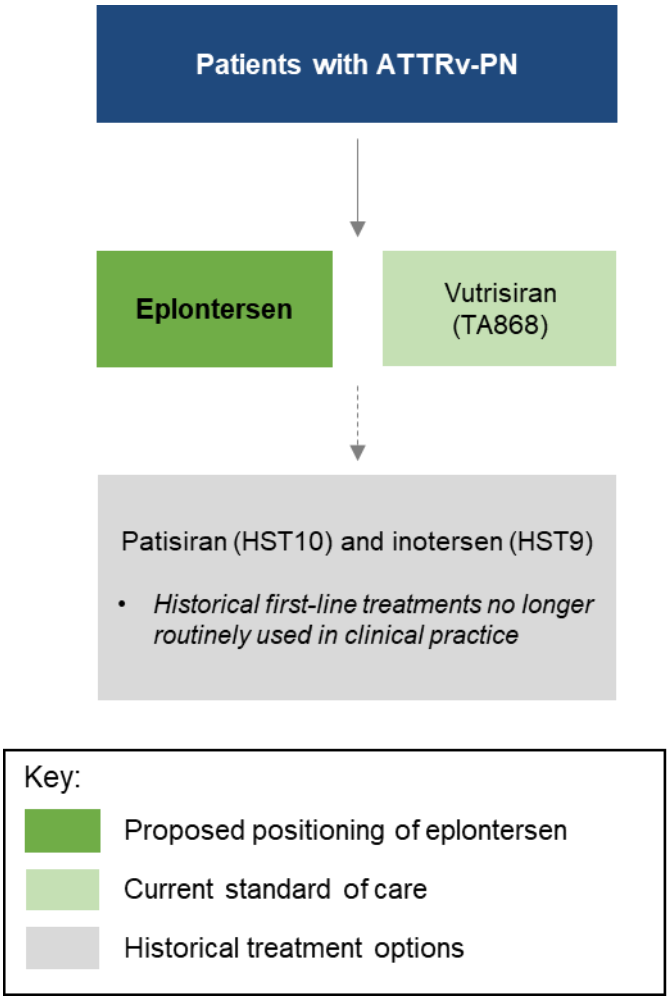
Proposed Positioning

The proposed positioning for eplontersen is as an alternative to vutrisiran for the treatment of patients with Stage 1 or Stage 2 ATTRv-PN. Unlike vutrisiran, eplontersen will be provided as a pre-filled pen (referred to as an auto-injector from hereon), allowing for self-administration. The administration routes cited are based on the SmPC for vutrisiran and the draft SmPC for eplontersen.[46, 49]

Eplontersen would offer a therapeutic option for slowing or halting progression of this irreversible, fatal condition and compared to vutrisiran, provides patients with greater autonomy through a more convenient administration profile, allowing them to keep their independence for as long as possible.

In the context of the existing NICE clinical pathway, eplontersen is anticipated to provide similar or greater health benefits at a similar or lower cost than those provided by vutrisiran in the identical patient population. As such, eplontersen is expected to be an alternative to vutrisiran as the standard of care treatment for this patient population, with UK clinical experts confirming this proposed positioning (Figure 1).[20]

Figure 1: Anticipated treatment pathway, including eplontersen, for patients in the UK with ATTRv-PN



Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy.

Benefits of Eplontersen Over Vutrisiran

Vutrisiran and eplontersen are associated with similar treatment effects for the treatment of ATTRv-PN (a detailed comparison of the clinical effectiveness and safety profiles of eplontersen and vutrisiran can be found in Section B.3). However, as further detailed in Section B.1.3.6, eplontersen offers benefits over vutrisiran due to its advantageous administration profile – eplontersen can be self-administered, or administered by a carer, via an auto-injector. This reduces the treatment burden on patients, caregivers and HCPs. A comparison of the key characteristics of vutrisiran and eplontersen is presented in Table 5.

Table 5. Characteristics of vutrisiran and eplontersen

	Vutrisiran[12, 48]	Eplontersen[49]
Mechanism of action	GalNAc-conjugated siRNA targeted to hepatocytes (via GalNAc platform), promoting degradation of *TTR* mRNA	GalNAc-conjugated ASO delivered to hepatocytes (via GalNAc), inducing cleavage of *TTR* mRNA
Intended use	Treatment of ATTRv amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy	Treatment of ATTRv amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy

	Vutrisiran[12, 48]	Eplontersen[49]
Dose and frequency	25 mg SC injection in pre-filled syringe; Q3M	45 mg solution for SC injection via auto-injector; QM
Method of administration	• Initial injection by an HCP at the NAC • Subsequent doses by HCP at patients' home, or other outpatient settings • Administration is assumed to require one hour of HCP time	• Initial injection by an HCP at the NAC • Subsequent injections can be self-administered or administered by a caregiver at home
Burden to healthcare system due to administration	• Initial injection requires limited incremental resource at NAC • Healthcare resource use for subsequent injections – HCP travel to the patient's home, HCPs at hospital/outpatient setting	• Initial injection requires limited incremental resource at NAC
Burden to patients and caregivers due to administration	• Travel to NAC for initial injection • Loss of time and productivity for patients (and caregivers), as up to four homecare visits a year required for subsequent injections	• Travel to NAC for initial injection

Abbreviations: ASO: antisense oligonucleotide; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; CM: cardiomyopathy; GalNAc: N-acetylglucosamine; HCP: healthcare professional; NAC: National Amyloidosis Centre; QM: monthly; Q3M: every three months; SC: subcutaneous; siRNA: small interfering ribonucleic acid; TTR: transthyretin.

Both treatments are administered at a fixed dose and require initial administration by an HCP at the NAC. Subsequent vutrisiran treatments are delivered by a SC injection, which must be administered by an HCP and requires HCPs to travel to the patients' home.[12] Conversely, eplontersen is delivered via a SC auto-injector, and therefore can be self-administered or administered by the patients' caregiver.[49]Following the initial injection, eplontersen is expected to almost completely eliminate the need for HCP involvement for administration, including the travel time for HCPs. [12, 50] As a result, eplontersen results in reduced costs for the NHS since following the first administration, all subsequent administrations of eplontersen would not be associated with an administration cost. Conversely, each administration of vutrisiran is associated with a cost of £36 (see Section B.4 for further details on the cost-comparison analysis).

The advantages of the administration profile of eplontersen, which would not require HCP involvement, were supported by a UK clinical expert and identified to be particularly important for active patients who prefer not to wait at home for HCP-administered treatments or those who wish to avoid taking time off work, potentially impacting employment. This is particularly significant given that approximately 30-40% of patients are of working age.[20] In summary, eplontersen would provide patients with a convenient treatment option that allows them to control their symptoms whilst maintaining their independence and normal daily routines for as long as possible. As well as minimising the HRQoL burden on patients, and their family and caregivers, eplontersen would decrease administration-related costs and pressure on HCPs associated with

regular administration of SC injections. Additionally, eplontersen would eliminate the need for patients and their caregivers to wait at home, and potentially take time off work, for HCP homecare visits. As such, eplontersen would decrease the productivity loss of patients and their caregivers and reduce the indirect costs of ATTRv-PN.

B.1.3.7 Equality considerations

The use of eplontersen in the UK is not expected to raise any issues related to equality given its clinical comparability with vutrisiran.[12]

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

B.2.1 Clinical outcomes and measures

As previously detailed in Section B.1.3.5, vutrisiran represents the only appropriate comparator to eplontersen in this evidence submission. Vutrisiran currently captures [redacted]% of the market share of ATTRv-PN treatments in England, and based on clinical expert feedback from the NAC, all newly diagnosed patients are currently expected to be treated with vutrisiran.[20] Vutrisiran was recommended by NICE in TA868 as a treatment for adults with stage 1 or 2 ATTRv-PN, the population of relevance to this appraisal.[12]

The similar treatment effects of vutrisiran and patisiran were demonstrated in TA868 through consideration of clinical trial data from HELIOS-A.[12] Vutrisiran was shown to be comparable to patisiran when assessed on change in serum TTR, mNIS+7, Norfolk QoL-DN, 10-meter Walk Test (10MWT), modified body mass index (mBMI) and Rasch-build Overall Disability Score (R-ODS) from baseline. A NMA was also conducted that included the vutrisiran and patisiran arms from HELIOS-A, and the patisiran and placebo arms from APOLLO, which further demonstrated comparable mNIS+7 change from baseline (CfB), comparable median difference in Norfolk QoL-DN score change, and comparable change in PND score CfB.

Vutrisiran (TA868) was appraised via the cost-comparison route against patisiran, which was appraised in HST10.[18] As no clinical outcome measures were appraised in TA868, clinical outcome measures associated with HST10 have been listed in Appendix K.

B.2.2 Resource use assumptions

Vutrisiran, the comparator for this cost-comparison analysis (CCA), was appraised through the cost-comparison route in TA868.[12] Vutrisiran demonstrated clinical efficacy that was deemed equivalent to that of patisiran, whilst also reducing cost to the healthcare system. The key differences between vutrisiran and patisiran in TA868 were:

- **Administration costs**: Patisiran can only be administered in a homecare setting after three well tolerated infusions at the NAC, whilst vutrisiran can be administered in a homecare setting following one injection at the NAC. There are cost savings associated with vutrisiran compared to patisiran for infusions administered both at the NAC and in a homecare setting, due to differing route of administration. Patisiran is administered via IV infusion which is a more costly and time-consuming mode of administration when compared to that of vutrisiran, which is administered via SC injection. In addition to this, vutrisiran is administered once every three months, while patisiran is administered once every three weeks.
- **Pre-medication costs**: Patients being administered patisiran must undergo a premedication regimen of IV corticosteroid (dexamethasone 10 mg or equivalent), H1 blocker (diphenhydramine 50 mg, or equivalent [chlorphenamine 10 mg is used in clinical practice]), H2 blocker (ranitidine 50 mg, or equivalent [in clinical practice oral famotidine 20mg is used]), and oral paracetamol. Conversely, vutrisiran does not require a pre-medication regimen.

B.2.2.1 Relevance to the decision problem for eplontersen

The comparable clinical effectiveness between eplontersen and vutrisiran demonstrated through an ITC showing comparable serum TTR outcomes, CfB in mNIS+7 and a statistically significant improvement in CfB in Norfolk QoL-DN, suggests similar disease outcomes, and by extension comparable HCRU needs for disease management. Comparable adverse event (AE) rates are also demonstrated through the ITC (Section B.3.9.6 and B.3.9.7).

Given the expected similarity in terms of these costs, this economic analysis submission is a CCA which does not include health state specific HCRU and associated costs, or AE costs in the base-case. The only HCRU differences expected between eplontersen and vutrisiran are from their different routes of administration, so this is included in the CCA. This assumption is aligned with TA868, where the only cost differentiators are administration cost and pre-medication costs, with the latter not relevant for this submission.[12]

B.3 Clinical effectiveness

Summary of Clinical Effectiveness Data

- NEURO-TTRansform was a Phase III, multicentre, open-label, randomised clinical trial that assessed the safety and efficacy of eplontersen for patients with Stage 1 or 2 hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN).[43] Patients received eplontersen or inotersen for 34 weeks before switching to eplontersen at Week 37.[4, 51] As part of the NEURO-TTRansform trial, the clinical efficacy of eplontersen was compared against an external placebo group from the NEURO-TTR trial.[4]
    - At Week 65 of NEURO-TTRansform, eplontersen treatment resulted in a least squares mean (LSM) change from baseline (CfB) in percent serum transthyretin (TTR) of -81.7% (95% confidence interval [CI]: -84.8%, -78.5%), compared with -11.2% (95% CI: -15.1%, -7.4%) in the external placebo group.[52, 53]
    - By Week 66, eplontersen also delayed polyneuropathic progression, as indicated by a LSM CfB of 0.3 (95% CI: -4.5, 5.1) in the modified Neuropathy Impairment Score+7 (mNIS+7) composite score for the eplontersen group at Week 66, with a higher score indicating poorer function. In comparison, the LSM CfB was 25.1 (95% CI: 20.2, 29.9) in the external placebo group.[53]
    - At Week 66, eplontersen-treated patients experienced an improvement in quality of life (QoL). At Week 66 of NEURO-TTRansform, a mean CfB of -5.5 (95% CI: -10.0, -1.0) in the Norfolk quality of life-diabetic neuropathy (QoL-DN) total score was observed in the eplontersen group, compared with 14.2 (95% CI: 9.5, 19.0) in the placebo arm. An increase in score indicates decline in QoL.[53]
- The proportion of patients experiencing treatment-emergent adverse events (AEs) was comparable between eplontersen in NEURO-TTRansform and vutrisiran in HELIOS-A.[53, 54]
- Unanchored matching-adjusted indirect comparisons (MAICs) and simulated treatment comparisons (STCs) showed no statistically significant differences in the absolute, mean and percent CfB in steady state serum TTR concentration between the eplontersen group (NEURO-TTRansform) and vutrisiran group (HELIOS-A).
- Similarly, the unanchored MAICs and STCs showed no significant differences between eplontersen and vutrisiran for the mNIS+7 composite score, whilst a statistically significant difference, in favour of eplontersen, was shown for the Norfolk QoL-DN total score.
- Unanchored MAICs and STCs also showed no significant differences in terms of the odds of a serious or severe AE, or treatment discontinuation event between eplontersen and vutrisiran.
- Overall, the comparative efficacy and safety data provide clear evidence that eplontersen and vutrisiran have similar treatment effects in patients with ATTRv-PN. This was confirmed by input from UK clinical experts.[20]

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify the most up-to-date, relevant clinical evidence. The SLR was conducted in July 2022 and updated in October 2023. In total, 2,446 records were identified and 385 publications, reporting on 239 unique studies, were included in the SLR. Two studies identified in the SLR investigated eplontersen.[53, 55] Of these, only NEURO-TTRansform was considered relevant for informing the efficacy evidence for eplontersen in this submission.[53] One study included in the SLR (HELIOS-A) was used to inform the efficacy evidence for vutrisiran.[54]

B.3.2 List of relevant clinical effectiveness evidence

A summary of the pivotal trial, NEURO-TTRansform, demonstrating the clinical effectiveness of eplontersen is provided in Table 6. NEURO-TTRansform was a Phase III, multicentre, open-label, randomised clinical trial that examined the safety and efficacy of eplontersen for patients with Stage 1 or 2 ATTRv-PN, defined by the FAP or Coutinho stage.[43] Patients were randomised 6:1 to receive eplontersen (45 mg; Q4W; SC) or inotersen (300 mg; QW; SC) for 34 weeks before switching to eplontersen at Week 37 (45 mg; Q4W; SC).[4, 51]

As part of the NEURO-TTRansform trial, the clinical efficacy of eplontersen was compared against an external placebo group from the NEURO-TTR trial.[4] The NEURO-TTR trial also included an inotersen group which was compared descriptively against the NEURO-TTRansform inotersen group, to validate efficacy comparisons between the two trials.[56]

Table 6: Clinical effectiveness evidence

Study	**NEURO-TTRansform** (NCT04136184)[4, 51]
Study design	Phase III, international, multi-centre, open-label randomised clinical trial
Population	Adults aged 18–82 years diagnosed with Stage 1 or 2 ATTRv-PN with a documented TTR mutation, and signs and symptoms consistent with ATTRv-PN, including an NIS 10–130 (n=168; randomised 6:1)
Intervention(s)	Eplontersen (45 mg) administered SC Q4W (n=144)
Comparator(s)	Inotersen (300 mg) administered QW SC for 34 weeks before switching to 45 mg Q4W SC eplontersen at Week 37 (n=24) Placebo: external control from NEURO-TTR trial (n=60; NCT01737398)
Indicate if study supports application for marketing authorisation (yes/no)	Yes
Reported outcomes[a]	Primary outcomes: • **Serum TTR** • Polyneuropathy impairment: **mNIS+7** • HRQoL: **Norfolk QoL-DN** Secondary outcomes: • Symptoms of polyneuropathy: **PND score** • HRQoL: **PSC score of SF-36** • Nutritional status: **mBMI** Exploratory/other endpoints: • Motor function:10MWT • Symptoms of polyneuropathy: NSC score • Symptoms of autonomic dysfunction: COMPASS-31 • HRQoL/PROs: PGIS, PGIC, R-ODS, **EQ-5D-5L** • **AEs** and other safety endpoints

Footnote: [a]Outcomes in **bold** are presented in this submission.

Abbreviations: AE: adverse event; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; COMPASS-31: Composite Autonomic Symptom Score-31; EQ-5D-5L: 5-level EuroQoL 5-dimension; HRQoL: health-related quality of life; mBMI: modified body mass index; mNIS: modified Neuropathy Impairment Score; NSC: Neuropathy Symptom and Change; NIS: Neuropathy Impairment Score; PSC: physical summary component; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PND: Polyneuropathy Disability Score; QOL-DN: quality of life-diabetic neuropathy; QW: every week; Q4W: every 4 weeks; R-ODS: Rasch-built Overall Disability Score; SC: subcutaneous; SF-36: 36-Item Short Form; TTR: transthyretin; 10MWT: 10-metre walk test.

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

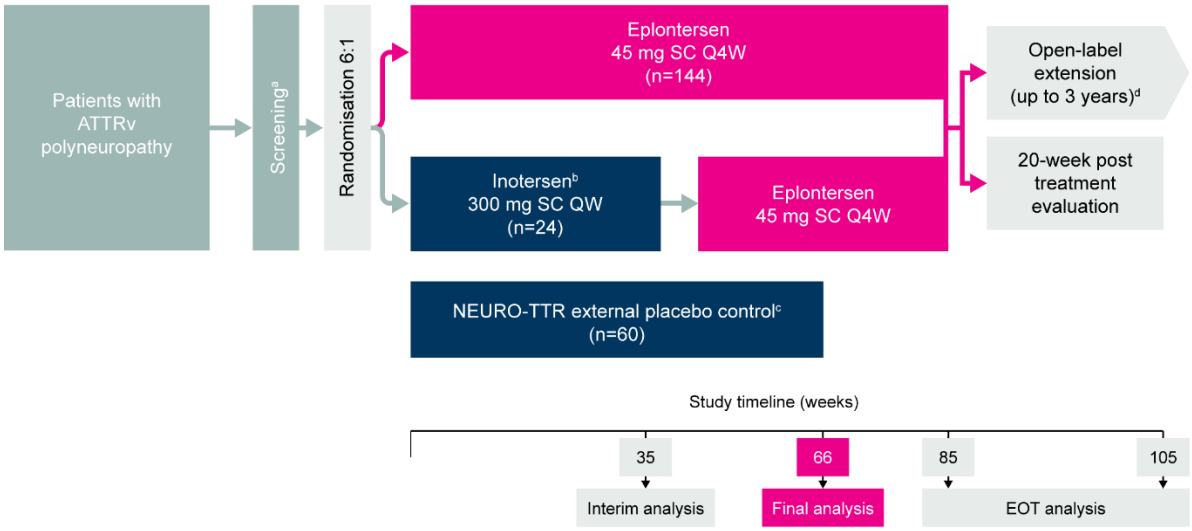
B.3.3.1 Summary of trial methodology

NEURO-TTRansform was a Phase III, multicentre, open-label, randomised clinical trial that examined the safety and efficacy of eplontersen for patients with Stage 1 or 2 ATTRv-PN. The study was conducted at 45 sites across 16 countries.[43] Patients were randomised 6:1 to receive eplontersen (45 mg; Q4W; SC) or inotersen (300 mg; QW; SC) for 34 weeks before switching to eplontersen at Week 37 (45 mg; Q4W; SC). Patients received treatment until Week 81, with a pre-specified interim analysis conducted at Week 35 and the final efficacy analysis at Week 65/66. End of treatment assessments were conducted at Week 85.[4, 51] The design of NEURO-TTRansform is summarised in Figure 2.

Due to the rarity of the condition, speed of progression, and number of available treatments for ATTRv-PN, inclusion of a randomised placebo group in NEURO-TTRansform was considered to be unethical.[4] International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidelines recommend that external comparisons are used for diseases with low prevalence and well-understood natural histories.[12] For example, the placebo arm from the APOLLO study was used as the external control group in HELIOS-A, the pivotal trial for vutrisiran.[12] Furthermore, as described in TA868, the ATTRibute-PN trial for acoramidis versus placebo was cancelled in February 2022 and redesigned as a single-arm study “after a careful review of the currently available treatments worldwide for patients with ATTR-polyneuropathy”, highlighting the ethical considerations surrounding placebo-controlled trials in ATTRv-PN.[12]

Therefore, the two treatment groups in NEURO-TTRansform were compared to two groups from an external study, NEURO-TTR (NCT01737398).[57] NEURO-TTRansform was designed to closely match the design of NEURO-TTR, as illustrated by Table 7, to support the use of the external placebo arm. Furthermore, as NEURO-TTR was designed to evaluate inotersen in ATTRv-PN,[4] the presence of an inotersen arm in both studies allowed for a comparison of the performance of patients in NEURO-TTRansform and NEURO-TTR.[4] The NEURO-TTRansform eplontersen arm was compared to the NEURO-TTR external placebo arm to demonstrate the efficacy and safety of eplontersen in ATTRv-PN.[4]

Figure 2: Design of NEURO-TTRansform



Footnotes: [a]Screening period could be up to 10 weeks if genetic testing required. [b]Patients randomised to the inotersen group switched to receive eplontersen at Week 37. [c]Use of a placebo in NEURO-TTRansform was deemed unethical due to the availability of ATTRv-PN treatments. [d]For patients not enrolled in the OLE, the final patient visit will be at Week 105.
Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; EOT: end of treatment; OLE: open-label extension; TTR: transthyretin.
Source: Khella 2023.[58]

A summary of the methodology of the NEURO-TTRansform and NEURO-TTR trials is provided in Table 7.

Table 7: Comparative summary of NEURO-TTRansform and NEURO-TTR trial methodology

Study	**NEURO-TTRansform** (NCT04136184)[4, 43, 51, 53]	**NEURO-TTR** (NCT01737398)[59]
Study design	Phase III, multi-centre, open-label randomised clinical trial	Phase III, multi-centre, double-blind, randomised, placebo-controlled trial
Location and study setting	Global (45 sites, 16 countries)	Global (24 sites, 10 countries)
Intervention	Eplontersen (45 mg) administered Q4W SC (n=144)	Inotersen (300 mg): 3 SC injections during Week 1 followed by QW SC injections (n=112)
Comparator	Inotersen: 300 mg; QW; SC for 34 weeks before switching to eplontersen at Week 37 (n=24)	Placebo: 3 SC injections during Week 1 followed by QW SC injections (n=60)
Patient population	• Adults aged 18–82 years with Stage 1 or 2 ATTRv-PN • Documented *TTR* mutation by genotyping • Signs and symptoms consistent with ATTRv-PN, including an NIS 10–130	• Adults aged 18-82 years with Stage 1 or 2 ATTRv-PN • Documented *TTR* mutation by genotyping • Biopsy-confirmed amyloid deposits
Total number of	168 (randomised 6:1)	173 (randomised 2:1)

Study	NEURO-TTRansform (NCT04136184)[4, 43, 51, 53]	NEURO-TTR (NCT01737398)[59]
randomised patients		
Primary outcomes	**Interim analysis co-primary efficacy outcomes**[a, b] • Percent CfB in serum TTR concentration at Week 35 • CfB in mNIS+7 at Week 35 **Final analysis co-primary efficacy outcomes** • Percent CfB in serum TTR concentration at Week 65 • CfB in mNIS+7 at Week 66 • CfB in Norfolk QOL-DN at Week 66	CfB in mNIS+7 and Norfolk QoL-DN scores at Week 66
Other relevant outcomes/outcomes specified in the scope	• mBMI • PND score • NSC score • AEs	• mBMI • Serum TTR

Footnote: [a]If the co-primary endpoints (TTR and mNIS+7) were not statistically significant at the interim analysis at Week 35, their corresponding tests would be performed in the full analysis at Week 65/66. [b]As results from the co-primary endpoints were statistically significant, Norfolk QoL-DN was tested as the key secondary endpoint at Week 35 in line with the statistical analysis plan.
Abbreviations: AE: adverse event; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; CfB: change from baseline; mBMI: modified body mass index; mNIS: modified Neuropathy Impairment Score; NIS: Neuropathy Impairment Score; NSC: neuropathy symptom and change; PND: polyneuropathy disability; QOL-DN: quality of life-diabetic neuropathy; QW: every week; Q4W: every 4 weeks; SC: subcutaneous; TTR: transthyretin; 10MWT: 10-metre walk test.

B.3.3.2 Eligibility criteria

The eligibility criteria for the NEURO-TTRansform and NEURO-TTR trials are presented in Table 8 and Table 9, respectively.

Table 8: Key inclusion and exclusion criteria for the NEURO-TTRansform study[4]

Inclusion Criteria	Exclusion Criteria

Adults aged 18–82 years with ATTRv-PN, as defined by meeting the following criteria:
• Stage 1 or 2 neuropathy, according to the FAP or Coutinho stage
• Documented mutation in the *TTR* gene
• Neuropathy symptoms consistent with ATTRv-PN, including an NIS 10–130
	• Prior liver transplant
	• NHYA functional classification ≥3
	• Alternative causes of polyneuropathy
	• Current or previous treatment with inotersen, patisiran or other ASO or siRNA therapies
	• Current treatment with tafamidis, diflusinal, doxycycline (alone or in combination with TUDCA)
	  ○ Previous treatment must have discontinued ≤2 weeks prior to study Day 1
	• Abnormal laboratory results:
	  ○ UPCR ≥1000 mg/g[a]

Inclusion Criteria	Exclusion Criteria
	○ Platelets <125 x 10^9/L ○ eGFR[b] <45 mL/min/1.73m^2

Footnote: [a]In the event of UPCR ≥1000 mg/g, eligibility can be confirmed by a repeat random urine test with UPCR <1000 mg/g or a quantitative total urine measurement of 1000 mg/24h. [b]Chronic Kidney Disease Epidemiology Collaboration equation 1 formula.
Abbreviations: ASO: antisense oligonucleotide; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; NIS: Neuropathy Impairment Score; siRNA: small interfering ribonucleic acid; TTR: transthyretin; TUDCA: tauroursodeoxycholic acid; UPCR: urine protein/creatine ratio.

Table 9: Key inclusion and exclusion criteria for the NEURO-TTR study[59]

Inclusion Criteria	Exclusion Criteria
Adults aged 18–82 years with ATTRv-PN, as defined by meeting the following criteria: • Stage 1 or Stage 2 neuropathy, according to the Coutinho stage • Documented mutation in the *TTR* gene • Documented amyloid deposits • Neuropathy symptoms consistent with ATTRv-PN, including an NIS 10–130	• Prior liver transplant • NHYA functional classification ≥3 • Use of tafamidis or diflunisal during the intervention period • Significant abnormalities in screening laboratory values • Karnofsky performance status score of 50 or less • Other causes of polyneuropathy

Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; NIS: Neuropathy Impairment Score; NYHA: New York Heart Association; TTR: transthyretin.

B.3.3.3 Baseline characteristics and demographics

A summary of the baseline characteristics of patients from NEURO-TTRansform is presented in Table 10, alongside the baseline characteristics of the NEURO-TTR external placebo and inotersen groups.[43] UK clinical experts confirmed that these characteristics were broadly generalisable to the UK population of patients with ATTRv-PN anticipated to receive eplontersen.[20, 43]

Overall, NEURO-TTRansform encompassed a diverse population of patients with ATTRv-PN. The study enrolled 168 patients across 15 countries/territories (North America: 15.5%; Europe: 38.1%; South America/Australia/Asia: 46.4%). The mean age was 52.8 years, with the majority of patients less than 65 years old and the most common ethnicity was white (78.0%).[43, 52] The majority of patients had Coutinho Stage 1 disease (79.2%), and slightly more than half of the patient population had early-onset disease (53.0%) compared with late-onset disease.[43]

Patient characteristics were similar overall between the NEURO-TTRansform eplontersen and NEURO-TTR external placebo arms. In both studies, the most common TTR mutation was V50M; the incidence of this mutation was similar between the NEURO-TTRansform eplontersen (59%) and NEURO-TTR external placebo groups (55%).[53] The mean duration of ATTRv-PN from the time of symptom onset was 67.7 and 64.0 months in the NEURO-TTRansform eplontersen group and NEURO-TTR external placebo group, respectively.[53]

At the time of enrolment, current or prior treatment with inotersen or patisiran was not permitted in NEURO-TTRansform.[51] In addition, concurrent use of tafamidis and off-label diflunisal were not permitted, and a washout period of two weeks was applied for patients who discontinued these treatments before enrolling in NEURO-TTRansform.[51] Whilst previous treatment with

tafamidis was permitted, both UK clinical experts confirmed that this would not impact the generalisability of the trial results to the UK, where tafamidis is not reimbursed.[20] Other medications were permitted in order to reflect real-world practice.[51] The frequency of concomitant medication use was the same across all groups (safety set population): at least one concomitant medication was used by [redacted] of patients in the NEURO-TTRansform eplontersen group (n=[redacted]), NEURO-TTR external placebo group (n=[redacted]), NEURO-TTRansform inotersen group (n=[redacted]) and NEURO-TTR external inotersen group (n=[redacted]).[60]

Table 10: Key demographic and characteristics for patients in NEURO-TTRansform and NEURO-TTR (all randomised patients)[53]

Parameter	NEURO-TTRansform		NEURO-TTR	
	Inotersen (n=24)	Eplontersen (n=144)	External placebo (n=60)	External inotersen (n=112)
Age, years, mean (SD)	51.1 (14.4)	53.0 (15.0)	59.5 (14.0)	59.0 (12.5)
Sex, n (%)				
Female	8 (33)	44 (31)	19 (32)	35 (31)
Male	16 (67)	100 (69)	41 (68)	77 (69)
Race, n (%)				
White	19 (83)	112 (78)	53 (88)	105 (94)
Asian	2 (9)	22 (15)	3 (5)	1 (1)
Black/African American	0	5 (3)	1 (2)	3 (3)
Other or multiple	2 (9)	4 (3)	3 (5)	3 (3)
Region, n (%)				
Europe	10 (42)	54 (38)	23 (38)	37 (33)
North America	5 (21)	21 (15)	26 (43)	56 (50)
South America/Australia/New Zealand/Asia	9 (38)	69 (48)	11 (18)	19 (17)
Previous treatment (tafamidis or diflunisal), n (%)	15 (63)	100 (69)	36 (60)	63 (56)
Disease stage (Coutinho stage), n (%)				
Stage 1 (ambulatory without assistance)	18 (75)	115 (80)	42 (70)	74 (66)
Stage 2 (ambulatory with assistance)	6 (25)	29 (20)	18 (30)	38 (34)
V50M *TTR* mutation, n (%)				
Yes	16 (67)	85 (59)	33 (55)	56 (50)

Parameter	NEURO-TTRansform		NEURO-TTR	
	Inotersen (n=24)	Eplontersen (n=144)	External placebo (n=60)	External inotersen (n=112)
No	8 (33)	59 (41)	27 (45)	56 (50)
mNIS+7 composite score,[a] mean (SD)	65.1 (33.5)	81.3 (43.4)	74.8 (39.0)	79.2 (37.0)
Norfolk QoL-DN total score, mean (SD)	40.1 (21.5)	*n=137* 44.1 (26.6)	*n=59* 48.7 (26.7)	*n=111* 48.2 (27.5)
mBMI, mean (SD), kg/m2 x g/L	*n=22* 1101.7 (246.5)	*n=138* 1025.8 (235.1)	1049.9 (228.4)	*n=111* 1010.9 (227.8)
NSC total score, mean (SD)	20.6 (10.5)	23.1 (12.4)	23.0 (12.6)	24.8 (13.1)
SF-36 PCS score, mean (SD)	39.7 (9.6)	39.7 (9.3)	37.2 (9.8)	*n=111* 35.7 (8.7)
PND score, n (%)		*n=143*		
I (sensory, but can walk)	12 (50)	56 (39)	23 (38)	32 (29.9)
II (difficulty walking, no aids)	8 (33)	61 (43)	19 (32)	42 (38)
IIIa (1 walking stick or crutch)	3 (13)	16 (11)	15 (25)	30 (27)
IIIb (2 walking sticks or crutches)	1 (4)	10 (7)	3 (5)	8 (7)
Duration from diagnosis or symptoms[b] mean (SD)				
Duration of disease from diagnosis, months	45.7 (54.1)	46.8 (58.1)	39.3 (40.3)	42.4 (51.2)
Duration from onset of symptoms, months	72.5 (111.0)	*n=143* 67.7 (50.9)	64.0 (52.3)	63.9 (53.2)
Patients with clinical diagnosis of ATTRv-CM,[c] n (%)	7 (29)	39 (27)	22 (37)	45 (50)

Footnotes: [a]mNIS+7 values are mNIS+7$_{Ionis}$. [b]Time from diagnosis or onset oof symptoms (collected as year and month only) to date of informed consent. [c]Patients with a clinical diagnosis of ATTRv-CM at baseline on their case report form.
Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; CM: cardiomyopathy; mBMI: modified body mass index; mNIS+7: modified Neuropathy Impairment Score plus 7; NSC: Neuropathy Symptom Change; PND: Polyneuropathy Disability; QOL-DN: quality of life-diabetic neuropathy; SD: standard deviation; SF-36: 36-Item Short Form; TTR: transthyretin.
Source: Coelho 2023[53]

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

B.3.4.1 Definitions of the patient population analysis sets

Full analysis set (FAS): All randomised patients who received at least one injection of the study drug, and who had a baseline and at least one post-baseline efficacy assessment for the modified neuropathy impairment score +7 (mNIS+7) and Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) questionnaire.[52]

Per-protocol set (PPS): Subset of the FAS who received at least 80% of the prescribed doses of the study drug and had no significant protocol deviations that would be expected to affect efficacy assessments.[52]

Safety set: All patients who were randomised and received at least one injection of the study drug.[52]

All efficacy outcomes were assessed for the FAS population and PPS population. The FAS was the basis of the primary efficacy analysis. All safety assessments were performed on the safety set population.[52]

B.3.4.2 Statistical Analysis

Sample Size

The sample size for NEURO-TTRansform was estimated based on the data from the NEURO-TTR clinical trial; power calculations assumed that percent reduction from baseline in serum TTR reduction would be 80%.[4] Approximately 140 patients were planned to be enrolled in NEURO-TTRansform to provide 108 evaluable patients, assuming a 10% dropout rate. With 52 evaluable completers in the placebo arm of NEURO-TTR, a sample size of 108 evaluable patients in the eplontersen arm of NEURO-TTRansform would provide statistical power for comparisons between the eplontersen-treated patients and the external placebo arm of the NEURO-TTR trial (two-sided alpha level, 0.025):[4]

- ≥95% power to detect a difference of 70.3% in the CfB in serum TTR
- ≥90% power to detect a 19.6-point difference in the CfB of mNIS+7
- ≥80% power to detect a 10.7-point difference in the CfB of the Norfolk QOL-DN score

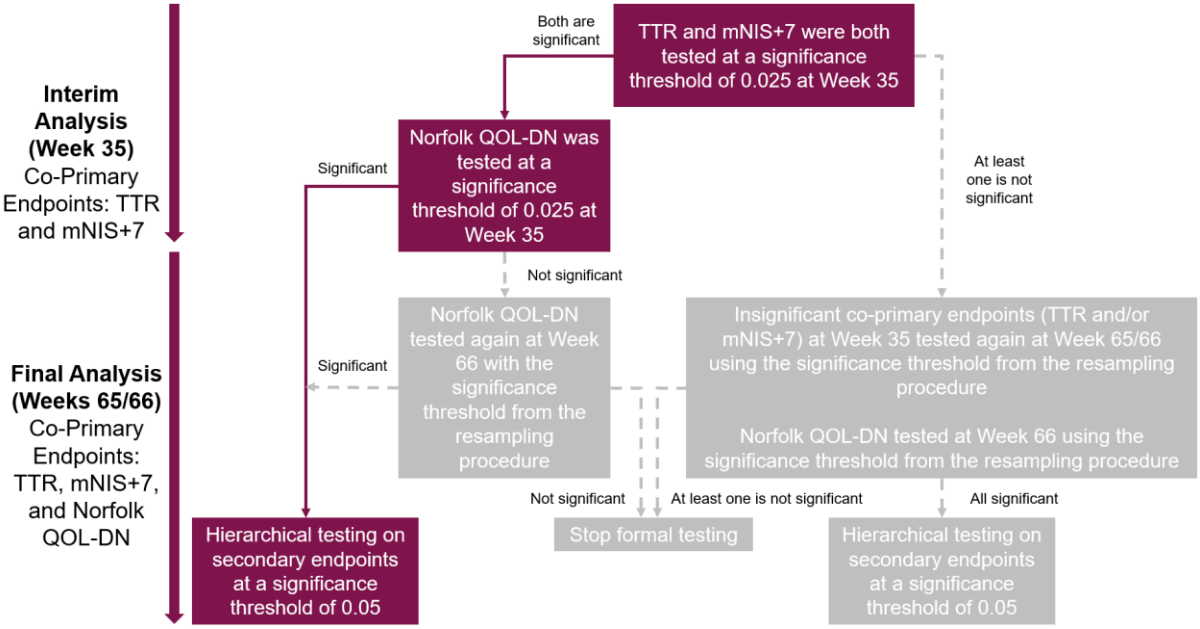
Statistical Analyses

- To ensure characteristics were well-balanced across the NEURO-TTRansform eplontersen group and NEURO-TTR external placebo group, propensity score weighting was carried out to balance the following variables: V50M *TTR* mutation, previous treatment and disease stage.[52, 56]
- Interim analysis was conducted at Week 35, to assess the efficacy and safety profile of eplontersen compared with the external placebo arm of NEURO-TTR.[4] V50M mutation (Yes/No), previous treatment with tafamidis or diflunisal (Yes/No), disease stage (Stage 1/Stage 2), and baseline value of the endpoint were included as covariates in the ANCOVA

models for efficacy analyses at this analysis timepoint.[56] Regardless of the interim analysis results, the study was planned to proceed with the final analysis being conducted at Week 65/66. A hierarchical testing procedure of endpoints at the interim (Week 35) and final (Week 65/66) was used to control the overall type 1 error rate at 0.05, as illustrated in Figure 3.

- Two co-primary endpoints were measured in the Week 35 interim efficacy analysis; percent CfB in TTR and CfB in mNIS+7. CfB in Norfolk QOL-DN was measured as a key secondary endpoint.[4] Since both co-primary endpoints were statistically significant at a two-sided alpha level of 0.025, the key secondary endpoint (Norfolk QOL-DN) was tested at the interim analysis at two-sided alpha level of 0.025 – this result was positive at the interim analysis. Given that these endpoints were statistically significant at Week 35, they were not formally re-tested in the final analysis (Week 65/66).[53]
- For the final analysis, percent CfB in TTR (measured at Week 65), CfB in mNIS+7 (measured at Week 66) and CfB in Norfolk QOL-DN (measured at Week 66) were analysed using the mixed-effects model with repeated measures (MMRM) which was adjusted by propensity score weights.[52, 61] The propensity score was calculated for each point using a logistic regression model with baseline covariates including disease stage, receipt of previous treatment and presence or absence of the V50M mutation. The MMRM model also included effects of treatment, time (categorical), disease stage, V50M mutation, previous treatment, treatment-by-time interaction, baseline TTR value and baseline-by-time interaction.[4]
- In the MMRM model, all available post-baseline assessments up to the Week 65/Week 66 endpoints during the treatment period for patients in the FAS were utilised. Endpoint treatment differences were derived via modelling of the within subject correlation structure and were adjusted to account for missing data. Missing data were not explicitly imputed. The normality assumptions for the MMRM model were formally tested using a Shapiro-Wilks test at the 0.01 significance level and assessed by inspection of plots. If the Shapiro-Wilks test assessing normality of the MMRM residuals was statistically significant at the 0.01 level, a stratified Wilcoxon Rank Sum Test was planned to be provided.[52]
- Multiple sensitivity analyses were conducted on the FAS for each co-primary endpoint at the final analysis. A sensitivity analysis, repeating the primary efficacy analysis, was conducted using the PPS.[52] Additional detail of all sensitivity analyses can be found in the CSR, presented as part of the reference pack for this submission.

Figure 3: Hierarchical testing flow for NEURO-TTRansform interim and final analysis

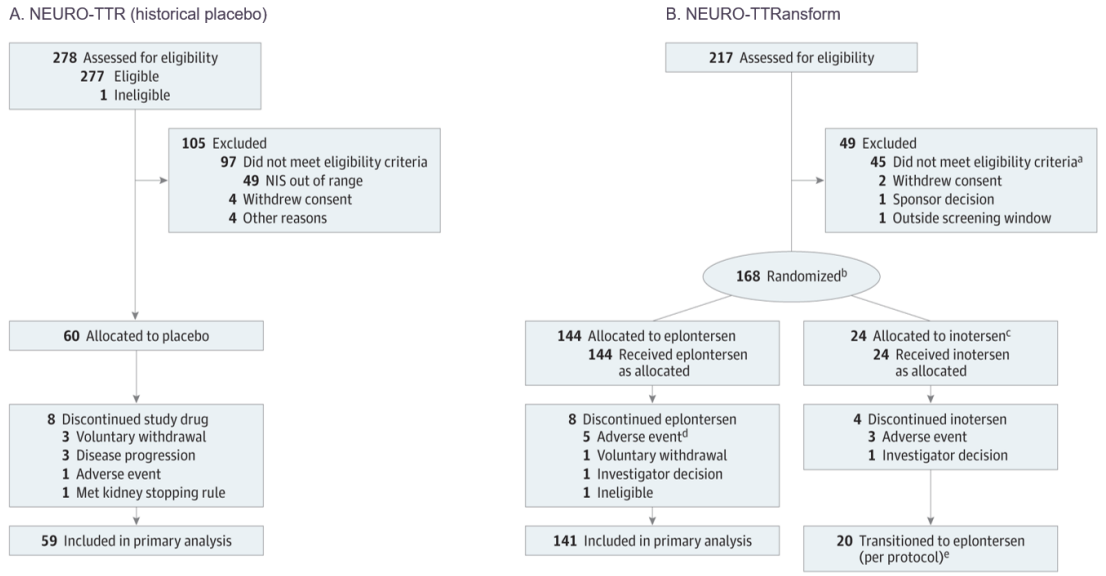


Footnotes: Dashed lines/grey boxes indicate that path was not taken based on the interim outcomes measured at Week 35. Purple boxes indicate statistical hierarchical testing route that was taken. Week 35 interim analyses showed significant outcomes for both TTR and mNIS+7.
Abbreviations: mNIS+7: modified Neuropathy Impairment Score +7; QoL-DN: Quality of Life-Diabetic Neuropathy; TTR: transthyretin.
Source: Coelho 2023[53]

B.3.4.3 Participant flow in the relevant randomised controlled trials

The participant flow in NEURO-TTRansform and NEURO-TTR is summarised in Figure 4.

Figure 4: Patient disposition in NEURO-TTR and NEURO-TTRansform



Abbreviations: NIS: Neuropathy Impairment Score.
Source: Coelho 2023[53]

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 11. Quality assessments of pivotal RCTs included in the clinical SLR assessed using the York CRD checklist[62]

Risk of bias and rationale							
Study	**Was randomisation carried out appropriately?**	**Was the concealment of treatment allocation adequate?**	**Were the groups similar at the outset of the study in terms of prognostic factors?**	**Were the care providers, participants, and outcome assessors blind to treatment allocation?**	**Were there any unexpected imbalances in drop-outs between groups?**	**Is there any evidence to suggest that the authors measured more outcomes than they reported?**	**Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**
NEURO-TTRansform, Coelho 2023	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
	Patients were randomly assigned 6:1 with a blocking schema (block size of 7) to open-label treatment with eplontersen or inotersen. Randomisation was facilitated using an interactive voice/web-response system (IxRS; Almac).	Treatment was not concealed; this was an open-label study with two treatments and an external placebo comparator.	The eplontersen and placebo groups were generally well balanced across baseline characteristics. Patients in the eplontersen group were slightly younger, had less severe disease, were more likely to have received previous treatment with stabilisers, and were more	Serum vitamin A levels were available to NEURO-TTRansform investigators (eplontersen group) but were blinded per protocol in NEURO-TTR (historical placebo group) to avoid unmasking the double-blind treatment	Unexpected imbalances in dropouts were not observed	Reported results matched the outcomes reported in methodological documents.	An intention-to-treat analysis was not included. The efficacy analysis population included all patients who received at least 1 dose of trial medication (eplontersen or historical placebo) and who had a baseline and at

Risk of bias and rationale							
Study	**Was randomisation carried out appropriately?**	**Was the concealment of treatment allocation adequate?**	**Were the groups similar at the outset of the study in terms of prognostic factors?**	**Were the care providers, participants, and outcome assessors blind to treatment allocation?**	**Were there any unexpected imbalances in drop-outs between groups?**	**Is there any evidence to suggest that the authors measured more outcomes than they reported?**	**Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**
			likely to have the V50M variant than those in placebo.	groups in the NEURO-TTR study.			least 1 post baseline mNIS+7 or Norfolk QoL-DN assessment. The safety analysis population included all patients who received at least 1 dose of trial medication (eplontersen or historical placebo).

Abbreviations: CRD: Centre for Reviews and Dissemination; IxRS: interactive voice/web response system; mNIS+7: modified neuropathy impairment score+7; QoL-DN: quality of life-diabetic neuropathy; RCT: randomised controlled trial; SLR: systematic literature review.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 Primary efficacy outcomes

Serum Transthyretin Concentration

In NEURO-TTRansform, serum TTR was measured to assess the change in circulating TTR protein. Eplontersen silences TTR gene expression in liver hepatocytes, leading to a reduction in TTR protein synthesis. Therefore, it is anticipated that serum TTR levels will decrease after treatment with eplontersen.[53]

In NEURO-TTRansform and NEURO-TTR, serum TTR concentrations were measured before study drug dosing and CfB was calculated.[12, 53] Serum TTR concentration was quantified using different assays in NEURO-TTRansform and NEURO-TTR. Therefore, to allow for cross-assay comparisons to be conducted across the two studies, serum TTR concentrations from NEURO-TTR were adjusted.[53]

The co-primary endpoint of percent CfB in serum TTR at Week 35 and Week 65 was met. At the Week 35 interim analysis, eplontersen was superior to the external placebo in reducing serum TTR concentration (Table 12). The difference in least squares mean (LSM) percent CfB in serum TTR between the NEURO-TTRansform eplontersen group and NEURO-TTR external placebo group was statistically significant, favouring eplontersen (-66.4%, 95% confidence interval [CI]: -71.4%, -61.5%; p<0.001).[52]

Table 12: Percent CfB in serum TTR concentration at Week 35 interim analysis[a]

	Eplontersen (n=140)	External Placebo (n=59)
n[b]	136	57
LSM % CfB (95% CI)	-81.2 (-84.6, -77.8)	-14.8 (-18.7, -10.8)
Difference (95% CI)	-66.4 (-71.4, -61.5)	
p-value	<0.001	

Footnote: [a]Prespecified interim analysis was performed when all patients in NEURO-TTRansform had completed the Week 35 assessments. Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; TTR: transthyretin.
Source: Coelho 2023[53]

At Week 65, the effect on serum TTR concentrations was maintained (Table 13). Eplontersen treatment resulted in LSM percent CfB in serum TTR concentration of -81.7% (95% CI: -84.8%, -78.5%) at Week 65. In comparison, a reduction of only -11.2% (95% CI: -15.1%, -7.4%) was observed for the external placebo group.[52, 53] The reduction in TTR observed in the placebo group may be explained by the association between declining TTR concentrations and malnutrition, as Figure 10 shows, the placebo group experienced a decrease in mBMI levels which indicates a decline in nutritional status.[63, 64]

The LSM difference in serum TTR between the eplontersen and external placebo groups at Week 65 was -70.4% (95% CI: -75.2%, -65.7%; p<0.001).[53]

The results for all sensitivity analyses, including the missing data and PPS analyses, were consistent with the primary analyses.[52] As shown in Figure 5, a notable reduction in serum TTR concentration was evident in eplontersen-treated patients by Week 5, the earliest timepoint at which TTR was measured.[53]

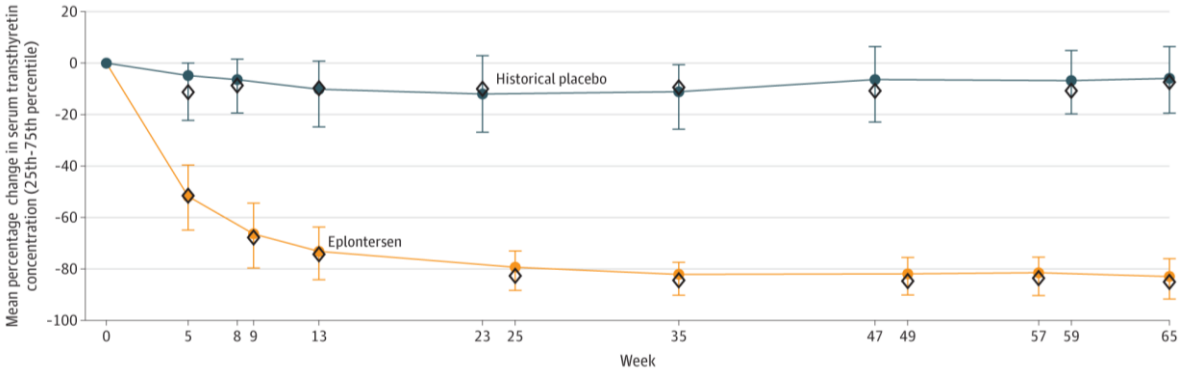
Results from Week 85 are presented in Appendix M.

Table 13: Percent CfB in serum TTR concentration at Week 65[a]

	Eplontersen (n=141)	External Placebo (n=59)
n[b]	135	51
LSM % CfB (95% CI)	-81.7 (-84.8, -78.5)	-11.2 (-15.1, -7.4)
Difference (95% CI)	-70.4 (-75.2, -65.7)	
p-value	<0.001	

Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; TTR: transthyretin.
Source: Coelho 2023[53] and AstraZeneca Data on File. 2022.[52]

Figure 5: CfB in percent change of serum TTR concentration to Week 65



Abbreviations: CfB: change from baseline; TTR: transthyretin.
Footnotes: Unadjusted means (filled circles), medians (open diamonds), and first and third quartiles (lower and upper ends of whiskers) for percentage changes from baseline in serum transthyretin concentration at each study visit.
Source: Coelho 2023[53]

Modified Neuropathy Impairment Score +7

The mNIS+7 scale was designed specifically to measure polyneuropathy progression in ATTRv-PN patients. The scale was adapted from the Neuropathy Impairment Score (NIS) scale and includes additional assessments that better quantify neuropathic impairment, it consists of the following components:[53, 65]

- NIS components (maximum of 244 points)
    - Motor strength/weakness (0 to 192 points)
    - Reflexes (0 to 20 points)
    - Sensation (0 to 32 points)

- Change in heart rate with deep breathing (HRdb) to assess autonomic function (-3.7 to 3.7 points)
- NCS, determined by measuring the function of small- and large-nerve fibres (-18.6 to 18.6 points)
- Standardised quantitative sensory testing (QST; investigating heat pain and touch pressure at multiple body sites; 0 to 80 points)

The mNIS+7 scale ranges from -22.3 to 346.3, with higher scores indicating poorer function. In NEURO-TTRansform, CfB in mNIS+7$_{ionis}$ score was measured to detect progression or improvement in polyneuropathy.

The co-primary endpoint CfB in mNIS+7 composite score at Week 35 and Week 66 was met.[53]

At Week 35, eplontersen was superior to the external placebo in improving the mNIS+7 score at Week 35 (Table 14). At Week 35, the difference in LSM CfB in mNIS+7 composite score was statistically significant, in favour of eplontersen (-9.01, 95% CI: -13.5, -4.5; p<0.001).[53]

Table 14: CfB in mNIS+7 at Week 35 Interim Analysis[a]

	Eplontersen (n=140)	External Placebo (n=59)
n[b]	140	59
LSM CfB (95% CI)	0.22 (-3.5, 3.9)	9.22 (5.5, 12.9)
Difference (95% CI)	-9.01 (-13.5, -4.5)	
p-value	<0.001	

Footnote: [a]Prespecified interim analysis was performed when all patients in NEURO-TTRansform had completed the Week 35 assessments. Analysis based on ANCOVA model adjusted by propensity score with the effects of treatment, disease stage, V50M mutation, previous treatment, and the baseline value. [b]Participants with missing mNIS+7 data at Week 35 had values imputed using an imputation model (based on Missing at Random assumption).
Abbreviations: ANCOVA: analysis of covariance; CfB: change from baseline; CI: confidence interval; LSM: least squares mean; mNIS+7: modified Neuropathy Impairment Score.
Source: Coelho 2023[53]

The effect on mNIS+7 was maintained at Week 66 (Table 15). At the Week 66 final analysis, the LSM CfB was 0.3 (95% CI: -4.5, 5.1) for the eplontersen group, and 25.1 (95% CI: 20.2, 29.9) for the external placebo group.[53] The LSM difference between eplontersen and the external placebo was -24.8 (95% CI: -31.0, -18.6; p<0.001).[53] As shown in Figure 6, the LSM mNIS+7 score remained stable over time for the eplontersen group but had increased for the external placebo group, indicating disease progression.[53] Results of all sensitivity analyses, including the missing data and PPS analyses, were consistent with the primary Week 66 final analysis.[52]

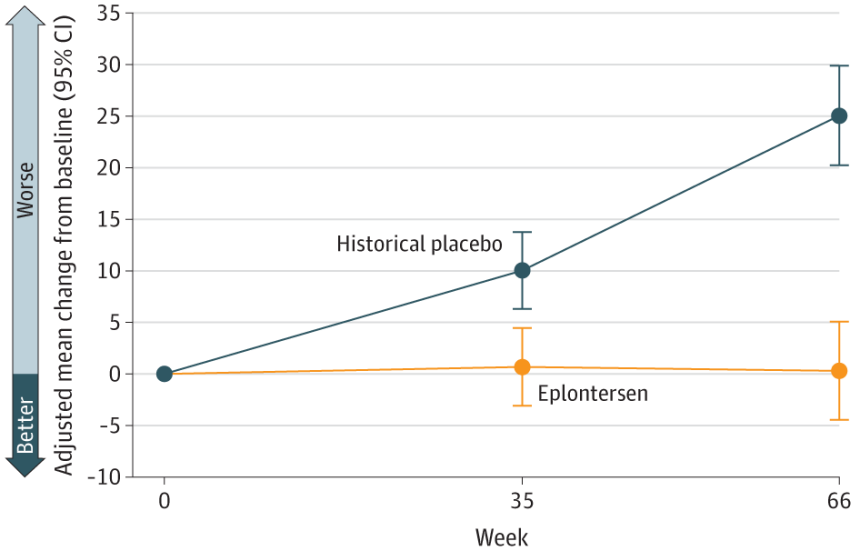
Results for Week 85 are presented in Appendix M.

Table 15: CfB in mNIS+7 at Week 66[a]

	Eplontersen (n=141)	External Placebo (n=59)
n[b]	128	52
LSM CfB (95% CI)	0.3 (-4.5, 5.1)	25.1 (20.2, 29.9)
Difference (95% CI)	-24.8 (-31.0, -18.6)	
p-value	<0.001	

Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; mNIS+7: modified Neuropathy Impairment Score.
Source: Coelho 2023[53]

Figure 6: CfB in mNIS+7 composite score to Week 66

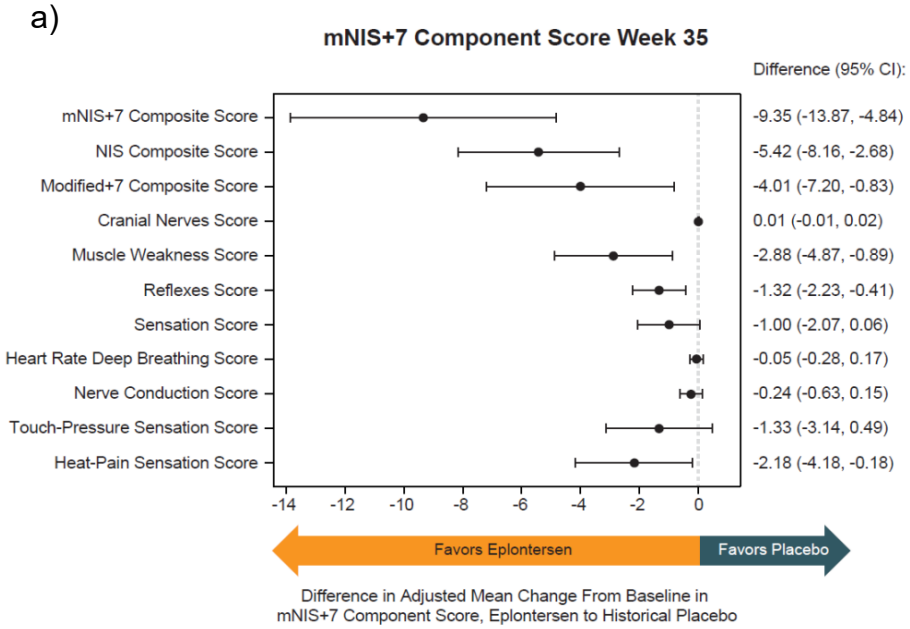


Footnotes: CfB (LSMs [filled circles] and 95% CIs [lower and upper ends of whiskers]) in the mNIS+7 composite score, which range from −22.3 to 346.3, with higher scores indicating poorer function (decrease in score indicates improvement).
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; mNIS+7: modified Neuropathy Impairment Score.
Source: Coelho 2023[53]

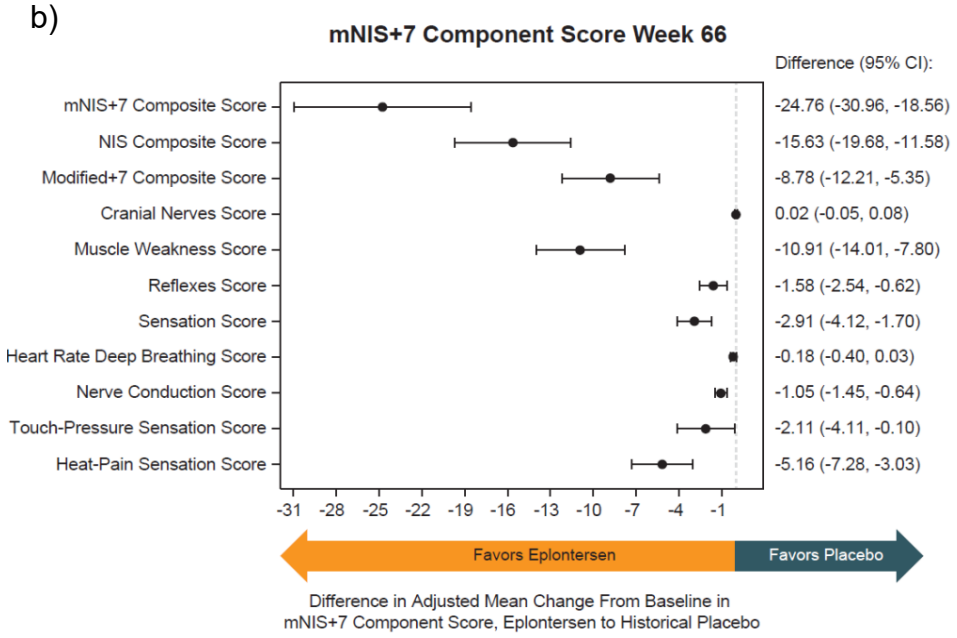
The treatment effect for eplontersen versus placebo was directionally consistent across all of the mNIS+7 component scores at Week 35 and Week 66 (Figure 7), with the LSM difference between the eplontersen and the external placebo groups greatest for CfB in the muscle weakness score at Week 66 (-10.9, 95% CI: -14.0, -7.8; p<0.001).[52, 53]

Figure 7: Treatment effect on mNIS+7 component scores at Week 35 (a) and Week 66 (b)

a)



b)



Footnotes: Difference in LSMs, CIs, and p-values are based on an MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, and disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.
Abbreviations: CI: confidence interval; MMRM: mixed-effects model with repeated measures; mNIS+7: modified Neuropathy Impairment Score; NIS: Neuropathy Impairment Score.
Source: Coelho 2023[53]

Norfolk Quality of Life Questionnaire-Diabetic Neuropathy

The Norfolk QoL-DN Questionnaire is a validated quality of life (QoL) instrument, validated to measure QoL for patients with neuropathy. Scores range from minus four to 136, with a higher score indicating poorer QoL.[53]

CfB in Norfolk QoL-DN was a key secondary endpoint at Week 35 and a co-primary endpoint at Week 66. The difference in LSM CfB between the eplontersen and placebo groups was statistically significant at both timepoints, in favour of eplontersen.[53]

At the Week 35 interim analysis (secondary endpoint), treatment with eplontersen resulted in an improvement in patient QoL, as indicated by a decrease in the Norfolk QoL-DN total score (Table 16). The difference in LSM CfB in Norfolk QoL-DN between the eplontersen group and external placebo group was -11.8 (95% CI: -16.8, -6.8; p<0.001), in favour of eplontersen.[53]

Table 16: CfB in Norfolk QoL-DN total score at Week 35 Interim Analysis[a]

	Eplontersen (n=140)	External Placebo (n=59)
n[b]	133	58
LSM CfB (95% CI)	-3.1 (-7.2, 1.0)	8.7 (4.5, 12.8)
Difference (95% CI)	-11.8 (-16.8, -6.8)	
p-value	<0.001	

Footnote: [a]Prespecified interim analysis was performed when all patients in NEURO-TTRansform had completed the Week 35 assessments. Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Participants with missing mNIS+7 data at Week 35 had values imputed using an imputation model (based on Missing at Random assumption.
Abbreviations: CfB: change from baseline; CI: confidence interval; MMRM: mixed-effects model with repeated measures; QoL-DN: Quality of Life Questionnaire-Diabetic Neuropathy.
Source: Coelho 2023[53]

Eplontersen was also superior to the external placebo in improving the Norfolk QoL-DN from baseline at Week 66 (primary endpoint) (Table 17). At Week 66, eplontersen treatment resulted in a LSM CfB of -5.5 (95% CI: -10.0, -1.0) in Norfolk QoL-DN total score. An increase of 14.2 (95% CI: 9.5, 19.0) was observed for the placebo group.[53]

The LSM difference between the eplontersen and external placebo group was -19.7 (95% CI: -25.6, -13.8; p<0.001) at Week 65.[53] Results of all sensitivity analyses, including missing data and PPS analyses, of CfB in Norfolk QoL-DN total score, were consistent with the primary analysis.[52]

Table 17: CfB in Norfolk QoL-DN total score at Week 66[a]

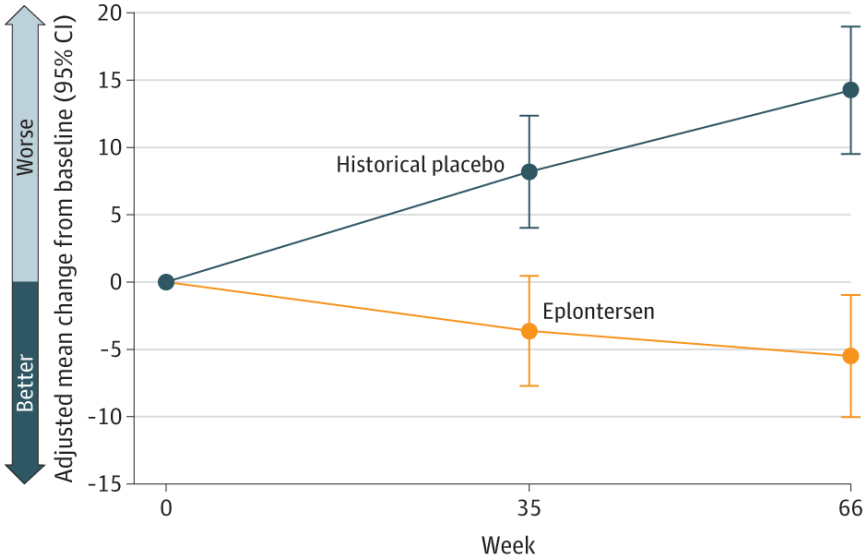
	Eplontersen (n=141)	External Placebo (n=59)
n[b]	128	52
LSM CfB (95% CI)	-5.5 (-10.0, -1.0)	14.2 (9.5, 19.0)
Difference (95% CI)	-19.7 (-25.6, -13.8)	
p-value	<0.001	

Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; QoL-DN: Quality of Life Questionnaire-Diabetic Neuropathy.
Source: Coelho 2023[53] and AstraZeneca Data on File. 2022[52]

Eplontersen improved patient QoL over time, as indicated by the decrease in mean Norfolk-QoL DN score from baseline to Week 66, whilst QoL worsened over time for the external placebo group (Figure 8).[53]

Results for Week 85 are presented in Appendix M.

Figure 8: CfB in Norfolk QoL-DN total score to Week 66



Footnotes: Changes from baseline (LSMs [filled circles] and 95% Cis [lower and upper ends of whiskers]) in Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN) total score, which range from −4 to 136, with higher scores indicative of poorer quality of life (decrease in score indicates improvement).
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; QoL-DN: Quality of Life-Diabetic Neuropathy.
Source: Coelho 2023.[53]

B.3.6.2 Secondary efficacy outcomes

Polyneuropathy Disability Score

The Polyneuropathy Disability (PND) Score measures mobility and is used to categorise patients with ATTRv-PN according to their level of functional impairment, a higher score indicates greater functional impairment. CfB in PND score was formally tested as a secondary endpoint. At Week 65, eplontersen was superior to the external placebo for CfB in PND score. Eplontersen resulted in an LSM CfB of [redacted] at Week 65, compared with [redacted] in the external placebo group. The difference in LSM CfB in PND score was [redacted] p<0.05) (Table 18).[52, 53] Results for the non-parametric and PPS sensitivity analyses were consistent with the primary Week 66 final analysis.[52]

Table 18: CfB in PND score at Week 65[a]

	Eplontersen (n=141)	External Placebo (n=59)
n[b]	134	51
LSM CfB (95% CI)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
p-value	<0.05	

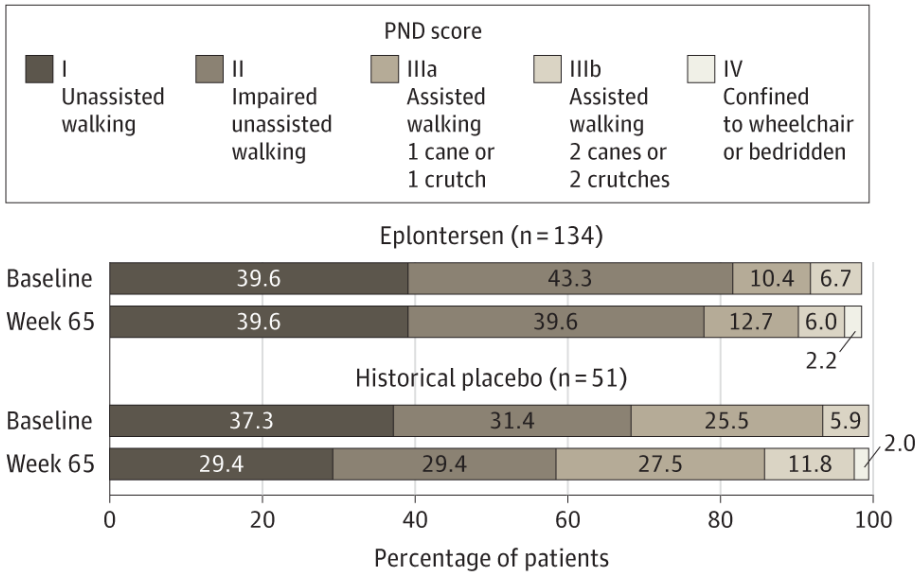
Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; PND: polyneuropathy disability.
Source: Coelho 2023[53] and AstraZeneca Data on File. 2022.[52]

The proportion of patients who could walk without assistance (PND score I) was unchanged from baseline at Week 65 (39.6% at both time points) in the eplontersen group (Figure 9). In the placebo group, 37.3% of patients had a PND score I at baseline, however this decreased to 29.4% at Week 65. The proportion of patients with a PND score of IIIb decreased from 6.7% at baseline to 6.0% at baseline in the eplontersen group but increased from 5.9% to 11.8% in the placebo group.[53]

Whilst the majority of patients remained in the same PND stage at Week 65 compared with baseline, more patients in the eplontersen group showed an improvement in PND score ([redacted]) compared with the external placebo group ([redacted]).[52]

Results for Week 85 are presented in Appendix M.

Figure 9: Proportion of patients with improved, no change or worsened PND scores compared with baseline to Week 65



Footnotes: Percentages are for patients with both baseline and Week 65 values.
Abbreviations: PND: polyneuropathy disability.
Source: Coelho 2023[53]

Modified Body Mass Index

Patients with ATTRv-PN can be affected by unintended weight loss and muscle wasting (cachexia and sarcopenia, respectively), and low serum albumin levels.[66, 67] Due to the high body mass index (BMI) values observed in oedematous malnourished patients as a result of low serum albumin, BMI is an unsuitable measurement for patients with ATTRv-PN.[66] To address these limitations, mBMI adjusts for low serum albumin, with higher scores indicating better nutritional status. mBMI is calculated by multiplying conventional BMI (kg/m^2) by serum albumin level (g/L).[66]

The key secondary endpoint CfB in mBMI at Week 65 was met.[53] At Week 65, the LSM CfB was -8.1 (95% CI: -28.6, 12.4) in the eplontersen group, compared with -90.8 (95% CI: -112.8, -68.7) in the external placebo group (Table 19). The difference in CfB was 82.7 (95% CI: 54.6, 110.8; p<0.001), in favour of eplontersen.[53] Results for both the non-parametric and PPS sensitivity analyses were consistent with the primary Week 66 Final analysis.[52]

Table 19: CfB in mBMI (kg/m2 x g/L) at Week 65[a]

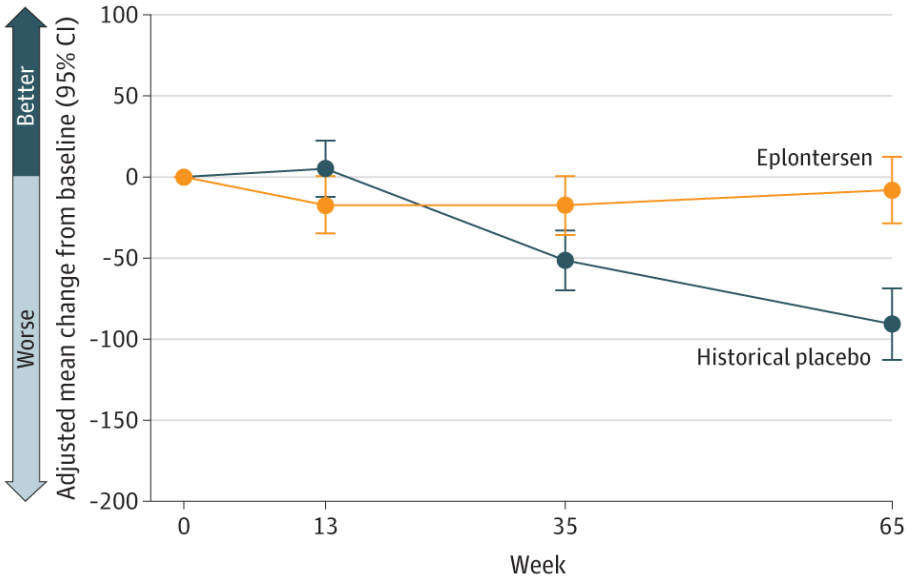
	Eplontersen (n=141)	External Placebo (n=59)
n[b]	130	49
LSM CfB (95% CI)	-8.1 (-28.6, 12.4)	-90.8 (-112.8, -68.7)
Difference (95% CI)	82.7 (54.6, 110.8)	
p-value	<0.001	

Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; mBMI: modified body mass index; MMRM: mixed-effects model with repeated measures.
Source: Coelho 2023[53]

Overall, LSM CfB mBMI remained fairly stable from baseline to Week 65 in the eplontersen group, whilst a decrease from Week 13 to Week 65 was observed in the external placebo group, indicating a decline in nutritional status (Figure 10).[53] This decline in nutritional status may explain the reduction in serum TTR concentration (Figure 5) seen in the external placebo group, given the association between malnutrition and low TTR concentrations.[64]

Results for Week 85 are presented in Appendix M.

Figure 10: CfB in mBMI (nutritional status) to Week 65



Abbreviations: CfB: change from baseline; CI: confidence interval; mBMI: modified body mass index.
Source: Coelho 2023[53]

36-Item Short Form Survey Physical Component Summary Score

The 36-Item short form (SF-36) is a QoL instrument consisting of eight multi-item scales, which can be aggregated into two summary scores: the Physical (PCS) and Mental (MCS) Component Summary scores. Scores range from zero to 100, with a higher score indicating greater QoL.[68]

The key secondary outcome CfB in the SF-36 PCS score at the final analysis (Week 65) was met.[53]

At Week 65, eplontersen treatment resulted in a LSM CfB of 0.9 (95% CI: -0.7, 2.4), indicating an improvement in QoL. By contrast, patients in the external placebo group experienced a decline in QoL, as indicated by a LSM CfB of -4.5 (95% CI: -6.1, -2.8) (Table 20). The LSM difference between treatment groups was 5.3 (95% CI: 3.2, 7.4; p<0.001), in favour of eplontersen.[53] Results for both the non-parametric and PPS sensitivity analyses were consistent with the primary Week 65 analysis.[52]

Table 20: CfB in SF-36 PCS score at Week 65[a]

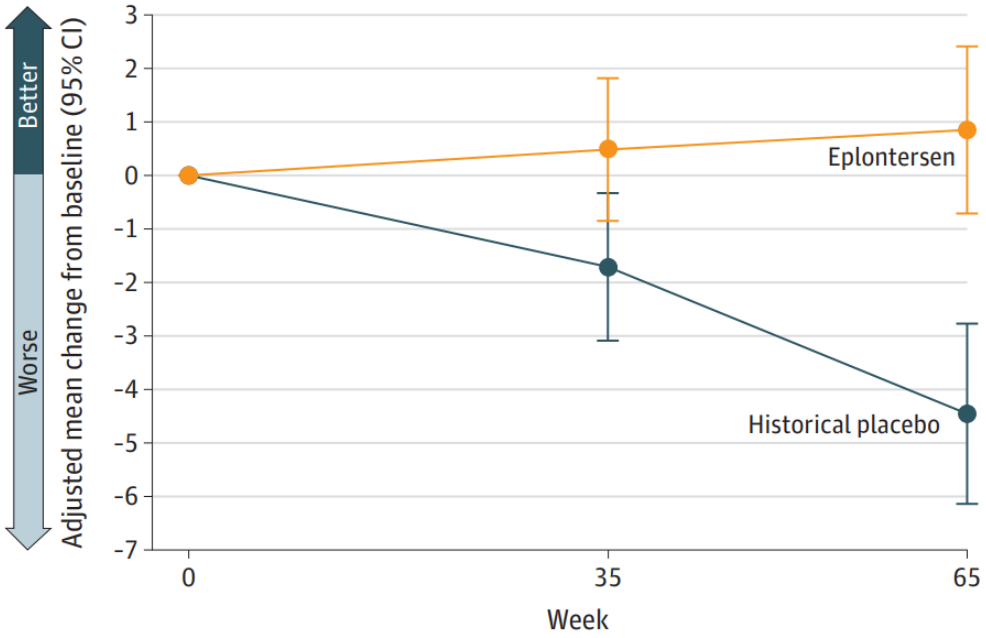
	Eplontersen (n=141)	External Placebo (n=59)
n[b]	136	50
LSM CfB (95% CI)	0.9 (-0.7, 2.4)	-4.5 (-6.1, -2.8)
Difference (95% CI)	5.3 (3.2, 7.4)	
p-value	<0.001	

Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; SF-36 PCS: 36-Item Short Form Survey Physical Component Summary.
Source: Coelho 2023[53]

The difference in LSM CfB SF-36 PCS score between the external placebo and eplontersen groups increased from Week 35 to Week 65. Although this was primarily driven by the continuous decrease in the external placebo group, a small but continuous increase was observed in the eplontersen group, indicating improvement over time (Figure 11).[53]

Results for Week 85 are presented in Appendix M.

Figure 11: CfB in SF-36 PCS score to Week 65



Abbreviations: CfB: change from baseline; CI: confidence interval; PCS: physical component summary; SF-36; 36-Item Short Form.
Source: Coelho 2023[53]

Neuropathy Symptoms and Change Score

The Neuropathy Symptoms and Change (NSC) questionnaire quantifies patients' neuropathy by considering the type, distribution and severity of muscle weakness, sensory symptoms, pain symptoms and autonomic symptoms. NSC scores range from zero to 114 (men) or 108 (women), with a higher score indicating worse symptoms.[69]

The key secondary endpoint CfB in NSC total score at the Week 66 final analysis were both met.[53] Results for both the non-parametric and PPS sensitivity analyses were consistent with the primary Week 66 final analysis.[52]

At Week 66, eplontersen treatment resulted in a LSM CfB of -0.03 (95% CI: -1.9, 1.9), with a reduction in score indicating improvement in symptoms. The LSM difference at Week 66 was statistically significant difference between the eplontersen and external placebo group (-8.2; 95% CI: -10.7, -5.8; p<0.001) (Table 21).[53]

Whilst there was little change in mean NSC score for the eplontersen group from baseline to Week 35 (0.8) and Week 66 (-0.03), an increase in mean NSC score was observed at both time points in the placebo group (4.7 at Week 35; 8.2 at Week 66) (Figure 12).[53] Results for Week 85 are presented in Appendix M.

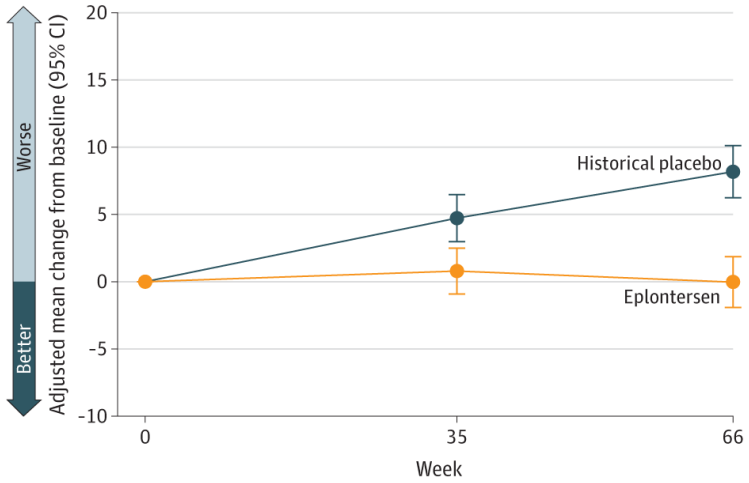
Table 21: CfB in NSC total score at Week 66[a]

	Eplontersen (n=141)	External Placebo (n=59)
n[b]	132	52
LSM CfB (95% CI)	-0.03 (-1.9, 1.9)	8.2 (6.2, 10.1)
Difference (95% CI)	-8.2 (-10.7, -5.8)	

	Eplontersen (n=141)	External Placebo (n=59)
p-value	<0.001	

Footnote: [a]Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. [b]Number of patients with non-missing data at the time point.
Abbreviations: CfB: change from baseline; CI: confidence interval; LSM: least squares mean; MMRM: mixed-effects model with repeated measures; NSC: neuropathy symptom and change.
Source: Coelho 2023[53]

Figure 12: CfB in NSC total score to Week 66

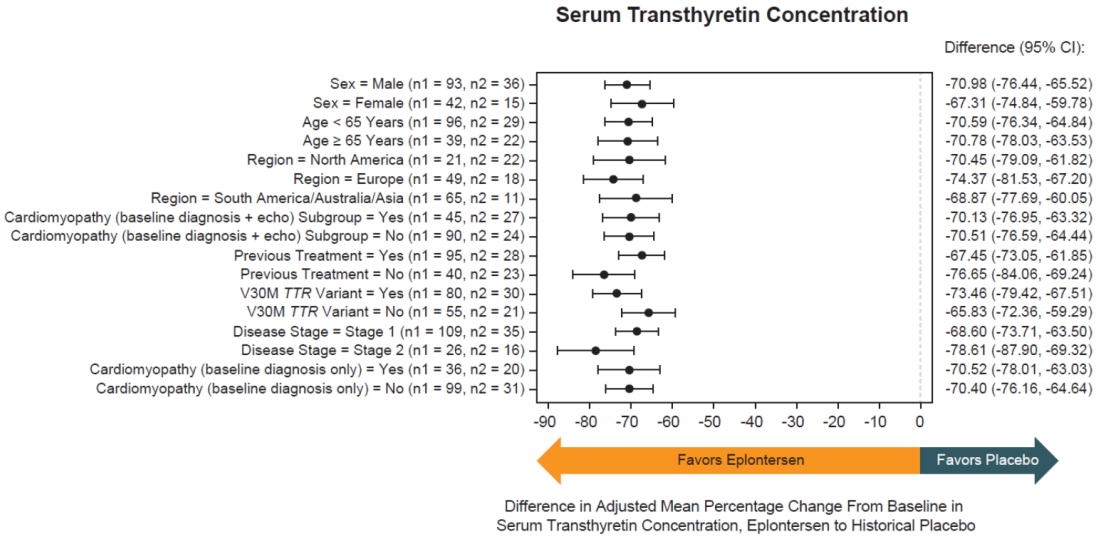


Footnotes: [a]Change from baseline in NSC total score at week 35 was also assessed in the final analysis (difference between eplontersen and historical placebo at week 35: −3.9 [95% CI, −6.1 to −1.8; P < .001]).
Abbreviations: CfB: change from baseline; CI: confidence interval; NSC: Neuropathy Symptoms and Change.
Source: Coelho 2023[53]

B.3.7 Subgroup analysis

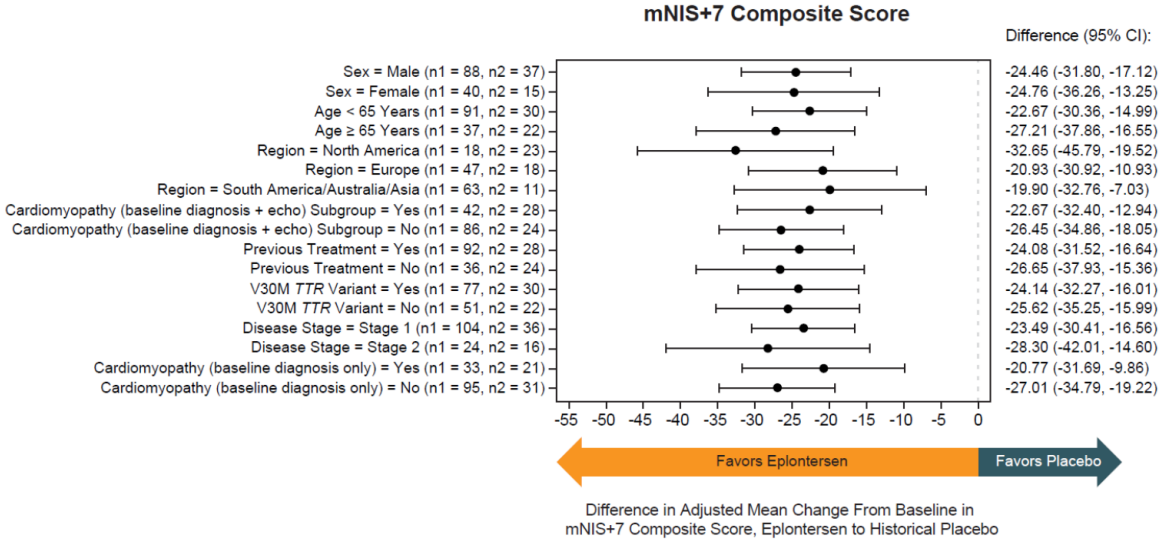
Subgroup analyses were conducted for serum TTR, mNIS+7 and Norfolk QoL-DN endpoints to test the impact of differences in patient demographics and disease characteristics.[52] All endpoints were examined for 19 subgroups.[53] Treatment effects on percent CfB in serum TTR, and CfB in mNIS+7 score and Norfolk QoL-DN score by subgroup are presented in Figure 13, Figure 14 and Figure 15, respectively. For all primary efficacy end points, a consistent treatment effect was demonstrated across pre-specified subgroups at Week 65/66.[53]

Figure 13: Treatment effect on percent CfB in serum TTR concentration for eplontersen vs placebo at Week 65



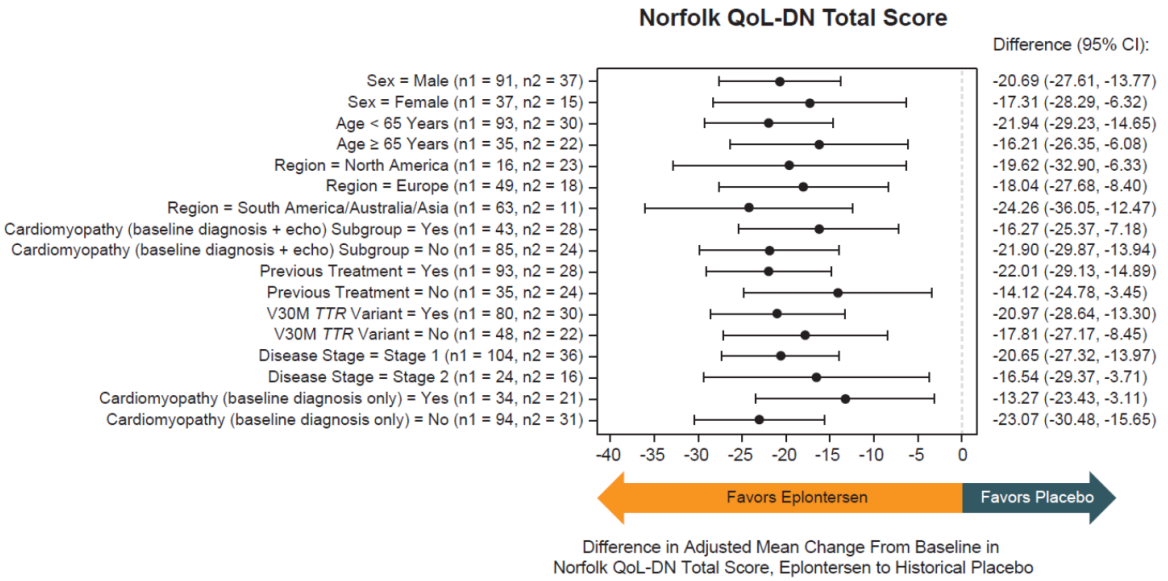
Footnotes: Subgroup analysis based on the MMRM adjusted by propensity score weights. The model included fixed categorical effects for treatment, time, disease stage, V50M variant, and previous treatment; treatment × time interaction; treatment × subgroup interaction; and treatment × time × subgroup interaction. The baseline value of the endpoint and the baseline × time interaction were included as covariates in the model. There were 2 cardiomyopathy subgroups with different definitions. The cardiomyopathy baseline diagnosis–only subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form. The cardiomyopathy baseline diagnosis plus echocardiography subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form (ie, the cardiomyopathy baseline diagnosis–only subgroup) or interventricular septum thickness 13 mm or greater on baseline echocardiogram plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of 150 mm Hg or greater at any time during the trial (including screening and baseline visits).
Abbreviations: CfB: change from baseline; CI: confidence interval; echo: echocardiography; n1: number of patients in eplontersen group; n2: number of patients in external placebo group; TTR: transthyretin.
Source: Coelho 2023[53]

Figure 14: Treatment effect on CfB in mNIS+7 for eplontersen vs placebo at Week 66



Footnotes: Subgroup analysis based on the MMRM adjusted by propensity score weights. The model included fixed categorical effects for treatment, time, disease stage, V50M variant, and previous treatment; treatment × time interaction; treatment × subgroup interaction; and treatment × time × subgroup interaction. The baseline value of the endpoint and the baseline × time interaction were included as covariates in the model. There were 2 cardiomyopathy subgroups with different definitions. The cardiomyopathy baseline diagnosis–only subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form. The cardiomyopathy baseline diagnosis plus echocardiography subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form (ie, the cardiomyopathy baseline diagnosis–only subgroup) or interventricular septum thickness 13 mm or greater on baseline echocardiogram plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of 150 mm Hg or greater at any time during the trial (including screening and baseline visits).
Abbreviations: CfB: change from baseline; CI: confidence interval; echo: echocardiography; mNIS+7: modified Neuropathy Impairment Score; n1: number of patients in eplontersen group; n2: number of patients in external placebo group.
Source: Coelho 2023[53]

Figure 15: Treatment effect on CfB in Norfolk QoL-DN for eplontersen vs placebo at Week 66



Footnotes: Subgroup analysis based on the MMRM adjusted by propensity score weights. The model included fixed categorical effects for treatment, time, disease stage, V50M variant, and previous treatment; treatment × time interaction; treatment × subgroup interaction; and treatment × time × subgroup interaction. The baseline value of the endpoint and the baseline × time interaction were included as covariates in the model. There were 2 cardiomyopathy subgroups with different definitions. The cardiomyopathy baseline diagnosis–only subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form. The cardiomyopathy baseline diagnosis plus echocardiography subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form (ie, the cardiomyopathy baseline diagnosis–only subgroup) or interventricular septum thickness 13 mm or greater on baseline echocardiogram plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of 150 mm Hg or greater at any time during the trial (including screening and baseline visits).
Abbreviations: CfB: change from baseline; CI: confidence interval; echo: echocardiography; n1: number of patients in eplontersen group; n2: number of patients in external placebo group QoL-DN: Quality of Life-Diabetic Neuropathy.
Source: Coelho 2023[53]

B.3.8 Meta-analysis

The NEURO-TTRansform trial is the only relevant trial for eplontersen in this indication. As such, a meta-analysis is not considered applicable for this appraisal.

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Methodology of the indirect treatment comparison

As previously highlighted in Section B.1.3.5, vutrisiran is the only treatment that is both established and used substantially in clinical practice for the treatment of patients with ATTRv-PN in England. As such, it is the only relevant comparator to eplontersen in this submission.[1]

An SLR was conducted to identify the most up-to-date, relevant clinical evidence in ATTRv-PN. The SLR was conducted in July 2022 and updated in October 2023. The review identified two relevant Phase 3 clinical trials reporting on data for eplontersen or vutrisiran: NEURO-TTRansform and HELIOS-A, as detailed in Table 22.

Table 22: Trials identified in the SLR

Trial name	Author, year	Cohort size	Intervention	Within-trial control group	External placebo (intervention group)
HELIOS-A (NCT03759379)	Adams 2022[54]	164	Vutrisiran	Patisiran	APOLLO
NEURO-TTRansform[a] (NCT04136184)	Coelho 2023[34, 53]	168	Eplontersen	Inotersen	NEURO-TTR

Footnotes: [a]NEURO-TTRansform (NCT04136184) data was extracted from the study design publication (Coelho 2021)[4] and from preliminary data presented at the XVIII International Symposium on Amyloidosis, Heidelberg, Germany, 04–08 September 2022. The primary NEURO-TTRansform publication, Coelho 2023,[53] had not been published when the indirect treatment comparison was initiated.
Abbreviations: SLR: systematic literature review.

Pairwise Comparison Methods

Initially, a feasibility assessment was conducted to consider the most appropriate type of ITC methodology, considering both Bucher ITCs as well as population-adjustment methods, including matching-adjusted indirect comparisons (MAICs) and simulated treatment comparisons (STCs). Due to differences in the underlying patient characteristics of each trial, population adjustment methods were deemed the most suitable methods for comparing treatments between trials.

The feasibility of both unanchored and anchored comparisons was considered. Unanchored comparisons were considered more suitable than anchored comparisons because unanchored comparisons do not rely on a common control arm. Despite HELIOS-A and NEURO-TTRansform using external placebo arms for comparison, the placebo groups were not considered to be comparable, due to differences in pre-medication. The APOLLO placebo arm (external placebo for HELIOS-A) used pre-medication, consisting of intravenous (IV) dexamethasone (10 mg), oral paracetamol (500 mg), IV H2 blocker, and IV H1 blocker at least 60 minutes prior to each three weekly IV infusion of placebo.[54] Conversely, there was no pre-medication in the NEURO-TTR placebo arm. As per NICE decision support unit (DSU) guidelines, unanchored population adjustments may be used when there is no connected evidence (i.e., if placebo arms cannot be deemed equivalent), or where comparisons involve single-arm studies.[70] As anchored comparisons were not considered to be appropriate, unanchored population-adjustment approaches were considered to represent the most robust ITC methodology.

Based on this, both an unanchored MAIC and an unanchored STC were conducted in order to assess the comparative efficacy of eplontersen versus vutrisiran.

The STCs and MAICs in this submission were undertaken in accordance with the NICE DSU Technical Support Document 18 (TSD18), which outlines the appropriate methodology for population-adjusted ITCs.[70]

As part of the MAIC, individual patient data (IPD) in NEURO-TTRansform were reweighted, such that the summary statistics for baseline characteristics, which are based on weighted data in NEURO-TTRansform, more closely match those reported for HELIOS-A. Comparisons of efficacy, safety and treatment discontinuation outcomes are based on the weighted data to provide treatment effect estimates for eplontersen in the HELIOS-A study population.

B.3.9.2 Indirect treatment comparison for efficacy, safety and treatment discontinuation endpoints

ITCs were conducted for the primary endpoints in the NEURO-TTRansform trial, as well as safety outcomes and treatment discontinuation. Specifically, the following outcomes were considered:

- Serum TTR outcomes, including:
    - Steady-state absolute serum TTR concentration
    - Steady-state absolute CfB in serum TTR concentration
    - Steady-state percent CfB in serum TTR concentration
- CfB in mNIS+7 composite score
- CfB in Norfolk QoL-DN total score
- Serious adverse events (AEs)
- Severe AEs
- Treatment discontinuation

In addition to assessing CfB, responder analyses were conducted for mNIS+7 composite score and Norfolk QoL-DN total score.

The ITC used data from the final analysis timepoint in NEURO-TTRansform and HELIOS-A for the mNIS+7 and Norfolk QoL-DN. For serum TTR outcomes, additional timepoints were included in the ITC analysis in order to estimate the steady state serum TTR. For safety and treatment discontinuation outcomes, data were collected from the full data timepoint of Week 66 and Week 78 for NEURO-TTRansform and HELIOS-A, respectively. The timepoint, alongside the outcomes of interest, are presented in Table 23.

An additional ITC for PND score was considered, however, change in PND score was not recorded in HELIOS-A. Consequently, conducting an ITC for PND score was not feasible.

Efficacy Outcome Endpoints

There are several versions of the mNIS+7 composite score, and the instrument used differed between the trials for eplontersen and vutrisiran. The mNIS+7$_{Ionis}$ was used in the NEURO-TTRansform and NEURO-TTR trials whereas the mNIS+7$_{Alnylam}$ was used in HELIOS-A and APOLLO. This presents a limitation as the scores are not directly comparable; the mNIS+7$_{Ionis}$ has an additional component for sensation that does not exist in the mNIS+7$_{Alnylam,}$ and the mNIS+7$_{Ionis}$ score ranges from -22 to 346 whereas the mNIS+7$_{Alnylam}$ score ranges from zero to 304. Further differences include the ranges of scores for various components, and use of postural blood pressure (BP) as a measure of autonomic impairment in mNIS+7$_{Alnylam}$, rather than HRdb which was used in mNIS+7$_{Ionis}$. The components and score ranges for the mNIS+7$_{Ionis}$ and mNIS+7$_{Alnylam}$ are presented in Appendix D.

As such, composite mNIS+7 scores are unlikely to be a reliable measure for comparison between these trials. To mitigate this, rescoring of the mNIS+7$_{Ionis}$ NCS and HRdb domains was conducted to allow for a better comparison between the two instruments.

In HELIOS-A, the majority of mean differences in continuous endpoints were reported as LSM differences, analysed using a MMRM. The MMRM analysis for outcomes included the baseline value as a covariate, as well as other factors (treatment group, visit timepoint genotype, age of disease onset and baseline NIS score [not included in model for NIS-related outcomes]), and treatment group by visit as an interaction term. The adjustment variables used in the models differ between HELIOS-A and NEURO-TTRansform (adjusted variables described in Section B.3.4.2), meaning the resulting LSMs are not strictly comparable. As such, comparisons between studies may not be true comparisons as “crude” means are not being compared. Despite these limitations, the methodology outlined is considered to present the best approach, given the limitations of the data reported by the HELIOS-A trial.

For the responder analyses, based on the occurrence of an event, the binary endpoint was converted to an odds ratio (OR). Responder analyses were conducted for mNIS+7 and Norfolk QoL-DN, with a patient considered to have responded if their CfB in score was negative. Endpoints were converted to binary measures using zero as the threshold for improvement. Further detail on how the analyses were carried out with respect to each endpoint can be found in Appendix D.

Safety Outcome and Treatment Discontinuation Endpoints

The safety and discontinuation of vutrisiran was assessed in the HELIOS-A clinical trial. Vutrisiran (n=122) was compared to a small patisiran group (n=42) and an external placebo arm (n=77) from the APOLLO trial, in which patisiran was compared to placebo. The outcomes reported in NEURO-TTRansform at the full data timepoint of 66 weeks and in HELIOS-A at the full data timepoint of 78 weeks were severe adverse events, serious adverse events and treatment discontinuation.

Serious and severe AEs were considered as separate outcomes. The definitions of AEs across NEURO-TTRansform and HELIOS-A, described below, were deemed to be comparable between trials:

- **HELIOS-A**: Any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
- **NEURO-TTRansform**: An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product

These endpoints were reported as a binary outcome and were converted to an odds ratio for analysis. Timepoint extrapolation was not possible for binary outcomes due to non-linearity. This represents a limitation of the analysis since the included trials have different durations and rates of discontinuation. Patient population adjustment was possible through a logistic regression model.

Time to discontinuation was not reported in HELIOS-A as a time to event outcome, so cannot be compared versus eplontersen. However, the proportion of patients who had discontinued at the end of the trial was reported, hence this was considered as a binary outcome. As such, this was converted to an odds ratio for analysis. Timepoint extrapolation was not possible due to non-

linearity of this outcome. The timepoint for treatment discontinuation for eplontersen and vutrisiran was Week 66 and Week 78, respectively – these differences in timepoints present a limitation of the analysis. Patient population adjustment was possible through a logistic regression model.

Table 23: Reporting and timepoints (weeks) of outcomes in key trials for full timepoints

Trial	Intervention	Outcome				
		mNIS+7	Norfolk QoL-DN	Steady-state serum TTR	Discontinuation	Adverse events[a]
		Final analysis timepoint				
NEURO-TTRansform	Eplontersen	66	66	Placebo controlled up to Week 65; observed up to Week 85	66	66
HELIOS-A	Vutrisiran	79–80[b]	79–80[b]	Placebo controlled up to Week 78	78	78

Footnotes: [a]Including serious and severe adverse events. [b]In HELIOS-A, the Month 18 timepoint was reported to be equivalent to a range of 79-80 weeks respectively, so the range is included in this table.
Abbreviations: mNIS+7: modified neuropathy impairment score; QoL-DN: quality of life-diabetic neuropathy; TTR, transthyretin.

Missing Data Imputation

The base case imputation method for missing data utilised multiple imputation of mean difference, in line with the methodology utilised in the HELIOS-A trial. Further details of the missing data imputation methods used are described in Appendix D.

Timepoint Adjustment for mNIS+7 and Norfolk QoL Endpoints

NEURO-TTRansform reported the final analysis timepoint in weeks (Week 66). Conversely, HELIOS-A reports in months and provides a time range in weeks; 18 months, with a week range of 79–80.

The applied extrapolation was performed to account for the differences between timepoints. This was compared against a sensitivity analysis without extrapolation to determine any impact of extrapolation on the results. For HELIOS-A, the latest timepoint of this range was used as the target extrapolation point. A linear extrapolation was used as change from baseline in observed mNIS+7 and Norfolk QoL-DN data from NEURO-TTRansform appears linear over time. It was also the view of one of the clinical experts engaged in the ITC study that there will be a continuous decline in mNIS+7 and Norfolk QoL-DN over time, in the absence of treatment, implying that the progression can be approximated by a linear change. Week 85 data from NEURO-TTRansform was available but was not used in the ITC because placebo control data is not available at this timepoint. This means that only observed values are available at the Week 85 timepoint, whereas the unanchored ITC has used adjusted values from an MMRM model. An analysis using the observed Week 85 data from NEURO-TTRansform would have the major limitation that observed values of eplontersen would be compared with adjusted values of vutrisiran, since observed values are not reported for most endpoints.

As such, for the ITCs presented below, the observed data for mNIS+7 and Norfolk QoL-DN from the NEURO-TTRansform trial at Week 65 and Week 66 were extrapolated to estimate the value at Week 80, to allow for comparison against the HELIOS-A data at the same time point. Extrapolation was performed by fitting a linear model to the observed measurements at baseline and at Week 66, then using these models to predict the values at 80 weeks.

Calculating Steady State Serum TTR

A comparison of percent CfB in serum TTR was not considered feasible since percent CfB is not normally distributed and, as such, could not be treated as a continuous variable. Additionally, in major clinical trials, initial drops in serum TTR concentrations are followed by plateaus which indicates that percent CfB in serum TTR does not behave linearly and consequently, extrapolation of serum TTR over time was not appropriate. Finally, it was not considered appropriate to compare a timepoint collected shortly after eplontersen dosing with one taken shortly prior to dosing of vutrisiran, due to the relationship between dosing and serum TTR.

Therefore, steady state serum TTR levels were estimated. Further detail on the calculation of steady state serum TTR levels is available in Appendix D. The steady state period for vutrisiran at Month 18 (from Month 6 to Month 18) does not necessarily correspond to that of eplontersen. Based on the tissue half-life of eplontersen (approximately 16 weeks), and the expectation that steady state is approximately three-times greater than the half-life, NEURO-TTRansform serum TTR measurements from Week 47/49 onwards were considered to be the most appropriate for calculation of eplontersen steady state serum TTR levels.

Treatment Effect Modifiers and Prognostic Factors

Prior to any population adjustment being implemented, a review of prognostic factors (PFs) and treatment effect modifiers (TEMs) was conducted, validated by clinical opinion. PFs predict the outcome of a disease or condition while TEMs influence how well an intervention works in affecting the outcome.[71]

One-to-one consultations were conducted with two clinical experts, from the US and UK, to validate PFs and TEMs obtained from review of pivotal trial publications. The consultations were independent from the clinician interviews conducted specifically to support this submission (previously cited in Section B.1.3). Since the ITC can only adjust for PFs and TEMs that are reported in the pivotal clinical trials for eplontersen and vutrisiran, each clinician was presented with a list of PFs and TEMs reported in NEURO-TTRansform and HELIOS-A (Table 22). The clinicians unanimously confirmed the final list of PFs and TEMs, which are presented in Table 24.

Table 24: Summary of PFs and TEMs

	Age[43]	Sex[34, 72, 73]	Race	Region	Disease stage (PND score)[74]	V50M Mutation[34, 75]	Prior treatment[59]	Cardiac involvement	Outcome at baseline[76, 77]
mNIS+7	✓	✓	✓	✗	✓	✓	✓	✓	✓
Norfolk QoL-DN	✓	✓	✓	✗	✓	✓	✓	✓	✓
Serum TTR	✓	✓	✓	✗	✓	✓	✓	✓	✓
Serious adverse events	✓	✓	✓	✗	✓	✓	✓	✓	✓
Severe adverse events	✓	✓	✓	✗	✓	✓	✓	✓	✓
Treatment discontinuation	✓	✓	✓	✗	✓	✓	✓	✓	✓

✓: variable considered a PF and TEM
✓ variable included as TEM only
✗: variable excluded from the analysis
Abbreviations: mNIS +7: modified neuropathy impairment score; PF: prognostic factor; PND: polyneuropathy disability; QoL-DN: quality of life-diabetic neuropathy; TEM: treatment effect modifier; TTR: transthyretin.

Following this identification step, references were sought via desk research for the support of each of the PFs or TEMs within the list. Desk research provided support for all previously identified factors and an additional factor, region, was identified as a potential PF. No references explicitly confirmed region as a PF, but evidence suggests that region may impact baseline disease score.[54] Therefore, region may be a surrogate variable for another PFs, e.g. race, V50M mutation or previous prescription of medication for ATTRv-PN. As a result, the decision was made to exclude region as a PF on the basis that evidence for its inclusion was not available and that the PFs which might be the reason for inclusion of region in the models have been included as variables in their own right.

Finally, the data from the NEURO-TTR and NEURO-TTRansform trials were used to support the inclusion of the identified PFs and TEMs into the models. Univariate analysis of each of the variables was used to identify which of the variables may be PFs within the patient-level data being used for the analysis (Table 25). All variables which had a p-value of less than 0.2 were considered to be PFs within the data set; 0.2 was chosen as the relatively small sample size means that statistically significant relationships are unlikely to be found at the standard 0.05 threshold. If a variable demonstrated a statistically significant relationship for mNIS+7 or Norfolk QoL-DN, it was deemed to be a PF.

In the univariate analysis, prior treatment and age did not reach the 0.2 p-value threshold and, consequently, did not meet the criteria for inclusion as PFs. Findings from the univariate analysis agreed with clinical reasoning that prior treatment does not affect the risk of disease. However, prior treatment was included in the ITC as a potential TEM as, in the opinion of clinicians, prior treatment could potentially affect subsequent treatment outcomes. Although age was not found to be a statistically significant PF for either outcome, age is known to be a prognostic factor for outcomes of patients with ATTRv-PN, and thus this variable was retained as a potential PF/TEM in the ITC.

All variables identified as PFs were also determined to be TEMs through the SLR, as well as observed differences in HELIOS-A subgroup analysis.

Table 25: Univariate analysis

Variable	mNIS + 7		Norfolk QoL-DN	
	Estimate	P-value	Estimate	P-value
Treatment	-9.81	0.000	-10.38	0.000
Age	0.00	0.960	0.08	0.364
Sex: male	5.42	0.034	0.38	0.898
Race: white	4.14	0.171	-0.88	0.794
Prior treatment	2.43	0.338	1.41	0.629
Genotype: V50M	-0.49	0.838	-3.83	0.160
Cardiac involvement	3.70	0.260	-5.19	0.165
FAP stage: I	-3.64	0.133	-5.42	0.051
Baseline mNIS+7	-0.05	0.103	-	-
Baseline Norfolk QoL-DN	-	-	-0.20	0.000

Abbreviations: FAP: familial amyloidotic polyneuropathy; mNIS + 7: modified neuropathy impairment score; QoL-DN, quality of life-diabetic neuropathy.

The impact of adjustment variable selection was assessed via the inclusion of a reference ITC model and an alternative ITC model for each method and outcome. The reference ITC model adjusted for all PFs and TEMs identified by clinicians (Table 24). The HELIOS-A publications reported all of the adjustment variables identified by clinicians.

The alternative ITC model adjusted for a smaller subset of the clinically-identified PFs and TEMs, formed through stepwise selection based on Akaike information criterion (AIC) (Table 26). Data from the eplontersen arm of NEURO-TTRansform were used to produce the alternative ITC model, which was subsequently used to adjust the NEURO-TTRansform data to HELIO-A aggregate data.

Table 26: Summary of adjustment variables used in reference and alternative models

Outcome	Reference model variables	Alternative model variables	Reference AIC	Alternative AIC
mNIS+7 outcomes				
mNIS+7 composite score	Age, sex, race, disease stage (PND score), V50M mutation, prior treatment, cardiac involvement, mNIS+7 at baseline	Previous treatment, FAP stage, baseline mNIS+7	748	743
mNIS+7 composite score responder analysis		Race, previous treatment, V50M mutation, FAP stage, baseline mNIS+7	175	173
Norfolk QoL-DN outcomes				
Norfolk QoL-DN total score	Age, sex, race, disease stage (PND score), V50M mutation, prior treatment, cardiac involvement, Norfolk QoL-DN score at baseline	Age, sex, baseline Norfolk QoL-DN	808	803
Norfolk QoL-DN total score responder analysis		FAP stage, previous treatment, cardiac involvement, baseline Norfolk QoL-DN	170	166
Steady-state serum TTR outcomes				
Absolute serum TTR at steady state	Age, sex, race, disease stage (PND score), V50M mutation, prior treatment, cardiac involvement, serum TTR concentration at baseline	Sex, V50M mutation, FAP stage, cardiac involvement	835	829
Absolute change from baseline serum TTR at steady state		Sex, V50M mutation, FAP stage, cardiac involvement, serum TTR baseline	835	831
Percentage change from baseline serum TTR at steady state		Sex, V50M mutation, FAP stage, cardiac involvement, serum TTR baseline	616	612
Safety and treatment discontinuation outcomes				

Outcome	Reference model variables	Alternative model variables	Reference AIC	Alternative AIC
Serious adverse events	Age, sex, race, disease stage (PND score), V50M mutation, prior treatment, cardiac involvement	FAP stage	137	132
Severe adverse events		Previous treatment, V50M mutation	106	99
Treatment discontinuation		Age	80	72

Abbreviations: AIC: Akaike Information Criterion; FAP: familial amyloidotic polyneuropathy; mNIS+7: Modified Neuropathy Impairment Score+7; PND: polyneuropathy disability score; QoL-DN: quality of life-diabetic neuropathy; TTR: transthyretin.

For mNIS+7 and Norfolk QoL-DN, both the mean CfB and the response were analysed. For these two measures, the alternative ITC model was estimated separately. This is because the optimal set of predictors for continuous CfB do not need to be the same as the optimal set of predictors for a response (i.e., change of a certain direction and at least a certain magnitude).

B.3.9.3 Indirect treatment comparison results: serum TTR

Mean Absolute Serum TTR at Steady State

The reference adjusted model produces summary statistics (Table 27) that match vutrisiran closely. The alternative model has small differences in age, race and prior treatment as these were the covariates not included in the alternative model.

Table 27: Trial population adjustments for absolute serum TTR concentration. Imputation: multiple imputation of absolute serum TTR concentrations at each measurement timepoint. Time adjustment: none

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative[a] (ESS=[redacted])
Age (mean)	57.80	52.63	[redacted]	[redacted]
Age (SD)	13.20	15.05	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.78	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.59	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.71	[redacted]	[redacted]
FAP I (proportion)	0.70	0.81	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]
Baseline absolute serum TTR (mean)	206.77	[redacted]	[redacted]	[redacted]

Footnotes: [a]Selection of step-wise variables for the absolute serum TTR were based on the Week 65 serum TTR data of the NEURO-TTRansform eplontersen arm.
Abbreviations: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; TTR: transthyretin; SD: standard deviation.

Unanchored MAIC and STC models showed no statistically significant differences between eplontersen and vutrisiran in absolute serum TTR concentration at steady state. The results of the alternative model were consistent with the reference model (Figure 16, Figure 17).

Figure 16: Mean difference in absolute serum TTR concentration (mg/L) at steady state between eplontersen and vutrisiran using unanchored MAIC, for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for sex, V50M mutation, FAP stage and cardiac involvement.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; PF: prognostic factor; STC: simulated treatment comparison; TEM: treatment effect modifier; TTR: transthyretin.

Figure 17: Mean difference in absolute serum TTR concentration (mg/L) at steady state between eplontersen and vutrisiran using unanchored STC, for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for sex, V50M mutation, FAP stage and cardiac involvement.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; PF: prognostic factor; STC: simulated treatment comparison; TEM: treatment effect modifier; TTR: transthyretin.

Mean Absolute Change from Baseline Serum TTR at Steady State

The reference adjusted model produces summary statistics (Table 27) that match vutrisiran closely. The alternative model has small differences in age, race and prior treatment as these were the covariates not included in the alternative model.

Table 28: Trial population adjustments for mean CfB (absolute and percent) serum TTR. Imputation: multiple imputation of absolute serum TTR concentrations at each measurement timepoint. Time adjustment: none

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative[a] (ESS=[redacted])
Age (mean)	57.80	52.48	[redacted]	[redacted]
Age (SD)	13.20	14.98	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.60	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.70	[redacted]	[redacted]
FAP I (proportion)	0.70	0.80	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.17	[redacted]	[redacted]
Baseline serum TTR concentration (mean)	206.77	[redacted]	[redacted]	[redacted]

Footnotes: [a]Selection of step-wise variables for the CfB in serum TTR were based on the Week 65 serum TTR data of the NEURO-TTRansform eplontersen arm.
Abbreviations: ESS: effective sample size; CfB: change from baseline; FAP: familial amyloidotic polyneuropathy; TTR: transthyretin; SD: standard deviation.

Unanchored MAIC and STC models show no statistically significant differences in absolute CfB in serum TTR concentration between treatments at steady state. The results of the alternative model were consistent with the reference model (Figure 18, Figure 19).

Figure 18: Mean difference in absolute CfB serum TTR concentration (mg/dL) at steady state between eplontersen and vutrisiran using unanchored MAIC, for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for sex, V50M mutation, FAP stage, cardiac involvement and baseline serum TTR.
Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; PF: prognostic factors; TEM: treatment effect modifier; TTR: transthyretin.

Figure 19: Mean difference in absolute CfB serum TTR concentration (mg/dL) at steady state between eplontersen and vutrisiran using unanchored STC, for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for sex, V50M mutation, FAP stage, cardiac involvement and baseline serum TTR.
Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; PF: prognostic factors; STC: simulated treatment comparison; TTR: transthyretin; TEM: treatment effect modifier.

Mean Percent Change from Baseline in Serum TTR at Steady State

The reference adjusted model produces summary statistics (Table 28) that match vutrisiran closely. The alternative model has small differences in age, race and prior treatment as these were the covariates not included in the alternative model.

Unanchored MAIC and STC models showed no statistically significant differences in percentage CfB serum TTR between treatments at steady state. The results of the alternative model were consistent with the reference model (Figure 20, Figure 21).

Figure 20: Mean difference in percent CfB in serum TTR at steady state between eplontersen and vutrisiran using unanchored MAIC, for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for sex, V50M mutation, FAP stage, cardiac involvement and baseline serum TTR.

Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; PF: prognostic factors; TEM: treatment effect modifier; TTR: transthyretin.

Figure 21: Mean difference in percent CfB in serum TTR concentration at steady state between eplontersen and vutrisiran using unanchored STC, for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for sex, V50M mutation, FAP stage, cardiac involvement and baseline serum TTR.
Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; PF: prognostic factors; STC: simulated treatment comparison; TEM: treatment effect modifier.

B.3.9.4 Indirect treatment comparison results: modified Neuropathy Impairment Score+7 composite score

Modified Neuropathy Impairment Score+7 Composite Score

Summary baseline characteristics for the eplontersen arm of NEURO-TTRansform and the adjusted eplontersen arm for the reference and alternative ITC are shown in Table 29. The baseline characteristics match those of the vutrisiran arm of HELIOS-A closely. For the variables not included in the alternative ITC model, small differences are observed for age, sex, race, and V50M mutation, and large differences are observed for cardiac involvement.

Table 29: Trial population adjustments for mNIS+7 composite score analysis.[a] Imputation: multiple imputation of mean difference. Time adjustment: linear extrapolation to Week 80

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.25	[redacted]	[redacted]
Age (SD)	13.20	15.01	[redacted]	[redacted]
Sex (proportion male)	0.65	0.69	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.6	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.72	[redacted]	[redacted]
FAP I (proportion)	0.70	0.82	[redacted]	[redacted]

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]
Baseline mNIS+7 (mean)[a]	60.55	66.32	[redacted]	[redacted]
Baseline mNIS+7 (SD) [a]	35.99	35.38	[redacted]	[redacted]

Footnote: [a] mNIS+7 values are $mNIS+7_{Alnylam}$. **Abbreviations**: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; mNIS+7: modified neuropathy impairment score; SD: standard deviation.

Both unanchored MAIC and STC showed no statistically significant differences between eplontersen and vutrisiran in terms of change in mNIS+7 composite score from baseline to Week 80. The results of the alternative model were consistent with the reference model (Figure 22, Figure 23).

Figure 22: Mean difference in CfB in mNIS+7 composite score at Week 80 between eplontersen and vutrisiran using unanchored MAIC for both the reference and alternative ITC model

[redacted]

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for previous treatment, FAP score, baseline mNIS+7.
Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NIS: neuropathy impairment score; PF: prognostic factors; TEM: treatment effect modifier.

Figure 23: Mean difference in CfB in mNIS+7 composite score at Week 80 between eplontersen and vutrisiran using unanchored STC for both the reference and alternative ITC model

[redacted]

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for previous treatment, FAP score, baseline mNIS+7.

Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; NIS: neuropathy impairment score; PF: prognostic factors; STC: simulated treatment comparison TEM: treatment effect modifier.

mNIS+7 Responder Analysis

The reference ITC model produces summary statistics that closely match vutrisiran, while the alternative ITC model has a small difference in age and sex, and a larger difference in cardiac involvement (Table 30).

Table 30: Trial population adjustments for mNIS+7 responder analysis.[a] Imputation: multiple imputation of mean difference. Time adjustment: linear extrapolation to Week 80

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.25	[redacted]	[redacted]
Age (SD)	13.20	15.01	[redacted]	[redacted]
Sex (proportion male)	0.65	0.69	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.6	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.72	[redacted]	[redacted]
FAP I (proportion)	0.70	0.82	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]
Baseline mNIS+7 (mean) [a]	60.55	66.32	[redacted]	[redacted]
Baseline mNIS+7 (SD) [a]	35.99	35.38	[redacted]	[redacted]

Footnote: [a]mNIS+7 values are $mNIS+7_{Alnylam}$. **Abbreviations**: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; mNIS+7: modified neuropathy impairment score; SD: standard deviation.

Unanchored MAIC and STC showed no statistically significant difference between eplontersen and vutrisiran in terms of the odds of a “response” in mNIS+7 between baseline and Week 80. The results of the alternative model were consistent with the reference model (Figure 24, Figure 25).

Figure 24: Log OR for mNIS+7 response (defined as a decrease from baseline) at Week 80 between eplontersen and vutrisiran using unanchored MAIC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for race, previous treatment, V50M mutation, FAP score, baseline mNIS+7.

Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NIS: neuropathy impairment score; OR: odds ratio; PF: prognostic factors; TEM: treatment effect modifier.

Figure 25: Log OR for mNIS+7 response (defined as a decrease from baseline) at Week 80 between eplontersen and vutrisiran using unanchored STC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for previous treatment, V50M mutation, FAP score, baseline mNIS+7.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; NIS: neuropathy impairment score; OR: odds ratio; PF: prognostic factors; STC: simulated treatment comparison TEM: treatment effect modifier.

B.3.9.5 Indirect treatment comparison results: Norfolk Quality of Life-Diabetic Neuropathy

Norfolk QoL-DN Total Score

The reference model adjusted ITC model produces summary baseline characteristics that match those for vutrisiran closely (Table 31). The alternative ITC model has small differences in race, V50M mutation, prior treatment, FAP stage and a larger difference in cardiac involvement.

Table 31: Trial population adjustments for Norfolk QoL-DN total score analysis. Imputation: multiple imputation of mean difference. Time adjustment: linear extrapolation to Week 80

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.48	[redacted]	[redacted]
Age (SD)	13.20	14.98	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.60	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.70	[redacted]	[redacted]
FAP I (proportion)	0.70	0.80	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.17	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.10	43.01	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.30	25.66	[redacted]	[redacted]

Abbreviations: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; Norfolk QoL-DN: Norfolk quality of life -diabetic neuropathy; SD: standard deviation.

The unanchored MAIC and STC showed a statistically difference, in favour of eplontersen, in CfB Norfolk QoL-DN score between treatments at Week 80 (Figure 26, Figure 27). The results of the alternative model were comparable to those of the reference model.

Figure 26: Mean difference in CfB in Norfolk QoL-DN total score at Week 80 between eplontersen and vutrisiran using unanchored MAIC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for age, sex, baseline Norfolk QoL-DN.
Abbreviations: CfB: change from baseline; CI: confidence interval; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NIS: neuropathy impairment score; PF: prognostic factors; QoL-DN: Quality of Life-diabetic neuropathy; TEM: treatment effect modifier.

Figure 27: Mean difference in CfB in Norfolk QoL-DN total score at Week 80 between eplontersen and vutrisiran using unanchored STC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians. The alternative model adjusted for age, sex, baseline Norfolk QoL-DN.
Abbreviations: CfB: change from baseline; CI: confidence interval; ITC: indirect treatment comparison; NIS: neuropathy impairment score; PF: prognostic factors; QoL-DN: Quality of Life-diabetic neuropathy; STC: simulated treatment comparison; TEM: treatment effect modifier.

Norfolk Quality of Life-Diabetic Neuropathy Responder Analysis

The reference adjusted ITC model produces summary statistics (Table 32) that match vutrisiran closely. The alternative ITC model has small differences in age, sex and race and a larger difference in cardiac involvement.

Table 32: Trial population adjustments for Norfolk QoL-DN response. Imputation: multiple imputation of mean difference. Time adjustment: linear extrapolation to Week 80

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.48	[redacted]	[redacted]

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (SD)	13.20	14.98	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.60	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.70	[redacted]	[redacted]
FAP I (proportion)	0.70	0.80	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.17	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.10	43.01	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.30	25.66	[redacted]	[redacted]

Abbreviations: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; QoL-DN: Quality of Life-diabetic neuropathy; SD: standard deviation.

None of the models showed a statistically significant difference between eplontersen and vutrisiran in terms of the odds of a "response" in Norfolk QoL-DN between baseline and Week 80 (Figure 28, Figure 29), i.e., an improvement in Norfolk QoL-DN score. The results of the alternative model were consistent with the reference model.

Figure 28: Log OR of Norfolk QoL-DN response (defined as a decrease from baseline) at Week 80 between eplontersen and vutrisiran using unanchored MAIC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for FAP stage, previous treatment, cardiac involvement, baseline Norfolk QoL-DN.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NIS: neuropathy impairment score; OR: odds ratio; PF: prognostic factors; QoL-DN: Quality of Life-diabetic neuropathy; TEM: treatment effect modifier.

Figure 29: Log OR of Norfolk QoL-DN response (defined as a decrease from baseline) at Week 80 between eplontersen and vutrisiran using unanchored STC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 26. The alternative model adjusted for FAP stage, previous treatment, cardiac involvement, baseline Norfolk QoL-DN.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; NIS: neuropathy impairment score; OR: odds ratio; PF: prognostic factors; QoL-DN: Quality of Life-diabetic neuropathy; STC: simulated treatment comparison; TEM: treatment effect modifier.

B.3.9.6 Indirect treatment comparison results: serious adverse events

The reference adjusted model for eplontersen produces summary statistics that closely match the summary statistics for vutrisiran (Table 33). The alternative model has differences in age, sex, proportion of white individuals (race), proportion of individuals with V50M mutation, proportion of individuals with prior treatment, and proportion of patients with cardiac involvement.

Table 33: Trial population adjustments for serious adverse events

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=140)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.63	[redacted]	[redacted]
Age (SD)	13.20	15.05	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.78	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.59	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.71	[redacted]	[redacted]
FAP I (proportion)	0.70	0.81	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]

Abbreviations: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; SD: standard deviation.

Unanchored MAIC and STC show no statistically significant difference in terms of the odds of a serious adverse event in patients treated with vutrisiran compared with eplontersen (Figure 30, Figure 31). Both reference and alternative models are consistent with each other.

Figure 30: Log OR for serious adverse events between eplontersen and vutrisiran using unanchored MAIC

Abbreviations: CI: confidence interval; MAIC: matching-adjusted indirect comparison; OR: odds ratio

Figure 31: Log OR for serious adverse events between eplontersen and vutrisiran using unanchored STC

Abbreviations: CI: confidence interval; OR: odds ratio; STC: simulated treatment comparison

B.3.9.7 Indirect treatment comparison results: severe adverse events

The reference adjusted model for eplontersen produces summary statistics that closely match the summary statistics for vutrisiran (Table 34). The alternative model has differences in age, sex, proportion of white individuals (race), proportion of individuals in FAP stage I, and proportion of patients with cardiac involvement.

Table 34: Trial population adjustments for severe adverse events

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=140)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.63	[redacted]	[redacted]
Age (SD)	13.20	15.05	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.78	[redacted]	[redacted]

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=140)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
V50M mutation (proportion)	0.44	0.59	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.71	[redacted]	[redacted]
FAP I (proportion)	0.70	0.81	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]

Abbreviations: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; SD: standard deviation.

Unanchored MAIC and STC show no statistically significant difference in terms of the odds of a severe adverse event in patients treated with vutrisiran compared with eplontersen (Figure 33).

Figure 32: Log OR for severe adverse events between eplontersen and vutrisiran using unanchored MAIC

Abbreviations: CI: confidence interval; MAIC: matching-adjusted indirect comparison; OR: odds ratio

Figure 33: Log OR for severe adverse events between eplontersen and vutrisiran using unanchored STC

Abbreviations: CI: confidence interval; OR: odds ratio; STC: simulated treatment comparison

B.3.9.8 Indirect treatment comparison results: treatment discontinuation

The reference adjusted model for eplontersen produces summary statistics that closely match the summary statistics for vutrisiran (Table 35). The alternative model has differences in sex, proportion of white individuals (race), and proportion of patients with V50M mutation, prior treatment, FAP I stage, and cardiac involvement.

Table 35: Trial population adjustments for treatment discontinuation

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=140)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.63	[redacted]	[redacted]
Age (SD)	13.20	15.05	[redacted]	[redacted]
Sex (proportion male)	0.65	0.70	[redacted]	[redacted]
Race (proportion white)	0.71	0.78	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.59	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.71	[redacted]	[redacted]
FAP I (proportion)	0.70	0.81	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]

Abbreviations: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; SD: standard deviation.

Unanchored MAIC and STC show no statistically significant difference in terms of the odds of a treatment discontinuation event in patients treated with vutrisiran compared with eplontersen (Figure 34, Figure 35).

Figure 34: Log OR for treatment discontinuation between eplontersen and vutrisiran using unanchored MAIC

Abbreviations: CI: confidence interval; MAIC: matching-adjusted indirect comparison; OR: odds ratio

Figure 35: Log OR for treatment discontinuation between eplontersen and vutrisiran using unanchored STC

Abbreviations: CI: confidence interval; OR: odds ratio; STC: simulated treatment comparison

B.3.9.9 Uncertainties in the indirect and mixed treatment comparisons

Multiple ITC methodologies were assessed for feasibility. Due to differences in the underlying patient characteristics of each trial, population adjustment methods (unanchored MAIC and STC) were deemed the most suitable methods for comparing treatments between the eplontersen and vutrisiran trials.

Despite representing the most suitable methodologies for the ITC analysis, given the evidence base available, unanchored MAIC and STC approaches are still subject to potential limitations. For example, MAIC requires a sufficient overlap in the populations between two trials, yet population differences were observed at baseline between clinical trials. The STC methodology is limited as can be difficult to accurately estimate outcomes for the comparator population, using individual-level patient data and regression techniques. Despite these potential limitations, unanchored MAIC and STC present the most suitable ITC methodologies given the limitations of the published evidence base for eplontersen and vutrisiran, and the absence of comparable placebo groups.

There were also differences between the instruments used to assess polyneuropathy progression – one of the primary efficacy outcomes. There are several forms of the mNIS+7 score, and the instrument used differed between trials. This presents a limitation as the scores were not exactly comparable, requiring the $mNIS+7_{Ionis}$ version to be rescored to align more closely with the $mNIS+7_{Alnylam}$ version. Additionally, treatment discontinuation was not reported as a time-to-event outcome in HELIOS-A. Instead, the proportion of patients who had discontinued at the end of the trial was considered as a binary outcome and compared with time-on-treatment data for eplontersen, representing an additional limitation of the analysis.

Whilst the selected ITC methodologies are associated with some potential uncertainties, this is to be expected given the lack of RCTs between eplontersen and vutrisiran, and the ethical considerations that restrict the opportunities to conduct placebo-controlled trials in ATTRv-PN. Unanchored MAIC and STC were consequently deemed to be the most appropriate ITC methodologies.

Furthermore, the analyses have shown there are no statistically significant differences between eplontersen and vutrisiran, or the difference is statistically significant in favour of eplontersen (CfB in Norfolk QoL-DN). The results were consistent across a range of sensitivity analyses, including exploring two different unanchored ITC approaches (MAIC and STC) and two different sets of adjustment variables (see Table 26). Unanchored MAICs and STCs showed no significant differences in terms of the odds of a serious or severe AE, or treatment discontinuation event between eplontersen and vutrisiran, with results consistent across two sets of adjustment variables.

Overall, the ITC results are strongly supportive of eplontersen and vutrisiran having a similar treatment effect in terms of clinical efficacy and safety. This is consistent with the feedback from UK clinical experts that eplontersen and vutrisiran are expected to demonstrate similar clinical efficacy and safety.[20]

B.3.10 Adverse reactions

HELIOS-A was the pivotal study assessing the safety and efficacy of vutrisiran.[12] To illustrate the comparable safety profiles of eplontersen and vutrisiran, safety data have been presented from NEURO-TTRansform (including the external placebo arm from NEURO-TTR) and HELIOS-A.

Where safety data were collected at multiple timepoints, data with the longest follow-up have been presented since they are likely to be the most representative. Conversely, efficacy data were presented at Week 66 in this appraisal, as efficacy endpoints at Week 85 were exploratory and assessed as a post hoc outcome. Additionally, efficacy data for the NEURO-TTR external placebo group were not collected beyond Week 66.

Treatment-Emergent Adverse Events

An overview of the treatment-emergent adverse events (TEAEs) from the final analysis of NEURO-TTRansform and HELIOS-A is presented in Table 36. In NEURO-TTRansform, the final analysis of safety data took place at Week 85 for the eplontersen arm and Week 66 for the external placebo arm. The final analysis in HELIOS-A took place at 18 months (78 weeks).

The number of patients who had experienced any TEAE was comparable across treatment groups with 98% of patients reporting TEAEs by Week 85 in the NEURO-TTRansform eplontersen group, and by Month 18 in the HELIOS-A vutrisiran group.[53, 54] The proportion of patients who discontinued study drug treatment due to TEAEs was slightly lower for vutrisiran (3%; by Month 18) compared with eplontersen (6%; by Week 85). The proportion of severe and serious TEAEs was lower in the eplontersen group (severe: 14%; serious 19%) compared with the vutrisiran group (severe: 16%; serious: 26%).[53, 54]

Deaths

During NEURO-TTRansform, [redacted] patients experienced fatal TEAEs by the Week 85 analysis, [redacted] of which were in the eplontersen group, although no deaths due to study drug were reported (Table 36).[52] The death rate as a proportion of eplontersen-exposed patients was 2% (3/144), which is equal to the rate of death in patients who received vutrisiran in HELIOS-A (2%).[53, 54]

Table 36: Summary of all TEAEs through end of treatment

	NEURO-TTRansform[53]	NEURO-TTR[53]	HELIOS-A[54]
	Eplontersen[a] (n=144)	External placebo (n=60)	Vutrisiran[b] (n=122)
Incidence, n (%)			
Any TEAEs[c]	141 (98)	60 (100)	119 (98)
TEAEs leading to study drug discontinuation	8 (6)	2 (3)	3 (3)
Severe TEAEs	20 (14)	13 (22)	19 (16)
Serious TEAEs	27 (19)	12 (20)	32 (26)
Serious TEAE related to study drug	0	1 (2)	-
Injection site reaction	13 (9)	-	5 (4)
Death	3 (2)	0	2 (2)
Death due to study drug	0	0	-

Footnotes: All percentages are rounded. [a]NEURO-TTRansform eplontersen data were collected up to Week 85 whilst NEURO-TTR external placebo data were collected up to Week 66, therefore exposure is longer in the NEURO-TTRansform eplontersen group than in the NEURO-TTR external placebo group; [b]HELIOS-A safety data was collected during 18-month treatment period; [c] In NEURO-TTRansform, TEAE is defined as an AE that first occurred or worsened after the first dose of study drug. In HELIOS-A, TEAE is defined as any AE with onset during or after administration of the study drug through 84 days following the last dose of vutrisiran.
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.
Source: Adams 2022[54]; Coelho 2023[53].

The TEAEs that occurred in ≥10% of patients in the NEURO-TTRansform trial are summarised in Table 37. The proportion of patients experiencing diarrhoea was comparable across the eplontersen (19%) and vutrisiran (14%) groups. Urinary tract infections were slightly higher in the eplontersen group (19%) compared with vutrisiran (13%).[53, 54] In the eplontersen group, 12% of patients experienced vitamin A deficiency, which is expected given the role of TTR in vitamin A transport.[53] Results for vitamin A deficiency were not reported in HELIOS-A.

Table 37: TEAEs[a] that occurred with incidence ≥10% in NEURO-TTRansform through end of treatment, for NEURO-TTRansform eplontersen and HELIOS-A vutrisiran

	NEURO-TTRansform	HELIOS-A
	Eplontersen[b] (n=144)	Vutrisiran[c] (n=122)
Preferred term	Patients, n (%)	
COVID-19	48 (33)	NR
Diarrhoea	28 (19)	17 (14)
Urinary tract infection	28 (19)	16 (13)
Vitamin A deficiency	17 (12)	NR
Nausea	16 (11)	12 (10)

Footnotes: [a]In NEURO-TTRansform, TEAE is defined as an AE that first occurred or worsened after the first dose of study drug. In HELIOS-A, TEAE is defined as any AE with onset during or after administration of the study drug through 84 days following the last dose of vutrisiran. [b]NEURO-TTRansform eplontersen data were collected up to Week 85; [c]HELIOS-A safety data was collected during 18-month treatment period.

Abbreviations: COVID-19: coronavirus disease 2019; NR: not reported; TEAE: treatment-emergent adverse event.
Source: Adams 2022[54]; Coelho 2023[53]

B.3.11 Conclusions about comparable health benefits and safety

Principle Findings from the Clinical Evidence Base

In NEURO-TTRansform, eplontersen (45 mg; Q4W; SC) was shown to result in greater benefit for patients with ATTRv-PN when compared to placebo across a range of clinically meaningful endpoints.

Eplontersen was effective in reducing serum TTR levels, demonstrating efficacy in targeting the source of TTR production. At the Week 35 interim analysis, treatment with eplontersen resulted in a -81.2% (95% CI: -84.6%, -77.8%) LSM CfB in serum TTR which was maintained at Week 65 with a -81.7% CfB (95% CI: -84.8%, -78.5%). The LSM difference in serum TTR between the eplontersen group and placebo group at Week 65 was statistically significant, with a -70.4% reduction in favour of eplontersen (95% CI: -75.2%, -65.7%; p<0.001) (Section B.3.6.1).

Eplontersen was also effective in preventing deterioration in polyneuropathy impairment. At the Week 35 interim analysis, the LSM CfB in mNIS+7 score was 0.22 (95% CI: -3.5, 3.9). This was maintained until Week 66, with a LSM CfB of 0.3 (95% CI: -4.5, 5.1). At Week 66, the LSM difference between eplontersen and the external placebo group was statistically significant, with a -24.8 reduction in mNIS+7 score in favour of eplontersen (95% CI: -31.0, -18.6; p<0.001).[53]

Treatment with eplontersen also resulted in reduced scores for patients completing the Norfolk QoL-DN questionnaire, indicating improvements in patient's quality of life, which given the high morbidity burden associated with ATTRv-PN, is an important outcome. Eplontersen was superior to the external placebo in reducing the Norfolk QoL-DN score from baseline at both Week 35 and Week 66. At Week 66, treatment with eplontersen resulted in a LSM CfB of -5.5 (95% CI: -10.0, -1.0) in Norfolk QoL-DN total score and the observed difference between the eplontersen and external placebo group was statistically significant, with a LSM difference of -19.7, in favour of eplontersen (95% CI: -25.6, -13.8; p<0.001).[53]

The results of the secondary endpoints were also positive, demonstrating that eplontersen results in improvements in mobility (PND score), nutritional status (mBMI), QoL (SF-36) and neuropathy (NSC) when compared to placebo.

Comparability to Vutrisiran

As described in Section B.1.3.5, UK clinical expert validation indicated that [redacted] patients with ATTRv-PN at the NAC are treated with vutrisiran, indicating that it is the only relevant comparator for eplontersen in UK clinical practice.[20] This was also confirmed in the response by NICE to the draft scope for this appraisal.[3] Since direct clinical evidence for eplontersen versus vutrisiran is not available, an unanchored MAIC and STC were conducted to compare the efficacy of eplontersen in the NEURO-TTRansform trial versus vutrisiran in the pivotal HELIOS-A trial.

The co-primary endpoints in the NEURO-TTRansform trial (serum TTR, mNIS+7, Norfolk QoL-DN) were considered in the ITCs, as clinically meaningful endpoints for patients with ATTRv-PN.

Unanchored MAIC and STC models showed no statistically significant differences in absolute serum TTR concentration, absolute CfB in serum TTR concentration or percent CfB in serum TTR between eplontersen and vutrisiran, at steady state. Similarly, both unanchored MAIC and STC showed no statistically significant differences between eplontersen and vutrisiran in terms of change in mNIS+7 composite score from baseline to Week 80.

Eplontersen treatment resulted in a sustained benefit in QoL. For the Norfolk QoL-DN, a statistically significant difference in CfB was observed between treatments at Week 80; both the MAIC and STC models showed that eplontersen statistically significantly reduced the Norfolk QoL-DN score from baseline (indicating an improvement in patient's quality of life) when compared to vutrisiran. No statistically significant difference was observed between eplontersen and vutrisiran in terms of the odds of a response (response defined as a CfB <0) in Norfolk QoL-DN at Week 80.

Combined, these ITC results demonstrate that vutrisiran and eplontersen have similar treatment effects, with statistically significant differences between the two treatments observed for the CfB in Norfolk QoL-DN, in favour of eplontersen. Input from UK clinical experts confirmed that eplontersen and vutrisiran have similar treatment effects.[20]

Safety Profile

Alongside similar treatment effects, the safety profile of eplontersen observed in the NEURO-TTRansform trial was generally tolerable and closely aligned with the safety profile for vutrisiran observed in HELIOS-A. At the final analysis (Week 85 for NEURO-TTRansform and 18 months for HELIOS-A), the proportion of severe and serious TEAEs was lower in the eplontersen group (severe: 14%; serious 19%) compared with the vutrisiran group (severe: 16%; serious: 26%).[9, 30]

Furthermore, unanchored MAICs and STCs showed no significant differences in terms of the odds of a serious or severe AEs, or treatment discontinuation events between eplontersen and vutrisiran.

Conclusion

Overall, the comparative efficacy and safety data provide clear evidence that the efficacy and safety of eplontersen should be considered to be similar to that of vutrisiran for the treatment of patients with ATTRv-PN. As such, a cost-comparison appraisal should be considered appropriate for eplontersen.

Compared to vutrisiran, eplontersen would offer a therapeutic option for slowing or halting progression of this irreversible, fatal condition that provides more autonomy and can be self-administered at home.

B.3.12 Ongoing studies

The ongoing open-label extension study of NEURO-TTRansform is ongoing (NCT05071300), with expected completion in [redacted].[78]

B.4 Cost-comparison analysis

Summary of Cost-Comparison Analysis

- The first dose of vutrisiran and eplontersen is expected to be administered at the National Amyloidosis Centre (NAC), the only specialised and commissioned center for patients living with amyloidosis in England.
  - In line with its Summary of Product Characteristics (SmPC),[46] subsequent doses of vutrisiran are delivered via a subcutaneous (SC) injection, which must be administered by an HCP, while eplontersen is supplied in an auto-injector which can be self-administered.
- A cost-comparison model was developed to evaluate the costs associated with eplontersen or vutrisiran to treat patients with Stage 1 or Stage 2 hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) from a UK NHS and personal social services (PSS) perspective.
  - Drug acquisition (simple patient access discount [PAS] for eplontersen; published list price for vutrisiran) were incorporated.
  - Administration costs were also incorporated, including the cost of the first dose for eplontersen and vutrisiran at the NAC, and subsequent doses of vutrisiran by a healthcare professional (HCP).
  - Inputs were validated by UK-based clinical experts.[20]
  - Time to treatment discontinuation (TTD) was included in the base case analysis and set equal for eplontersen and vutrisiran.
  - Costs were compared over a 5-year period.
- Base-case results showed that, due to its reduced administration requirements, eplontersen is associated with a saving in administration costs of [redacted] per patient, when compared with vutrisiran. There is an overall cost differential of [redacted] between the two treatments, showing eplontersen to be cost-saving in terms of acquisition and administration costs. This comparison is based on the with-PAS price for eplontersen and list price for vutrisiran.
- Cost savings for patients treated with eplontersen were maintained in scenario analyses.

B.4.1 Changes in service provision and management

B.4.1.1 Administration setting

The NAC is currently the only specialised and commissioned center for patients living with amyloidosis in England, and all patients diagnosed with ATTRv-PN will have treatment initiated by clinicians at the NAC.

Like vutrisiran, the first dose of eplontersen is expected to be administered at the NAC. While subsequent doses of vutrisiran require an HCP to administer the treatment in a homecare setting Q3M, eplontersen offers patients more autonomy over the management of their condition, with subsequent doses being self-administered by the patient or their caregiver monthly using an auto-injector, alleviating the need for homecare HCP visits. The real-world administration setting for vutrisiran and proposed administration setting for eplontersen were validated by clinical experts.[20]

Assumptions on resource use for eplontersen and vutrisiran regarding administration in a homecare and clinical setting are detailed further in Section B.4.2.7.

B.4.1.2 Administration-related resource use

Vutrisiran is delivered via a SC injection, which must be administered by an HCP, while eplontersen is supplied in an auto-injector, allowing for self-administration.[49, 79] Time requirements for administration of eplontersen and vutrisiran are expected to be comparable. The first administration for both treatments is held at the NAC, with subsequent administrations by an HCP in a homecare setting for vutrisiran and self-administered for eplontersen. Cost requirements for administration of the first dose at the NAC are comparable; however, eplontersen does not require HCP involvement for subsequent administrations, whilst in line with the treatment SmPC, vutrisiran requires an HCP to visit patients at home to administer subsequent treatment doses (see Table 40 for more details).[46]

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The CCA evaluated the costs associated with using eplontersen or vutrisiran to treat patients with ATTRv-PN from a UK NHS and personal social services (PSS) perspective.

The CCA model was developed in Microsoft Excel®. The model compares the costs associated with the use of eplontersen or vutrisiran for treating patients with ATTRv-PN in the UK over a 5-year period. The model incorporates drug acquisition and administration costs. The details of the economic evaluation are summarised in Table 38.

Table 38: Summary of economic evaluation

Component	Description
Type of economic evaluation	Cost-comparison analysis
Population	Adult patients (⩾18 years of age) with FAP or Coutinho Stage 1 or 2 ATTRv-PN
Intervention	Eplontersen 45 mg QM; SC
Comparator	Vutrisiran 25 mg Q3M; SC
Time horizon	5 years
Cycle length	1 month
Discounting	Costs were not discounted
Costs	Drug acquisition costs Administration costs
Perspective	UK NHS healthcare and PSS perspective
Outcomes	Total treatment costs per patient
Primary Target Audience	The National Institute for Health and Care Excellence

Abbreviations: ATTRv-PN: hereditary amyloid transthyretin amyloidosis with polyneuropathy; NHS: National Health Service; PSS: personal social services; Q3M: every 3 months; SC: subcutaneous; UK: United Kingdom.

B.4.2.2 Population

The population included in the CCA were adult patients (≥18 years of age) with FAP or Coutinho Stage 1 or 2 ATTRv-PN, in line with the NEURO-TTRansform trial population.[53] Unlike in the appraisal of TA868 in which a comparison was made to patisiran which has weight-based dosing, this comparison includes eplontersen and vutrisiran which are dosed independently of weight-based characteristics.[12] Therefore, weight as a baseline characteristic is not used as an input in the CCA. Other specific baseline characteristics, such as age and gender are also assumed to be independent of treatment so have also not been included in the analysis.

B.4.2.3 Intervention and comparators

The intervention in the CCA is eplontersen (45 mg; QM; SC) and the comparator is vutrisiran (25 mg; Q3M; SC).

B.4.2.4 Cycle length and time horizon

The model uses a monthly cycle length, as this aligns with the anticipated license for eplontersen (QM) and the treatment cycle of vutrisiran (Q3M). The base-case time horizon is 5 years as this is considered long enough to demonstrate differences in the costs associated with eplontersen and vutrisiran and is in alignment with a recent CCA submitted to NICE for vutrisiran.[12] A longer time horizon was deemed unnecessary given that many aspects of treatment costs (e.g. monitoring, dose frequency) either do not vary over time or are likely to remain constant after the second dose. For example, eplontersen and vutrisiran administration costs are higher during the first dose which is administered at the NAC, and then remain at a reduced cost thereafter when administered in the homecare setting, with vutrisiran administration costs remaining slightly higher due to HCP involvement. Alternative time horizons of 1, 2 and 10 years were assessed as scenario analyses in the CCA.

B.4.2.5 Discounting

In the NICE user guide for submitting single technology cost-comparison assessments, it is stated that discounting of costs is not normally required for a cost-comparison.[80] Therefore, the discount rate is set to zero.

B.4.2.6 Treatment discontinuation

Time to treatment discontinuation (TTD) was included in the base-case analysis, and was set equal for both eplontersen and vutrisiran. This approach was validated by clinical experts who have experience in treating patients with ATTRv-PN and who were familiar with the clinical trial data (see Section B.4.2.12 Clinical expert validation).[20] The approach is also supported through the ITC which showed similar treatment discontinuation for the two treatments (see Section B.3.9.8). This is in line with TA868 which also assumed equal TTD between treatment arms (patisiran was set equal to vutrisiran).[12] Following treatment discontinuation all patients were switched to best supportive care (BSC).

Eplontersen TTD was calculated from Week 85 NEURO-TTRansform IPD. Time on treatment data for each patient were used to generate Kaplan-Meier data up to Week 85. This was then extrapolated out to the model time horizon using parametric models fitted to the time to event

data. Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) estimators were used to evaluate the relative quality of the parametric models considered, namely exponential, Weibull, Gompertz, log-logistic, lognormal, gamma and generalised gamma. The curve with the lowest BIC by more than 2.5 points was exponential, and whilst exponential did not have the lowest AIC, it was within 0.5 points of the lowest. The exponential curve was selected for the model base-case and was validated as clinically appropriate by clinical experts (see Section B.4.2.12 Clinical expert validation).[20]

See Appendix I for a summary of AIC and BIC for each extrapolation method assessed.

B.4.2.7 Costs in the cost-comparison analysis

Costs in the CCA include drug acquisition costs (reflecting a proposed simple discount patient access scheme [PAS] for eplontersen, and the published list price for vutrisiran) and administration costs (including HCP visits for vutrisiran). A simple PAS is available for vutrisiran, however as this is confidential, the list price for vutrisiran has been assumed for this analysis. Costs relating to adverse events were not included in the model base-case but were included in a scenario analysis.

B.4.2.8 Intervention and comparators' acquisition costs

Drug acquisition costs for vutrisiran were obtained from the British National Formulary (BNF).[81] The proposed PAS price for eplontersen is [redacted] per month/dose and [redacted] per year, representing a discount of [redacted] on the anticipated list price of [redacted] per month/dose and [redacted] per year.

The dose of vutrisiran was aligned with the prescribing information detailed by the SmPC, and the dose of eplontersen was aligned with the draft SmPC.[82] Treatment acquisition costs and dosing assumptions are shown in Table 39. Concomitant medication costs and recommended supplemental vitamin A levels are assumed equal across both treatments and are therefore excluded from the analysis as these costs will cancel out across the two treatments.[82] Costs associated with BSC are assumed to be zero as these costs are equal amongst both treatment arms.

Table 39. Acquisition costs of the intervention and comparator technologies per patient

Treatment	Dose per administration (mg)	Vial size (mg)	Cost per unit	Annual cost	Source
Eplontersen	45	45	[redacted]	[redacted]	Proposed simple PAS, AstraZeneca
Vutrisiran	25	25	£95,862.36	£383,449.44	Published list price, BNF[81]

Abbreviations: BNF: British National Formulary; mg: milligram; PAS: patient access scheme.

B.4.2.9 Intervention and comparators' administration costs

To incorporate administration costs into the model, the route and location of administration for each treatment was evaluated (Table 40). Costs associated with HCP travel to the homes of patients treated with vutrisiran were excluded as a conservative assumption. The costs for self-

administration or administration by a caregiver are assumed to be zero. All administration costs and dosing frequencies were validated by clinical experts (see B.4.2.12 Clinical expert validation), and costs used for administration of vutrisiran are aligned with those used in TA868.[12]

The methodology for the identification of costs is summarised in Appendix G.

Table 40. Location and cost of administration for each treatment

	Eplontersen	Vutrisiran[6]
Route and frequency of administration	SC QM	SC Q3M
Administration location and cost for first administration	Location: Assumed to be at the NAC Cost: £119.00 Rationale: NHS reference costs 21/22 – HRG code: N10AF[4]	Location: At the NAC Cost: £119.00 Rationale: NHS reference costs 21/22 – HRG code: N10AF[4]
Administration location and cost for subsequent administrations	Location: Self-administered or administered by a caregiver at home Cost: £0.00 Rationale: Assumption and validated by clinical experts	Location: Homecare - administered by a nurse at the patient's home Cost: £33.00 Rationale: Band 4 nurse wage: PSSRU 2022[4] (Assuming 1 hour nurse time, in line with TA868)[12]
Yearly administration costs	£119.00 (first year) £0.00 (subsequent years)	£218.00 (first year) £132.00 (subsequent years)

Abbreviations: HRG: Healthcare Resource Group; NAC: National Amyloidosis Centre; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; QM: every month; Q3M: every three months; SC: subcutaneous.

B.4.2.10 Adverse event costs

Adverse events were not incorporated into the CCA base case analysis due to the similar rates of AEs reported for eplontersen in NEURO-TTRansform and vutrisiran in HELIOS-A.[53, 54] Further evidence in support of this similarity was provided by the clinical experts consulted as part of this submission, and by the results of the safety ITC analysis which demonstrated that the rate of serious and severe AEs is similar between eplontersen and vutrisiran (see Section B.3.9.6 and B.3.9.7). This assumption is also aligned with the approach taken in TA868.[12] Adverse event costs were included as part of a scenario analysis, and all inputs relating to this have been included in Appendix J.

B.4.2.11 Miscellaneous unit costs and resource use

All costs included in the CCA have been described in earlier sections.

B.4.2.12 Clinical expert validation

To validate the current clinical practice in ATTRv-PN, and validate model inputs, assumptions and approaches from an economic perspective, AstraZeneca arranged video interviews with two UK based clinical experts. The criteria for clinical expert inclusion were:

- Clinicians based at the NAC or neurologists who work at the National Hospital for Neurology and Neurosurgery (Queen Square) and who work in close partnership with the NAC
- Clinicians with experience in the treatment of ATTRv-PN with vutrisiran, patisiran and/or inotersen
- Clinicians with knowledge of the NEURO-TTRansform, HELIOS-A and APOLLO clinical trials

Two UK-based clinical experts who met the above criteria were approached and agreed to participate in the interviews: [redacted] and [redacted] Both experts engaged in 90-minute video interviews in November 2023. A pre-read of the NEURO-TTRansform and HELIOS-A trials was provided beforehand.

Validated inputs:[20]

- All ATTRv-PN patients are diagnosed and initiate treatment at the NAC.
- Inotersen and patisiran are not relevant comparators as [redacted]% of diagnosed ATTRv-PN patients are treated with vutrisiran and all new patients are currently initiated on vutrisiran.
- The modelled administration profile of vutrisiran (i.e., first injection delivered at the NAC and subsequent injections delivered via HCPs in homecare) is aligned with administration of vutrisiran in real-world practice.
- The administration cost assumptions in the model were validated.
- The monitoring tests and concomitant treatments (such as Vitamin A) were agreed to be comparable for vutrisiran and eplontersen.
- Similar TTD would be expected for a patient regardless of whether they are treated with vutrisiran or eplontersen, and assuming that 72% remain on treatment after five years is reasonable.
- NEURO-TTRansform patient characteristics were broadly generalisable to the UK population of patients with ATTRv-PN anticipated to receive eplontersen.
- The self-administration profile of eplontersen is advantageous, specifically for patients of working age.

B.4.2.13 Uncertainties and input assumptions

The CCA is aligned with the approved UK SmPC for vutrisiran and the expected SmPC for eplontersen in terms of administration practices, and real-world implementation of these practices were validated by clinical experts.[49, 79] The assumptions included in the CCA are presented in Table 7.

Table 41. Model assumptions and justifications

Assumption	Justification
Subsequent treatment	
Following discontinuation all patients move onto BSC	This assumption is aligned with the approach taken in TA868[12]
Clinical effectiveness	

Eplontersen is assumed to have equal efficacy (including equal mortality) to vutrisiran	This is in line with the results for the indirect treatment comparison (Section B.3.9) and was further validated through clinical expert interviews[20]
Eplontersen is assumed to have equal safety and adverse events to vutrisiran	Adverse event profiles were deemed as comparable through an ITC (see Section B.3.9.6 and B.3.9.7). Observed serious adverse event rates in NEURO-TTRansform and HELIOS-A are also comparable, so adverse event costs were excluded from the base case analysis in line with TA868[12, 43, 54]
Effect of treatment on mortality was not included in the model	In NEURO-TTRansform, there were very few observed deaths over the trial follow-up period, and this was not an endpoint of the study. This means that it was not possible to adequately assess the effect of eplontersen on mortality. In addition, given the similar efficacy between eplontersen and vutrisiran, there is no evidence that there is any mortality difference between treatments and therefore the potential effect of mortality was not modelled in the CCA. This approach is in line with the recent NICE submission for vutrisiran and was validated by clinical experts[12]
Treatment discontinuation for eplontersen is assumed equal to that of vutrisiran	TTD was set equal for both eplontersen and vutrisiran, which was validated by clinical experts. The approach is also supported through an ITC which showed similar treatment discontinuation for the two treatments (see Section B.3.9.8. This is in line with the vutrisiran NICE submission which also assumed equal TTD between treatment arms (patisiran was set equal to vutrisiran) and was an approach validated by clinical experts[20]
Cost and resource use	
The first SC injection of eplontersen and vutrisiran are administered at the NAC	This assumption was validated through clinical expert interviews[20]
There is no cost of administration of eplontersen at home	Based on expected SmPC, eplontersen can be self-administered. This assumption was validated through clinical expert interviews[20]
There is a cost of administration of vutrisiran via homecare	Based on approved SmPC for vutrisiran.[46] The cost of SC administration of vutrisiran at home was assumed to be represented by the cost associated with one hour of a community-based nurse.[83, 84]This assumption was based on TA868 and was validated through clinical expert interviews[12]
Vitamin A supplementation costs are excluded from the analysis	Recommended supplemental Vitamin A levels are similar for both treatments. This assumption was validated through clinical expert interviews[20]

Abbreviations: BSC: best supportive care; CCA: cost-comparison analysis; ITC: indirect treatment comparison; NAC: National Amyloidosis Centre; SC: subcutaneous; SmPC: Summary of Product Characteristics; TTD: time to treatment discontinuation.

B.4.3 Base-case results

The results of the base-case analysis are presented in Table 42. These costs represent the total costs per patient over 5 years. The incremental costs of eplontersen (at the with-PAS price) compared to vutrisiran (at list price) are also presented, with a negative value representing a cost saving for eplontersen. Due to its reduced administration requirements, eplontersen is associated with a saving in administration costs of [redacted] per patient, when compared with vutrisiran. Overall, there is a cost differential of [redacted] between the two treatments, showing eplontersen to be cost-

saving in terms of acquisition and administration costs for the treatment of patients with ATTRv-PN.

Table 42. Base-case result

Results	Eplontersen[a]	Vutrisiran	Eplontersen vs vutrisiran
Acquisition costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Footnote: [a]Results based on eplontersen at with-PAS price. **Abbreviations**: vs: versus.

B.4.4 Sensitivity and scenario analyses

B.4.4.1 One-way sensitivity analysis

A one-way sensitivity analysis (OWSA) was conducted to explore parameter uncertainty related to treatment administration costs. Each parameter was varied to its upper and lower value and the subsequent impact that this had on total costs was assessed. Standard errors were not available for any of the parameters therefore upper and lower values were defined as an arbitrary 10% variance; this is in line with the vutrisiran NICE submission.[12] Results for eplontersen versus vutrisiran are presented in Figure 36. All scenarios had a small impact on results, with no incremental difference exceeding [redacted] over a 5-year period.

Figure 36: OWSA results for eplontersen vs vutrisiran

Abbreviations: GBP: Great British Pounds; OWSA: one-way sensitivity analysis; vs: versus.

B.4.4.2 Scenario analysis

Scenario analyses were conducted to explore the structural uncertainty in the model. A scenario analysis was included in the model to explore the impact of excluding TTD data. Excluding TTD assumed that all patients remain on treatment for the duration of the model time horizon. Additional scenarios were also included to assess a model time horizon of 1, 2, and 10 years, and to assess the impact of including adverse events.

The total costs and incremental costs for eplontersen versus vutrisiran in each scenario are presented in Table 43. Results demonstrate that eplontersen is cost-saving compared to vutrisiran in all the scenarios that were assessed. Scenarios altering the time horizon between 1,

2 and 10 years had a large impact on incremental costs, with greater cost savings in scenarios with a longer time horizon. Excluding TTD resulted in greater cost savings for eplontersen versus vutrisiran. Similarly, including serious AEs also improved the incremental costs of eplontersen versus vutrisiran.

Table 43. Scenario analysis results

	Total cost		Incremental cost
	Eplontersen[a]	Vutrisiran	Eplontersen vs vutrisiran
Base-case	[redacted]	[redacted]	[redacted]
1-year time horizon	[redacted]	[redacted]	[redacted]
2-year time horizon	[redacted]	[redacted]	[redacted]
10-year time horizon	[redacted]	[redacted]	[redacted]
Inclusion of serious adverse events	[redacted]	[redacted]	[redacted]
Excluding TTD	[redacted]	[redacted]	[redacted]

Footnote: [a]Results based on eplontersen at with-PAS price.
Abbreviations: BSC: Best supportive care; TTD: Time to Treatment Discontinuation; vs: versus.

B.4.5 Subgroup analysis

Subgroup analyses were not included in the CCA.

B.4.6 Interpretation and conclusions of economic evidence

The clinical effectiveness of eplontersen is comparable to that of vutrisiran (as shown Section B.3.9) for the treatment of adults with ATTRv-PN. Costs are equivalent for the initial administration of both treatments at the NAC but are reduced with eplontersen subsequent doses as these are self-administered by the patient or their caregiver.

Treatment costs are examined over a 5-year time horizon in the base-case, in keeping with the time horizon for the base case analysis of vutrisiran in TA868.[12] The analysis was conducted from a UK NHS and PSS perspective, with all model inputs representing and comparing current clinical practice for vutrisiran and expected clinical practice for eplontersen.

Results from the base case analysis demonstrate cumulative cost-savings of [redacted] for treatment with eplontersen over 5 years, compared to treatment with vutrisiran. These cost savings are attributed to the reduced acquisition cost for eplontersen ([redacted]), and drug administration costs ([redacted]). The scenario analysis demonstrates that cost savings are maintained for patients treated with eplontersen when the model considers a one-year, two-year or 10-year time-horizon. Cost savings associated with the treatment of eplontersen are also demonstrated when TTD is excluded, and when serious AEs are included. Results from the OWSA showed that variability in administration costs had a small impact on the estimated difference in costs between eplontersen and vutrisiran, with no incremental difference exceeding [redacted] over a 5-year period.

Eplontersen offers a clinically effective and safe treatment option for patients with ATTRv-PN that can be self-administered without the need for HCP involvement. Consequently, the self-administration profile of eplontersen provides patients with greater autonomy compared to

vutrisiran, whilst reducing the financial and resource use burden associated with homecare delivery of treatment.

References

1. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022.
2. AstraZeneca UK Ltd. Data on File. ID: REF-218954. February 2024.
3. National Institute for Health and Care Excellence. Eplontersen for treating hereditary transthyretin amyloidosis [ID6337]: Response to stakeholder organisation comments on the draft remit and draft scope. Available from: https://www.nice.org.uk/guidance/gid-ta11392/documents/scope-consultation-comments-and-responses. Last accessed: February 2024. 2024.
4. Coelho T, Ando Y, Benson MD, et al. Design and Rationale of the Global Phase 3 NEURO-TTRansform Study of Antisense Oligonucleotide AKCEA-TTR-L(Rx) (ION-682884-CS3) in Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. Neurology and Therapy 2021;10:375-389.
5. Crooke ST, Baker BF, Xia S, et al. Integrated Assessment of the Clinical Performance of GalNAc(3)-Conjugated 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides: I. Human Volunteer Experience. Nucleic Acid Therapeutics 2019;29:16-32.
6. Luigetti M, Conte A, Del Grande A, et al. TTR-related amyloid neuropathy: Clinical, electrophysiological and pathological findings in 15 unrelated patients. Neurological Sciences 2013;34:1057-1063.
7. 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. Current Opinion in Neurology 2016;29 Suppl 1:S3-S13.
8. Akinrodoye MA, Lui F. Neuroanatomy, Somatic Nervous System. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., 2022.
9. Lovley A, Raymond K, Guthrie SD, et al. Patient-reported burden of hereditary transthyretin amyloidosis on functioning and well-being. Journal of Patient-Reported Outcomes 2021;5:3.
10. Waxenbaum JA, Reddy V, Varacallo M. Anatomy, Autonomic Nervous System. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., 2022.
11. UK ATTR Amyloidosis Patients Association. About ATTR Amyloidosis: Hereditary amyloidosis, 2021.
12. National Institute for Health and Care Excellence. TA868. Vutrisiran for treating hereditary transthyretin-related amyloidosis. Committee Papers. Available at: https://www.nice.org.uk/guidance/ta868/documents/committee-papers. Accessed: June 2023., 2023.
13. Dodet P, Adams D, Redolfi S, et al. Sleep disorders in patients with hereditary transthyretin amyloid neuropathy. Journal of the Peripheral Nervous System 2015:129-129.
14. Lopes A, Fonseca I, Sousa A, et al. Psychopathological Dimensions in Portuguese Subjects with Transthyretin Familial Amyloid Polyneuropathy. Biomedicine Hub 2017;2:1-14.
15. Yarlas A, Gertz M, Dasgupta N, et al. Burden of Hereditary Transthyretin Amyloidosis on Quality of Life. Muscle & Nerve 2019;60.
16. Acaster S, Lo SH, Nestler-Parr S. A survey exploring caregiver burden and health-related quality of life in hereditary transthyretin amyloidosis. Orphanet Journal of Rare Diseases 2023;18:17.
17. Inês M, Coelho T, Conceição I, et al. Societal costs and burden of hereditary transthyretin amyloidosis polyneuropathy. Amyloid 2020;27:89-96.

18. National Institute for Health and Care Excellence. HST10. Patisiran for treating hereditary transthyretin amyloidosis 2019.

19. National Institute for Health and Care Excellence. HST9. Inotersen for treating hereditary transthyretin amyloidosis. 2019.

20. AstraZeneca UK Ltd. Data on File. ID: REF-218937. February 2024.

21. Gertz M, Adams D, Ando Y, et al. Avoiding misdiagnosis: Expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner. BioMed Central Family Practice 2020;21:198.

22. Hawkins PN, Ando Y, Dispenzeri A, et al. Evolving landscape in the management of transthyretin amyloidosis. Annals of Medicine 2015;47:625-38.

23. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. Journal of Neurology 2021;268:2109-2122.

24. Magalhães J, Eira J, Liz M. The role of transthyretin in cell biology: impact on human pathophysiology. Cellular and Molecular Life Sciences 2021;78.

25. Adams D, Koike H, Slama M, et al. Hereditary transthyretin amyloidosis: A model of medical progress for a fatal disease. Nature Reviews Neurology 2019;15:387-404.

26. CADTH. Clinical Review Report: Inotersen (Tegsedi): (Akcea Therapeutics, Inc.): Indication: Stage I or II polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2020.

27. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: A multinational natural history study. Neurology 2015;85:675-82.

28. Coutinho PS, AMd; Lopes, J. Forty years of experience with type I amyloid neuropathy. Review of 483 cases. Amyloid and Amyloidosis. Excerpta Medica 1980.

29. Dohrn MF, Auer-Grumbach M, Baron R, et al. Chance or challenge, spoilt for choice? New recommendations on diagnostic and therapeutic considerations in hereditary transthyretin amyloidosis with polyneuropathy: The German/Austrian position and review of the literature. Journal of Neurology 2021;268:3610-3625.

30. Wixner J, Mundayat R, Karayal ON, et al. THAOS: gastrointestinal manifestations of transthyretin amyloidosis-common complications of a rare disease. Orphanet journal of rare diseases 2014;9:1-9.

31. Adams D, Algalarrondo V, Polydefkis M, et al. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet journal of rare diseases 2021;16:1-17.

32. Rintell D, Heath D, Braga Mendendez F, et al. Patient and family experience with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) amyloidosis: Results of two focus groups. Orphanet Journal of Rare Diseases 2021;16:70.

33. Stewart M, Shaffer S, Murphy B, et al. Characterizing the High Disease Burden of Transthyretin Amyloidosis for Patients and Caregivers. Neurology and Therapy 2018;7:349-364.

34. Coelho T, Conceição I, Waddington-Cruz M, et al. A natural history analysis of asymptomatic TTR gene carriers as they develop symptomatic transthyretin amyloidosis in the Transthyretin Amyloidosis Outcomes Survey (THAOS). Amyloid 2022;29:228-236.

35. Galan L, Gonzalez-Moreno J, Martínez-Sesmero JM, et al. Estimating the annual economic burden for the management of patients with transthyretin amyloid polyneuropathy in Spain. Expert Review of Pharmacoeconomics & Outcomes Research 2021;21:967-973.

36. Di Stefano V, Lupica A, Alonge P, et al. Genetic screening for hereditary transthyretin amyloidosis with polyneuropathy in western Sicily: Two years of experience in a neurological clinic. European Journal of Neurology 2023.

37. Hazenberg B. The cost of disease progression n ATTRv amyloidosis. Department of Internal Medicine UMCG 2020.

38. Bolte FJ, Langenstroer C, Friebel F, et al. Patient-reported outcomes on familial amyloid polyneuropathy (FAP). Orphanet Journal of Rare Diseases 2020;15:287.

39. Waddington-Cruz M, Ando Y, Amass L, et al. Feasibility of assessing progression of transthyretin amyloid polyneuropathy using nerve conduction studies: Findings from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Journal of the Peripheral Nervous System 2021;26:160-166.

40. Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. Journal of Neurology 2013;260:2802-14.

41. Yarlas A, Lovley A, McCausland K, et al. Early Data on Long-term Impact of Inotersen on Quality-of-Life in Patients with Hereditary Transthyretin Amyloidosis Polyneuropathy: Open-Label Extension of NEURO-TTR. Neurology and Therapy 2021;10:865-886.

42. Waddington-Cruz M, Schmidt H, Botteman MF, et al. Epidemiological and clinical characteristics of symptomatic hereditary transthyretin amyloid polyneuropathy: A global case series. Orphanet Journal of Rare Diseases 2019;14:34.

43. Coelho T, Waddington Cruz M, Chao CC, et al. Characteristics of Patients with Hereditary Transthyretin Amyloidosis-Polyneuropathy (ATTRv-PN) in NEURO-TTRansform, an Open-label Phase 3 Study of Eplontersen. Neurology and Therapy 2023;12:267-287.

44. Elmoamly S, Obici L. Amyloidosis: Pathogenesis, Types, and Diagnosis. Paraproteinemia and Related Disorders: Springer, 2022:101-112.

45. European Medicines Agency. Tegsedi: EPAR - Product information 2018

46. European Medicines Agency. Amvuttra (vutrisiran). Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf. Last Accessed: January 2024.

47. European Medicines Agency. Onpattro: EPAR - Medicine Overview. 2018.

48. European Medicines Agency. Amvuttra: EPAR - Medicine Overview. 2022.

49. AstraZeneca DoF. Eplontersen: Summary of Product Characteristics (SmPc).

50. Holmes J. The NHS crisis has been years in the making. Volume 380: British Medical Journal Publishing Group, 2023.

51. Clinicaltrials.gov. NEURO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. Available at: https://clinicaltrials.gov/ct2/show/study/NCT04136184. Accessed: November 2022.

52. AstraZeneca DoF. Clinical Study Report: 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 (Final Analysis). 2023.

53. Coelho T, Marques W, Dasgupta NR, et al. Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. JAMA 2023.

54. 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.

55. ClinicalTrials.gov. Evaluate the Safety and Tolerability, as Well as the Pharmacokinetic and Pharmacodynamic Profiles of Single and Multiple Doses of Eplontersen Administered Subcutaneously to Healthy Volunteers and Patients With Hereditary Transthyretin-Mediated Amyloidosis (hATTR). ClinicalTrials.gov identifier: NCT03728634. Volume 2023, 2024.

56. AstraZeneca Data on File. Statistical Analysis Plan (v2.3): 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, 2023.

57. Clinicaltrials.gov. Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy (NCT01737398). Available at: https://clinicaltrials.gov/study/NCT01737398. Accessed: October 2023.

58. Khella S, Marques Jr W, Dasgupta NR, et al. Eplontersen in hereditary ATTR-polyneuropathy: week 66 final analysis of the phase 3 NEURO-TTRansform study, In 2023 Annual Meeting of the American Academy of Neurology (AAN), 2023.

59. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. New England Journal of Medicine 2018;379:22-31.

60. AstraZeneca UK Ltd. Data on File. Clinical Study Report. Table 1.17. Summary of Concomitant Medications by Preferred Term.

61. AstraZeneca DoF. Statistical Analysis Plan (v2.3): 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. 2023.

62. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York, 2008.

63. Carroll A, Dyck PJ, De Carvalho M, et al. Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis. Journal of Neurology, Neurosurgery & Psychiatry 2022;93:668-678.

64. Tóthová C, Nagy O. Transthyretin in the evaluation of health and disease in human and veterinary medicine. Pathophysiology-Altered Physiological States: IntechOpen, 2017.

65. Dyck PJB, González-Duarte A, Obici L, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: from NIS to mNIS+ 7. Journal of the neurological sciences 2019;405:116424.

66. Suhr OB, Conceição IM, Karayal ON, et al. Post hoc analysis of nutritional status in patients with transthyretin familial amyloid polyneuropathy: impact of tafamidis. Neurology and therapy 2014;3:101-112.

67. Von Haehling S, Ebner N, Dos Santos MR, et al. Muscle wasting and cachexia in heart failure: mechanisms and therapies. Nature Reviews Cardiology 2017;14:323-341.

68. Ogura K, Yakoub MA, Christ AB, et al. What are the minimum clinically important differences in SF-36 scores in patients with orthopaedic oncologic conditions? Clinical orthopaedics and related research 2020;478:2148.

69. Dyck PJB, Coelho T, Waddington Cruz M, et al. Neuropathy symptom and change: Inotersen treatment of hereditary transthyretin amyloidosis. Muscle & Nerve 2020;62:509-515.

70. Phillippo D, Ades T, Dias S, et al. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. 2016.

71. Deeks J, Higgins J, (editors) DA. Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions. Volume 6.3, 2022.

72. Campbell CM, LoRusso S, Dispenzieri A, et al. Sex Differences in Wild-Type Transthyretin Amyloidosis: An Analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Cardiol Ther. 2022;11:393-405.

73. Dispenzieri A, Coelho T, Conceição I, et al. Clinical and genetic profile of patients enrolled in the Transthyretin Amyloidosis Outcomes Survey (THAOS): 14-year update. Orphanet Journal of Rare Diseases 2022;17:236.

74. Ungerer MN, Hund E, Purrucker JC, et al. Real-world outcomes in non-endemic hereditary transthyretin amyloidosis with polyneuropathy: a 20-year German single-referral centre experience. Amyloid 2021;28:91-99.

75. Benson MD, Dasgupta NR, Rao R. Diagnosis and Screening of Patients with Hereditary Transthyretin Amyloidosis (hATTR): Current Strategies and Guidelines. Ther Clin Risk Manag 2020;14:749-758.

76. Amass L, Li H, Gundapaneni BK, et al. Influence of baseline neurologic severity on disease progression and the associated disease-modifying effects of tafamidis in patients with transthyretin amyloid polyneuropathy. Orphanet Journal of Rare Diseases 2018;13:225.

77. Quan D, Obici L, Berk JL, et al. Impact of baseline polyneuropathy severity on patisiran treatment outcomes inthe APOLLO trial. Amyloid 2022.

78. Clinicaltrials.gov. A Study to Assess the Long-Term Safety and Efficacy of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Patients With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. Accessed from: https://www.clinicaltrials.gov/study/NCT05071300. Accessed on: October 2023.

79. Medicines Healthcare Regulatory Agency (MHRA). Amvuttra (vutrisiran). Summary of Product Characteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/8960be212216be27fd25941d615e1ad645631ad3. Date accessed: December 2023.

80. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation. Last Accessed: December 2023.

81. National Institute for Health and Care Excellence. British National Formulary. Vutrisiran. Available at: https://bnf.nice.org.uk/drugs/vutrisiran/medicinal-forms/. Last Accessed: December 2023.

82. Electronic Medicines Compendium. Amvuttra 25 mg solution for injection in pre-filled syringe. 2023. Available at: https://www.medicines.org.uk/emc/product/14060. Last Accessed: December 2023.

83. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2022. Available at: https://kar.kent.ac.uk/100519/1/Unit%20Costs%20of%20health%20and%20Social%20Care%202022%20%28amended%2013%20July%202023%29.pdf. Last Accessed: December 2023.

84. NHS Employers. Mileage allowances FAQs. 2023. Available at: https://www.nhsemployers.org/articles/mileage-allowances-faqs. Last Accessed: December 2023.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Eplontersen for treating hereditary transthyretin-related amyloidosis [ID 6337]

Addendum

Corrected results: mNIS+7 composite score ITC results

April 2024

File name	Version	Contains confidential information	Date
ID6337_Eplontersen_NICE_ Addendum [CON_REDACTED]	Final	Yes	18th April 2024

Summary of corrections and impact to results

The Company has identified an error in its results for the Modified Neuropathy Impairment Score+7 (mNIS+7) with re-scoring at Week 85, where some patients were not being re-scaled correctly and still had the Ionis version mNIS+7 composite score in the indirect treatment comparison (ITC). Corrected results for Eeek 85 were provided to NICE 17 April. On further investigation this issue also impacts results at Week 66.

The Company apologises for this error and has provided corrected results to NICE as soon as possible. These corrections have minimal impact on the mNIS+7 results, and all results are numerically closer to null or favour eplontersen. Therefore, all corrected results continue to demonstrate comparability between eplontersen and vutrisiran, supporting the original conclusions. For completeness the Company has provided a single addendum with all corrected results.

The Company can confirm the mNIS+7 re-scaling prior to Week 66 is not impacted.

Please see Table 1 for the summary of corrected Tables/Figures in this addendum and the corresponding Tables/Figures in the company submission and EAG clarification questions response.

Company submission corrections: The results of the main ITC of mNIS+7 composite score and responder analysis at Week 80 (extrapolated from Week 66) between eplontersen and vutrisiran are consistent after the correction of the re-scaling of mNIS+7 composite score, for the matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) and both Reference and Alternative models. The point estimates shift in favour of eplontersen and the confidence intervals continue to encompass the null hypothesis of no difference, supporting the conclusion of comparability between eplontersen and vutrisiran.

EAG clarification questions response corrections: The results of the ITC including additional requested variables, of mNIS+7 composite score at Week 80 (extrapolated from Week 66) between eplontersen and vutrisiran, are consistent after the correction of the re-scaling of mNIS+7 composite score. The results of the ITC of mNIS+7 composite score using data at Week 66 or Week 85 without extrapolation, between eplontersen and vutrisiran, are consistent after the correction of the re-scaling of mNIS+7 composite score. Similarly, the point estimates shift in favour of eplontersen and the confidence intervals continue to encompass the null hypothesis of no difference, supporting the conclusion of comparability between eplontersen and vutrisiran.

Table 1: Summary of corrected Tables/Figures in this addendum and the corresponding Tables/Figures in the company submission and EAG clarification questions response

Corrected Table/Figure in Addendum	Corresponding Section and Table/Figure in Company Submission	Corresponding Question and Table/Figure in EAG Clarification Questions Response
Table 2	Section B.3.9.2; Table 26	N/A
Table 3	Section B.3.9.4; Table 29	N/A
Figure 1	Section B.3.9.4; Figure 22	N/A
Figure 2	Section B.3.9.4; Figure 23	N/A
Table 4	Section B.3.9.4; Table 30	N/A
Figure 3	Section B.3.9.4; Figure 24	N/A
Figure 4	Section B.3.9.4; Figure 25	N/A
Table 5	N/A	Question A1; Table 1
Table 6	N/A	Question A3; Table 4
Table 7	N/A	Question A3; Table 11
Table 8	N/A	Question A7; Table 17
Figure 5	N/A	Question A10; Figure 2
Figure 6	N/A	Question A10; Figure 7

Corrections to the Company Submission

Table *2*: Summary of adjustment variables used in reference and alternative models

Outcome	Reference model variables	Alternative model variables	Reference AIC	Alternative AIC
mNIS+7 outcomes				
mNIS+7 composite score	Age, sex, race, FAP stage, V50M mutation, previous treatment, cardiac involvement, mNIS+7 at baseline	Sex, previous treatment, FAP stage, baseline mNIS+7	810	805
mNIS+7 composite score responder analysis		Age, sex, race, previous treatment	190	186

Abbreviations: AIC: Akaike Information Criterion; FAP: familial amyloidotic polyneuropathy; mNIS+7: Modified Neuropathy Impairment Score+7; V50: Val50 genetic mutation.

Table 3: Trial population adjustments for mNIS+7 composite score analysis.[a] Imputation: multiple imputation of mean difference. Time adjustment: linear extrapolation to Week 80

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.25	[redacted]	[redacted]
Age (SD)	13.20	15.01	[redacted]	[redacted]
Sex (proportion male)	0.65	0.69	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.59	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.72	[redacted]	[redacted]
FAP I (proportion)	0.70	0.82	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]
Baseline mNIS+7 (mean)[a]	60.55	66.32	[redacted]	[redacted]
Baseline mNIS+7 (SD) [a]	35.99	35.38	[redacted]	[redacted]

Footnote: [a] mNIS+7 values are $mNIS+7_{Alnylam}$. **Abbreviations**: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; mNIS+7: modified neuropathy impairment score; SD: standard deviation.

Figure 1: Mean difference in CfB in mNIS+7 composite score at Week 80 between eplontersen and vutrisiran using unanchored MAIC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 2. The alternative model adjusted for sex, prior treatment, FAP stage, baseline mNIS+7.
Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NIS: neuropathy impairment score; PF: prognostic factors; TEM: treatment effect modifier.

Figure 2. Mean difference in CfB in mNIS+7 composite score at Week 80 between eplontersen and vutrisiran using unanchored STC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 2. The alternative model adjusted for sex, prior treatment, FAP stage, mNIS+7 at baseline.
Abbreviations: CfB: change from baseline; CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; NIS: neuropathy impairment score; PF: prognostic factors; STC: simulated treatment comparison TEM: treatment effect modifier.

Table 4: Trial population adjustments for mNIS+7 responder analysis.[a] Imputation: multiple imputation of mean difference. Time adjustment: linear extrapolation to Week 80

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=141)	Eplontersen adjusted	
			Reference (ESS=[redacted])	Alternative (ESS=[redacted])
Age (mean)	57.80	52.25	[redacted]	[redacted]
Age (SD)	13.20	15.01	[redacted]	[redacted]
Sex (proportion male)	0.65	0.69	[redacted]	[redacted]
Race (proportion white)	0.71	0.77	[redacted]	[redacted]
V50M mutation (proportion)	0.44	0.59	[redacted]	[redacted]
Prior treatment (proportion)	0.62	0.72	[redacted]	[redacted]
FAP I (proportion)	0.70	0.82	[redacted]	[redacted]
Cardiac involvement (proportion)	0.33	0.16	[redacted]	[redacted]
Baseline mNIS+7 (mean)[a]	60.55	66.32	[redacted]	[redacted]
Baseline mNIS+7 (SD) [a]	35.99	35.38	[redacted]	[redacted]

Footnote: [a]mNIS+7 values are $mNIS+7_{Alnylam}$. **Abbreviations**: ESS: effective sample size; FAP: familial amyloidotic polyneuropathy; mNIS+7: modified neuropathy impairment score; SD: standard deviation.

Figure 3. Log OR for mNIS+7 response (defined as a decrease from baseline) at Week 80 between eplontersen and vutrisiran using unanchored MAIC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 2. The alternative model adjusted for age, sex, race, prior treatment.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NIS: neuropathy impairment score; OR: odds ratio; PF: prognostic factors; TEM: treatment effect modifier.

Figure 4: Log OR for mNIS+7 response (defined as a decrease from baseline) at Week 80 between eplontersen and vutrisiran using unanchored STC for both the reference and alternative ITC model

Footnotes: The reference model adjusted for all PFs and TEMs identified by clinicians, as presented in Table 2. The alternative model adjusted for age, sex, race, prior treatment.
Abbreviations: CI: confidence interval; FAP: familial amyloidotic polyneuropathy; ITC: indirect treatment comparison; NIS: neuropathy impairment score; OR: odds ratio; PF: prognostic factors; STC: simulated treatment comparison TEM: treatment effect modifier.

Corrections to the EAG clarification questions

Table 5: MAICs including additional variables identified in question A1a

Endpoint	Model variables	Point estimate	Lower 95% CI	Upper 95% CI
mNIS+7 change from baseline	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30M mutation • NT-proBNP baseline (>3000) • Cardiac population • mNIS+7 baseline	[redacted]	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7 Ionis version was rescored to approximately match mNIS+7 Alnylam version. Negative values favour eplontersen and positive values favour vutrisiran, for all endpoints.
Abbreviations: CI, confidence interval; FAP, familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; NT-proBNP, N-terminal pro b-type natriuretic peptide; V30/V50, Val30/Val50 genetic mutation.

Table 6: Baseline characteristics before and after applying the original reference MAIC, for change from baseline in mNIS+7 composite score

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline TTR (mean)	206.110	[redacted]	[redacted]
Baseline TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (50 - 100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline Norfolk (SD)	47.100	[redacted]	[redacted]
Baseline Norfolk (mean)	26.300	[redacted]	[redacted]
Baseline R-ODS (SD)	34.100	[redacted]	[redacted]
Baseline R-ODS (mean)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7 Ionis version was rescored to approximately match mNIS+7 Alnylam version. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline mNIS+7 composite score.

Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 7: Baseline characteristics before and after applying the new MAIC with additional variables identified in question A1a, for change from baseline in mNIS+7 composite score

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline TTR (mean)	206.110	[redacted]	[redacted]
Baseline TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (50 - 100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline Norfolk (SD)	47.100	[redacted]	[redacted]
Baseline Norfolk (mean)	26.300	[redacted]	[redacted]
Baseline R-ODS (SD)	34.100	[redacted]	[redacted]
Baseline R-ODS (mean)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7 Ionis version was rescored to approximately match mNIS+7 Alnylam version. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, and baseline mNIS+7 composite score.

Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 8: MAICs without extrapolation

Endpoint	Model	Point estimate	Lower 95% CI	Upper 95% CI
Using data at week 66				
mNIS+7 composite score	Reference	[redacted]	[redacted]	[redacted]
	Alternative	[redacted]	[redacted]	[redacted]
Using data at week 85				
mNIS+7 composite score	Reference	[redacted]	[redacted]	[redacted]
	Alternative	[redacted]	[redacted]	[redacted]

Footnotes: Adjustment variables included in the reference model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline measurement of the outcome (mNIS+7 composite score or Norfolk QoL-DN total score). Adjustment variables included in the alternative model for mNIS+7 using week 66 data without extrapolation were: sex, prior treatment, FAP stage and baseline mNIS+7 composite score. Adjustment variables included in the alternative model for mNIS+7 using week 85 data were: age, sex, prior treatment, FAP stage and baseline mNIS+7 composite score.
Abbreviations: CI, confidence interval; FAP, familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; V30/V50, Val30/Val50 genetic mutation.

Figure 5: Histogram of patient weights, after applying the original reference MAIC, for change from baseline in mNIS+7 composite score

Footnotes: Adjustment variables included in model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline mNIS+7 composite score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; V30/V50, Val30/Val50 genetic mutation.

Figure 6: Histogram of patient weights, after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in mNIS+7 composite score

Footnotes: Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, and baseline mNIS+7 composite score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Eplontersen for treating polyneuropathy caused by hereditary transthyretin-related amyloidosis [ID 6337]

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID6337_Eplontersen_NICE_SIP [noCON]	Final	No	26th February 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Eplontersen

Brand name: Not yet known

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

The medicine is under consideration for the treatment of adult patients with **polyneuropathy** associated with **hereditary transthyretin-related amyloidosis** (ATTRv).

Hereditary **amyloidosis** is a **genetic disease**, resulting from **inherited changes** called **mutations** in the **gene** that makes a **protein** called **transthyretin**. There are two types of hereditary amyloidosis:

- Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN): patients mainly experience damage to the **nerves** outside of the brain and spinal cord (known as **peripheral nerves)**.
- Hereditary transthyretin amyloidosis with **cardiomyopathy** (ATTRv-CM): patients mainly experience damage to the heart.

In addition to ATTRv, there is another form of transthyretin amyloidosis, called wild-type transthyretin amyloidosis (ATTRwt). ATTRwt tends to occur in older individuals, and is not

caused by a mutation in the gene that makes transthyretin. (1) ATTRwt is not relevant to this submission.

In this submission, eplontersen is being considered for patients with Stage 1 or Stage 2 ATTRv-PN. Further details about the condition and staging are provided in **Section** Error! Reference source not found. and **2b**) Diagnosis of the condition (in relation to the medicine being evaluated) of this document.

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section**

4b) Glossary of terms). Cross-references to other sections or documents are highlighted in **orange**.

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

The **Medicines and Healthcare products Regulatory Agency** (**MHRA**) is reviewing whether eplontersen should be approved and granted **marketing authorisation** as a treatment for adults with hereditary transthyretin-related amyloidosis. The **marketing authorisation** for eplontersen is therefore pending. Further details can be found in **Section B.1.2** of the Company Submission.

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

AstraZeneca UK Limited engages with the following patient advocacy group in amyloidosis, with the aims of strengthening patient insights and responding to requests for information: Amyloidosis UK (formerly UPATPA).

AstraZeneca has worked with, and provided honoraria to, members of Amyloidosis UK to gain insights into the experiences and perspectives of patients living with amyloidosis and their caregivers in the UK.

Funding provided to UK patient groups is published annually on our website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

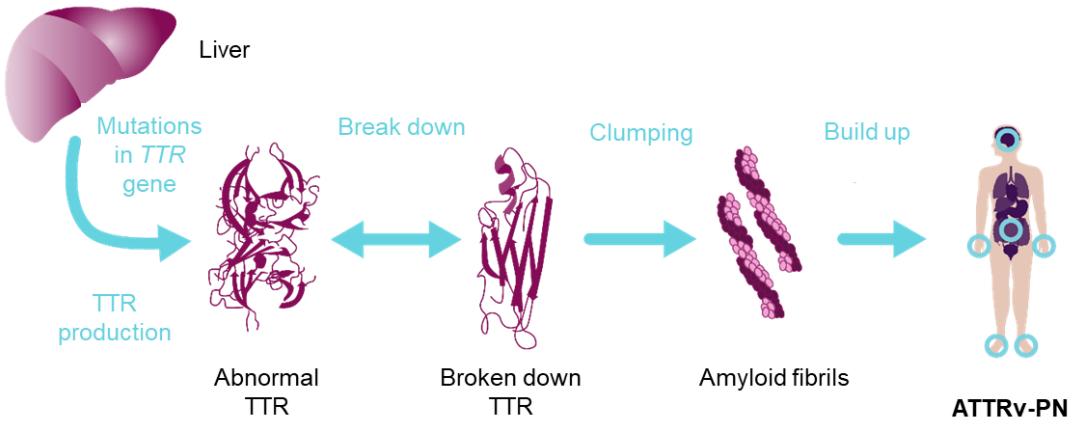
Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly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

What is hereditary transthyretin amyloidosis with polyneuropathy?

Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a chronic, progressive life-threatening condition that results from inherited mutations in the gene that makes a protein called transthyretin (TTR). There are multiple types of amyloidosis and hereditary amyloidosis refers to the genetic form of the disease. (2, 3)

Transthyretin is a normal protein that is made in the liver, then released into the blood stream. In ATTRv-PN, inherited mutations result in an abnormal form of the TTR protein being produced. (2, 3) The abnormal protein is less stable and can break apart, resulting in the protein pieces clumping together to form amyloid fibrils. (4) In ATTRv-PN, the amyloid fibrils mainly build up in the peripheral nerves can result in worsening and permanent polyneuropathy. (2, 3) An illustration of this process is shown in Error! Reference source not found..

Figure 1: An overview of the process which leads to ATTRv-PN



Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; TTR: transthyretin.
Source: Adapted from Garcia-Pavia 2021 (5)

How common is ATTRv-PN?

ATTRv-PN is an **endemic** disease, meaning it is commonly found in a specific group of people or region. The mutation that causes ATTRv-PN is more common in some populations and regions than others. (4) In the UK, ATTRv-PN is rare with approximately

210 patients diagnosed with the disease. (6) Individuals of Irish descent exhibit the most common genetic mutation in the UK. This mutation is known as T80A (previously known as T60A). (7, 8)

What is the impact of ATTRv-PN?

Life expectancy

Historically, patients with ATTRv-PN have been expected to live for approximately five years after diagnosis, ranging from three to 15 years after symptoms begin. (9) It is important to note that diagnosis can take many years, meaning that patients may have lived with ATTRv-PN for multiple years before diagnosis.

Symptoms of ATTRv-PN and their physical impact

The build-up of amyloid fibrils in peripheral nerves affects both the voluntary and involuntary branches of the nervous system, meaning that ATTRv-PN affects multiple organ systems and body functions. (10, 11) The first symptoms of ATTRv-PN vary but may include pain, pins and needles, and numbness in the hands and feet. (12) Patients can develop problems relating to cardiac, kidney, central nervous system and visual function. (4) Autonomic symptoms include sexual dysfunction and **orthostatic hypotension** (sudden drops in blood pressure that occur when an individual stands up after sitting or lying down), which can result in fainting. (13) Patients with ATTRv-PN may also experience digestive problems, including constipation, diarrhoea and loss of voluntary control over bowel function, all of which can result in serious malnutrition. (14)

ATTRv-PN is progressive and irreversible, meaning the condition worsens from the onset of symptoms. The progression of ATTRv-PN is typically experienced as sensory loss, loss of automatic responses to environmental changes (**reflexes**), reduced body control and movement and muscle weakness. (12) Historically, patients with ATTRv-PN have typically required support with walking within 3–5 years of symptom onset and have utilised a wheelchair for mobility within 5–10 years of symptom onset. (15)

Impact on quality of life

The severe and debilitating symptoms caused by ATTRv-PN are associated with a large quality of life impact for patients. The disease has a large impact on patients' mobility and physical functioning, and patients may avoid leaving their home as a result of their symptoms. In research, the physical and mental health of patients are referred to as **health-related quality of life (HRQoL).** The HRQoL of patients are typically measured through patient questionnaires, and their scores are compared to those of the general population to assess the impact of disease. A study investigating the HRQoL of patients with ATTRv-PN found HRQoL was significantly worse in patients with ATTRv-PN compared to the general population, and the greatest differences were observed for scores relating to physical functioning. (16)

In addition to the physical symptoms associated with the disease, ATTRv-PN also significantly impacts patients' mental and emotional health. Patients with ATTRv-PN are at greater risk of experiencing psychological distress and mental health problems compared

to the general population. In particular, anxiety and depression are more common in patients with ATTRv-PN compared to the general population and are most common in patients with more advanced disease. (16-18)

Finally, due to the impact on mobility and physical functioning, ATTRv-PN reduces the ability of individuals to work. One clinical study reported that 69% of patients with ATTRv-PN were unable to work. (13)

Impact on families and carers

Progression of ATTRv-PN results in a decline in patients' independence and requires extensive support from caregivers. A study exploring the care received by patients with ATTRv-PN reported that patients required an average of 45.9 hours of caregiver time per week. (19) The time spent caring for patients limits the employment opportunities of caregivers and can place a significant burden on carers' emotional wellbeing. Families and carers of patients with ATTRv-PN are more likely to experience problems sleeping and stress when compared with caregivers of patients with chronic conditions. (20) Additionally, family members have reported feelings of loss, associated with the negative impact of ATTRv-PN on their relative's life. (19-21) The impact on caregivers' mental and physical health is estimated to be similar to that of caregivers of people with Alzheimer's disease. (20)

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

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

How is ATTRv-PN diagnosed?

Since ATTRv-PN is a rare disease with symptoms that are shared with other conditions, it can be difficult to diagnose and can be confused with other diseases.

In the UK, if ATTRv-PN is suspected in an individual, they will be referred to a specialised medical centre in London called the **National Amyloidosis Centre (NAC)**. The NAC is a health service that diagnoses and treats all patients with ATTRv-PN.

Diagnosis of ATTRv-PN involves multiple tests which typically include (22, 23):

- Tissue samples**:** a small sample, known as a **biopsy**, is taken from the individual's tissues to identify amyloid deposits and determine which protein is causing the deposits
- Genetic tests: since ATTRv-PN is caused by an inherited mutation, a genetic test is used to determine the type of mutation causing the production of abnormal TTR
- **Amyloid typing**: amyloidosis is common to multiple conditions and typing by light microscopy immunohistochemistry or immunoelectron microscopy is conducted to determine the specific type of amyloidosis

Staging

Several systems have been developed to group patients with ATTRv-PN into stages, based on the severity of disease. The three main **staging systems** are:

- The Coutinho scale: stages 0–3 (24)
- The familial amyloidotic polyneuropathy (FAP) scale: stages 0–3 (15)
- The **polyneuropathy disability (PND) score**: stages 0–IV (12)

For each scale, a score of 0 indicates that patients have no symptoms, whilst a higher score reflects worsening symptoms.

2c) Current treatment options:

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for ATTRv-PN?

Current recommended therapies

Historically, some patients with ATTRv-PN were treated with **liver transplants**. However, since the introduction of drugs to treat the disease, liver transplants are rarely used in the UK. (25)

The only group of therapies recommended by NICE for ATTRv-PN are called **silencers**. Examples of silencers include inotersen, patisiran and vutrisiran. Inotersen is rarely used as it is associated with numerous **side effects** and patients receiving inotersen require additional monitoring. Additionally, patisiran is not commonly used as it requires **intravenous** (IV) administration. This is more complicated and time-consuming to give to patients, compared to other treatments like vutrisiran. For example, patients must receive a specialised treatment regimen before each dose of patisiran to reduce the risk of experiencing complications associated with IV administration. (9)

Currently, the majority of patients in the UK with ATTRv-PN are treated with vutrisiran as it is the safest and most convenient silencer currently available. (9, 26) Vutrisiran is administered every three months by **healthcare professionals** (HCPs), meaning that HCPs need to visit the patient's home every three months, after receiving their first dose at the NAC. (9)

As vutrisiran is the main treatment used to treat patients with ATTRv-PN, it is the most relevant treatment to compare eplontersen with.

What is a silencer?

Silencers are a group of drugs that "switch off" the gene which codes for TTR, to prevent the production of abnormal TTR protein. This stops new amyloid fibrils developing and can slow progression of ATTRv-PN. Examples of silencers include: (27)

- Inotersen
- Patisiran
- Vutrisiran

Alternative Therapies

Diflunisal and tafamidis, which belong to a group of therapies called **stabilisers**, can also be used to treat ATTRv-PN. However, these treatments are not recommended for use by NICE and therefore are not available on the NHS. (9)

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

Context:

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

matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

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

Disease from the patient perspective

Physical and mental impact:

The progressive, devastating symptoms associated with ATTRv-PN can have a significant impact on the HRQoL of patients, their caregivers and families, as highlighted in Section 2a) The condition – clinical presentation and impact. In a UK survey, patients with ATTRv-PN describe **neuropathic pain** affecting their sleep: "It's like a constant shooting pain that's going down your feet all the time… And in bed as well, it seems to be worse because it keeps me awake at night". (13) Additionally, muscle weakness can lead to difficulties walking, standing and gripping onto objects: "Now, when I physically start to walk I get really tired, my legs ache, [I] get out of breath." (13)

Bowel and bladder problems also impact patients' day-to-day lives, impacting their sleep and ability to leave the house: "Issues with constipation and diarrhoea, unexpected and just out of the blue… You have to prepare in advance… [I would like] not to have to worry about embarrassing myself in public."(28)

The physical impact of the disease, combined with delays in receiving a diagnosis, and a lack of effective treatments, can seriously affect the emotional well-being of patients. (28, 29) In a survey of 14 patients, the majority reported feelings of fear, anxiety and frustration, which often impaired the ability of individuals to communicate with family and friends and engage in social activities. (28)

The physical and mental impact of ATTRv-PN also affects patients' ability to continue working, with one clinical study reporting 69% of patients as unable to work. (13)

Impact on caregivers and relatives:

As described in Section 2a) The condition – clinical presentation and impact, ATTRv-PN can impact the physical and mental health of patients' carers and relatives. When patients with ATTRv-PN become less independent, they become more reliant on their caregivers and relatives. In a UK survey, caregivers reported "frustration at being restricted to the house for hours yet having nothing to do…the carer couldn't leave in case the patient awoke or arose in their absence." (13)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

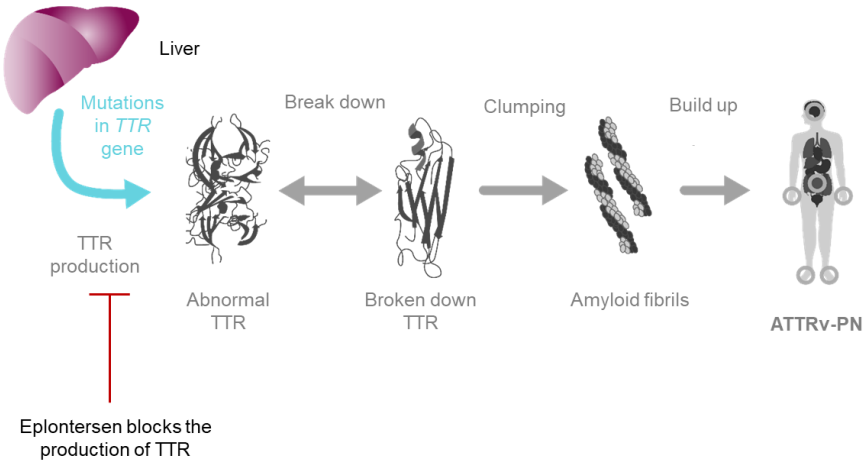
- If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

What is eplontersen and how does it work?

In ATTRv-PN, an abnormal form of the TTR protein is produced, which can break down and form amyloid fibrils. Build-up of these fibrils around the body can cause damage to nerves and other organs, causing symptoms associated with the disease. (4)

Eplontersen is a type of silencer (see Section 2c) containing a small piece of synthetic material which can enter cells, then bind to and block the **genetic information** (or "instructions") in the cell required to produce the TTR protein. Eplontersen is designed to target liver cells, as this is the main site of TTR production in the body. (30, 31) A diagram showing how eplontersen treats ATTRv-PN is shown in Figure 2.

Figure 2: An illustration showing how eplontersen treats ATTRv-PN



Abbreviations: ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; TTR: transthyretin.
Source: Adapted from Garcia-Pavia 2021 (5)

Blocking the production of TTR protein has a number of benefits:

- Shrinking existing amyloid fibrils (27)
- Preventing new amyloid fibrils forming (27)
- Slowing disease progression by protecting organs from further damage (27)
- Relieving symptoms (30)

3b) Combinations with other medicines

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

- Yes / No

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

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

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

Eplontersen is not intended to be used with any other treatment for ATTRv-PN in this patient population.

3c) Administration and dosing

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

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

How is eplontersen taken?

- Eplontersen is delivered once a month as an injection under the patient's skin – this is known as a **subcutaneous injection** (32)
- The injection is delivered via an autoinjector pen at a dose of 45 mg, and can be self-administered into the abdomen or upper thigh, or into the upper arm if administered by a caregiver or HCP
- The first injection is performed under the guidance of an appropriately qualified HCP. Subsequent injections can be self-administered at home, or administered by a caregiver or HCP

3d) Current clinical trials

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

Studies of eplontersen in ATTRv-PN

The NEURO-TTRansform trial (NCT04136184) was an open-label, randomised **clinical trial**, which means that the treatment each patient received in the trial was decided randomly, and that patients knew which treatment they were being treated with. (31) The trial studied how well eplontersen works (its **efficacy**) in treating patients with Stage 1 or Stage 2 ATTRv-PN, the impact eplontersen has on patients' HRQoL and how safe it was compared to a different ATTRv-PN treatment (inotersen). (31)

NEURO-TTRansform was carried out from December 2019 until April 2023, and included 168 patients from 15 different countries. These patients either received eplontersen or inotersen (another drug belonging to the same group as eplontersen; see **Section**

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for ATTRv-PN?

Current recommended therapies

Historically, some patients with ATTRv-PN were treated with **liver transplants**. However, since the introduction of drugs to treat the disease, liver transplants are rarely used in the UK. (25)

The only group of therapies recommended by NICE for ATTRv-PN are called **silencers**. Examples of silencers include inotersen, patisiran and vutrisiran. Inotersen is rarely used as it is associated with numerous **side effects** and patients receiving inotersen require additional monitoring. Additionally, patisiran is not commonly used as it requires **intravenous** (IV) administration. This is more complicated and time-consuming to give to patients, compared to other treatments like vutrisiran. For example, patients must receive a specialised treatment regimen before each dose of patisiran to reduce the risk of experiencing complications associated with IV administration. (9)

Currently, the majority of patients in the UK with ATTRv-PN are treated with vutrisiran as it is the safest and most convenient silencer currently available. (9, 26) Vutrisiran is administered every three months by **healthcare professionals** (HCPs), meaning that HCPs need to visit the patient's home every three months, after receiving their first dose at the NAC. (9)

As vutrisiran is the main treatment used to treat patients with ATTRv-PN, it is the most relevant treatment to compare eplontersen with.

What is a silencer?

Silencers are a group of drugs that "switch off" the gene which codes for TTR, to prevent the production of abnormal TTR protein. This stops new amyloid fibrils developing and can slow progression of ATTRv-PN. Examples of silencers include: (27)

- Inotersen
- Patisiran
- Vutrisiran

Alternative Therapies

Diflunisal and tafamidis, which belong to a group of therapies called **stabilisers**, can also be used to treat ATTRv-PN. However, these treatments are not recommended for use by NICE and therefore are not available on the NHS. (9)

).(31) To be included in the study, patients had to have the following characteristics: (31)

- Aged 18 to 82 years
- Stage 1 or Stage 2 ATTRv-PN
- A mutation in the gene that codes for the TTR protein
- Signs and symptoms associated with ATTRv-PN
- A **neuropathy impairment score** (NIS) of 10 to 130

Some clinical trials will test the effect of a drug by comparing it to a **placebo** (a treatment which appears real but does not treat the disease). Due to the severity of ATTRv-PN, and the availability of proven effective treatments, it was thought to be unethical for some patients in NEURO-TTRansform to receive placebo. Therefore, the effects of eplontersen were compared to inotersen instead. (9) However, the results for patients who received eplontersen in NEURO-TTRansform were also compared to those for patients with Stage 1 or Stage 2 ATTRv-PN who received placebo in another study (NEURO-TTR). (31)

NEURO-TTR (NCT01737398) was a clinical trial which studied how well inotersen works, and how safe it is, as a treatment for ATTRv-PN. (33) In this study, patients were randomly divided into two treatment groups, with one group receiving inotersen and the other receiving placebo. The characteristics required for patients to be included in NEURO-TTR were very similar to those required for NEURO-TTRansform. (33)

More information about NEURO-TTRansform and NEURO-TTR can be found here:

NEURO-TTRansform

- Coelho *et al.,* 2023 (31)
- ClinicalTrials.gov (NEURO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen [Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx] in Participants With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy | ClinicalTrials.gov) (34)

NEURO-TTR

- Benson *et al.,* 2018 (35)
- ClinicalTrials.gov (Study Details | Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy | ClinicalTrials.gov)(33)

3e) Efficacy

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

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

Trial results

In NEURO-TTRansform, the efficacy of eplontersen was measured according to how well it improved various outcomes after patients are treated for a fixed period of time. The key outcomes from the trial are described here:

- Levels of TTR in the **serum** (blood)
- Nerve damage: this was measured using a scale called **modified neuropathy impairment+7** (mNIS+7)
- Symptoms of ATTRv-PN**:** this was measured using the PND staging system (described in **Section 2b**) Diagnosis of the condition (in relation to the medicine being evaluated)) and the **neuropathy symptom and change** (NSC) score
- Weight and levels of nourishment (**nutritional status**): this was measured using a **modified version of body mass index** (mBMI)
- HRQoL: this was measured using two different questionnaires; the **Norfolk Quality of Life-Diabetic Neuropathy** (QoL-DN), 36-Item Short Form Survey Physical Component Summary (SF-36 PCS) and 5-level EQ-5D (EQ-5D-5L) visual analogue scale

As described in **Section 3d**) Current clinical trials, the NEURO-TTRansform trial compared eplontersen against inotersen. However, the results in the following section compare the efficacy of eplontersen against the placebo group of the NEURO-TTR trial. This comparison will indicate whether treatment with eplontersen is better than no treatment at all. A comparison of the efficacy of eplontersen versus vutrisiran is described in the **indirect treatment comparison** section below. Vutrisiran is the most relevant treatment to compare eplontersen with in this submission as it is the only treatment used substantially to treat patients with ATTRv-PN in the UK.

Data from the NEURO-TTRansform trial below are the latest available published data, presented by Coelho *et al*. 2023. (31) There are additional unpublished data from NEURO-TTRansform, including the EQ-5D-5L visual analogue scale scores and indirect treatment comparison results, presented in the Company Submission.

Serum TTR

The aim of eplontersen is to reduce the production of TTR protein (see Section

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for ATTRv-PN?

Current recommended therapies

Historically, some patients with ATTRv-PN were treated with **liver transplants**. However, since the introduction of drugs to treat the disease, liver transplants are rarely used in the UK. (25)

The only group of therapies recommended by NICE for ATTRv-PN are called **silencers**. Examples of silencers include inotersen, patisiran and vutrisiran. Inotersen is rarely used as it is associated with numerous **side effects** and patients receiving inotersen require additional monitoring. Additionally, patisiran is not commonly used as it requires **intravenous** (IV) administration. This is more complicated and time-consuming to give to patients, compared to other treatments like vutrisiran. For example, patients must receive a specialised treatment regimen before each dose of patisiran to reduce the risk of experiencing complications associated with IV administration. (9)

Currently, the majority of patients in the UK with ATTRv-PN are treated with vutrisiran as it is the safest and most convenient silencer currently available. (9, 26) Vutrisiran is administered every three months by **healthcare professionals** (HCPs), meaning that HCPs need to visit the patient's home every three months, after receiving their first dose at the NAC. (9)

As vutrisiran is the main treatment used to treat patients with ATTRv-PN, it is the most relevant treatment to compare eplontersen with.

What is a silencer?

Silencers are a group of drugs that "switch off" the gene which codes for TTR, to prevent the production of abnormal TTR protein. This stops new amyloid fibrils developing and can slow progression of ATTRv-PN. Examples of silencers include: (27)

- Inotersen
- Patisiran
- Vutrisiran

Alternative Therapies

Diflunisal and tafamidis, which belong to a group of therapies called **stabilisers**, can also be used to treat ATTRv-PN. However, these treatments are not recommended for use by NICE and therefore are not available on the NHS. (9)

for further detail on how eplontersen works). Therefore, looking for a decrease in the levels of TTR in the blood can indicate how well eplontersen is working. (31)

After 65 weeks of treatment with eplontersen, TTR levels decreased by 81.7% from baseline, indicating an improvement in disease status. In contrast, TTR levels only decreased by 11.2% in patients treated with placebo and it is possible that this decrease was actually due to **malnourishment**, rather than a change in disease status. (31, 36, 37)

mNIS+7

The mNIS+7 scale measures a variety of components, such as muscle strength, reflexes, how well individuals can feel sensations like touch, vibration and heat. Taken together, these measures are used to indicate whether a patient's nerve damage has progressed and, if so, by how much. An increase in score means the polyneuropathy has worsened, whilst a decrease in score indicates improvement. (31)

After 66 weeks of treatment, the mNIS+7 score for patients receiving eplontersen showed almost no change (+0.3). For the group of patients receiving placebo, the score increased by 25.1. (31)

HRQoL

During NEURO-TTRansform patients were asked to answer questions about their HRQoL, using the Norfolk QoL-DN and SF-36 PCS questionnaires, and EQ-5D-5L visual analogue scale. (31)

The Norfolk QoL-DN questionnaire is completed by patients and is designed specifically to measure HRQoL in patients with **neuropathy**. A higher Norfolk QoL-DN score indicates a poor HRQoL. (31)

SF-36 is a tool used to measure HRQoL and is not specific to a certain disease. The questions in SF-36 that relate to physical health, such as pain and energy, make up the SF-36 PCS A higher SF-36 PCS score indicates better HRQoL. (38) Another tool used to measure general HRQoL is EQ-5D-5L, which consists of a visual analogue scale component. This scale asks patients to label how they feel their HRQoL is, from a score of 0 to 100. A score of 0 means 'the worst health you can imagine', and a score of 100 represents 'the best health you can imagine'. (39)

The Norfolk QoL-DN score reduced by 3.1 after 66 weeks of treatment with eplontersen, indicating an improvement in HRQoL. In contrast, HRQoL consistently worsened over time in patients receiving placebo, with the score increasing by 8.7 after 66 weeks of treatment. (31) Additionally, the indirect treatment comparison described in **Section 3e)** showed that eplontersen was better at improving patients' Norfolk QoL-DN score, compared with vutrisiran.

Similarly, in patients receiving eplontersen, the SF-36 PCS score increased by 0.9 after 65 weeks of treatment, which indicates a small improvement in HRQoL after 65 weeks. However, patients treated with placebo experienced a decrease of 4.5 in SF-36 PCS score, suggesting a worsening in HRQoL. (31)

The EQ-5D-5L visual analogue scale scores also showed that the eplontersen improved the HRQoL of patients over time, because, after 37 and 81 weeks, the score had increased from baseline in patients treated with eplontersen. (40)

PND stage and NSC score

A patient's PND stage (or score) indicates the severity of ATTRv-PN symptoms by looking at how well they are able to move around. A higher stage indicates worsened symptoms. (25, 41) For example, Stage 1 disease means patients are still able to walk, whilst Stage 4 means patients cannot move around without a wheelchair or are unable to leave their bed. (25, 41)

After 65 weeks of treatment, the average increase in PND score was slightly lower for the patients receiving eplontersen, when compared with those receiving placebo. Additionally, more patients who received eplontersen showed an improvement in their PND stage, when compared with the group receiving placebo.(31, 40)

The NSC score is based on a questionnaire which asks patients various questions about their symptoms, including muscle weakness, pain and the inability to feel sensations like touch. An increase in score means symptoms have worsened, whilst a decrease in score indicates improvement.(42)

After 66 weeks of treatment with eplontersen, there was very little change (-0.03) in NSC score, whilst the score increased (+8.2) for patients receiving placebo.(31)

mBMI

The effects of ATTRv-PN on the digestive system mean that patients may experience unintended weight loss and malnourishment. Body mass index is a measure which takes

into account an individual's height and weight and therefore can be used to indicate their nutritional status. mBMI also takes into account levels of a protein called albumin in an individual's serum. This is because low serum albumin can cause fluid build up (**oedema**), increasing a patient's weight and making it difficult to work out if they are malnourished. (43)

Between baseline and Week 65 of eplontersen treatment, mBMI remained fairly stable. However, mBMI declined after 65 weeks of treatment with placebo, which suggests that nutritional status worsened over time for patients receiving placebo. (31)

Additional outcomes measured

A number of other outcomes, such as the **10-Metre Walk Test** (10MWT) and **Composite Autonomic Symptom Score-31** (COMPASS-31), were also assessed in NEURO-TTRansform. Patients treated with eplontersen experienced an improvement in these additional outcomes.

Indirect treatment comparison

When there are no data directly comparing how well two drugs work, an **indirect treatment comparison** may be performed. This is a type of analysis where differences between the studies evaluating each of the two drugs are adjusted for, allowing their outcomes to be compared.

An indirect treatment comparison was performed for eplontersen in the NEURO-TTRansform and vutrisiran in the HELIOS-A trial. Vutrisiran is currently the standard treatment received by patients with ATTRv-PN in England. This comparison was conducted to determine whether eplontersen could provide patients with similar or greater health benefits than vutrisiran. An indirect treatment comparison was also performed to compare the safety of eplontersen and vutrisiran. Further information of this comparison is provided in Section 3g) Safety of the medicine and side effects.

Overall, the results of the indirect treatment comparison showed that eplontersen and vutrisiran have a similar treatment effect and are equally safe in patients with ATTRv-PN.

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

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

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

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

Quality of life impact of eplontersen

In the NEURO-TTRansform study, HRQoL was measured using the Norfolk QoL-DN, SF-36 PCS and EQ-5D-5L visual analogue scale scores. Further detail of these questionnaires, and their results, are available in Section 3e) .(31)

3g) Safety of the medicine and side effects

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

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

Every medicine has its own side effects and the same medicine can produce different reactions in different people. The safety of eplontersen in NEURO-TTRansform was compared to that of vutrisiran in HELIOS-A. These safety results were collected after 85 weeks in NEURO-TTRansform, and after 18 months (~78 weeks) in HELIOS-A. Overall, eplontersen was generally well **tolerated**, and broadly similar to vutrisiran in terms of safety.

The most common side effects, which affected more or equal to 10% of patients in NEURO-TTRansform, are summarised in **Table 1** below. The proportions of patients experiencing these side effects in each treatment group were similar.

Table 1. Summary of the most common side effects experienced by patients during NEURO-TTRansform and HELIOS-A

Side effect	Trial: NEURO-TTRansform	Trial: HELIOS-A
	Eplontersen (144 patients)	Vutrisiran (122 patients)
	Percentage of patients	
COVID-19	33%	Not reported
Diarrhoea	19%	14%
Urinary tract infection	19%	13%
Vitamin A deficiency	12%	Not reported

Nausea	11%	10%

Note: further explanation of the terms in **orange** are provided in the glossary (Section 4b).
Source: Coelho 2023 (NEURO-TTRansform) (31) and Adams 2022 (HELIOS-A) (44)

The proportion of patients who experienced a more serious side effect or stopped their treatment ("discontinued") because of side effects during NEURO-TTRansform is shown in **Table 2**. There was a higher number of more serious side effects in patients who were treated with vutrisiran compared with those receiving eplontersen.

Table 2. Summary of serious side effects and treatment discontinuations during NEURO-TTRansform and HELIOS-A

	Trial: NEURO-TTRansform	Trial: HELIOS-A
	Eplontersen (144 patients)	Vutrisiran (122 patients)
	Percentage of patients	
Serious side effect	19%	26%
Side effect leading to discontinuation	6%	3%

Source: Coelho 2023 (NEURO-TTRansform) (31) and Adams 2022 (HELIOS-A) (44)

An indirect treatment comparison was used to compare the safety of eplontersen and vutrisiran. The indirect treatment comparison showed that eplontersen was at least as safe as vutrisiran as a treatment for ATTRv-PN.

Managing side effects

A very common side effect (may affect more than 1 in 10 people) of eplontersen treatment is a reduction in the levels of vitamin A in the blood. This side effect is manageable with supportive care: patients will take a daily vitamin A supplement during treatment and will have their vitamin A levels monitored. (45)

Common side effects (may affect up to 1 in 10 people) include vomiting, and redness, itching or pain where the injection was given. (45)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Vutrisiran is currently the main treatment offered to patients with ATTRv-PN. However, the administration of vutrisiran has some limitations, as it must be administered by an HCP in

the patient's home, or patients must travel to a medical facility. This can significantly impact the daily lives of patients and their carers as they will need to wait at home, and potentially take time off work, for these regular visits. There is a need for a treatment that can be administered at home, to allow patients to manage their symptoms whilst keeping their independence and normal daily routines for as long as possible. (9)

The key benefits of eplontersen to patients with ATTRv-PN include:

Delayed disease progression and symptom improvement: Results from the NEURO-TTRansform trial highlight that eplontersen is effective in slowing down the progression of ATTRv-PN and reducing the severity of symptoms associated with it, such as poor mobility and nutritional status, muscle weakness and reflexes.

Convenient treatment administration: Eplontersen can be administered by patients themselves, or their carers, at home. The convenience offered by eplontersen could reduce the treatment burden on patients, relatives and carers.

Tolerable safety profile: The results of the NEURO-TTRansform trial showed that eplontersen is generally well tolerated and the majority of patients can continue receiving it for a long period of time. Side effects of eplontersen can be minimised with regular monitoring and managed with supportive care.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

Eplontersen is generally well-tolerated and is effective in delaying the progression of ATTRv-PN and reducing the severity of symptoms in some patients. However, there are some things that patients may want to consider before starting treatment such as:

Efficacy

Eplontersen does not work for everyone and some people might not experience any improvement in ATTRv-PN. Patients for whom eplontersen does not work may still experience side effects, which are detailed further below.

Side effects

Like all medicines, some patients may experience side effects while they are taking eplontersen, as described in Section 3g) Safety of the medicine and side effects. These are usually manageable, and most patients do not need to stop treatment because of their side effects. Vitamin A deficiency is the most common side effect and to minimise the risk of this, patients treated with eplontersen are required to take a vitamin A supplement and have their vitamin A levels monitored regularly.

Administration

Eplontersen can be administered by patients with an easy-to-use auto-injector pen every month for the rest of their life. However, some patients may be unable to administer the injection themselves, so will need to seek support from carers to administer the treatment. Overall, eplontersen will provide patients and their carers with more autonomy than vutrisiran.

3i) Value and economic considerations

Introduction for patients:

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

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

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

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines, by looking at the costs and benefits of the new medicine. The

pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**.

As described in Section 3e) and 3f) Quality of life impact of the medicine and patient preference information, the health benefits (or efficacy) of the new treatment (eplontersen) and the standard of care (vutrisiran) are very similar. Therefore, in this submission, the pharmaceutical company uses the health economic model to perform a **cost-comparison** analysis, which compares the costs of eplontersen with vutrisiran.

Modelling how the costs of treatment differ with the new treatment

The economic model was designed to estimate the costs for patients receiving vutrisiran, compared with patients receiving eplontersen, over a 5-year period. A time period of 5 years was chosen because after the second dose of eplontersen or vutrisiran, most of the costs associated with these treatments are unlikely to change much over time.

Various costs are included in the model for the different ATTRv-PN treatments (vutrisiran and eplontersen). These costs include:

- The cost of the medicine itself
- The costs of administering the medicine
- If patients discontinued vutrisiran or eplontersen, the cost of the subsequent treatment they would receive

In practice, vutrisiran is provided to the NHS at a discount, however this discount is not available to the public, or other companies, so the discounted price could not be used in the economic model. Instead, the full cost of vutrisiran was used.

Cost-comparison analysis results

The results of the cost-comparison analysis showed that eplontersen is expected to reduce some costs for the NHS compared to vutrisiran for the treatment of patients with ATTRv-PN. This is driven by the different administration requirements of eplontersen versus vutrisiran. The first dose of vutrisiran must be administered at the NAC, then all other injections are given by an HCP who travels to the patient's home. Conversely, after the first injection of eplontersen is administered by an HCP, all subsequent injections can be administered at home without an HCP. Therefore, by removing the requirement for an HCP to regularly travel to a patient's home, eplontersen reduces the costs incurred by the NHS.

Uncertainty

There are various assumptions that were made in the model. Information on these assumptions can be found in Document B, Section B.4.2.7.

The cost of administering vutrisiran and eplontersen were assumed for the model, based on how patients would normally receive the treatment. However, a variation of these estimated costs was tested in the model. Using these different costs, eplontersen was still shown to reduce costs in patients with ATTRv-PN compared to vutrisiran.

Variations of other inputs in the model were also tested, with the results of these tests also showing that eplontersen is expected to reduce costs compared with vutrisiran. Further details of these tests can be found in **Document B, Section B.4.4.**

Benefits of eplontersen not captured in the economic analysis

As described in Section 3h) Summary of key benefits of treatment for patients, eplontersen will provide patients with a convenient treatment option that can be administered at home by patients or their carers. Therefore, it is expected to improve the HRQoL of patients, and their carers and relatives, when compared with vutrisiran. However, this benefit is not captured in the economic analysis used in this submission, as HRQoL was not considered in the model.

3j) Innovation

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

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

Eplontersen is an innovative treatment which would represent an important advancement in the treatment of ATTRv-PN.

ATTRv-PN is a progressive, irreversible, often fatal condition that can have a significant impact on the mental and emotional wellbeing, and HRQoL, of patients and their carers. However, as described in **Section**

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for ATTRv-PN?

Current recommended therapies

Historically, some patients with ATTRv-PN were treated with **liver transplants**. However, since the introduction of drugs to treat the disease, liver transplants are rarely used in the UK. (25)

The only group of therapies recommended by NICE for ATTRv-PN are called **silencers**. Examples of silencers include inotersen, patisiran and vutrisiran. Inotersen is rarely used as it is associated with numerous **side effects** and patients receiving inotersen require additional monitoring. Additionally, patisiran is not commonly used as it requires **intravenous** (IV) administration. This is more complicated and time-consuming to give to patients, compared to other treatments like vutrisiran. For example, patients must receive a specialised treatment regimen before each dose of patisiran to reduce the risk of experiencing complications associated with IV administration. (9)

Currently, the majority of patients in the UK with ATTRv-PN are treated with vutrisiran as it is the safest and most convenient silencer currently available. (9, 26) Vutrisiran is administered every three months by **healthcare professionals** (HCPs), meaning that HCPs need to visit the patient's home every three months, after receiving their first dose at the NAC. (9)

As vutrisiran is the main treatment used to treat patients with ATTRv-PN, it is the most relevant treatment to compare eplontersen with.

What is a silencer?

Silencers are a group of drugs that “switch off” the gene which codes for TTR, to prevent the production of abnormal TTR protein. This stops new amyloid fibrils developing and can slow progression of ATTRv-PN. Examples of silencers include: (27)

- Inotersen
- Patisiran
- Vutrisiran

Alternative Therapies

Diflunisal and tafamidis, which belong to a group of therapies called **stabilisers**, can also be used to treat ATTRv-PN. However, these treatments are not recommended for use by NICE and therefore are not available on the NHS. (9)

, there is a need for novel treatments that slow, or halt, progression of ATTRv-PN and can be administered conveniently. This would reduce the impact of treatment administration on the day-to-day lives of patients and their carers, providing them with greater independence.

Eplontersen has been shown to be as effective and safe as the current standard of care, vutrisiran. However, eplontersen can be administered by patients or their carers at home, without an HCP. This would provide patients with an alternative treatment option that allows them to control their symptoms whilst maintaining their independence and normal daily routines for as long as possible. Overall, these benefits would result in an improvement in HRQoL for patients, and their families and carers.

A positive recommendation of eplontersen for use in patients with Stage 1 or Stage 2 ATTRv-PN would address the critical unmet need for a new treatment option in UK clinical practice, which is more convenient than the current standard of care.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No potential equality issues are anticipated for the use of eplontersen in patients with Stage 1 or Stage 2 ATTRv-PN.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on ATTRv-PN: • Amyloidosis UK website: Amyloidosis UK - The UK ATTR Amyloidosis Patients' Association • Amyloidosis Patient Information Site: ATTR Amyloidosis - Amyloidosis Patient Information Site **Further information on NICE and the role of patients:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • The International Network of Agencies for Health Technology Assessment (INAHTA): http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: https://iris.who.int/handle/10665/332207

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Amyloid fibrils	Abnormal **transthyretin protein** can become unstable and break apart. The pieces of **protein** can then build up together and form clumps called amyloid fibrils.
Amyloid typing	**Amyloidosis** can be caused in a variety of ways. To help identify the cause, the type of **protein** causing amyloidosis is studied – this is called amyloid typing.
Amyloidosis	A condition caused by the build-up of **proteins** to form **amyloid fibrils**.
Biopsy	A medical procedure that involves taking a small sample of tissue from an area of the body, to examine in the laboratory. The procedure can be used to diagnose a disease, or understand how severe the disease is.
Cardiomyopathy	A condition which affects the size, shape or thickness of the heart muscle. This makes it harder for the heart to pump blood around the body.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Composite Autonomic Symptom Score-31 (COMPASS-31)	A questionnaire designed to measure how severe and widespread patients' symptoms are. In particular, it focuses on problems with responses that should happen automatically, such as bowel functions and **reflexes**.

Cost-comparison analysis	A type of analysis used to predict and compare the costs associated with different treatments for a disease, in a particular patient group.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial.**
Endemic	A condition or disease which is commonly found among a particular geographic area or population of people.
Gene	A gene is a part of a cell in a living thing that controls physical characteristics, growth and development.
Genetic disease	A disease caused by abnormalities in one or more **genes**.
Genetic information	The biological information of an individual which contains the instructions needed for them to function.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a **clinical trial**.
Healthcare professionals (HCPs)	A trained individual who is qualified to provide healthcare treatment and advice.
Health-related quality of life (HRQoL)	The overall enjoyment of life. Many **clinical trials** assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Hereditary transthyretin amyloidosis (ATTRv)	A disease caused by a change in the gene which codes for the **protein transthyretin**. This change results in the formation of

	abnormal **proteins**, which can build up to form **amyloid fibrils**.
Indirect treatment comparison	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised trial.
Inherited change	A change in **genetic information** which is passed on from parent to child.
Intravenous	A method of administering treatment through an injection directly into the patient's vein.
Liver transplant	An operation that removes an individual's unhealthy liver and replaces it with a healthy liver from another person (a donor).
Malnourishment	A condition where an individual is not taking in enough nutrients from their diet.
Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MRHA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the United Kingdom.
Modified body mass index (mBMI)	The body mass index takes into account an individual's height or weight to work out if their weight is healthy or unhealthy. The modified version of this measure also accounts for levels of a **protein** called serum albumin, because low **serum** albumin can cause **oedema**. This can make a patient's weight seem unhealthy, even if it is not (and vice versa).
Modified neuropathy impairment score+7 (mNIS+7)	An altered version of the **neuropathy impairment score** which measures a wider range of signs associated with damage to the

	peripheral nerves, compared to the neuropathy impairment score.
Mutations	A permanent alteration in a **gene,** in an individual.
National Amyloidosis Centre (NAC)	A specialised medical centre in London, responsible for diagnosing and treating all patients with ATTRv-PN in the UK.
National Institute for Heath and Care Excellence (NICE)	The body in England that decides whether to approve new medicines for funding on the NHS based on whether they can be demonstrated to be value for money.
Nerves	Specialised cells which carry information from one part of the body to the other.
Neuropathic pain	A type of pain that is caused by damage to an individual's nerves. Examples of neuropathic pain include burning, tingling, numbing, or itching.
Neuropathy	A condition caused by damage to an individual's **nerves**.
Neuropathy impairment score (NIS)	A scale which is used by doctors to accurately measure signs of damage to the **peripheral nerves**.
Neuropathy symptom and change (NSC) score	A scale designed to assess the types of symptoms associated with polyneuropathy, and how severe those symptoms are.
Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) Questionnaire	A questionnaire which is filled out by patients with neuropathy, and used to measure their **HRQoL**.
Nutritional status	A measure of how well-nourished an individual is.

Oedema	Swelling in the body caused by fluid trapped in tissues, such as the feet and ankles.
Orthostatic hypotension	A type of low blood pressure that happens when you stand up after sitting or lying down.
Peripheral nerves	All **nerves** outside of the brain and spinal cord.
Placebo	A treatment that appears real, but does not treat the disease. It is used in clinical trials to assess the effects of a new treatment, versus no treatment.
Polyneuropathy	A condition caused by damage to an individual's **peripheral nerves**.
Polyneuropathy disability (PND) score	A type of **staging system** which categorises patients based on how well they are able to move around.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Reflexes	A response to a trigger that happens almost immediately and does not require any conscious thought. An example of this is quickly pulling back your hand after touching something hot.
Regulatory bodies	Legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
Serum	The clear, watery component of blood, which carries various **proteins**, and other substances, around the body.

Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Silencers	A group of treatments for ATTRv that “switch off” the **gene** that codes for the protein **transthyretin**. This prevents production of the **protein**.
Stabilisers	A group of treatments that bind to **transthyretin** and prevent it breaking down and forming **amyloid fibrils**.
Staging system	A method of classifying patients’ disease based on various characteristics, such as how severe it is.
Subcutaneous injection	A method of delivering a drug by injecting it just beneath the patient’s skin.
Tolerated	The ability of a patient to put up with the **side effects** of treatment.
Transthyretin (TTR)	A **protein** which travels around the body in the blood and is mainly produced in the liver.
Vitamin A deficiency	A condition where individuals do not have enough vitamin A in their body. Vitamin A is a nutrient needed for various processes in the body, so not having enough of it can cause health problems.
10-Metre Walk Test (10MWT)	A test to measure how fast a patient can walk. The test involves timing how long it takes patients to walk 10 metres without any assistance.

4c) References

1. UK ATTR Amyloidosis Patients Association. About ATTR Amyloidosis: Wild-type amyloidosis 2021 [Available from: https://amyloidosisuk.org/wild-type-amyloidosis/.

2. Luigetti M, Conte A, Del Grande A, Bisogni G, Madia F, Lo Monaco M, et al. TTR-related amyloid neuropathy: Clinical, electrophysiological and pathological findings in 15 unrelated patients. Neurological Sciences. 2013;34(7):1057-63.

3. Parman Y, Adams D, Obici L, Galán L, Guergueltcheva V, Suhr OB, 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. Current Opinion in Neurology. 2016;29 Suppl 1(Suppl 1):S3-S13.

4. UK ATTR Amyloidosis Patients Association. Hereditary amyloidosis. Available at: https://www.ukatpa.org/hereditary-amyloidosis/. Last Accessed: January 2024.

5. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. European heart journal. 2021;42(16):1554-68.

6. National Institute for Health and Care Excellence. Resource Impact Report: Vutrisiran for treating hereditary transthyretin related amyloidosis (TA868). 2023.

7. Gillmore JD, Reilly MM, Coats CJ, Cooper R, Cox H, Coyne MR, et al. Clinical and genetic evaluation of people with or at risk of hereditary ATTR amyloidosis: an expert opinion and consensus on best practice in Ireland and the UK. Advances in therapy. 2022;39(6):2292-301.

8. UK ATTR Amyloidosis Patients Association. About ATTR Amyloidosis: Link between genetic variants and ethnicity. Last accessed: January 2024 2021 [Available from: https://amyloidosisuk.org/ethnicity-and-geography/.

9. National Institute for Health and Care Excellence. TA868. Vutrisiran for treating hereditary transthyretin-related amyloidosis. Committee Papers. Available at: https://www.nice.org.uk/guidance/ta868/documents/committee-papers. Accessed: June 2023. 2023 [

10. Waxenbaum JA, Reddy V, Varacallo M. Anatomy, Autonomic Nervous System. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

11. UK ATTR Amyloidosis Patients Association. About ATTR Amyloidosis: Hereditary amyloidosis 2021 [Available from: https://amyloidosisuk.org/hereditary-amyloidosis/.

12. Adams D, Ando Y, Beirão JM, Coelho T, Gertz MA, Gillmore JD, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. Journal of Neurology. 2021;268(6):2109-22.

13. National Institute for Health and Care Excellence. HST10. Patisiran for treating hereditary transthyretin amyloidosis 2019.

14. Wixner J, Mundayat R, Karayal ON, Anan I, Karling P, Suhr OB. THAOS: gastrointestinal manifestations of transthyretin amyloidosis-common complications of a rare disease. Orphanet journal of rare diseases. 2014;9:1-9.

15. Adams D, Algalarrondo V, Polydefkis M, Sarswat N, Slama MS, Nativi-Nicolau J. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet journal of rare diseases. 2021;16(1):1-17.

16. Yarlas A, Gertz M, Dasgupta N, Obici L, Pollock M, Ackermann E, et al. Burden of Hereditary Transthyretin Amyloidosis on Quality of Life. Muscle & Nerve. 2019;60.

17. Dodet P, Adams D, Redolfi S, Amulf I, Leu S, Similowski T, et al. Sleep disorders in patients with hereditary transthyretin amyloid neuropathy. Journal of the Peripheral Nervous System. 2015:129-.

18. Lopes A, Fonseca I, Sousa A, Branco M, Rodrigues C, Coelho T, et al. Psychopathological Dimensions in Portuguese Subjects with Transthyretin Familial Amyloid Polyneuropathy. Biomedicine Hub. 2017;2(3):1-14.

19. Acaster S, Lo SH, Nestler-Parr S. A survey exploring caregiver burden and health-related quality of life in hereditary transthyretin amyloidosis. Orphanet Journal of Rare Diseases. 2023;18(1):17.

20. Stewart M, Shaffer S, Murphy B, Loftus J, Alvir J, Cicchetti M, et al. Characterizing the High Disease Burden of Transthyretin Amyloidosis for Patients and Caregivers. Neurology and Therapy. 2018;7(2):349-64.

21. Adams D, Coelho T, Obici L, Merlini G, Mincheva Z, Suanprasert N, et al. Rapid progression of familial amyloidotic polyneuropathy: A multinational natural history study. Neurology. 2015;85(8):675-82.

22. Elmoamly S, Obici L. Amyloidosis: Pathogenesis, Types, and Diagnosis. Paraproteinemia and Related Disorders: Springer; 2022. p. 101-12.

23. UK ATTR Amyloidosis Patients Association. Living with Amyloidosis: Diagnosis. Last Accessed: January 2024 [Available from: https://amyloidosisuk.org/diagnosis/.

24. Coutinho PS, AMd; Lopes, J. Forty years of experience with type I amyloid neuropathy. Review of 483 cases. Amyloid and Amyloidosis Excerpta Medica. 1980.

25. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Annals of Medicine. 2015;47(8):625-38.

26. AstraZeneca UK Ltd. Data on File. ID: REF-218937. February 2024.

27. UK ATTR Amyloidosis Patients Association. Living with Amyloidosis: Treatment. Available at: https://www.ukatpa.org/treatment/. Last Accessed: January 2024.

28. Lovley A, Raymond K, Guthrie SD, Pollock M, Sanchorawala V, White MK. Patient-reported burden of hereditary transthyretin amyloidosis on functioning and well-being. Journal of Patient-Reported Outcomes. 2021;5(1):3.

29. Rintell D, Heath D, Braga Mendendez F, Cross E, Cross T, Knobel V, et al. Patient and family experience with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) amyloidosis: Results of two focus groups. Orphanet Journal of Rare Diseases 2021;16(1):70.

30. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: A model of medical progress for a fatal disease. Nature Reviews Neurology. 2019;15(7):387-404.

31. Coelho T, Marques W, Dasgupta NR, Chao C-C, Parman Y, França MC, et al. Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. JAMA. 2023.

32. (GOSH) GOSHfC. Giving subcutaneous injections. Available at: https://www.gosh.nhs.uk/conditions-and-treatments/procedures-and-treatments/giving-subcutaneous-injections/. Last Accessed: January 2024.

33. Clinicaltrials.gov. Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy (NCT01737398). Available at: https://clinicaltrials.gov/study/NCT01737398. Accessed: October 2023 [

34. Clinicaltrials.gov. NEURO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. Available at: https://clinicaltrials.gov/ct2/show/study/NCT04136184. Accessed: November 2022. [

35. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. New England Journal of Medicine. 2018;379(1):22-31.

36. Carroll A, Dyck PJ, De Carvalho M, Kennerson M, Reilly MM, Kiernan MC, et al. Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis. Journal of Neurology, Neurosurgery & Psychiatry. 2022;93(6):668-78.

37. Tóthová C, Nagy O. Transthyretin in the evaluation of health and disease in human and veterinary medicine. Pathophysiology-Altered Physiological States: IntechOpen; 2017.

38. Farivar SS, Cunningham WE, Hays RD. Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V. 1. Health and quality of life outcomes. 2007;5(1):1-8.

39. EURO-QoL. EQ-5D-5L User Guide. Last Accessed: January 2024. Available from: https://euroqol.org/wp-content/uploads/2023/11/EQ-5D-5LUserguide-23-07.pdf.

40. AstraZeneca DoF. Clinical Study Report: 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 (Final Analysis). 2023.

41. CADTH. Clinical Review Report: Inotersen (Tegsedi): (Akcea Therapeutics, Inc.): Indication: Stage I or II polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020.

42. Dyck PJB, Coelho T, Waddington Cruz M, Brannagan III TH, Khella S, Karam C, et al. Neuropathy symptom and change: Inotersen treatment of hereditary transthyretin amyloidosis. Muscle & Nerve. 2020;62(4):509-15.

43. Suhr OB, Conceição IM, Karayal ON, Mandel FS, Huertas PE, Ericzon BG. Post hoc analysis of nutritional status in patients with transthyretin familial amyloid polyneuropathy: impact of tafamidis. Neurology and therapy. 2014;3:101-12.

44. Adams D, Tournev IL, Taylor MS, Coelho T, Planté-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.

45. AstraZeneca DoF. Eplontersen: Summary of Product Characteristics (SmPc).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Eplontersen for treating polyneuropathy caused by hereditary transthyretin-related amyloidosis [ID6337]

Clarification questions

April 2024

Section A: Clarification on effectiveness data

Indirect treatment comparisons

A1. Priority question. Based on input from a clinical expert, the EAG notes the following additional baseline variables that are considered to be potential prognostic factors and are reported in the HELIOS-A study: early onset V30/V50 mutation, mNIS+7 score, NIS score and NT-proBNP levels. Please can the company:

a) Discuss whether these factors were identified as part of the clinical interviews or literature review used to inform the selection of adjustment variables and, if so, the rationale for their exclusion from the ITC adjustment;

Early onset V30/V50 mutation, mNIS+7 score, NIS score and NT-proBNP levels were all identified as part of the clinical expert consultations and literature review used to inform the selection of adjustment variables. There are different definitions of early onset V30/V50 mutation. In HELIOS-A this was defined by a dichotomous variable, as age <50 years at disease onset and V30/V50 mutation vs. all others (including late onset V30/V50 mutation and non-V30/V50 mutation). The original reference MAICs included both age as a continuous variable and V30/V50 mutation as a dichotomous variable. Early onset V30/V50 mutation was considered and discussed with clinical experts but the Company deemed that the added value of including this variable did not outweigh the value of including both age and V30/V50 mutation. The clinical experts agreed with this approach. When adding early onset V30/V50 mutation, the variable for V30/V50 mutation (regardless of age at onset) must be dropped from the original reference MAICs to avoid issues with collinearity. The NIS is a subset of the mNIS+7, constituting two thirds of the range (0 to 244 points in NIS, and -22.3 to 346.3 points in $mNIS+7_{Ionis}$). It is therefore not appropriate to include both mNIS+7 and NIS in the same analysis. In HELIOS-A, mNIS+7 was reported as a continuous variable whereas NIS was reported as a categorical variable (<50, ≥50 to <100, ≥100 points). The value of adjusting for mNIS+7 was therefore deemed greater than the potential value of adjusting for NIS. Baseline mNIS+7 composite score (rescored to approximate $mNIS+7_{Alnylam}$) was included in the original reference MAICs for mNIS+7 but not for other outcomes, since the approach was to include the baseline value of each outcome variable in the MAIC for the same outcome. In HELIOS-A, NT-proBNP was reported as a dichotomous variable (≤3000, >3000 ng/L) but was not included in the original reference MAICs since it was considered a prognostic factor for patients with cardiomyopathy in addition to polyneuropathy, but not for patients with only polyneuropathy.

b) Provide scenarios for the reference MAICs that include these additional variables in the adjustment. The EAG considers that this could be limited to the following outcomes

i. Absolute and percentage change from baseline in steady state serum TTR;

ii. Change from baseline in mNIS+7;

iii. Change from baseline in Norfolk QoL-DN;

iv. Severe and serious AEs;

v. Treatment discontinuation.

Table 1 summarises the ITC results for new MAICs, excluding V30/V50 mutation but including the other original variables in the reference MAICs, in addition to: early onset V30/V50 mutation, baseline mNIS+7 composite score, and baseline NT-proBNP. The NIS is not included for the reasons described in Clarification Question A1a. This is presented for each of the outcomes specified in Clarification Question A1b. The results are very consistent with the original reference MAICs and the inclusion of additional variables in the MAIC did not affect any conclusions. One notable change was the point estimate for severe adverse events (AEs), which was [redacted] in the original reference MAIC and [redacted] in the new MAIC, but the confidence interval and conclusion remain consistent with the original reference MAIC.

Table 1. MAICs including additional variables identified in question A1a

Endpoint	Model variables	Point estimate	Lower 95% CI	Upper 95% CI
Absolute change from baseline in serum TTR (mean difference)	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline serum TTR • Baseline mNIS+7 • Baseline NT-proBNP (>3000)	[redacted]	[redacted]	[redacted]
Percentage change from baseline in serum TTR (mean difference)	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement	[redacted]	[redacted]	[redacted]

	• FAP stage (stage I) • Baseline serum TTR • Baseline mNIS+7 • Baseline NT-proBNP (>3000)			
mNIS+7 change from baseline (mean difference)	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline mNIS+7 • Baseline NT-proBNP (>3000)	[redacted]	[redacted]	[redacted]
Norfolk QoL-DN change from baseline (mean difference)	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline mNIS+7 • Baseline NT-proBNP (>3000) • Baseline Norfolk QoL-DN	[redacted]	[redacted]	[redacted]
Serious AEs (log odds ratio)	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline mNIS+7 • Baseline NT-proBNP (>3000)	[redacted]	[redacted]	[redacted]
Severe AEs (log odds ratio)	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline mNIS+7 • Baseline NT-proBNP (>3000)	[redacted]	[redacted]	[redacted]
Treatment discontinuation (log odds ratio)	• Age • Sex (male) • Race (white) • Prior treatment	[redacted]	[redacted]	[redacted]

	• Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline mNIS+7 • Baseline NT-proBNP (>3000)			

Footnotes: For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. Negative values favour eplontersen and positive values favour vutrisiran, for all endpoints.
Abbreviations: AE, adverse event; CI, confidence interval; FAP, familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

A2. The EAG notes a number of additional outcomes where data should be available for both eplontersen and vutrisiran (based on the Adams 2022 paper) but were not included in ITCs.[1] Please could the company:

a) Explain the rationale for not including ITCs for modified body mass index (mBMI), 10 metre walk test and Rasch-build Overall Disability Score;

An ITC was not submitted for 10-metre walk test (10-MWT) and Rasch-Built Overall Disability Score (R-ODS) as these were exploratory outcomes in NEURO-TTRansform that were not deemed critical for indirect comparisons by the Company and the clinical experts. Furthermore, these outcomes were not captured in NEURO-TTR so there were no placebo-controlled estimates of treatment effect available for eplontersen. Consequently, an ITC was not performed for outcomes where there was no demonstration that both treatments had shown efficacy versus an appropriate control.

b) Consider providing a MAIC for the mBMI outcome, which was indicated as a potentially useful additional outcome by the EAG's clinical expert.

Please ensure that the additional variables mentioned in question A1 above are included in the adjustment, in addition to other variables already included in reference MAICs for other outcomes and the baseline value of this outcome.

Table 2 summarises the reference MAIC results for mBMI, R-ODS, and 10-MWT, and the results of the new MAICs containing the additional variables identified in Clarification Question A1a. Note that higher values represent better nutritional status in mBMI and better physical function in 10-MWT. The results for the reference MAIC and the results from the MAICs including additional variables are consistent for mBMI, R-ODS, and 10-MWT, supporting the conclusion of comparable efficacy between eplontersen and vutrisiran.

Table 2. MAICs for mBMI, R-ODS and 10 MWT

Endpoint	Model	Point estimate	Lower 95% CI	Upper 95% CI

mBMI: Original reference MAIC (mean difference)	• Age • Sex • Race (white) • Prior treatment • V30/V50 • FAP stage I • Cardiac involvement • Baseline mBMI	[redacted]	[redacted]	[redacted]
mBMI: Including additional variables identified in question A1a (mean difference)	• Age • Sex • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage I • Baseline mNIS+7 • Baseline NT-proBNP (>3000)	[redacted]	[redacted]	[redacted]
R-ODS: Original reference MAIC (mean difference)	• Age • Sex • Race (white) • Prior treatment • V30/V50 • FAP stage I • Cardiac involvement • Baseline R-ODS	[redacted]	[redacted]	[redacted]
R-ODS: Including additional variables identified in question A1a (mean difference)	• Age • Sex • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage I • Baseline mNIS+7 • Baseline NT-proBNP (>3000) • Baseline R-ODS	[redacted]	[redacted]	[redacted]
10-MWT: Original reference MAIC (mean difference)	• Age • Sex • Race (white) • Prior treatment • V30/V50 • FAP stage I • Cardiac involvement • Baseline 10-MWT	[redacted]	[redacted]	[redacted]

10-MWT: Including additional variables identified in question A1a (mean difference)	• Age • Sex • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage I • Baseline mNIS+7 • Baseline NT-proBNP (>3000) • Baseline 10-MWT	[redacted]	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. Negative values favour eplontersen and positive values favour vutrisiran, for all endpoints except for mBMI (measured in kg/m2 x g/L) and 10-MWT (measured in m/s) because in these outcomes higher (more positive) values are better. NEURO-TTRansform recorded 10-MWT results at "comfortable" and "fast" pace. HELIOS-A do not report the pace at which 10-MWT was performed, only stating that it is "gait speed". As such, results presented here are based on the "comfortable" pace results in NEURO-TTRansform, which is a conservative approach.
Abbreviations: 10-MWT, 10-metre walk test (comfortable pace); FAP, familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified Neuropathy Impairment Score+7; NT-proBNP, N-terminal pro b-type natriuretic peptide; V30/V50, Val30/Val50 genetic mutation.

A3. Priority question. In order to assess how well-balanced the HELIOS-A and adjusted NEURO-TTRansform populations are following the ITCs, it is important that all baseline characteristics for the adjusted NEURO-TTRansform population are reported, rather than just those included in the adjustment, which is currently the case in Tables 27 to 35 of the CS. Please can these tables be updated to include the additional baseline characteristics listed in the table below for the vutrisiran, eplontersen unadjusted and eplontersen adjusted (reference) populations. For continuous variables, please indicate in each case whether values are means or medians.

Please also provide this for any additional analyses performed in response to questions A1 and A2 above.

Error! Reference source not found.–Table 9 summarise the baseline characteristics of the eplontersen population before and after applying the original reference MAICs, for each outcome in Clarification Question A1b and also for the outcomes requested in Clarification Question A2b (mBMI, R-ODS, and 10-MWT). Table 10–Table 16 summarise the baseline characteristics of the eplontersen population before and applying the new MAICs including the additional variables identified in Clarification Question A1a (adding mNIS+7 composite score at baseline, NT-proBNP, early onset V30/V50 mutation and removing V30/V50 mutation).

Table 3. Baseline characteristics before and after applying the original reference MAIC, for absolute and percent change from baseline in serum TTR

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference

			(ESS=[redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline serum TTR.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, mBMI, modified body index; modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 4. Baseline characteristics before and after applying the original reference MAIC, for change from baseline in mNIS+7 composite score

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference (ESS=[redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]

V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	26.300	[redacted]	[redacted]
Baseline R-ODS (SD)	34.100	[redacted]	[redacted]
Baseline R-ODS (mean)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline mNIS+7 composite score.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 5. Baseline characteristics before and after applying the original reference MAIC, for change from baseline in Norfolk QoL DN total score

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference (ESS=[redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference (ESS=[redacted])
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline Norfolk QoL-DN total score.

Abbreviations: 10-MWT, 10-metre walk test (comfortable pace); ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 6. Baseline characteristics before and after applying the original reference MAIC, for serious AEs, severe AEs, and treatment discontinuation

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference (ESS=[redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, and cardiac involvement.
Abbreviations: AE, adverse event; ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 7. Baseline characteristics before and after applying the original reference MAIC, for change from baseline in mBMI

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference (ESS=[redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
Early onset V30/V50 (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline mBMI.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, mBMI, modified body index; modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 8. Baseline characteristics before and after applying the original reference MAIC, for change from baseline in 10-MWT

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n=[redacted])	Eplontersen adjusted, reference

			(ESS=[redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30M mutation (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline 10-MWT (mean)	1.006	[redacted]	[redacted]
Baseline 10-MWT (SD)	0.393	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. NT-proBNP is measured in ng/L, mBMI is measured in kg/m2 x g/L, and 10-MWT is measured in m/s. NEURO-TTRansform recorded 10-MWT results at “comfortable” and “fast” pace. HELIOS-A do not report the pace at which 10-MWT was performed, only stating that it is “gait speed”. As such, results presented here are based on the “comfortable” pace results in NEURO-TTRansform, which is a conservative approach. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline 10-MWT.

Abbreviations: 10-MWT, 10-metre walk test (comfortable pace); ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 9. Baseline characteristics before and after applying the original reference MAIC, for change from baseline in R-ODS

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline R-ODS.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 10. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for absolute and percent change in serum TTR

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline serum TTR.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 11. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in mNIS+7 composite score

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	26.300	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	47.100	[redacted]	[redacted]
Baseline R-ODS (mean)	11.000	[redacted]	[redacted]
Baseline R-ODS (SD)	34.100	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, and baseline mNIS+7 composite score.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 12. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in Norfolk QoL-DN total score

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline Norfolk QoL-DN total score.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 13. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for serious AEs, severe AEs, and treatment discontinuation

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, and baseline mNIS+7 composite score.
Abbreviations: AE, adverse event; ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 14. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in mBMI

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline mBMI.
Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 15. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in 10-MWT

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30M mutation (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]
Baseline 10-MWT (mean)	1.006	[redacted]	[redacted]
Baseline 10-MWT (SD)	0.393	[redacted]	[redacted]

Footnotes: For all analyses baseline $mNIS+7_{Ionis}$ was rescored to approximately match $mNIS+7_{Alnylam}$. NT-proBNP is measured in ng/L, mBMI is measured in kg/m2 x g/L, and 10-MWT is measured in m/s. NEURO-TTRansform recorded 10-MWT results at “comfortable” and “fast” pace. HELIOS-A do not report the pace at which 10-MWT was performed, only stating that it is “gait speed”. As such, results presented here are based on the “comfortable” pace results in NEURO-TTRansform, which is a conservative approach. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline 10-MWT.

Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

Table 16. Baseline characteristics before and after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in R-ODS

Variable	Vutrisiran (n=122)	Eplontersen unadjusted (n= [redacted])	Eplontersen adjusted, reference (ESS = [redacted])
Age (mean)	57.800	[redacted]	[redacted]
Age (SD)	13.200	[redacted]	[redacted]
Sex (male) (proportion)	0.648	[redacted]	[redacted]
Race (white) (proportion)	0.705	[redacted]	[redacted]
V30/V50 (proportion)	0.443	[redacted]	[redacted]
Prior treatment (proportion)	0.615	[redacted]	[redacted]
FAP Stage I (proportion)	0.697	[redacted]	[redacted]
Cardiac involvement (proportion)	0.328	[redacted]	[redacted]
Baseline NT-proBNP (>3000) (proportion)	0.082	[redacted]	[redacted]
Region (Western Europe) (proportion)	0.352	[redacted]	[redacted]
Region (North America) (proportion)	0.221	[redacted]	[redacted]
Region (Rest of World) (proportion)	0.426	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (mean)	3.350	[redacted]	[redacted]
Duration since ATTR diagnosis (years) (SD)	3.690	[redacted]	[redacted]
V30/V50 early onset (proportion)	0.205	[redacted]	[redacted]
Baseline serum TTR (mean)	206.110	[redacted]	[redacted]
Baseline serum TTR (SD)	61.030	[redacted]	[redacted]
Baseline NIS (≥100) (proportion)	0.041	[redacted]	[redacted]
Baseline NIS (≥50 to <100) (proportion)	0.320	[redacted]	[redacted]
Baseline mBMI (mean)	1057.500	[redacted]	[redacted]
Baseline mBMI (SD)	234.000	[redacted]	[redacted]
Baseline mNIS+7 (mean)	60.550	[redacted]	[redacted]
Baseline mNIS+7 (SD)	35.990	[redacted]	[redacted]
Baseline Norfolk QoL-DN (mean)	47.100	[redacted]	[redacted]
Baseline Norfolk QoL-DN (SD)	26.300	[redacted]	[redacted]
Baseline R-ODS (mean)	34.100	[redacted]	[redacted]
Baseline R-ODS (SD)	11.000	[redacted]	[redacted]

Footnotes; For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. NT-proBNP is measured in ng/L and mBMI is measured in kg/m2 x g/L. Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline R-ODS.

Abbreviations: ATTR; transthyretin mediated amyloidosis; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body index; mNIS+7, modified neuropathy impairment score+7; NIS, Neuropathy impairment score; NT-proBNP, N-terminal pro b-type natriuretic peptide; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; SD, standard deviation; TTR, Transthyretin; V30/V50, Val30/Val50 genetic mutation.

A4. Priority question. On page 56 of the CS, missing data imputation is said to have been performed in the base case MAICs/STCs in line with methodology used in HELIOS-A. Please provide details of where this information for HELIOS-A was obtained from, as the EAG could not find mention of any additional imputation for 18-month outcomes other than inclusion in the MMRM.

The HELIOS-A interim analysis was based on ANCOVA with multiple imputation (MI), assuming missing at random (MAR). The mixed-effects model with repeated measures (MMRM) used in the HELIOS-A analysis at 18 months also assumes MAR, implicitly imputing missing outcome values as part of the correlations in the covariance structure. Taking this implicit imputation approach reduces traceability in the ITC, while MI MMRM allows for better understanding of the impact of the missing data handling and the MAR assumption. Given the same underlying assumptions for missing data, MMRM (implicit imputation) and MI MMRM are expected to yield equivalent results. For this reason, the ITCs were performed using MI MMRM, assuming MAR. The imputation approach mimicked the approach described in the HELIOS-A SAP for the interim analysis (see Amendment 3, Section 4.4.1.1).[2]

A5. Priority question. Please provide further details of the following for eplontersen TTR data used in analyses in Section B.3.9.3 of the CS and comment on how this compares to the HELIOS-A trial data/methods for this outcome:

a) **Multiple imputation method mentioned as being used for these analyses;**

The ITCs of serum TTR used the same approach to multiple imputation as explained in the response to Clarification Question A4.

b) **Population analysed (e.g. was this the full analysis set described in Section B.3.4.1 of the CS?).**

The population analysed was the randomised set (all patients who were randomised, N=144) with patients being excluded from the model if they had missing data on any of the demographic or baseline characteristics included in the MAIC, or if they had missing data on change from baseline for the outcome variable.

A6. Priority question. Please clarify the following regarding the decision to extrapolate week 80 outcomes from week 66 data for mNIS+7 and Norfolk QoL-DN outcomes instead of using week 85 observed data:

a) **The rationale for this is stated to be so that adjusted values from an MMRM model can be used, in line with the data available for HELIOS-A. Does this mean that adjusted individual patient data for the eplontersen patients based on MMRM models have been extrapolated?**

The extrapolation was performed on individual patient data, assuming linear behaviour from baseline to week 66, prior to inclusion in MMRM.

b) **Please outline exactly what the MMRM models mentioned in part a above adjusted for. Given the external placebo control group has been deemed irrelevant to the ITCs in the submission, the EAG would consider it unusual to use data from MMRM models that adjust to this group in the ITCs.**

The MMRM models in the ITC only included baseline value of the outcome, V30/V50, disease stage, and prior treatment, which is not equivalent to adjustment to the placebo group. The MMRM models in the ITC did not include the adjustment to the placebo group (i.e., propensity score adjustment), as explained in the response to Clarification Question A14.

c) **If adjustment to the placebo group has been performed as part of the MMRM data used for eplontersen, please provide scenarios for these MAICs without this adjustment to the placebo group included. Please also consider performing these scenarios for the additional analyses requested in question A1.**

As the MMRM models did not include propensity scores, no additional analyses are warranted based on this question.

d) **Please provide full details of the methodology used for this extrapolation, including model selection and a visual assessment and details of model fit.**

While many approaches to extrapolation were available, a simple linear extrapolation accompanied by a sensitivity analysis without extrapolation, was deemed appropriate for outcomes other than serum TTR (see response to Clarification Question A7c below). The choice of extrapolating from week 66 data (week 65 for serum TTR and mBMI) was based on using the last time point in NEURO-TTRansform where there were treatment difference estimates for eplontersen versus placebo. No modelling was done for the linear extrapolation, so no model fit was assessed. To assess sensitivity of the results and conclusions to the impact of linear

extrapolation, sensitivity analyses were performed without extrapolating data, using week 66 data as observed.

e) **Please describe in more detail the concerns about using observed week 85 data from NEURO-TTRansform and HELIOS-A data resulting from adjusted MMRM models. For example, are there any specific concerns the company has based on factors included in the MMRM model and in which direction would any bias be anticipated?**

The week 85 time point, while clinically important, only supports exploratory endpoints when there is no control group available in NEURO-TTR so there is no placebo-controlled treatment effect estimate available for eplontersen at week 85. However, the Company agrees that for the unanchored ITCs, the lack of a control group in NEURO-TTR is not a major issue, as clarified in the response to Clarification Question A7b.

A7. Priority question. Related to question A6 above, the EAG considers that the difference in time-points between studies, and methods used to account for this, represent uncertainties. While each of the approaches may be associated with different limitations, it is important that the results of different approaches are explored. Therefore, please provide the following scenario results for mNIS+7 and Norfolk QoL-DN change from baseline MAICs (STCs can be omitted) so that the impact of different approaches on the results can be assessed:

a) **A scenario without extrapolation of week 66 data (said on page 56 of the CS to have already been performed);**

Table 17 summarises the results of analyses without extrapolation, using either week 66 data or week 85 data for eplontersen. When week 66 data is used without extrapolation, the ITC for mNIS+7 shows no statistically significant differences between eplontersen and vutrisiran, whilst the ITC for Norfolk QoL-DN results show significant differences in favour of eplontersen.

b) **A scenario where observed week 85 data is used for NEURO-TTRansform.**

When week 85 data is used, the results for mNIS+7 significantly favour vutrisiran and the results for Norfolk QoL-DN significantly favour eplontersen. Here, both the mNIS+7 results and the Norfolk QoL-DN (alternative model) results are significant, but the confidence limits are close to zero, still suggesting that the treatments are comparable. It is also important to acknowledge the additional uncertainty present in all ITCs of mNIS+7 due to the rescoring, described in the response to Clarification Question A8a. This analysis is shown in Table 17.

c) Please also consider providing the above scenarios for the additional analyses requested in question A1.

Further analyses for the additional items outlined in A1 were explored and were not deemed relevant in this case. To match the definition of steady-state serum TTR used in HELIOS-A, in the analysis of absolute and percentage change from baseline in serum TTR, the steady-state serum TTR values for eplontersen were calculated using pre-dose serum TTR measurements available between month 6 and 18. In NEURO-TTRansform, the first pre-dose serum TTR measurement between month 6 and 18 is at Week 49 and the final measurement is at week 85. Therefore, the Company presented week 85 data for the serum TTR and, as extrapolation is not performed due to the steady-state calculation, it is not feasible to perform corresponding analyses using "week 65/66" or "week 85" without changing the steady-state definition. Restricting the pre-dose measurements of serum TTR in NEURO-TTRansform to those taken prior to week 66 would limit measurements to three values, week 49, week 57 and week 65, and would no longer match the steady-state definition used in HELIOS-A. Further analyses were therefore not deemed relevant for serum TTR. No extrapolation was performed for binary outcomes because all available information was already included for the endpoints serious AEs, severe AEs, and treatment discontinuation. Further analyses were therefore not deemed relevant for serious AEs, severe AEs, and treatment discontinuation.

Table 17. MAICs without extrapolation

Endpoint	Model	Point estimate	Lower 95% CI	Upper 95% CI
Using data at week 66				
mNIS+7 composite score	Reference	[redacted]	[redacted]	[redacted]
	Alternative	[redacted]	[redacted]	[redacted]
Norfolk QoL-DN total score	Reference	[redacted]	[redacted]	[redacted]
	Alternative	[redacted]	[redacted]	[redacted]
Using data at week 85				
mNIS+7 composite score	Reference	[redacted]	[redacted]	[redacted]
	Alternative	[redacted]	[redacted]	[redacted]
Norfolk QoL-DN total score	Reference	[redacted]	[redacted]	[redacted]
	Alternative	[redacted]	[redacted]	[redacted]

Footnotes: Adjustment variables included in the reference model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline measurement of the outcome (mNIS+7 composite score or Norfolk QoL-DN total score). Adjustment variables included in the alternative model for mNIS+7 using week 66 data without extrapolation were: sex, prior treatment, FAP stage and baseline mNIS+7 composite score. Adjustment variables included in the alternative model for mNIS+7 using week 85 data were: age, sex, prior treatment, FAP stage and baseline mNIS+7 composite score. Adjustment variables included in the alternative model for Norfolk QoL-DN were: age, sex, baseline Norfolk QoL-DN total score.
Abbreviations: CI, confidence interval; FAP, familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; V30/V50, Val30/Val50 genetic mutation.

A8. Page 54 of the CS describes attempts to align the two versions of the mNIS+7 score between trials as part of the ITCs. However, it is unclear how exactly this was achieved and what the limitations of this were. Please provide more detail regarding this process, including:

a) **A detailed, step-by-step description of the rescoring process performed on the NEURO-TTRansform data and any references to support the use of this method;**

The mNIS+7 composite score is the sum of the scores of each component. The $mNIS+7_{Ionis}$ has many similarities to the $mNIS+7_{Alnylam}$ version, in terms of components and component scores. But there are also important differences (see Figure 2 of Coelho et al. [2023]).[3] The $mNIS+7_{Ionis}$ has a range of -22.3 to 346.3 points, whereas the $mNIS+7_{Alnylam}$ has a range of 0 to 304 points. Both versions contain the weakness and reflexes components of the NIS (NIS-W and NIS-R). They also contain the same quantitative sensory testing (QST) component. The nerve conduction studies (NCS) component which exists in both versions is scored differently. In the $mNIS+7_{Ionis}$, the NCS value is normalised and is scored based on how many standard deviations the value is from the mean of a healthy age-matched reference population (the range is -18.6 to 18.6 points). In the $mNIS+7_{Alnylam}$, the NCS is scored based on the 95th and 99th percentiles of a healthy age-matched reference population, assigning 0 points if the value is within the 95th percentile, assigning 1 point if the value is between the 95th and 99th percentile, and assigning 2 points if the value is beyond the 99th percentile. Using the 95th and 99th percentiles, the NCS component in the $mNIS+7_{Ionis}$ could be rescored to exactly match the NCS component in the $mNIS+7_{Alnylam}$ score, attaining the same range and outcome space {0, 1, 2}.The autonomic domain is captured differently in the $mNIS+7_{Ionis}$ from the $mNIS+7_{Alnylam}$. In the $mNIS+7_{Ionis}$ of the mNIS+7 composite score, autonomic dysfunction is assessed in the heart rate with deep breathing (HRdb) component (the range is -3.7 to 3.7 points). In the $mNIS+7_{Alnylam}$, autonomic dysfunction is assessed in the postural blood pressure (BP), or hypotension, component by comparing to a healthy age-matched reference population, assigning 0 points if the value is within the 95th percentile, assigning 1 point if the value is between the 95th and 99th percentile, and assigning 2 points if the value is beyond the 99th percentile. Since this assessment was not performed in NEURO-TTRansform, there was no way of exactly deriving this component of the $mNIS+7_{Alnylam}$. Instead, the autonomic dysfunction component of the $mNIS+7_{Ionis}$ was rescored using the 95th and 99th percentiles (instead of standard deviations), assigning 0 points if the value is within the 95th percentile, assigning 1 point if the value is between the 95th and 99th percentile, and assigning 2 points if the value is beyond the 99th percentile. In this way, the same range and outcome space {0, 1, 2} are attained.

b) **How the lack of a "sensation" component in mNIS+7Alnylam was addressed;**

The $mNIS+7_{Ionis}$ includes an additional sensation component (NIS-S), which the $mNIS+7_{Alnylam}$ does not contain. For the rescoring of the NIS components, the NIS-S was dropped from the $mNIS+7_{Ionis}$.

c) Whether the composite score range was the same in both versions once the amendments had been made;

After rescoring mNIS+7$_{Ionis}$ using the approach described above, the exact range of the mNIS+7$_{Alnylam}$ is attained.

d) Comment on the potential bias introduced by any differences that could not be resolved and any limitations of the approach used.

In the APOLLO study of patisiran versus placebo, all components for both versions (mNIS+7$_{Ionis}$ and mNIS+7$_{Alnylam}$) of the mNIS+7 composite score were collected. In the Adams 2022 publication, the mean mNIS+7$_{Alnylam}$ version composite score at baseline was reported to be 74.6 points in the APOLLO placebo arm (see Table 2 in Adams et al. [2022]).[4] In a previous paper, the mean mNIS+7$_{Ionis}$ score for the same placebo arm was reported to be 96.5 points (see Table 1 in Gorevic et al. [2021]).[5] Since all components for both scores were collected in APOLLO, the rescoring could be done exactly (without approximation), and the results show that the mNIS+7$_{Ionis}$ score is on average [redacted] points higher than in the mNIS+7$_{Alnylam}$. This highlights how critical rescoring is for any comparison of mNIS+7 across trials. Furthermore, despite the ranges and outcome spaces being identical after rescoring based on using HRdb to approximate postural BP, this does not eliminate the risk of systematic bias due to the underlying difference arising from the autonomic dysfunction component being measured using fundamentally different tests; a neurological test (HRdb) versus a neurologist's assessment (postural BP). The ITCs of mNIS+7 should always be interpreted with greater caution than the ITCs of Norfolk QoL-DN, regardless of the approach taken, due to this underlying uncertainty caused by the lack of data required for an exact rescoring.

A9. Priority question. Please can the following additional details be provided in terms of the steady state TTR analyses performed:

a) References to support the company's assumption that the steady state period should begin at ~47/49 weeks for eplontersen based on the relationship between half-life and steady state described on page 57 of the CS;

To match the definition of steady state serum TTR used in HELIOS-A, the steady state serum TTR values for eplontersen and inotersen were calculated using pre-dose serum TTR measurements available between month 6 and 18 to match the period used in HELIOS-A. In NEURO-TTRansform, the first pre-dose serum TTR measurement between month 6 and 18 is at Week 49. In NEURO-TTR, the first pre-dose serum TTR measurement between month 6 and 18 is at Week 47.

b) Comment on whether the same relationship between half-life and steady state is the reason behind the vutrisiran steady state starting at 6 months, if this information is available;

No rationale for the choice of steady state period used in HELIOS-A was provided in the statistical analysis plan (SAP) for HELIOS-A. The SAP states that "Time-averaged trough TTR

percent reduction through month 18 is defined as the average trough (ie, predose) TTR percent reduction from Month 6 to 18, which is the steady state period for both vutrisiran and patisiran." (HELIOS-A SAP, Amendment 3, Section 4.4.3.3). [2]

c) Comment on whether any differences between the assays used to measure TTR exist between NEURO-TTRansform and HELIOS-A, including differences in the lower limit of detection of these assays;

Information on the assay used by Alnylam is not publicly available, so the Company cannot ascertain the lower limit of detection of that assay and compare it to what was used in NEURO-TTRansform. The Company can only access qualitative data on the Alnylam assay from publications and other publicly available sources. In NEURO-TTRansform, a Meso Scale Discovery (MSD) assay based on electrochemiluminescence detection was used, whereas an Enzyme Linked Immunosorbent Assay (ELISA) based on colorimetric detection was used in HELIOS-A. It is possible that differences exist in the analytical performance of these assays, including assay precision and the lower limit of detection. Whilst this information is available for the MSD assay, it is not publicly available for the Alnylam ELISA. Since the Company do not have data for both assays for matched samples, it is not possible to conduct a comparison. If there would be considerable differences between the assays, this would be present both at baseline and at follow-up and so the impact on change from baseline would be reduced. Furthermore, the impact on percent change from baseline would be expected to be even lower, as that is expressed as a fraction of the baseline value. From this perspective, the consistency between ITC results of absolute and percent change from baseline in serum TTR supports the assumption that potential differences between the assays are not of a magnitude that would impact the overall conclusion of the ITC of serum TTR.

d) Related to part c, whether any adjustments for this were performed (similar to what is described when comparing the external placebo control group to eplontersen on the third page of the Coelho 2023 publication under the "outcomes" heading).[3]

The correction factor mentioned in the Coelho 2023 was developed based on a cross-comparison of an immunoturbidimetry assay and an ECL assay, using matched samples for NEURO-TTRansform. This adjustment was used throughout the ITCs of serum TTR.

A10. For the MAICs described in Section B.3.9 of the CS, for each "reference" analysis, please provide graphs showing the distribution of patient weights within the eplontersen population following adjustment to the HELIOS-A population so that an assessment of any extreme weightings can be made. Please also provide these for any new analyses that are presented in response to questions A1 and A2.

Figure 1–Figure 5 show the distribution of patient weights after applying the original reference MAICs, for each outcome in Clarification Question A1b (i-v) and also for mBMI, as requested in Clarification Question A2b. Figure 6Figure 10 show the distribution of patient weights after applying the new MAICs including the additional variables identified in Clarification Question A1a. No indication of extreme weights was observed for any of the original reference MAICs or new MAICs.

Figure 1. Histogram of patient weights, after applying the original reference MAIC, for absolute and percent change from baseline in serum TTR

Footnotes: Adjustment variables included in model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline serum TTR.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

Figure 2. Histogram of patient weights, after applying the original reference MAIC, for change from baseline in mNIS+7 composite score

Footnotes: Adjustment variables included in model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline mNIS+7 composite score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; V30/V50, Val30/Val50 genetic mutation.

Figure 3. Histogram of patient weights, after applying the original reference MAIC, for change from baseline in Norfolk QoL DN total score

Footnotes: Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline Norfolk QoL-DN total score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; V30/V50, Val30/Val50 genetic mutation.

Figure 4. Histogram of patient weights, after applying the original reference MAIC, for serious AEs, severe AEs, and treatment discontinuation

Footnotes: Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, and cardiac involvement.
Abbreviations: AE, adverse event; FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; V30/V50, Val30/Val50 genetic mutation.

Figure 5. Histogram of patient weights, after applying the original reference MAIC, for change from baseline in mBMI

Footnotes: Adjustment variables included in the model were: age, sex, race, V30/V50, prior treatment, FAP stage, cardiac involvement, and baseline mBMI.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body mass index; V30/V50, Val30/Val50 genetic mutation.

Figure 6. Histogram of patient weights, after applying the new MAIC with additional variables identified in Clarification Question A1a, for absolute and percent change from baseline in serum TTR

Footnotes: Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline serum TTR.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation

Figure 7. Histogram of patient weights, after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in mNIS+7 composite score

Footnotes: Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, and baseline mNIS+7 composite score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

Figure 8. Histogram of patient weights, after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in Norfolk QoL-DN total score

Footnotes: Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline Norfolk QoL-DN total score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

Figure 9. Histogram of patient weights, after applying the new MAIC with additional variables identified in Clarification Question A1a, for serious AEs, severe AEs, and treatment discontinuation

Footnotes: Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, and baseline mNIS+7 composite score.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

Figure 10. Histogram of patient weights, after applying the new MAIC with additional variables identified in Clarification Question A1a, for change from baseline in mBMI

Footnotes: Adjustment variables included in the model were: age, sex, race, early onset V30/V50, prior treatment, FAP stage, cardiac involvement, baseline NT-proBNP, baseline mNIS+7 composite score, and baseline mBMI.
Abbreviations: FAP, Familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mBMI, modified body mass index; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

A11. The company states on page 57 of the CS that a comparison of percent change from baseline in serum TTR was not considered feasible. However, percent change from baseline analyses are presented in Figures 20 and 21 of the CS. Please clarify how these analyses differ from those that were said not to be feasible – is it because steady state levels have been used?

An ITC of percent change from baseline in serum TTR at a given time point was not considered an optimal approach for a comparison of eplontersen and vutrisiran since this information was not explicitly available from HELIOS-A and required digitising graphs, a process which is associated with additional uncertainty. Furthermore, percent change from baseline in serum TTR is not normally distributed, inherently having a ceiling and floor, so treating it as a continuous variable in an ITC may be inappropriate. The differences in data collection time points between NEURO-TTRansform and HELIOS-A are also more impactful in the ITC of serum TTR, than in the ITCs of mNIS+7 composite score or Norfolk QoL-DN total score, where a more linear behaviour can be assumed. The serum TTR is dose-dependent and therefore more sensitive to the measurement time point relative to the dosing frequency in the study and the half-life of the drug.

The ITCs using steady state calculations were deemed appropriate as this was how serum TTR results were reported in HELIOS-A and a very similar calculation could be performed using available data from NEURO-TTRansform. This approach minimises the impact of serum TTR measurement timings relative to dosing and the need to extrapolate or interpolate individual values to adjust for differences in time points. The approach to look at absolute change from baseline, described in the response to Clarification Question A12, also removed the issues arising from the non-normality of the percent change from baseline in serum TTR.

A12. Please clarify how mean absolute and mean absolute change from baseline in steady-state serum TTR levels were obtained for vutrisiran, as the Adams 2022 paper only appears to report this as a percentage change from baseline.[1] Were these data presented in a separate publication or were calculations performed?

Due to the paucity of granular data on serum TTR levels in HELIOS-A, absolute serum TTR (mg/L) at baseline and at steady state at month 6 to 18 were extracted from Table 29 in the Amvuttra EPAR, for vutrisiran (and patisiran) in the "TTR per protocol population".[6] From these values, the mean absolute change from baseline was approximated by the difference between the baseline and the steady state at month 6 to 18.

A13. Please can the company comment on whether it is aware of any thresholds that could be used as minimal clinically important differences from baseline (or between treatments) for serum TTR, mNIS+7, Norfolk QoL-DN and mBMI outcomes. The EAG is aware that these may exist in related amyloid conditions and it considers that, in the absence of any directly relevant thresholds, these may still be informative even if they are as yet unproven in the population covered by this appraisal.

Please note that that the following information is sourced from a draft manuscript that is intended for publication but has not been approved or published. Consequently, the information provided below should be treated as confidential.

Clinically important differences are instrument- and population-specific and aim to derive a magnitude of difference between treatments that is clinically important to the patient. For hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN), minimal clinically important differences are not available in the published literature as the natural history of ATTRv-PN is that of a chronic progressive condition which, when left untreated, is fatal. As such, any halting of progression is widely accepted as clinically meaningful.

[redacted]

[redacted]

A14. Please clarify whether the baseline characteristics described for the eplontersen unadjusted population (n=141) in Table 29 of the CS (and subsequent tables) represents data with or without propensity matching to the external placebo group described in Section B.3.4.2 of the CS.

No propensity score adjustment is included in the ITC, as this would represent double-accounting for variables that are already included in the MAIC or STC, namely the V30/V50, FAP stage, and prior treatment.

Trials

A15. Priority question. Please provide a breakdown of patients in the eplontersen arm of NEURO-TTRansform that had:

a) The early-onset V30/V50 mutation;

The NEURO-TTRansform trial did not record the number of patients with the early-onset V50M (previously known as V30M) and, consequently, this data is unavailable.

However, the population of patients with the early-onset V50M can be specified in terms of the definition used in the primary publication for the HELIOS-A trial. Adams et al. (2022) define early-onset as patients aged <50 years at disease onset.[4]

In line with this definition, the proportion of early-onset V50M patients in the eplontersen arm of NEURO-TTRansform is [redacted] of randomised patients.

b) The T60A/T80A mutation.

The mutation profiles of patients in the NEURO-TTRansform trial are available in the Clinical Study Report (CSR) (CS3 Section 14-1; Table 1.10) included as part of the reference pack for this submission and are presented in Table 18 below. In the eplontersen arm of NEURO-TTRansform, [redacted] of patients exhibited the T60A/T80A mutation.

Table 18. TTR mutations in NEURO-TTRansform

TTR mutation, n (%)	**NEURO-TTRansform**	
	Inotersen (n=24)	**Eplontersen (n=144)**
V50M	16 (66.7)	85 (59.0)
Non-V50M	8 (33.3)	59 (41.0)
E89Q/E109Q	[redacted]	[redacted]
L58H/L78H	[redacted]	[redacted]
F64L/F84L	[redacted]	[redacted]
S50R/S70R	[redacted]	[redacted]
S77Y/S97Y	[redacted]	[redacted]
T49A/T69A	[redacted]	[redacted]
T60A/T80A	[redacted]	[redacted]
V122I/V142I	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations: TTR: transthyretin.
Source: AstraZeneca Data on File. 2022.[8]

A16. Discussions with the EAG's clinical expert highlighted that the distribution of mutations in the NEURO-TTRansform study is quite different to what would be seen in a UK population. Specifically, the proportion of patients with the V30/V50 mutation is much higher than would be seen in the UK, where the majority of patients would likely have the T60A/T80A mutation. Furthermore, those with the V30/V50 mutation in the UK would most likely manifest with later onset disease rather than early onset (before ~55 years of age), the latter of which is more common in Portugal and there is thought to be a difference in phenotype and prognosis between early and late onset. The mean age in the NEURO-TTRansform trial is ~53 years, suggesting that even if the proportion with V30/V50 mutations was more in line with UK practice, those captured by the trial may be more reflective of those with V30/V50 mutation early onset disease.

Please can the company comment on the potential implications of these observations on the generalisability of the results to UK clinical practice.

The Company acknowledges that there is a lower proportion of patients exhibiting the T60A/T80A mutation in the eplontersen arm of the NEURO-TTRansform trial than what might be expected in UK clinical practice. However, this is not anticipated to influence the generalisability of the results since evidence from the NEURO-TTRansform trial demonstrates the efficacy of eplontersen is independent of the specific TTR mutation. To ensure that any potential impacts of mutation type and disease onset were captured in NEURO-TTRansform, pre-specified subgroup analyses for age and TTR mutation type were conducted at Week 65/66 for serum TTR, mNIS+7 and Norfolk QoL-DN endpoints (see Section 3.7, Document B).[9] The results of these analyses

show a consistent treatment effect across all pre-specified subgroups, including age (<65 years versus ≥65 years) and TTR mutation status (V50M versus non-V50M mutation).[9] This demonstrates that the clinical benefits of eplontersen are independent of the specific TTR mutation, and age of onset, and supports that the results of NEURO-TTRansform can therefore be considered generalisable to UK clinical practice.

Furthermore, in a Phase II/III trial of inotersen versus placebo in patients with ATTRv-PN (NCT01737398), the distribution of TTR gene mutations was not found to be a strong predictive factor for the efficacy of inotersen.[10] Inotersen is a silencer therapy and, consequently, has a similar mechanism of action as eplontersen; TTR mRNA synthesis is blocked, limiting the production of TTR protein. Given the similarity in mechanisms of action and the evidence supporting the absence of mutation-related treatment effects demonstrated in the NCT01737398 trial, it was not considered necessary to ensure a particular mutation distribution amongst patients in NEURO-TTRansform.[9, 10] Instead, the impact of mutation type was investigated in pre-specified subgroup analyses as described above.[9]

These conclusions are further supported by feedback from UK clinical experts from the National Amyloidosis Centre (NAC) who confirmed that the NEURO-TTRansform population was broadly generalisable to the UK patient population and patients observed in UK clinical practice.[11] Additionally, the clinical experts did not raise any concerns regarding the mutation profile of patients in the eplontersen arm of NEURO-TTRansform, suggesting this is not a key consideration in clinical settings and in the treatment of patients with ATTRv-PN.

In summary, the efficacy of eplontersen is considered to be independent of the specific TTR mutation. Consequently, any differences in the distribution of mutation types between the NEURO-TTRansform cohort and the target UK patient population with ATTRv-PN are not expected to impact the generalisability of the results to UK clinical practice.

A17. Please clarify why the proportion with cardiac involvement for eplontersen in Table 10 of the CS appears to be very different to the proportion reported in Table 27 (and other ITC baseline characteristics tables) for the eplontersen unadjusted subgroup. Was the original definition used in Table 10 updated to match those used in the HELIOS-A study for indirect comparisons?

The definitions of cardiac involvement in NEURO-TTRansform and HELIOS-A are based on different criteria, as defined in their corresponding Statistical Analysis Plans.[2, 12] Consequently, to allow for comparison, it was necessary to align their definitions, so the definition for the eplontersen treatment group was updated to match the definition used in HELIOS-A. This resulted in an adjustment to the proportion of patients with cardiac involvement at baseline reported in Table 10 (from NEURO-TTRansform) and the post-adjustment proportion reported in Table 27 (used in the indirect treatment comparison [ITC]).

The definition of cardiac involvement used in NEURO-TTRansform was patients with either:[12]

- A diagnosis of TTR cardiomyopathy at study entry.
- Baseline interventricular septum thickness ≥13 mm on echocardiogram AND no hypertension in past medical history or diagnosed on study AND no two consecutive systolic blood pressure readings of ≥150 mmHg at any time during the study (including screening and baseline visits).

The definition used in HELIOS-A was:[2]

- Patients who had pre-existing evidence of cardiac amyloid involvement, defined as patients with baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history.

A18. Please provide a breakdown of the proportion of patients in NEURO-TTRansform that were able to administer eplontersen at home themselves (or with the help of a carer) rather than by a healthcare professional following the first dose and whether this was maintained for all subsequent doses.

The proportion of injections in NEURO-TTRansform that were self-administered or administered by a trained relative was [redacted].[13] It is important to note that the NEURO-TTRansform trial involved mandatory in-clinic visits for patient monitoring that aligned with dose administration days (see Appendix A of the NEURO-TTRansform protocol). Of the 21 dose administration days, 12 (60%) coincided with mandatory in-clinic visits. During these visits, eplontersen would have been administered by on-site personnel or trained healthcare professionals (HCPs) by default. Consequently, the proportion of injections that were self-administered in the trial is lower than what is anticipated in clinical practice, as patients who were able and willing to self-administer eplontersen in the trial did not do so, due to the mandated in-clinic visits and trial design. Given the parameters of the trial, the proportion of injections that were self-administered or administered by a trained relative is considerably significant.

As explained further in the response to Clarification Question B1, for patients who may not be able to or prefer to not self-administer, the Company plans to develop a fully funded homecare program which will support with the delivery of the medicine to the patients home and offer HCP administration, where required. Scenario analyses indicate that if a proportion of patients express a preference for HCP administration, the resulting financial impact would be negligible, [redacted]

A19. Please clarify where the 9-month adverse event data for HELIOS-A were obtained from, as mentioned in Appendix J of the CS.

The primary HELIOS-A publication (Adams et al. 2022) only reported the incidence of adverse events (AEs) occurring in ≥10% of patients at 18 months.[4] The Company submission used 9-month data for serious adverse events (SAEs) for vutrisiran in the HELIOS-A trial, derived from the European Public Assessment report for vutrisiran. The relevant reference for these data is:

European Medicines Agency. Amvuttra (vutrisiran) – Assessment Report. Available from: https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf

A20. Please clarify whether any data from the open-label extension study of NEURO-TTRansform (NCT05071300) is currently available.

Data from the open-label extension study of NEURO-TTRansform is available for the April 2023 data cut-off. The CSR presenting these data has been provided alongside the clarification

question responses. Please note that these data are unpublished and consequently, should be treated as confidential.

Section B: Clarification on cost-effectiveness data

Treatment administration

B1. Priority question. The EAG's clinical experts outlined that a proportion of eplontersen patients may not be able to self-administer due to the progression of ATTR impairing limb movement, or may prefer to not self-administer. If the company considers that treatment with eplontersen would be continued and administered by a healthcare professional (HCP), please conduct a scenario in which a proportion of eplontersen patients receive treatment from a HCP. If the company has no way of estimating what proportion of patients might be unwilling to self-administer, consider conducting a range of scenarios where 5%, 10%, 15% of patients don't self-administer to test the sensitivity of the results to the assumption of 100% self-administration and comment on the plausibility of those scenarios.

The ITC included as part of the Company submission demonstrates similar clinical efficacy between eplontersen and the key comparator, vutrisiran, but unlike eplontersen, vutrisiran must be administered by an HCP. Eplontersen will be supplied in an autoinjector (pre-filled pen), providing increased flexibility for patients who are of working age and physically able to self-inject, or for patients who have caregivers who may be able to support with administration. For patients who may not be able to or prefer to not self-administer, [redacted]

As requested, since it is unclear what proportion of patients might be unwilling to self-administer or do not have a caregiver to support with administration, the Company has considered a range of scenarios where 5%, 10% and 15% of patients do not self-administer (see xxxxxxxxxxxxx

Table 19 below and the updated model provided alongside the clarification question responses). [redacted] and are therefore conservative. As seen below, the influence of these scenarios on the base case is minimal, with the most extreme scenario (15% HCP administration) resulting in an increase of [redacted] per patient over the model 5-year time horizon compared to the base case (0% HCP administration). Therefore, should a proportion of patients express a preference for HCP administration, the resulting financial impact would be negligible, [redacted]

Table 19. Base case and scenario analyses assessing various eplontersen HCP administration assumptions in the model

Proportion of patients requiring HCP administration of eplontersen	Total cost (GBP)		Incremental Cost (GBP)
	Eplontersen	Vutrisiran	
Base case (0%)	[redacted]	[redacted]	[redacted]
5%	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]
15%	[redacted]	[redacted]	[redacted]

Abbreviations: GBP: Great British Pound; HCP: healthcare professional.

B2. Based on HST4 and Boye *et al. 2010,*[14] *please* explore the use of disutility associated with invasive administrations, such as:

a) Consider the possibility and implications of the inclusion of an injection disutility given the difference in administration frequencies between eplontersen (Q1M) and vutrisiran (Q3M).

b) Please estimate the potential QALY loss with eplontersen and vutrisiran due to injections.

The Company firmly believes that the inclusion of an additional disutility associated with the self-administration of eplontersen to be inappropriate, as the inclusion of disutility values is not in the scope of the NICE cost-comparison guidelines.[15] In addition, health-related quality of life (HRQoL) data were collected as part of the NEURO-TTRansform trial and, as demonstrated by the results of the ITC, eplontersen was associated with a statistically significant improvement in Norfolk QoL-DN total score in both the unanchored matching-adjusted indirect comparisons (MAIC) and simulated treatment comparisons (STC) compared with vutrisiran. As HRQoL data were captured as part of the clinical trial, any administration-related decrement would inherently be captured in the assessment of HRQoL. Therefore, any attempt to include an additional administration-related disutility would result in double counting.

The proposal to include the utility estimates presented in Boye *et al.* 2010[14] appears to be arbitrary and not identified systematically. The population and issues discussed in this publication are not generalisable to the population relevant to this appraisal; nor is the treatment pathway. Boyle *et al*. 2010 reports disutilities associated with the management of diabetes in 2010, during which the mainstay therapeutic goal was glycaemic control. Patients with type 2 diabetes mellitus (T2DM) who are being treated with injectable insulin will have previously failed treatment with multiple oral antidiabetic medicines and therefore represent an optimised, intensified population of patients. In addition, the authors report particular challenges associated with injectable insulin therapy which is not representative of the treatment approach for patients with ATTRv-PN. In particular, the authors state:

"The first injection attribute is dose frequency, which varies greatly among injectable treatments for type 2 diabetes. Some types of insulin are administered multiple times daily, while other treatments such as insulin glargine and liraglutide usually require only one daily injection. More recently, once-weekly injectable treatments are being developed."

And

"*The second attribute examined in the current study is dose flexibility with regard to mealtimes. Most injectable treatments for type 2 diabetes must be administered at a time coordinated with meals. For example, human short-acting insulin must be administered within 30 min prior to eating. Other medications have been developed that have a more flexible dosing regimen, allowing for injections at any time of day regardless of when a patient eats. Injection regimens that have greater flexibility with respect to mealtimes and eating patterns are thought to be associated with greater treatment satisfaction and quality of life among patients with type 2 diabetes.*"

It is therefore evident from the publication that the challenges associated with the administration of injectable insulin are very different to those for patients with ATTRv-PN, who would be offered monthly injection via self-administration with an autoinjector. The utilities reported in Boye *et al.* 2010 would therefore inappropriately and significantly overestimate any treatment-related disutility associated with the administration of eplontersen.

Whilst the Company remains content that any administration-related disutility would inherently be captured as part of the HRQoL assessment conducted in NEURO-TTRansform, it would also be feasible that the comparator would be associated with a greater disutility due to the need for HCP administration and the subsequent impact this could have on the flexibility of patients' lives. As such, the current approach to exclude additional disutilities for both eplontersen and vutrisiran is already likely to be conservative.

Finally, inclusion of disutilities was also not considered appropriate in TA868 where differences in dosing frequencies and time requirements for treatment administration are more pronounced.[16] Vutrisiran is administered every three months, with treatment lasting less than 5 minutes, whilst patisiran is administered every three weeks, with treatment lasting several hours. Therefore, to adhere to NICE's methods and ambition to ensure consistency in its decision making, the Company firmly disagrees with any additional attempt to include an administration-related disutility.[16]

Treatment discontinuation

B3. Priority question. The company has outlined that the HELIOS-A study did not report time to treatment discontinuation (TTD). Therefore, an odds ratio was calculated from the number of patients who had discontinued treatment by the end of the study, which was compared to eplontersen treatment discontinuation from NEURO-TTRansform. Please can the company provide the odds ratios (mean and 95% confidence interval) and the calculations informing them.

The log odds ratio and the associated 95% confidence interval (CI) in Table 1 (for Clarification Question A1b) and Table 2 (for Clarification Question A2b) for the ITC of treatment discontinuation can be converted to odds ratios by applying the exponential function to the differences between the log odds. The log odds and its associated variance were calculated from the HELIOS-A data, in the following manner:

$$\text{Log odds} = \log(E / (T - E)) ,$$

$$\text{Variance of the log odds} = 1 / ((T \times (E / T)) \times (1 - (E / T)))$$

where E is the number of patients with events, and T is the total number of patients.

During the review for this response an error in the underlying numbers in the ITC of treatment discontinuation was discovered. In the original ITCs, five patients were counted as discontinuing treatment in HELIOS-A. This was a miscalculation because two deaths were counted as discontinuations in addition to the three reported discontinuation. But the two deaths were already counted among the three discontinuations, as explained in the HELIOS-A publication:[4]

Three (2.5%) patients in the vutrisiran group discontinued treatment, and also stopped study participation, due to AEs by Month 18 (two of which were due to death).

This error only impacted the ITC of treatment discontinuation. Therefore, all ITCs of treatment discontinuation have been updated to the correct figure of three (not five) patients discontinuing treatment in HELIOS-A. The results of the corrected analyses were consistent with the original ITC and did not affect the conclusion of comparability.

Table 20 shows the ITCs for treatment discontinuation, for the reference MAIC (updated to reflect the correct number of patients discontinuing treatment in HELIOS-A) and the new MAICs containing the additional variables identified in Clarification Question A1a.

Table 20. MAICs for treatment discontinuation

		Model variables	Point estimate	Lower 95% CI	Upper 95% CI
Treatment discontinuation (log odds ratio)	Original reference MAIC	• Age • Sex (male) • Race (white) • Prior treatment • V30/V50 • Cardiac involvement • FAP stage (stage I)	[redacted]	[redacted]	[redacted]
	Including additional variables identified in question A1a	• Age • Sex (male) • Race (white) • Prior treatment • Early onset V30/V50 • Cardiac involvement • FAP stage (stage I) • Baseline mNIS+7 • Baseline NT-proBNP (>3000)	[redacted]	[redacted]	[redacted]

Footnotes: For all analyses baseline mNIS+7$_{Ionis}$ was rescored to approximately match mNIS+7$_{Alnylam}$. Negative values favour eplontersen and positive values favour vutrisiran, for all endpoints.
Abbreviations: CI, confidence interval; FAP, familial amyloid polyneuropathy; MAIC, matching adjusted indirect comparison; mNIS+7, modified Neuropathy Impairment Score+7; NT-proBNP, N-terminal pro b-type natriuretic peptide; TTR, transthyretin; V30/V50, Val30/Val50 genetic mutation.

Adverse events

B4. Priority question. When calculating the per cycle adverse event probabilities for vutrisiran, a study duration of nine months has been assumed in the model while a duration of 18 months is reported in the CS. Please can the company confirm the true value and update the calculations if required.

The AE probabilities for vutrisiran currently used in the model are correct. SAE rates for vutrisiran were taken from HELIOS-A trial data at 9-months, as information relating to the incidence of AE occurring in ≥10% of patients was only reported for the 18-month trial data. Please see the response to Clarification Question A19 for more detail.

Treatment costs

B5. Priority question. In the economic model, the company has applied a cost of vutrisiran at a third of the price every month instead of the full cost every three months so that a cost can be applied monthly given this is the model cycle length. As a scenario, please cost the full price of vutrisiran every three months instead of a third of the cost every month. In the scenario, please also

adjust the administration costs so they are in line with the monthly administration frequency.

The totality of vutrisiran acquisition and administration costs applied once every three months has been included as a model scenario analysis (see Table 21 below and updated model provided alongside the clarification question responses). This scenario results in an incremental cost increase of [redacted] per patient for vutrisiran over the 5-year time horizon used in the model.

Table 21. Base case and scenario analysis assessing how the cost of vutrisiran is applied in the model

Cost of vutrisiran applied	Total cost (GBP)		Incremental Cost (GBP)
	Eplontersen	Vutrisiran	
Base case At a third each cycle	[redacted]	[redacted]	[redacted]
Every three cycles	[redacted]	[redacted]	[redacted]

Abbreviations: GBP: Great British Pound.

B6. Priority question. The EAG considers that discounting should be applied given time preferences are still applicable. As such, please include standard discounting of costs and utilities in the model.

The Company does not believe inclusion of discounting of costs is appropriate for the base case analysis in this cost-comparison submission. According to Section 4.4.2 of the NICE cost-comparison user guide,[15] discounting is not normally required in a cost-comparison analysis without rationale. Discounting was not considered appropriate in TA868 where time preferences were more pronounced, with vutrisiran administered every three months, whilst patisiran is administered every three weeks.[16] Given the comparable mechanism of action between vutrisiran and eplontersen, both of which are silencers (see Section B.1.3.5, Document B) if discounting is applied to this analysis there would be inconsistency in the application of NICE methods. As a scenario analysis, a cost discount rate of 3.5% has been included in the model to explore the impact of this variable, resulting in an incremental cost decrease of [redacted] per patient over the model 5-year time horizon (see Table 22 below and updated model provided alongside the clarification question responses). Finally, as discussed in response to Clarification Question B2, the incorporation of any disutilities has not been conducted therefore discounting to utilities is not relevant for the analysis presented here.

Table 22. Base case and scenario analysis assessing annual discount rates applied in the model

Discount rate	Total cost (GBP)		Incremental Cost (GBP)
	Eplontersen	Vutrisiran	
Base case (0%)	[redacted]	[redacted]	[redacted]
3.5%	[redacted]	[redacted]	[redacted]

Abbreviations: GBP: Great British Pound.

Section C: Textual clarification and additional points

Indirect treatment comparison

C1. Priority question. Please clarify whether polyneuropathy disability (PND) score or familial amyloidotic polyneuropathy (FAP) was the staging variable used in the MAIC adjustments. Tables 24 and 26 of the CS suggest that PND was included, whereas Tables 27 to 36 of the CS and the sample MAIC code provided suggest this was FAP stage instead.

Familial amyloidotic polyneuropathy (FAP) was the staging variable used in the MAIC adjustments. Tables 24 and 26 in the CS included PND score, as this was the initial staging variable assessed for treatment effect modification; however, due to the availability of aggregate data and small number of patients with PND score IIIb in both trials, FAP was used instead of PND score. If PND score would have been used, it would likely have to be collapsed into fewer categories, which then defeats the purpose of having a more granular variable.

C2. Priority question. For Figures 30 to 33 in the CS, can the company confirm that the x-axis labels should be swapped? The EAG notes that when the log ORs in Figures 30, 31 and 33 are converted to ORs, the point estimate ORs are [redacted], suggesting [redacted] events with eplontersen if the results are presented as eplontersen vs vutrisiran. Currently the x-axis labels in these figures suggest [redacted] events with vutrisiran based on point estimates. The opposite is observed in Figure 32.

Reviewing the plots, the Company agrees that for these plots the x-axis labels, namely “Favours Eplontersen” or “Favours Vutrisiran”, should be switched.

Treatment storage and administration

C3. Priority question. Can the company confirm if patients will be expected to store eplontersen at home? If so, is eplontersen required to be stored under specific conditions? For example, below a specific temperature. Can the company provide the ‘Instructions for Use’ indicated in the draft SPC and any other information for patients that will explain how the prefilled pen is used and stored?

Information on how patients should store eplontersen at home is available in the draft SmPC.[17] As per the ‘Instructions for Use’, the conditions for the storage of eplontersen are as follows:

- The pre-filled pen should be refrigerated by patients at a temperature between 2ºC and 8ºC. The pre-filled pen should not be frozen.

- The pre-filled pen should be removed from refrigerated storage at least 30 minutes before use and allowed to reach room temperature prior to injection. The pre-filled pen should not be positioned within direct sunlight.
- If needed the pre-filled pen can be stored at room temperature up to 30°C in the original carton for up to 6 weeks. The pre-filled pen should be thrown away if it is kept at room temperature for 6 weeks but is not used.

The 'Instructions for Use' for the eplontersen pre-filled pen are available on pages 31–35 of the draft SmPC.[17]

C4. Please provide a RIS file that can be used to import references used within the CS.

A RIS file has been shared alongside the clarification question responses.

Additional Questions Received by Email

Please can the company clarify if "n=140" for the unadjusted eplontersen population is correct for ITCs of adverse events and discontinuation in Tables 33 to 35 of the CS is correct or whether the full safety population of n=144 was analysed for these outcomes. If n=140 is correct, please outline why n=4 patients from the safety set were not included.

The Company confirms that n=140 is correct as this number is based on the original set of randomised patients (safety population) in NEURO-TTRansform. The final number included in the analysis is the number of patients with available data on all baseline variables included in the ITC adjustments. The n=4 patients were excluded because they did not have data on all adjustment variables included in the reference ITCs for AEs and treatment discontinuations.

For Tables 27 to 32 of the CS, is "n=141" correct for the unadjusted eplontersen population for all outcomes? Does this represent the FAS population or were certain patients excluded given they would not be eligible for inclusion in HELIOS-A? If the latter, please outline the reasons for n=3 patients being excluded.

The Company confirms that n=141 is correct and is the number of patients in the FAS, defined in the NEURO-TTRansform SAP (See Section 4.5.3) as all randomised patients who received at least one injection of eplontersen and who have a baseline and at least one post-baseline assessment for mNIS+7 composite score or Norfolk QoL-DN total score.[18]

For the additional MAICs provided in response to CQ A2 (mBMI, 10MWT and R-ODS), are these results based on extrapolated week 65/66 data (as per the process originally used for mNIS+7 and Norfolk QoL-DN outcomes) or were week 85 observed data used for these ITCs?

The additional MAIC provided in the response to CQ A2 for mBMI is based on extrapolated week 65 data for mBMI, as per the process originally used for mNIS+7 and Norfolk QoL-DN outcomes.

The additional MAICs provided for 10-MWT and R-ODS are based on observed Week 81 data, as 10-MWT and R-ODS are not captured at Week 65/66 or at Week 85.

In Table 17 of the CQ responses for the week 85 data analysis, the "reference" MAIC point estimate for Norfolk QoL-DN appears to be very different to other Norfolk QoL-DN results in this table (including the "alternative" MAIC directly below it) - please can this result be reviewed and corrected if required.

We agree that the difference between the reference MAIC and alternative MAIC, for Norfolk QoL-DN using week 85 observed data, show notably different point estimates. We have reviewed and verified these analyses, and we can confirm that the results are correct.

The reason for the difference in point estimates is that the alternative MAIC for Norfolk QoL-DN using Week 85 observed data does not include V30/V50M, which is the variable with the largest variation between the NEURO-TTRansform trial and the HELIOS-A trial (variables included in each model are described in the footnotes to Table 17 of the CQ responses). In the NEURO-TTRansform trial, 59% of patients in the eplontersen arm had V30/V50M, compared with 44.3% in the vutrisiran arm of the HELIOS-A trial [1, 3]. This means that the effective sample size (ESS) in the ITC is more than doubled by removing V30/V50M from the reference MAIC (from [redacted] to [redacted]). The results were consistent with the main ITC results, both when V30/V50M is included in the MAIC and when it is not, supporting a conclusion of comparable efficacy for eplontersen and vutrisiran.

References

1. 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 2023;30:1-9.
2. Alnylam Pharmaceuticals. 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). Statistical Analysis Plan. 2021. Available at: https://classic.clinicaltrials.gov/ProvidedDocs/79/NCT03759379/SAP_001.pdf. Last Accessed: March 2024.
3. Coelho T, Marques W, Jr., Dasgupta NR, et al. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. Jama 2023;330:1448-1458.
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. Gorevic P, Franklin J, Chen J, et al. Indirect treatment comparison of the efficacy of patisiran and inotersen for hereditary transthyretin-mediated amyloidosis with polyneuropathy. Expert Opin Pharmacother 2021;22:121-129.
6. European Medicines Agency. Amvuttra: EPAR - Assessment Report. Available at: https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf. . 2022.
7. Folkvaljon F, Gertz, M., Gillmore, J.D., Khella, S., Masri A., Maurer, M.S., Waddington-Cruz, M., Wixner, J., Chen, J., Reicher, B., Kwoh, J., Yarlas, A., Berk, J.L. AstraZeneca UK Ltd. DOF. Estimating meaningful differences in measures of neuropathic impairment, health-related quality of life and nutritional status in patients with hereditary transthyretin amyloidosis. [Manuscript] 2024.
8. AstraZeneca UK Ltd. Data on File. Clinical Study Report (Section 14: Tables, Figures and Graphs).
9. AstraZeneca DoF. Clinical Study Report: 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 (Final Analysis). 2023.
10. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. New England Journal of Medicine 2018;379:22-31.
11. AstraZeneca UK Ltd. Data on File. ID: REF-218937. February 2024.
12. AstraZeneca Data on File. Statistical Analysis Plan (v2.3): 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, 2023.
13. AstraZeneca UK Ltd. Data on File. Eplontersen administration methods summary v1.3 20240328.
14. Boye KS, Matza LS, Walter KN, et al. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. The European Journal of Health Economics 2011;12:219-230.
15. National Institute for Health and Care Excellence. User guide for the cost comparison company evidence submission template. Available at: https://www.nice.org.uk/process/pmg32/chapter/cost-comparison-analysis. .
16. National Institute for Health and Care Excellence. TA868. Vutrisiran for treating hereditary transthyretin-related amyloidosis. Committee Papers. Available at: https://www.nice.org.uk/guidance/ta868/documents/committee-papers. Accessed: June 2023., 2023.
17. AstraZeneca DoF. Eplontersen: Summary of Product Characteristics (SmPc).
18. AstraZeneca DoF. Statistical Analysis Plan (v2.3): 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. 2023.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Eplontersen for treating polyneuropathy caused by hereditary transthyretin-related amyloidosis [ID6337]

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	Amyloidosis UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a small charity run by and for ATTR amyloidosis patients. We have 6 trustees and one, part time member of staff. We are funded through donations, fund raising and grants from the pharmaceutical industry.
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.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Speaking directly to patients and their carers, attending relevant patient and professional events, and through lived experience.

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?	**hTTR Amyloidosis is a debilitating, progressive and ultimately fatal disease that affects all aspects of a patient's life.** Patients describe living with disease as painful, depressing and disabling "As the disease progresses you are unable to do simple day to day things without support". Patients experience a wide range of challenges because of having hATTR. These include: -Very difficult to control diarrhoeas. This result is weight loss and can often lead to social isolation and not being able to hold a job or even go out of the house. Treatments like codeine may help on the day but they can have a rebound effect the following day when symptoms are even worse. -Diarrhoea and pain at night is very common and seriously disturbs rest. This is a big problem when it happens every night. -Neurogenic pain feels like suddenly being stabbed, out of the blue, with very intense pain that is short in duration, and aches that last a long time. The pains usually start in the feet, and then progress proximally as the neuropathy advances. It then affects the hands. Sometimes the pain feels like burning or like being scalded. This type of pain does not respond well to usual painkillers, and even gabapentin and pregabalin do not seem very effective. -Autonomic nerve symptoms include those related to hypotension (feeling light headed and fainting), digestive (vomiting, problems swallowing, abdominal pain, diarrhoea), sexual (including impotence), and urinary (difficulty voiding leading to frequent urinary infections). -Cardiac involvement often start with tiredness and shortness of breath. This affects walking distance and later, the ability to self-care. Often palpitations and arrythmias require a pacemaker, some patients also require an implantable cardioverter-defibrillator. -The numbness due to neuropathy starts in the feet. This causes problems with shoes causing ulcers, similar to diabetic foot problems. Patients also develop sensory ataxia leading to poor coordination and balance. For example, it is difficult to just stand up and balance, movements can make them look like they are drunk. -Weakness and muscle atrophy causes difficulty, first walking, then using the hands. progresses to the hands fine motor skills such as buttoning up clothes and opening packets, wallets etc. which further increase the challenges of daily life. The weakness progresses proximally and in advanced stages, even breathing is difficult. The first to be lost is usually employment, then hobbies, then social life, then the ability to self-care. -The fact that this is a familial disease means that the patients have often seen relatives with the disease degenerate and die, so they are very aware of what is waiting for them. Psychologically this is devastating.

	-There is often a profound concern about children, since it is possible, even likely, that they will develop the disease at some point in their lives. There are also situations where multiple family members are affected, which makes the situation extremely difficult for the carers. -The eyes are often involved in the disease with glaucoma, vitreous opacification and loss of sight as a result. Being blind and having numb hands is a devastating combination, completely disabling. -Advanced cases develop central nervous degeneration, with headaches and progressive dementia. -Advanced stages of the disease, with a patient in pain, unable to walk or stand, unable to use his or her hands, unable to selfcare, with diarrhoea, with pressure ulcers and blind, results in a situation worse than death. Even in the early stages symptoms significantly reduce an individual's quality of life, rendering them unable to do things they used to enjoy. It increases their need for care and reduces their ability to participate fully in their own lives, including their ability to maintain employment. The financial implications for families are 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. TTR Amyloidosis causes a heavy burden on families and carers. The symptoms mentioned above make it difficult to live independently so have a major impact on family members. Patients often become a different person, as they deal with constant pain and discomfort. This can result in them being distant and 'living in their own bubble' of the disease. Carers are often required to leave or change their jobs to allow them more time for their role as carer. Closeness between a couple where Amyloidosis affects one of them can be reduced. Patience and love are often tested, and relationships can change significantly from how they were prior to amyloidosis. Physically carers often take over the tasks that their loved one with hATTR can no longer do, in addition to the physically demanding role of carer.

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, the need for 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, it can take months or years. For a progressive condition like this, any delay reduces the quality of life and reduces the impact of treatment. Current care consists mainly of symptom management. There are three disease modifying treatments currently available in the UK patisiran, vutisiran and inotersen. Two of these, patisiran and vutisiran are essentially the same treatment in a different form. This means that in practice there are still only two disease modifying treatments available. The third treatment, inotersen, is effective but has some serious, if relatively rare side effects. Patients who are on inotersen must undergo weekly administration injections and frequent blood tests to monitor for side effects. For those who can access them, treatments have completely changed the quality of life and the outlook of hATTR patients and their carers, yet there is still a great need for improvement in the treatment and care of hATTR amyloidosis in the UK.
8. Is there an unmet need for patients with this condition?	Yes. While existing treatments offer some symptomatic relief and a slowing of disease progression, there remains a great unmet need for improved, safe, disease modifying treatments. Patients need access to treatments that have a longer lasting and/or deeper positive impact. Treatment options for hATTR patients in the UK remain very limited and the burden of disease is great, even when a patient is receiving treatment. Some patients are not able to tolerate either of the currently available treatments. More effective, and more convenient treatments are urgently needed to reduce the huge burden this disease places on patients and their families.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	This technology gives the same benefits as the existing Inotersen with an improved delivery method which reduces the dose and frequency of administration needed to gain the same benefits. This reduces side effects, risks and the number of interventions the patient is subjected to. Patients tell us that even small improvements to their condition, or improvements to their treatment protocol can transform their quality of life. Allowing them to retain more independence and maintain a better quality of life, for longer. Eplontersen represents a significant improvement over inotersen for patients, the lower doses needed also means that patients who are unable to tolerate inotersen may be able to tolerate eplontersen. For hATTR patients the treatment options remain incredibly limited, so patients are keen to have access to another, improved treatment option. Any new treatment also brings with it hope for the future, which is often all too lacking for the affected families.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who are currently on Inotersen treatment will benefit most from this technology, as it offers the same benefits as Inotersen with a reduced dose and frequency of administration. Eplontersen represents a material improvement in treatment and will make a significant difference to patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• hTTR Amyloidosis is a debilitating, progressive and fatal disease that affects every aspect of a patient's life. The disease puts a huge burden on the whole family. • Better disease modifying treatments are urgently needed. • Even small improvements in their condition can transform the quality of life for patients and their families. • From the patient perspective there are no disadvantages. • Eplontersen offers significant advantages for patients over inotersen.

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

NICE National Institute for Health and Care Excellence

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

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Eplontersen for treating polyneuropathy caused by hereditary transthyretin-related amyloidosis [ID6337]

Professional organisation submission

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

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

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

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 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists Neuromuscular Advisory Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	Association of British Neurologists Neuromuscular Advisory Group.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Slow disease progression, prevent progression of disability, prolong survival.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In current practice, neuropathy in patients with hereditary transthyretin amyloidosis (ATTRv) is stratified by Coutinho stage (1 ambulatory without assistance, 2 ambulatory with assistance, 3 wheelchair dependent/ bedbound). Outcome measures used in previous clinical trials have included: • Modified Neuropathy Impairment Score +7 (mNIS+7) • Norfolk Quality of Life Questionnaire-diabetic neuropathy Norfolk QoL-DN) We would hope that treatment would result in disease stabilisation or slowing of disease progression by remaining in the earlier stages of the disease with a better quality of life. Previous NICE appraisals have considered a 2-point change in mNIS+7 score to be a minimum clinically important difference based on a consensus report from the Peripheral Nerve Society, but there is no minimally clinically important difference for the Norfolk QoL-DN reported in the literature. Previous studies have also looked at serum TTR reduction as a surrogate marker for amyloidosis and an important indicator of response to treatment, with an 80% reduction in TTR levels generally associated with a better prognosis than patients with smaller reductions. Prior clinical trials have shown the following changes: - Patisiran vs placebo showed Δ mNIS+7 -34, Δ Norfolk QOL-DN -21.1 over 18 months - Vutrisiran vs. historical placebo Δ mNIS+7 -28.55, Δ Norfolk QOL-DN -21 over 18 months - Inotersen Δ mNIS+7 -19.7, Δ Norfolk QOL-DN -11.7 over 66 weeks. Eplontersen was studied over 65/66 weeks with comparable Δ mNIS+7 -24.8, Δ Norfolk QOL-DN -19.7 There are several additional outcome measures including DPD scintigraphy, neurological and cardiological assessments, nerve conduction studies, clinical examination, intraepidermal nerve fibre density assessment, autonomic assessment with heart rate variability, sudoscan, mIBG scintigraphy, BNP/nt-proBNP, troponin, echocardiography, cardiac MRI, bone scintigraphy and skin biopsy, and more novel biomarkers including MRI and US, neurophysiological assessments (QST) under evaluation as potential secondary outcome measures.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	ATTRv neuropathy is a life altering and life-shortening inherited condition which has a significant impact on patients, carers and healthcare providers. There are licenced, effective gene silencing therapies for ATTRv neuropathy which are more effective when commenced early in the disease course. Greater understanding of the role of genetic therapies earlier in the disease course is needed. Inotersen/Patisiran/Vutrisiran are available and what must be established is whether Eplontersen provides 1) treatment to a wider range of patients, 2) an improved side effect profile, 3) an easier treatment journey, 4) a cost saving to all or some patients. There is also a need to raise awareness of the condition now that therapies are available to promote early diagnosis.

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

9. How is the condition currently treated in the NHS?	Inotersen, Patisiran, Vutrisiran. (Liver transplant for selected patients, rarely in the UK due to poorer outcomes in those with ATTRv variants with greater cardiac involvement, which are more common here) Tafamadis is not available in England, Diflunisal rarely used off label due to contraindication/increased risk of cardiac, hepatic or renal failure.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	https://www.nice.org.uk/guidance/hst10/resources/patisiran-for-treating-hereditary-transthyretin-amyloidosis-pdf-50216252129989 https://www.nice.org.uk/guidance/ta868 https://www.nice.org.uk/guidance/hst9
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In England care is provided through the National Amyloidosis Centre.
9c. What impact would the technology have on the current pathway of care?	Provides an additional subcutaneous option with a longer dosing interval and possibly better side effect profile.
10. Will the technology be used (or is it already used)	Yes.

in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Eplontersen: 4 weekly subcut injection – likely with blood monitoring Inotersen: weekly subcut injection with blood monitoring Vutrisiran: 3 monthly subcut Patisiran: 3 weekly IV
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics. It may be possible for some of these medications to be delivered more locally.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	In England, the infrastructure is in place. Some patients have to travel to receive care.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It possibly provides an additional subcutaneous treatment option with a wider dose interval and better side effect profile.
11a. Do you expect the technology to increase length of life more than current care?	It is difficult to say whether the differences in outcome measures between treatment and contemporary or historical placebo groups across the four therapeutic options is meaningful in terms of life expectancy, as there are no head-to-head comparisons between Eplontersen and other disease modifying treatments listed above. Certainly, treatment with one of these options has a meaningful impact on quality of life and survival compared with placebo.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Possibly. Helpful to have additional options due to the range of contraindications seen in patients with ATTRv neuropathy.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not to our knowledge though this may become clearer with observational cohort/natural history studies, it may be the case in the future that ATTRv carriers who are presymptomatic are shown to benefit from treatment. Individuals with stage 3 neuropathy have not been studied.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is generally accepted that the subcutaneous delivery is simpler than intravenous delivery for most patients, and Eplontersen could be evaluated for possibly being delivered at the patient's home rather than a daycare or inpatient admission, saving travel time and costs, and providing greater flexibility.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The current Eplontersen trials recruited patients with Coutinho stage 1 and 2 ATTRv neuropathy – these would be considered to start treatment, and stoppage criteria that have been previously considered included a lack of clinical benefit, progression to stage 3, or if serum TTR reduction was not maintained.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is likely that there are quality of life benefits that are not measured by QALYs in this patient group. There is a convenience factor that comes with subcutaneous delivery and a longer dosage interval that is not considered.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Possibly. The conjugation of the ASO is thought to significantly increase to the pharmacological potency of the molecules allowing for substantially lower effective doses, which may increase the efficiency of ATTR reduction, and Eplontersen is given as a SC injection every 4 weeks compared to weekly Inotersen SC injections. Current studies have shown significant differences in outcome measures compared to historical placebo, but not compared directly/head-to-head with other disease modifying treatments currently available. The study suggests an improved side effect profile.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. siRNAs and ASOs have revolutionised care for ATTRv neuropathy. Compared to Inotersen for example, Eplontersen appears to provide a more convenient dosing regimen with similarly efficacious results.
16b. Does the use of the technology address any particular unmet need of the patient population?	Possibly, this requires further study.
17. How do any side effects or adverse effects of the technology affect the management of the	The treatment appears to have a good side effect profile on current studies, but there may be long term effects of ASO therapies that we do not currently understand. We anticipate that these treatments will

condition and the patient's quality of life?	not affect TTR production within the CNS and we may see CNS-TTR amyloidosis become more of a problem with prolonged survival of patients with ATTRv. Prolonged survival of individuals with ATTRv Neuropathy may result in a patient group with different care needs e.g. following treatment with liver transplant in some subtypes of ATTRv amyloidosis some survivors experienced intracranial haemorrhage.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No UK patients were included in the NEURO-TTRansform trial; however it was a 40-site trial and included patients from healthcare systems similar to the UK, and Inotersen, trialled in the similar NEURO-TTR study, is already delivered in England. The participants in the trial were individuals with manifesting neuropathy (stage I-II) and proven ATTRv, which reflects patients who would currently be offered this therapy in the UK.
18a. If not, how could the results be extrapolated to the UK setting?	See above.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	mNIS+7 and Norfolk QOL-DN, designed to capture disability from neuropathy, as well as serum TTR reduction, a surrogate outcome measure of disease activity are important outcome measures and were considered the primary outcome measures in the NEURO-TTRansform study. Other secondary end points included neuropathy symptom/change total score, SF-36 physical component summary score, PND score and modified body index score, which provide further additional useful information. We would

	also hope to see a survival benefit in longer term follow up studies, which may not be apparent in shorter initial studies.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Greater serum TTR reduction is generally associated with better prognosis, but this requires further study for example in a natural history/observational cohort study.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA868?	No.
21. How do data on real-world experience compare with the trial data?	Not known.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The T60A mutation predominantly affects individuals of Irish descent. The V122I mutation predominantly effects individuals of Afro-Caribbean descent.
22b. Consider whether these issues are different from issues with current care and why.	To our knowledge, this does not affect current care. Historically, liver transplant has been most useful for individuals with V30M mutations, which is not a commonly seen variant in the UK. We note also the discussion regarding Inotersen as a treatment for individuals with late onset disease[1] (which is typically but not always the case in the UK) and highlight that it may in the future be the case that treatment earlier in life in mutation carriers may be thought to be beneficial, though further study is much needed in this regard. 1. https://www.nice.org.uk/guidance/hst9/documents/equality-impact-assessment-guidance-development

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Eplontersen is associated with a significant fall on serum transthyretin and disability scales in ATTRv neuropathy compared to historical placebo, with a good side effect and safety profile. • There are no direct head-to-head studies comparing the efficacy and side effect profile of Eplontersen and the current disease modifying genetic therapies, although it does seem to be comparable to Inotersen on limited qualitative comparisons in the NEURO-TTRansform study. • Compared to current disease modifying genetic therapies, it is a monthly SC injection, compared to weekly SC injections/IV infusions, offering a more convenient dosing regimen for patients and clinicians. • The cost of delivering this therapy compared to other current treatment options will be important in determining its use within NHS clinical practice.

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.

BMJ TAG

Eplontersen for treating hereditary transthyretin amyloidosis [ID6337]

Cost-comparison Technology Appraisal

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165030.

Title:	Eplontersen for treating hereditary transthyretin amyloidosis [ID6337]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Nicole Downes, Senior Clinical Evidence Analyst, BMJ-TAG, London Archie Walters, Health Economist, BMJ-TAG, London Victoria Wakefield, Clinical Evidence Manager, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	01/05/2024
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165030.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Professor Philip Hawkins (Professor and Consultant Physician, University College London & National Amyloidosis Centre, Royal Free Hospital, London) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report. The EAG would also like to thank Dr Caroline Coats (Consultant Cardiologist, NHS Greater Glasgow and Clyde, Queen Elizabeth University Hospital, Glasgow) for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Downes N, Walters A, Wakefield V. Eplontersen for treating hereditary transthyretin amyloidosis: A Cost-comparison Technology Appraisal. BMJ Technology Assessment Group, 2024.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical methods section.
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

10-MWT	10-metre walk test
^{99m}Tc-DPD scintigraphy	Tc-labelled 3,3-diphosphono-1,2propanodicarboxylic acid scintigraphy
ADAs	Anti-drug antibodies
AEs	Adverse events
AESI	Adverse events of special interest
AIC	Akaike information criterion
ASO	Antisense oligonucleotide silencer
ATTRv	Hereditary transthyretin-mediated amyloidosis
ATTRv-CM	Hereditary transthyretin-mediated amyloidosis with cardiomyopathy
ATTRv-PN	Hereditary transthyretin-mediated amyloidosis with polyneuropathy
ATTRwt	Wild-type transthyretin-mediated amyloidosis
BIC	Bayesian Information Criterion
BSC	Best supportive care
CCE	Cost-comparison evaluation
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Controlled Register of Trials
CFB	Change from baseline
CIs	Confidence intervals
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
ES	Effect size
ESS	Effective sample size
FAP	Familial Amyloid Polyneuropathy
FAS	Full analysis set
HCP	Healthcare professional
HRdb	Heart rate with deep breathing
HRQoL	Health-related quality of life
HST	Highly specialised technology
HTAD	Health Technology Assessment Database
IPD	Individual patient data
ITC	Indirect treatment comparison

ITT	Intention to treat
KPS	Karnofsky Performance Status
LLOD	Lower limit of detection
LSM	Least squares mean
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
mBMI	Modified body mass index
MCID	Minimum clinically important difference
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed effects models with repeated measures
mNIS+7	Modified Neuropathy Impairment Score +7
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
N/A	Not applicable
NAC	National Amyloidosis Centre
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIS	Neuropathy Impairment Score
NMA	Network meta-analysis
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NSC	Neuropathy Symptoms and Change
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OAEI	Other adverse events of interest
OR	Odds ratio
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Pharmacodynamic
PFs	Prognostic factors
PGIC	Patients' Global Impression of Change
PK	Pharmacokinetic
PN	Polyneuropathy
PND	Polyneuropathy disability
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
RCT	Randomised controlled trial
ROC	Receiver-operating characteristic
R-ODS	Rasch-built Overall Disability Scale

SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SF-36 GH	36-item short form questionnaire – general health domain
SF-36 PCS	36-item short form questionnaire – physical component summary
siRNA	Small interfering RNA
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SRM	Standardised response mean
STC	Simulated treatment comparison
TA	Technology appraisal
TEAEs	Treatment-emergent adverse events
TEMs	Treatment effect modifiers
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTR	Transthyretin

1 Summary of EAG's view of the company's cost-comparison evaluation case

A cost-comparison evaluation (CCE) was submitted by the company to assess eplontersen compared to vutrisiran for the treatment of adults with hereditary transthyretin (TTR)-mediated amyloidosis who present with stage 1 or stage 2 polyneuropathy (PN), which may be termed stage 1 or 2 ATTRv-PN. As discussed in Section 2, the External Assessment Group (EAG) considers that the population covered in this appraisal is those with ATTRv with stage 1 or 2 PN who may or may not also have cardiac involvement (up to New York Heart Association [NYHA] class II); it does not cover patients that had cardiac involvement but no stage 1 or stage 2 PN or whose NYHA class was III or IV based on the inclusion criteria in the eplontersen trial (NEURO-TTRansform).

For a CCE to be appropriate, the National Institute for Health and Care Excellence (NICE) requires evidence that the intervention under review is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication. The EAG notes that vutrisiran has been recommended by NICE as part of TA868,[1] which was assessed using a CCE against the comparator of patisiran. However, the EAG highlights that there is inherently more uncertainty in this CCE compared to the one for vutrisiran given the reliance on indirect treatment comparisons (ITCs) here, whereas direct comparative evidence for the comparison between vutrisiran and patisiran was available in NICE TA868.

The EAG considers the population covered by the company in this appraisal to be appropriate given it is within the company's anticipated marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA); while the marketing authorisation is not specific to stage 1 or 2 PN, limiting the assessment to this group is in line with the population that vutrisiran was recommended for as a result of NICE TA868 (Section 3.1).[1] Furthermore, the EAG considers the inclusion of vutrisiran as the only comparator in this appraisal to be appropriate (Section 3.3).

While it is noted that the NEURO-TTRansform study lacks applicability to the UK population in terms of mutation type, age and PN stage, similar is true for the HELIOS-A study for vutrisiran. Based on clinical expert feedback, the EAG is satisfied that the relative efficacy and safety of eplontersen vs vutrisiran (and conclusions about the similarity of treatments made based on ITCs in Section 4.3.3) would not be expected to differ across different populations given these factors have been accounted for in the ITC adjustments (Section 3.1).

While the vutrisiran NICE appraisal (TA868) did not include explicit modelling of outcomes given it was also a CCE,[1] the EAG is satisfied that most of the outcomes used for decision-making in the vutrisiran CCE (and NICE final scope for eplontersen) have been covered by the ITCs in this appraisal (Section 3.4).[2]

As noted in Section 2, while both drugs act to reduce TTR levels, there are differences in the pathways involved, meaning there is scope for there being differences in safety and/or efficacy.

The EAG's conclusions and limitations of the clinical evidence are summarised in Sections 4.4 and 8. In the EAG's preferred matching-adjusted indirection comparisons (MAICs; summarised in Table 1 below), while the point estimates for a couple of outcomes favour vutrisiran (modified body mass index [mBMI] and treatment discontinuation), others favour eplontersen, including degree of serum TTR level reduction which is the key pharmacological determinant of clinical response to treatment based on clinical expert feedback (Section 3.4). Therefore, based on an overall assessment across the range of outcomes included in ITCs, the EAG considers it likely that eplontersen and vutrisiran are broadly similar in terms of efficacy and safety. Furthermore, point estimates for all outcomes are generally not above the minimum clinically important differences (MCIDs) identified by the EAG or the view of the EAG's clinical expert, or there is a small difference in terms of the number of events observed. For adverse events (AEs), the EAG reviewed naïve comparative data for specific AEs (Section 4.3.3.6) as well as the ITCs for serious and severe AEs (Section 4.3.3.6) and considered it likely that the AE profile of the two treatments is similar. Therefore, despite some uncertainty based on the 95% confidence intervals (CIs), the EAG considers it likely that eplontersen and vutrisiran are broadly similar in terms of efficacy and safety and that a CCE may, therefore, be appropriate.

While the EAG's preferred MAICs are not without their limitations, including limitations specific to these analyses as well as general uncertainty associated with unanchored MAICs,[3] the EAG does not consider its conclusions about clinical similarity would be likely to change were these to be fully resolved.

With respect to costs, the annual acquisition costs for eplontersen and vutrisiran are [redacted] when considering the list prices. However, there is a difference in administration costs as eplontersen patients are able to self-administer treatment and therefore do not require health care practitioner assistance unlike vutrisiran patients. The EAG notes that the cost difference due to administration costs composites a small proportion of the total cost difference between treatments, which is driven by acquisition costs.

Overall, the EAG considers that appropriate measures have been taken to address the uncertainty where data is missing or limited. Given the similarities in efficacy and costs, the EAG considers that patient choice between treatments may be guided by the differences in administration frequencies (every month compared to every three months), and methods of administration (flexibility to self-administer or administered by a healthcare professional for eplontersen, and administered by a healthcare professional for vutrisiran).

Based on the inclusion of the patient access scheme (PAS) discount for eplontersen and list price for vutrisiran, eplontersen remains cost saving under the company's base case and scenario analyses and the EAG's preferred assumptions. However, a confidential PAS discount is available for vutrisiran and so results that include this discount, are presented in a confidential appendix to this report.

Table 1. Summary of EAG conclusions on similarity of eplontersen and vutrisiran in terms of clinical outcomes

Outcome	Point estimate (95% CI)	Smallest MCID identified in literature*	EAG conclusion†	Comment‡
Serum TTR percentage change from baseline at steady-state, mean difference	[redacted]	10 percentage points	The EAG considers that there is unlikely to be a clinically meaningful difference between treatments. The point estimate and 95% CI do not cross the lowest MCID identified.	Some limitations remain in terms of analyses but the EAG considers these to be minor or unresolvable uncertainties, with the size and direction of bias unclear.
mNIS+7 change from baseline score, mean difference	[redacted]	1.8 points	The point estimate slightly favours eplontersen but is not higher than any of the MCID thresholds identified by the EAG. Although the 95% CI crosses some of the MCID thresholds identified, it does not cross the threshold that the EAG's clinical expert considered to be a better indicator of a clinically important difference (12.2-point threshold). Therefore, the EAG is satisfied that there is unlikely to be a clinically important difference between treatments for this outcome.	Additional adjustment was not included in the week 85 analysis preferred by the EAG but it is unlikely that this would change results to the extent that the EAG's conclusions would change. It was not possible to completely align the two mNIS+7 versions used in the MAICs for this outcome, meaning the results for this outcome are associated with increased uncertainty, although the impact may be small given the domain that could not be aligned was the smallest domain within the mNIS+7.
Norfolk QoL-DN change from baseline score, mean difference	[redacted]	1.4 points	The point estimate slightly favours eplontersen but this does not exceed any of the MCIDs identified for this outcome. Uncertainty exists based on the 95% CI. The EAG is satisfied that there is unlikely to be a clinically important difference between the two treatments for this outcome.	Additional adjustment was not included in the week 85 analysis preferred by the EAG but it is unlikely that this would change results to the extent that the EAG's conclusions would change.

mBMI change from baseline score, mean difference	[redacted]	9.8 points	The point estimate suggests a slight benefit of vutrisiran and is above the smallest MCID identified. However, this is highly uncertain based on the 95% CI. The EAG's clinical expert did not consider a 10-point difference to be clinically meaningful, with even a difference of ~50 points considered to be small. Overall, the, the EAG considers it possible that there is a slight benefit of vutrisiran for this outcome but that there is uncertainty associated with this and it may not be a clinically meaningful difference.	These results are based on the extrapolation of week 65 data rather than use of observed data at week 85 for eplontersen. The EAG would have preferred that week 85 observed data was used instead and cannot rule out the possibility that results for mBMI may favour vutrisiran slightly more if the week 85 observed data had been. However, the EAG considers it unlikely that it would change its conclusion with regards to this outcome and the EAG's overall conclusion about similarity of the treatments based on all outcomes.
10-MWT change from baseline score, mean difference	[redacted]	0.04 m/s	The point estimate is slightly in favour of vutrisiran but the difference is not larger than the lowest identified MCID. Uncertainty exists based on the 95% CI. The EAG is satisfied that no clinically important difference is likely to exist between treatments for this outcome.	The EAG is satisfied that additional requested variables have been included in the adjustment and observed data has been used rather than extrapolation.
R-ODS change from baseline score, mean difference	[redacted]	N/A	The point estimate is slightly in favour of eplontersen but the difference is small considering a scale of 0 to 48 for this outcome. Uncertainty exists based on the 95% CI. The EAG is satisfied that no clinically important difference is likely to exist between treatments for this outcome.	The EAG is satisfied that additional requested variables have been included in the adjustment and observed data has been used rather than extrapolation.
Serious AEs, OR	[redacted]	N/A		

Severe AEs, OR	[redacted]	N/A	The point estimates suggest reduced events with eplontersen, with uncertainty based on 95% CIs. The EAG is satisfied that, based on point estimates from these MAICs, serious and severe AEs for eplontersen are unlikely to be worse compared to vutrisiran.	These MAICs included week 66 rather than week 85 data for eplontersen. However, the EAG is not concerned that use of week 85 data would change the results to the extent that the EAG's conclusions about similarity between treatments would change.
Treatment discontinuation, OR	[redacted]	N/A	The point estimate suggests increased events with eplontersen, with uncertainty based on the 95% CI. However, the difference in the absolute number of patients discontinuing treatment is fairly small at the end of each study (n=5 for vutrisiran at week 78 and n=[redacted] for eplontersen at week 85). Therefore, the EAG considers it unlikely that there are any large differences in treatment discontinuation between the two treatments.	While the treatment effect in this table is based on week 66 data rather than week 85 data for eplontersen, the EAG has considered the absolute number of patients discontinuing at the end of each study (a naïve comparison) when making its conclusion.

*see Appendix 10.4 for MCIDs identified and considered by the EAG. While these were the smallest MCIDs identified, where point estimates crossed these thresholds the EAG sought clinical expert feedback to validate whether or not the thresholds represent clinically meaningful changes from baseline or differences between treatment; †see the respective results sections for each outcome in Section 4.3.3; ‡see Sections 4.3.2.3 and 4.3.3 for details.

No MCIDs were identified for R-ODS or the ORs reported for serious AEs, severe AEs and treatment discontinuation.

Abbreviations: 10-MWT, 10-metre walk test; AEs, adverse events; CI, confidence interval; EAG, External Assessment Group; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; MCID, minimum clinically important difference; mNIS+7, Modified Neuropathy Impairment Score +7; N/A, not applicable; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; OR, odds ratio; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin;

2 Background

The description of the disease area and treatment pathway of this cost-comparison evaluation (CCE) are presented in Section B.1.3 of the company submission (CS). The clinical expert consulted by the External Assessment Group (EAG) considered this to be an accurate reflection of the experience in UK clinical practice. While there are various types and presentations of amyloidosis (Section B.1.3 of the CS), this appraisal is specific to adults with hereditary transthyretin (TTR)-mediated amyloidosis who present with polyneuropathy (PN), which may be termed ATTRv-PN. Specifically, patients with stage 1 or stage 2 PN are the focus of this appraisal (Section B.1.1 of the CS). Marketing authorisation for this indication is anticipated to be granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) in [redacted], for a slightly broader population of adults with ATTRv-PN (not specific to stage 1 or 2 PN).[4] See Section 3 of this report for a more detailed discussion of the decision problem for this appraisal.

ATTRv is the genetic form of the disease and is distinct from wild-type ATTR amyloidosis (ATTRwt), which is caused by age-related deposition of misfolded TTR amyloid fibrils in the absence of an identified *TTR* mutation. Aside from ATTRv-PN, which is characterised by damage to the peripheral and autonomic nerves, patients with ATTRv can also be classified as ATTRv with cardiomyopathy (ATTRv-CM), which is characterised by amyloid fibril infiltration of the heart; many patients with ATTRv have both PN and cardiomyopathy. The clinical trial used to support this submission (NEURO-TTRansform) does not exclude patients with cardiac involvement completely, with subgroup results for those with and without cardiac involvement presented in the CS, but it did exclude those with New York Heart Association (NYHA) class III or IV, which also applied to the HELIOS-A trial for vutrisiran.[5, 6]

The EAG's clinical expert noted that most patients in clinical practice in England with ATTRv-PN will also have cardiac involvement. The EAG considers that the population covered in this appraisal is those with ATTRv with stage 1 or 2 PN who may or may not also have cardiac involvement (up to NYHA class II); it does not cover patients that had cardiac involvement but no stage 1 or stage 2 PN or whose NYHA class was III or IV. However, the identification of patients with cardiac involvement in NEURO-TTRansform and HELIOS-A may not be robust, as this relied on echocardiography parameters or criteria that were unclear and based on a diagnosis of ATTRv-CM recorded on the patient's case report form, rather than specific methods such as heart failure symptoms combined with cardiac magnetic resonance imaging (MRI) and/or Tc-labelled 3,3-diphosphono-1,2propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy, which were highlighted by the EAG's clinical

expert as being more reliable. There are ongoing trials of eplontersen (CARDIO-TTRansform; NCT04136171) and vutrisiran (HELIOS-B; NCT04153149) in ATTR-CM, which includes ATTRv-CM and ATTRwt-CM. [7, 8]

Eplontersen is being considered in a CCE in this indication as the company considers there is sufficient evidence that it has similar efficacy and safety (and is likely to be associated with similar or lower costs) compared to vutrisiran, which has been recommended by the National Institute of Health and Care Excellence (NICE) in an identical population (TA868) as result of a CCE against patisiran.[1] The company deemed vutrisiran to be the only relevant comparator for this appraisal based on clinical expert feedback; the EAG's clinical expert agreed with this conclusion given the vast majority of NHS patients (>95%) with ATTRv-PN are currently receiving vutrisiran, with most of those remaining on inotersen or patisiran likely doing so due to patient preference rather than a specific clinical reason.

The mechanism of action of eplontersen is described in Section B.1.2 of the CS; it is an antisense oligonucleotide silencer (ASO) that reduces TTR levels by interfering with messenger RNA (mRNA) for its production, with liver-specific targeting. TTR in the plasma is the amyloid fibril precursor protein in ATTRv amyloidosis, which undergoes misfolding and aggregation, and progressively accumulates in different tissues and organs to cause the various clinical manifestations in patients with ATTRv amyloidosis. The EAG's clinical expert noted that eplontersen's mechanism of action differs to that of vutrisiran as it is an ASO rather than a small interfering RNA (siRNA), the pathways of which both act to reduce production of TTR by the liver. ASO and siRNA pharmaceuticals are, however, substantially different, and comparable efficacy or safety between the two approaches cannot be assumed. The EAG considers that while both drugs lead to the same outcome (reduced TTR levels), differences in how these drugs work exist and it is plausible that differences in terms of ASO vs siRNA could lead to some differences in efficacy (for example, extent of TTR knockdown) or safety.[9]

The EAG's conclusion regarding the appropriateness of a CCE for this treatment and indication is summarised in Section 1 of this report and discussed in more detail throughout.

3 Critique of the decision problem in the company's submission

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE),[2] together with the rationale for any deviation from it, in Section B.1.1 of the company submission (CS). This is summarised in Table 2 below and more detailed comments from the External Assessment Group (EAG) are provided in the subsections that follow.

Overall, the EAG considers the decision problem addressed, and the evidence used to address it, to be in line with the NICE final scope apart from certain outcomes which were either not included in the eplontersen trial (NEURO-TTRansform) at all or were not selected for indirect treatment comparison (ITC) analyses against vutrisiran (see Section 3.4).[5]

There is some concern that the NEURO-TTRansform trial for eplontersen may not be reflective of the population of patients with hereditary transthyretin-mediated amyloidosis (ATTRv) and stage 1 or 2 polyneuropathy (ATTRv-PN) in the UK based on feedback from the EAG's clinical expert that the proportion with V50M (formerly V30M) mutations is much higher in the trial than would be expected in the UK, which may also contribute to the lower-than-expected age and proportion with stage 2 PN observed in the trial when considering a UK population (see Section 3.1).[5] Of note, most UK patients with the V50M mutation are much older than those in 'endemic' countries, and almost without exception have significant cardiac amyloidosis.

However, the EAG notes that similar concerns are associated with the HELIOS-A trial for vutrisiran used to inform the NICE recommendation in this indication and the EAG's clinical expert noted that there was no reason to believe that the relative efficacy or safety of eplontersen vs vutrisiran would differ across the different mutation types (or age or PN stage subgroups) as long as these factors are adjusted for in any comparison that is made between trials.[1, 6] As discussed in Section 4.3.2.2, mutation type, PN stage and age have been accounted for in the indirect treatment comparisons (ITCs). Therefore, although the trials may lack applicability to the UK population in terms of mutation type, age and PN stage, conclusions made using the ITCs included in this submission in terms of whether or not eplontersen can be considered clinically similar to vutrisiran should still be relevant to the UK population because:

1. The trials are similar in this regard and any differences in the aforementioned characteristics between the two trials have been accounted for as part of the ITCs, meaning the ITC results for eplontersen vs vutrisiran should be robust;

2. Feedback from the EAG's clinical expert was that the relative efficacy of eplontersen vs vutrisiran would not be expected to differ across different populations as long as key differences have been accounted for in the ITCs comparing eplontersen with vutrisiran, which the EAG is satisfied has been done.

In response to clarification question (CQ) A16, the company acknowledges the difference between the trials and the UK population in terms of mutation status but considers the results from NEURO-TTRansform to be generalisable to the UK population (see Section 3.1).

Table 2. Summary of decision problem as outlined in the CS – adapted from Table 1 of the CS

	Final scope issued by NICE[2]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with hereditary ATTR amyloidosis who have stage 1 or stage 2 polyneuropathy	As per NICE final scope.	N/A	The population addressed in the CS and trials matches the NICE final scope but some limitations in terms of the applicability of the NEURO-TTRansform and HELIOS-A trials to the UK population are noted. These applicability issues are not likely to impact conclusions about whether eplontersen is similar to vutrisiran in terms of efficacy and safety as all variables mentioned are adjusted for as part of the ITCs. See Section 3.1 for further discussion.
Intervention	Eplontersen	As per NICE final scope.	N/A	The intervention covered in the CS and NEURO-TTRansform trial matches the NICE final scope and draft SmPC. There is the option for patients/carers to administer treatment themselves following the first treatment. The treatment should be given alongside the recommended daily vitamin A allowance; it is unclear how well this was adhered to in the NEURO-TTRansform trial. See Section 3.2 for further discussion.
Comparator(s)	• Vutrisiran	• Vutrisiran	NICE guidance states that the chosen comparator for a	Based on feedback received from the EAG's clinical expert, the EAG agrees that the

	• Patisiran • Inotersen		cost-comparison submission must be established, and have substantial use, in clinical practice in England.[10] Based on these requirements, vutrisiran is considered to be the only relevant comparator for patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) in England. This is demonstrated by prescribing data from the NAC where [redacted] of [redacted] of patients with ATTRv-PN receive vutrisiran, compared to [redacted] ([redacted]) receiving patisiran and [redacted] [redacted] receiving inotersen. These data are aligned with UK prescribing data from Blueteq, which show that [redacted] patients commenced treatment with vutrisiran in Q2 and Q3 of 2023, and [redacted] initiated treatment on patisiran or inotersen.[11] Consequently, patisiran and inotersen do not meet the criteria for relevant comparators, as defined by NICE.	inclusion of vutrisiran as the only comparator is reasonable. HELIOS-A is an appropriate source of data for vutrisiran as used in the UK. Vutrisiran should also be given alongside the recommended daily vitamin A allowance; it is unclear how well this was adhered to in the HELIOS-A trial. No direct comparative data are available and unanchored ITCs have been required, which are generally associated with increased uncertainty compared to comparative trial evidence and there are differences between trials which could not be completely accounted for. See Section 3.3 for further discussion.

			In line with this, NICE has confirmed that vutrisiran is the key comparator to eplontersen, with patisiran and inotersen only included in the list of comparators for completeness, given that both are recommended by NICE.[12]	
Outcomes	• Overall survival • Neurological impairment • 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	• Neurological impairment • Symptoms of polyneuropathy • Autonomic function (including the effects on the gastrointestinal system and postural hypotension) • Weight loss (nutritional status) • Serum TTR • Motor function • Adverse effects of treatment • HRQoL	• Overall survival, cardiac function and the effects of amyloid deposits in other organs such as the eye were not measured in NEURO-TTRansform • Cardiac function was not measured in NEURO-TTRansform and is not a relevant outcome for this patient population	Most outcomes in the NICE final scope have been covered as part of the ITCs against vutrisiran, including an additional outcome provided in response to CQ A2 (mBMI to capture weight loss/nutritional status). Additional analyses for 10-MWT and R-ODS outcomes were also provided in response to CQ A2. The EAG considers that cardiac function was measured in NEURO-TTRansform, but has not requested ITCs for this outcome due to limitations in terms of the methods used to identify patients with cardiac involvement in the trial and the much smaller sample size analysed for these outcomes in NEURO-TTRansform. Ongoing trials in patients with ATTRv-CM will be better placed to compare the impact on cardiac outcomes for patients that have ATTRv-CM. The lack of data for overall survival and effects of amyloid deposits in other organs and tissues may be a limitation but this was also the case in the vutrisiran CCE.[1]

				Outcome definitions and/or choice of instruments are not unreasonable but some issues in terms of alignment between trials exist and are not completely resolvable. Focus on the overall population rather than subgroups is considered reasonable. See Section 3.4
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. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. • 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.	• A cost-comparison model has been developed for comparison of eplontersen vs vutrisiran, which is the current standard of care for patients in the UK with ATTRv-PN • Costs are considered from an NHS and PSS perspective	N/A	N/A

	• Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			

Abbreviations: 10-MWT, 10-metre walk test; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRv-CM, hereditary transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; CCE, cost-comparison technology appraisal; CQ, clarification question; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; ITC, indirect treatment comparison; mBMI, modified body mass index; N/A, not applicable; NAC, National Amyloidosis Centre; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; R-ODS, Rasch-built Overall Disability Score; SmPC, Q1, first quarter; Q3, third quarter; Summary of Product Characteristics; TTR, transthyretin.

3.1 Population

Alignment to NICE final scope

The population outlined by the company in its submission is in line with the NICE final scope population (adults with ATTRv who have stage 1 or stage 2 PN) and the key trial used to inform the efficacy and safety of eplontersen (NEURO-TTRansform) matches this population.[2, 5] Specifically, the following inclusion criteria in the NEURO-TTRansform capture this population:

- Aged 18-82 years;
- Stage 1 (ambulatory without assistance) or stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy (FAP) or Coutinho stage;
- Documented genetic mutation in the transthyretin (*TTR*) gene;
- Symptoms and signs consistent with neuropathy associated with ATTR, including Neuropathy Impairment Score (NIS) ≥10 and ≤130.

The population covered by this appraisal is slightly narrower than the anticipated marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA), which covers a broader population of adults with ATTRv-PN (not specific to stage 1 or 2 PN; Table 2 of the CS).[4] The EAG considers this narrower population to be reasonable and notes that it is in line with the population that vutrisiran (the only comparator covered by the company in this cost-comparison evaluation [CCE]) was recommended for as a result of NICE TA868.[1]

The population enrolled in HELIOS-A (the key trial for the vutrisiran appraisal and used to adjust eplontersen results to in this submission as part of the ITCs) also aligns with the population outlined in the NICE final scope for eplontersen; while inclusion criteria for PN in HELIOS-A involved the polyneuropathy disability (PND) score rather than the Coutinho or FAP score used in NEURO-TTRansform, the EAG's clinical expert confirmed that the requirement for PND stage ≤IIIb in HELIOS-A can be considered equivalent to stage 1 or 2 on the Coutinho or FAP score in terms of PN stage. There are other differences compared to NEURO-TTRansform in terms of requirement for baseline NIS (≥5 to ≤130 rather than ≥10 to ≤130) and Karnofsky Performance Status (KPS; ≥60% rather than >50%), which the EAG's clinical expert considered to be minor differences. Differences between NEURO-TTRansform and HELIOS-A are described in more detail in Section 4.3.

Alignment to UK population

On review of the baseline characteristics of the NEURO-TTRansform trial for eplontersen (Table 10 of the CS), the EAG's clinical expert noted that there is some concern about how applicable the trial population is to the population with ATTRv-PN seen in UK clinical practice. The primary concern is that the proportion with the V50M (formerly V30M) mutation in the trial (59%) is much higher than would be expected in the UK population as most patients in the UK would have the T80A (formerly T60A) mutation (whereas only [redacted] patients [redacted] treated with eplontersen in NEURO-TTRansform had this mutation). Patients with the T80A mutation usually aren't diagnosed until at least 55 years of age and it is associated with a rapid, severe disease course that always affects the heart and causes a lot of autonomic symptoms. For this reason, the clinical expert considered that the non-V50M mutation group within the trial may be a better representation of the UK population with ATTRv-PN.

This difference relative to the UK population in terms of mutation type likely also contributes to the lower-than-expected age (~53 years) and proportion of patients with stage 2 PN (20%) for a UK population, as mutation type influences the onset and presentation of the disease. Furthermore, these additional observations could also be linked to the fact that the same mutation has been observed to present differently in different populations; for example, most patients in the UK that do have the V50M mutation usually present with late onset disease including cardiomyopathy, whereas this mutation in countries such as Portugal typically leads to presentation at a much earlier age and rarely causes cardiomyopathy. In response to CQ A15, the company notes that [redacted] % of patients treated with eplontersen in NEURO-TTRansform had a V50M mutation and were considered to have early onset disease (<50 years of age).

The EAG notes that no UK patients were included in NEURO-TTRansform which may explain these observations given certain mutations occur more frequently in specific countries; for example, V50M is common in European countries such as Portugal, Spain, France and Sweden, which were captured by the trial.[13]

In response to CQ A16, the company also acknowledged the differences in terms of the applicability of the mutation types observed in the NEURO-TTRansform trial to the UK population but noted that subgroup analyses from NEURO-TTRansform and NEURO-TTR do not indicate any difference in efficacy across mutation types for eplontersen or inotersen (which has a similar mechanism to eplontersen).[14, 15] Therefore, the company considers the results from NEURO-TTRansform to be generalisable to UK clinical practice.

Given that baseline characteristics and results from the eplontersen arm of NEURO-TTRansform are adjusted to the HELIOS-A study population as part of the ITCs, the applicability of this trial to the UK population was also explored. The EAG notes that similar limitations in terms of applicability to the UK population may also apply but to a lesser extent; the proportion with the V50M mutation is lower (44%) compared to NEURO-TTRansform but still much higher than would be expected for a UK population. The median age (60 years) and proportion with stage 2 disease (22.9%; considered to be reflected by PND stage IIIa or IIIb) were also slightly higher and while this is potentially more in line with the UK population, applicability may still be limited. Of note, some UK patients did appear to be included in HELIOS-A.[6]

While these limitations in terms of applicability to the UK population are important to note, as long as they are accounted for in the ITC adjustments, the EAG's clinical expert did not consider that there was any reason to believe that the relative efficacy or safety of eplontersen vs vutrisiran would be impacted significantly by any of the differences noted above (i.e. the impact of these differences in population on the efficacy and safety of the two drugs would be expected to be the same and there is no reason why one drug would be affected differently to the other). The EAG notes that V50M mutation, age and PN stage were all included in the original ITCs performed by the company; given the discussion above about early-onset vs late-onset V50M mutations, the EAG requested that the company consider including this as an additional factor in the ITCs and versions of the analyses with this factor included were provided in response (CQ A1; see Section 4.3.2.2 for further discussion).

Overall, although the EAG considers that the points raised above may mean the evidence from the trials may be less applicable to the UK population, conclusions made using the ITCs included in this submission in terms of whether or not eplontersen can be considered clinically similar to vutrisiran should still be relevant to the UK population as it is not considered likely that the comparative efficacy and safety of eplontersen and vutrisiran would differ across different populations and important variables have been accounted for in the ITCs.

3.2 Intervention

The intervention addressed in the CS matches the NICE final scope.[2] The dose of eplontersen used in the NEURO-TTRansform trial matches that described in the draft Summary of Product Characteristics (SmPC), which is 45 mg administered by subcutaneous injection once monthly.[4] Vitamin A supplementation at ~2500 to 3000 IU (but not exceeding this) is also advised in the draft SmPC for patients receiving eplontersen; the NEURO-TTRansform trial required that patients took oral

supplementation of ~3000 IU daily but based on Table 1.17 of the clinical study report (CSR) provided for NEURO-TTRansform, only ~[redacted]% of patients may have taken this as a plain vitamin A supplement and among these patients it is unclear if they adhered to the once daily regimen.[4, 15] A further group of patients may have taken this as part of a multivitamin supplement but the breakdown of this is unclear. Other concomitant treatments used in the trial are not considered to be unreasonable. Importantly, prior or concomitant use of other TTR silencers (such as vutrisiran, patisiran or inotersen) and concomitant use of TTR stabilisers (tafamidis or diflunisal) was not permitted.

The draft SmPC states that treatment should be prescribed and supervised by a treating physician knowledgeable in the management of patients with amyloidosis. It also describes the drug as a pre-filled pen that can be used for self-administration. It explains that the first injection by the patient or caregiver should be performed under the guidance of an appropriately qualified healthcare professional, with training in the subcutaneous administration provided to patients and/or caregivers. Requirements for the appropriate storage and temperature of the drug before administration are also provided in the draft SmPC.[4]

At clarification, the EAG requested that the company provide a breakdown of the proportion of patients or carers that were able to self-administer the treatment in NEURO-TTRansform following the first dose, and whether this was maintained for all subsequent doses (CQ A18); the response outlined that the proportion of injections that were self-administered or administered by a trained relative was [redacted]. While this may be considered to be quite low, the company explained that 12 of the 21 dose administration days (60%) coincided with mandatory in-clinic visits, at which the default was for on-site personnel or trained healthcare professionals (HCPs) to administer eplontersen. The EAG agrees that this means the proportion of self-administered or carer-administered doses from the trial may not be a good indicator of the proportions in UK clinical practice that would be able to administer treatment without a HCP. As discussed in Section 5.2.4.2, scenario analyses assuming that different proportions of patients are unable to self-administer eplontersen have been performed and the company notes that it plans to develop a [redacted] homecare program to support eplontersen delivery by a HCP for those that prefer this option.

3.3 Comparators

Inotersen, patisiran and vutrisiran are listed as relevant comparators in the NICE final scope.[2] The company has only included vutrisiran based on prescribing data from the National Amyloidosis

Centre (NAC; the only centre in the UK specialising in amyloidosis), demonstrating that [redacted]% of patients with ATTRv-PN currently receive vutrisiran, with only [redacted]% and [redacted]% receiving patisiran and inotersen, respectively.[11] The EAG validated this with its clinical expert, who agreed that vutrisiran is the only relevant comparator and that the other two treatments are used infrequently. However, the EAG's clinical expert noted that as of April 2024 ~99% of ~200 patients in England with ATTRv-PN currently receive vutrisiran, with less than 1% receiving patisiran and none receiving inotersen. The EAG's clinical expert confirmed that there is not a group of patients who would not be eligible for vutrisiran but could have patisiran or inotersen. The minor exception would be patients that experienced adverse events (AEs) on vutrisiran, but this was considered to be very rare in UK clinical practice. The EAG's clinical expert noted that most patients currently continuing on treatment with inotersen or patisiran were likely doing so based on patient preference rather than there being a clinical reason for not switching to vutrisiran. Therefore, the EAG is satisfied that the inclusion of only vutrisiran as a comparator is appropriate in this appraisal.

There is no direct evidence comparing eplontersen with vutrisiran and the company has performed ITCs to demonstrate similar efficacy and safety between the two drugs in ATTRv-PN. These analyses are described in detail in Section 4.3, but the EAG notes that comparative evidence from ITCs in general is likely to be associated with increased uncertainty in terms of conclusions compared with had a trial directly comparing the two been available. This is particularly true in this case given unanchored ITCs have been required and because there are underlying differences between trials in terms of certain outcomes that cannot be completely addressed. The EAG notes that this represents a key difference from the vutrisiran cost-comparison evaluation (CCE; NICE TA868) as there was direct comparative evidence for the comparison between vutrisiran and patisiran as part of HELIOS-A.[1, 6]

HELIOS-A has been used as the source of data for vutrisiran in the ITCs within this appraisal.[6] The EAG considers this to be reasonable given this was the trial used to inform the vutrisiran appraisal (NICE TA868) and the vutrisiran dose used in this trial (25 mg subcutaneously once every 3 months) matches that outlined in the SmPC and, therefore, UK clinical practice.[1, 16] The EAG's clinical expert confirmed that there is no option for the patient to self-administer vutrisiran currently (although this may be an option in the future) and that HCPs usually visit the patient at home to administer the treatment.

As mentioned in Section 3.3 for eplontersen, vitamin A supplementation at ~2500 to 3000 IU (but not exceeding this) is also advised in the SmPC for patients receiving vutrisiran; the HELIOS-A trial

required that patients took the recommended daily vitamin A allowance but it is unclear from publicly available data how well this was adhered to in the trial.[6, 16] Concomitant or prior use of other TTR silencers, or concomitant use of TTR stabilisers, was not permitted in HELIOS-A.[6]

3.4 Outcomes

The EAG considers that the following outcomes listed in the NICE final scope are captured in the ITCs against the comparator of interest, vutrisiran (results for modified body mass index [mBMI], 10-metre walk test [10-MWT] and Rasch-built Overall Disability Scale [R-ODS] were provided in response to CQ A2):

- Neurological impairment (modified Neuropathy Impairment Score +7 [mNIS+7]);
- Symptoms of polyneuropathy (mNIS+7);
- Autonomic function (mNIS+7);
- Weight loss (mBMI)
- Serum TTR;
- Motor function (mNIS+7 and 10-MWT);
- Adverse effects of treatment (serious and severe AEs, and treatment discontinuation);
- Health-related quality of life (HRQoL; Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QoL-DN] and R-ODS).

Clinical expert feedback to the EAG was that the mNIS+7 is designed to capture elements of neurological impairment, symptoms of PN, autonomic function and motor function described in the NICE final scope. However, the EAG's clinical expert considered that mNIS+7 may not be as good at capturing the adverse daily impact of autonomic dysfunction as it is for peripheral neurological sensory impairment and motor function. In the absence of any other outcome data for NEURO-TTRansform and HELIOS-A trials that could be used to provide stronger evidence for autonomic dysfunction, the EAG considers that the use of mNIS+7 to capture these outcomes is reasonable.

Of the reported efficacy outcomes, feedback from the EAG's clinical expert was that the degree of reduction in serum TTR levels is the key pharmacological determinant of clinical response to treatment which may lead to reduced disease progression and deterioration of patients in terms of physical function or quality of life, as captured by measures such as mNIS+7 and Norfolk QoL-DN. The EAG notes that while some patients may experience improvement in efficacy outcomes such as mNIS+7 and Norfolk QoL-DN following treatment if they are at an early stage of disease, most commonly TTR lowering treatments will merely reduce the rate of progression rather than improve their condition given that considerable irreversible damage to nerves and other tissues is likely to be present. However, these two outcomes, in addition to others presented in Section 4.3.3, were considered to be useful additional measures for assessing the impact on physical functioning and quality of life-based outcomes.

The EAG considers the focus on severe or serious AEs in the ITCs to be reasonable but also provides comment on the breakdown of more specific events between treatments in Section 4.3.4.1 based on naïve comparisons. With respect to AEs in the company's model, given the similarity of AEs and their incidences between treatments, the company did not include AE costs in their cost comparison model base case but explored these costs in a scenario, which led to a minimal change in the cost difference. As such, the EAG agrees with the exclusion of AE costs from the model base case and similarly excludes them from the EAG base case.

Definitions and/or choice of instrument for other outcomes captured in NEURO-TTRansform and ITCs do not appear to be unreasonable but there are some differences between trials that have required attempts at alignment that may not be completely resolvable, and responder analyses included for mNIS+7 and Norfolk QoL-DN outcomes were not considered clinically useful by the EAG's clinical expert (see Section 4.3).

Outcomes listed in the NICE final scope but not covered in the ITCs against vutrisiran are:

- Overall survival (OS);
- Cardiac function;
- Effects of amyloid deposits in other organs and tissues (including the eye).

The company states that OS and effects of amyloid deposits in other organs and tissues (including the eye) were not measured in NEURO-TTRansform, which the EAG has validated. The EAG notes that the lack of OS data is a limitation given the life-limiting nature of this disease, but acknowledges that it is a limitation that also applied in the vutrisiran CCE (NICE TA868).[1] Deaths are captured as part of the safety data and are covered in Section 4.3.4.1. Similarly, a lack of data for the "effects of amyloid deposits in other organs and tissues" outcome also applied in NICE TA868.[1]

The company also states that cardiac function outcomes were not measured in NEURO-TTRansform. However, the EAG considers that cardiac function outcomes were captured as the CSR for this study includes change from baseline measures of N-terminal pro b-type natriuretic peptide (NT-proBNP) as an exploratory endpoint within the subgroup that had PN and cardiac involvement, as well as other measures of cardiac function and structure (echocardiogram features).[15] While similar data are available in a separate publication for HELIOS-A and many patients with ATTRv-PN also present with cardiac involvement,[17] the EAG did not request that an ITC be performed for this outcome for the following reasons:

- The EAG's clinical expert did not consider the criteria used to identify patients with cardiomyopathy in the two trials to be robust, as they only included echocardiography criteria (NEURO-TTRansform and HELIOS-A) or a clinical diagnosis of cardiomyopathy on their case form (NEURO-TTRansform) – a clinical diagnosis requiring cardiac magnetic resonance imaging (MRI) with or without symptoms of heart failure, or Tc-labelled 3,3-diphosphono-1,2propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy, would be much more reliable approaches to identifying this subgroup with cardiomyopathy related to ATTRv;[5, 6]

- There are ongoing trials for both eplontersen and vutrisiran to determine the impact on patients with cardiomyopathy (HELIOS-B and CARDIO-TTRansform) – the exact inclusion criteria for cardiomyopathy are unclear for HELIOS-B but CARDIO-TTRansform requires ^{99m}Tc-DPD scintigraphy mentioned above as being a more reliable method and is, therefore, likely to provide more useful results for the impact on cardiomyopathy-related measures;[7, 8]
- Sample sizes for the cardiac involvement subgroup in both trials are small (<50 patients), which would reduce further once adjustment was applied and mean that results would be associated with even more uncertainty than those for other outcomes in the full population.[5, 6]

The EAG has not included a naïve comparison of cardiac outcomes either given the limitations described above. The lack of more robust data for cardiac function outcomes could be considered a limitation given patients often present with cardiac involvement alongside PN in the UK population.

The EAG considers that the analysis of the full trial population for NEURO-TTRansform, rather than analysis of separate subgroups, is appropriate and is in line with the population considered for decision-making in the vutrisiran CCE.[1] Results of subgroup analyses from NEURO-TTRansform are briefly discussed in Appendix 10.3.3 but the EAG's clinical expert did not consider that there was any reason to believe that the relative efficacy or safety of eplontersen vs vutrisiran would be impacted by any particular subgroup (i.e. a different subgroup should not impact how similar the two treatments are in terms of efficacy or safety and there is no reason why one drug would be affected differently to the other).

3.5 Other relevant factors

No equality issues were outlined in the NICE final scope and neither were any raised by the company in the CS. A confidential patient access scheme (PAS) has been proposed by the company (see Section 5.2.4.1) and a PAS is also available for vutrisiran.

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company describes the methods used to perform the clinical systematic literature review (SLR) in Appendix D.1 of the company submission (CS). The SLR was used to identify clinical evidence on the efficacy and safety of eplontersen and its relevant comparators in the treatment of polyneuropathy (PN) caused by hereditary transthyretin-mediated amyloidosis (ATTRv). The company reported that the population included in the SLR (which included adults with ATTRv and considered patients with PN and cardiomyopathy) was broader than that specified in the National Institute for Health and Care Excellence (NICE) final scope (adults with ATTRv who have stage 1 or stage 2 PN [ATTRv-PN; see Section 3.1]),[2] to ensure that no relevant publications were missed.

The SLR was reported to have been performed according to a pre-specified protocol and using methodology recommended by Cochrane and detailed in the University of York's Centre for Reviews and Dissemination (CRD) guidelines.[18, 19] It was conducted in July 2022 with the most recent update to the searches performed in October 2023. The External Assessment Group (EAG)'s critique of the SLR methods are presented in Table 16 of Appendix 10.1 and it is noted that a total of three studies were identified as suitable for inclusion by the SLR:

- ION-682884-CS1 (NCT03728634) (eplontersen and placebo arms);[20]
- HELIOS-A (NCT03759379) (vutrisiran, patisiran and external placebo arms);[6] and
- NEURO-TTRansform (eplontersen, inotersen and external placebo arms).[5]

The ION-682884-CS1 study of eplontersen was a phase I/II that comprised of only healthy volunteers, as the planned Cohort D of patients with ATTRv was never initiated (due to a limited number of suitable participants with ATTRv). The EAG notes that the primary efficacy data for eplontersen used in the CS and in the indirect treatment comparisons (ITCs) is from the NEURO-TTRansform and the EAG agrees with the company that this is the most relevant study of eplontersen for addressing the decision problem. A critique of and results from this trial are provided in Section 4.2 and Appendix 10.3 of this report.

The EAG notes that an open-label extension phase of NEURO-TTRansform (NCT05071300) is currently ongoing (see Section 4.2), with data currently available up to [redacted].[21]

In summary, the EAG considers that the methodology used in the SLR process is reasonable and that it is unlikely that relevant trials of eplontersen or vutrisiran in adults with hereditary ATTR amyloidosis who have stage 1 or stage 2 PN, have been missed.

4.2 Critique of trials of eplontersen and comparator interventions

4.2.1 Trials included and quality assessment

As discussed in Section 4.1, one study for eplontersen (NEURO-TTRansform) and one study for vutrisiran (HELIOS-A) in adults with ATTRv with stage 1 or 2 PN were identified for inclusion in the ITCs and the EAG does not consider that any relevant studies have been missed.[5, 6] These were both randomised controlled trials (RCTs). The company provided a risk of bias assessment for these two studies in Table 26 of the CS appendices; this suggests that the two studies are similar in terms of risk of bias for most domains.

Overall, the EAG considers the two trials to have been well-performed but some risk of bias is introduced, largely due to the open-label nature of the studies. The EAG generally agrees with the company's assessment but does not consider NEURO-TTRansform to be at a lower risk than HELIOS-A based on blinding of care providers, participants and outcome assessors to treatment allocation – while the external placebo trial used for NEURO-TTRansform (NEURO-TTR) may have involved blinding to treatment, this was not the case for eplontersen in NEURO-TTRansform and bias for eplontersen results would still, therefore, be expected.[5, 22] Furthermore, the trial used as an external placebo group for HELIOS-A (APOLLO) also involved blinding to treatment so the same argument made by the company could apply here.[23]

The main risk of bias issue that the EAG considers important to mention is that for both trials, treatment was not concealed (studies were open-label), meaning patients, investigators and outcome assessors were aware of assignment to eplontersen or vutrisiran in the respective studies – given the alternative treatments in the trials were inotersen or patisiran, respectively, rather than placebo, it is unclear how knowledge of the treatment would have impacted results (i.e. in which direction bias may occur) but the introduction of bias is possible. Furthermore, comparisons made against external placebo groups in the two trials may be limited as only a few variables that were imbalanced at baseline were adjusted for, meaning some bias is likely to remain and could impact relative treatment effect estimates.

It is also noted that intention to treat (ITT) analyses were not provided for either study and that slightly different populations were used in NEURO-TTRansform and HELIOS-A. The EAG considers there may be slightly less bias for modified Neuropathy Impairment Score +7 (mNIS+7) and Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) outcomes in HELIOS-A compared to NEURO-TTRansform given the number randomised to vutrisiran matches those analysed (n=122), whereas 141/144 randomised eplontersen patients in NEURO-TTRansform were analysed; however, this is unclear for the serum transthyretin (TTR) outcome in HELIOS-A as a different population was used for this outcome with the number of patients excluded, and potential resulting bias, being unclear. A detailed breakdown of the risk of bias of the two trials as assessed by the EAG is presented in Appendix 10.2.

An open-label extension phase of NEURO-TTRansform (NCT05071300) is currently ongoing, with data currently available from the [redacted] data cut-off, which was provided to the EAG. This is of limited use in this appraisal given efficacy data and analyses are not yet available, but the EAG includes anything of note in Section 4.3.4.1 below, including immunogenicity and adverse events (AEs).[21]

4.2.2 Results from NEURO-TTRansform

In this section, the EAG focuses on week 85 outcome data for eplontersen from NEURO-TTRansform, given this is the latest time-point at which data are available from the study and is the time-point that the EAG considers most appropriate in terms of making comparisons against vutrisiran (see Section 4.3.2.3). These results are observed values from the trial given there were no external placebo group data at this time-point to compare to. Observed data at week 65/66 are also included in the tables presented here.

Results comparing eplontersen from NEURO-TTRansform to the external placebo group from NEURO-TTR up to week 65/66 are detailed in Appendix 10.3 ,which was the main focus of the NEURO-TTRansform study.[5, 22] The EAG considers the results vs external placebo to be of limited relevance for decision-making in this appraisal for reasons described in Section 4.3.2.1 but it has reported them in Appendix 10.3. Results of subgroup analyses for comparisons against external placebo are also mentioned briefly in Appendix 10.3.3.

As noted in Section 4.3.2.3, the EAG has a preference for ITC analyses performed using observed data at the latest available time-point (85 weeks) for eplontersen. Results for eplontersen at 85

weeks from NEURO-TTRansform are covered in the text below. While a small inotersen group was included until week 36, formal comparisons to this group were not included as part of the analyses in NEURO-TTRansform and data have not been included here by the EAG. Furthermore, inotersen was not considered to be a relevant comparator in this appraisal.

Baseline characteristics for eplontersen can be found in Table 10 of the CS. As noted by the EAG in Section 4.2.1 and Appendix 10.1, the study was open-label, which could introduce bias. Limitations in terms of the applicability of the NEURO-TTRansform population to the population seen in UK practice are described in Section 3.1.

A breakdown of AEs from NEURO-TTRansform for eplontersen is provided in Section 4.3.4.1, where a comparison to those observed in HELIOS-A for vutrisiran is included. Serious and severe AEs, as well as treatment discontinuations, were also included by the company in the ITCs against vutrisiran (Section 4.3.3.4).

4.2.2.1 Primary efficacy outcomes

Primary efficacy outcomes presented in CS Section B.3.6.1 and Appendix M include change from baseline assessments of serum TTR (percentage change), mNIS+7 score and Norfolk QoL-DN. Reductions in all three outcomes indicate better outcome. Scales for mNIS+7 and Norfolk QoL-DN are -22.3 to 346.3 and -4 to 136, respectively. Serum TTR is a measure of how well the treatment reduces levels of TTR, which accumulates and causes the symptoms of ATTRv-PN. mNIS+7 assesses PN progression in ATTRv-PN and includes various assessments of neurological function, and Norfolk QoL-DN is a validated quality of life instrument for use in patients with neuropathy, although it was designed for use in diabetic neuropathy rather than ATTRv-PN specifically.

Data for eplontersen from NEURO-TTRansform at week 85 are available in Appendix M of the CS, with further details available in the CSR.[15] These results show that eplontersen improves all outcomes at week 85 compared to baseline and that the impact on outcomes observed at week 65/66 appear to be largely maintained or improved further for all three outcomes, as indicated in Table 3 below. Figure 1 shows that TTR levels appear stable from week 65 to week 85 in the eplontersen treatment group from NEURO-TTRansform.

Table 3. Eplontersen results from NEURO-TTRansform at 65/66 and week 85 – change from baseline in serum TTR, mNIS+7 and Norfolk QoL-DN* - adapted from Tables 20, 25 and 30 of the CSR

Parameter	Serum TTR (percentage CFB)		mNIS+7		Norfolk QoL-DN	
	Week 65	Week 85†	Week 66	Week 85	Week 66	Week 85
n‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change (or percentage change for serum TTR) from baseline Mean, 95% CI§	[redacted]	-81.83, [redacted]	-0.21, [redacted]	[redacted]	[redacted]	-6.23, [redacted]

*n=141 included at baseline for eplontersen. Analyses were at week 65 for serum TTR and week 66 for mNIS+7 and Norfolk QoL-DN; †week 85 is based on nominal visit. It includes all data collected on Week 85 visit without visit windows implemented; ‡number of patients with non-missing data at the time-point; §the EAG calculated 95% CIs from reported sample size, mean and SD as these were not presented in the CSR.

Abbreviations: CFB, change from baseline; CI, confidence interval; CSR, clinical study report; EAG, External Assessment Group; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; TTR, transthyretin.

Figure 1. Percentage change in serum TTR concentration to week 85 – NEURO-TTRansform eplontersen group – reproduced from Figure 4 of the CSR

[redacted]

Abbreviations: CSR, clinical study report; ION-682884, eplontersen; NA, not applicable; Q4W, once every four weeks; TTR, transthyretin.

4.2.2.2 Secondary efficacy outcomes

Various secondary endpoints were also reported in the CS in Section B.3.6.2, including change from baseline in polyneuropathy disability (PND) score, modified body mass index (mBMI), and 36-item short form questionnaire – physical component summary (SF-36 PCS) and Neuropathy Symptoms and Change (NSC) questionnaires. The EAG presents results of PND and mBMI below as these are important measures of disease stage and nutritional status, respectively, and the EAG requested that mBMI be included in the ITCs against vutrisiran (clarification question [CQ] A2). The same was

not requested for PND given data for HELIOS-A does not appear to be available for this outcome. Results for the other two outcomes listed above are briefly mentioned. Higher scores for mBMI indicate better outcome whereas lower scores for PND are better as they indicate less impairment. PND is scored on a 0-4 scale, with patients grouped into 0, 1, 2, 3 or 4 based on level of impairment (categorical rather than continuous measure).

Observed eplontersen results for secondary outcomes at week 65/66 were largely maintained up to week 85, with results for PND score and mBMI presented in Table 4 below. While mBMI appears to have reduced compared to baseline at week 65 and reduced further by week 85, this may not be unexpected given progression of the disease can still occur with treatment. This difference is relatively small compared to what was observed in the external placebo group from baseline to week 65 in Table 19 of Appendix 10.3.2. Changes in PND score appear to be [redacted] at both time-points compared to baseline.

Table 4. Eplontersen results from NEURO-TTRansform at 65 and week 85 – change from baseline in PND and mBMI* - adapted from Tables 2.114 and 39 and of the CSR

Parameter	PND score		mBMI	
	Week 65	Week 85	Week 65	Week 85
n†	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline Mean, 95% CI‡	[redacted]	[redacted]	-4.63, [redacted]	-9.73, [redacted]

*n=141 included at baseline for eplontersen; ‡number of patients with non-missing data at the time-point; ‡the EAG calculated 95% CIs from reported sample size, mean and SD as these were not presented in the CSR.

Abbreviations: CI, confidence interval; CSR, clinical study report; EAG, External Assessment Group; mBMI, modified body mass index; PND, polyneuropathy disability.

4.3 Summary and critique of the indirect treatment comparisons

4.3.1 Comparability of included studies

The EAG has provided a critique of the two trials in terms of risk of bias associated with methodology in Section 4.2.1 and Appendix 10.2 of this report. This section focuses on the comparability of the two trials and a critique of any differences that may be important to consider in terms of the ITCs.

The company has commented on various similarities and differences between NEURO-TTRansform and HELIOS-A throughout the submission.[5, 6] The EAG considers the inclusion and exclusion criteria in the trials to be broadly similar; differences in terms of Neuropathy Impairment Score (NIS) and

Karnofsky Performance Status (KPS) requirement between the trials were not considered important by the EAG's clinical expert (Section 3.1).

Some differences in terms of baseline characteristics are noted between the trials. Most of these were already included as variables for adjustment in the ITCs but based on clinical expert feedback the EAG requested that some additional variables be considered for inclusion for all outcomes, which the company performed in response to CQ A1 (see Section 4.3.2).

The study designs are similar in that they are both open-label trials with comparisons against other active treatments (inotersen for NEURO-TTRansform and patisiran for HELIOS-A), with comparisons against placebo made via external placebo groups. The EAG does not consider the active comparator or external placebo groups to be of great relevance to this appraisal but has included the main results from NEURO-TTRansform in Section 4.2.2 and Appendix 10.3. Trial procedures appear to be similar, with similar prohibitions in terms of prior and concomitant treatments.

Differences start to arise when considering outcome definitions and methods of analysis, one of which the company has introduced via the methods it has chosen in terms of the ITCs. The EAG discusses these in more detail in Section 4.3.2.3.

Overall, there are a number of differences between studies in terms of outcomes and analysis that could impact the comparative estimates obtained from the ITCs. The different mNIS+7 versions used and time-point at which NEURO-TTRansform data is obtained (and whether extrapolated or observed data is used) are thought to be the most important but choice of imputation, potential differences in the lower limit of detection (LLOD) of serum TTR assays and population analysed for serum TTR are also worth noting. The company's rationale for its chosen methodology and methods of exploring these uncertainties are described in further detail in Section 4.3.2.3 below.

4.3.2 Critique of the methods and approach to indirect treatment comparisons

4.3.2.1 Methods used to perform indirect treatment comparisons

Following a feasibility assessment, the company chose to use population-adjustment methods for ITCs comparing eplontersen with vutrisiran, including matching-adjusted indirect comparisons (MAICs) and simulated treatment comparisons (STCs), instead of Bucher ITCs given there were thought to be important differences in the patient characteristics of NEURO-TTRansform and HELIOS-A trials. Unanchored analyses were favoured over anchored analyses as differences in pre-

medication were noted between the two external placebo groups used in the trials, which the company suggests means they could not be considered a "common" control group that is required for anchored ITCs.

MAICs and STCs were performed in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, which outlines methodology for population-adjusted ITCs.[3] This process involved reweighting individual patient data (IPD) from NEURO-TTRansform so that the summary baseline characteristics matched HELIOS-A more closely. This reweighting was then applied to IPD for efficacy, safety and discontinuation outcomes from NEURO-TTRansform, providing an estimate of eplontersen outcomes in a population more similar to the HELIOS-A study population. Reweighted IPD for outcomes were then compared to aggregate outcome data for the HELIOS-A study. Analyses were performed in R software version 4.0.3 or higher using various external packages.

EAG comment

The EAG considers the use of population-adjusted methods such as MAICs and STCs to be appropriate given the noted differences in patient characteristics between eplontersen and vutrisiran studies. While the company has presented results for MAICs and STCs for each outcome, the EAG has a slight preference for MAICs given a measure of overlap (effective sample size; ESS) is obtained from these analyses, which is not the case for STCs. For this reason, and because results were very similar for most outcomes across the two methods, the EAG only briefly mentions results for STCs in Section 4.3.3 and focused its requests for further analyses on MAICs in its CQs to the company.

The EAG agrees with the company's decision to perform unanchored rather than anchored MAICs, although for additional reasons. In addition to the company's concerns about differences in pre-medication between placebo groups, the EAG notes that the placebo groups were not randomised components of the NEURO-TTRansform and HELIOS-A trials themselves.[5, 6] In both trials, the placebo group used for comparative purposes was external to the trial, with covariates included the analyses to adjust for some differences in baseline characteristics to improve the robustness of comparisons to placebo. Given only three or four variables were included in this adjustment, which did not cover all of the observed imbalances, the EAG considers that inclusion of these placebo arms in the ITCs would have introduced an additional source of uncertainty given the differences between intervention and external placebo arm may not have been adequately addressed. ITCs including

these placebo groups would be using data from four different studies and there would be uncertainty as to the comparability of intervention and placebo groups within each trial on top of uncertainty resulting from comparing eplontersen to vutrisiran. Therefore, the EAG considers the use of unanchored ITCs to be more appropriate in this situation.

The EAG considers that the methods used to perform ITCs are valid and in line with NICE DSU guidance.[3] The EAG reviewed the sample code provided and considers it to be appropriate but it has not validated the results of the analyses by rerunning them given the analyses involve IPD.

4.3.2.2 Variables included in adjustment and population analysed

While Section D.1.6 of the CS appendices suggests that patients in NEURO-TTRansform who did not meet the inclusion criteria for HELIOS-A were excluded prior to calculation of patients weights, the company clarified that no patients were excluded from ITC analyses based on HELIOS-A inclusion criteria. Numbers analysed for the unadjusted eplontersen group in each MAIC are presented in response to CQ A3, with exclusions due to a lack of baseline data on factors adjusted for in the ITCs.

The company identified potential prognostic factors (PFs) and treatment effect modifiers (TEMs) for inclusion in adjusted ITCs through clinical expert consultation and references were subsequently sought to validate their status as PFs or TEMs. The only additional factor that was identified through publications was region, which was not ultimately included in adjustments given it was considered likely to be a surrogate variable for other PFs already included. Data from NEURO-TTR and NEURO-TTRansform trials were also used to support the status of PFs and TEMs used in the adjusted ITCs through univariate and multivariate analyses to assess the relationship between variable and outcome within the trials. However, clinical expert feedback and evidence from the literature held the most weight in terms of deciding which variables to include in the adjustment for "reference" models as some that did not achieve significance in the trial analyses were still included in the reference ITCs. The company also explored alternative models for each outcome with fewer variables included in the adjustment, which were selected based on stepwise selection using Akaike information criterion (AIC; see Table 26 of the CS for variables included in the two models for each outcome). In response to CQ A1, the company also provided a third version of MAICs for certain outcomes with additional variables requested by the EAG based on its clinical expert feedback.

EAG comment

The EAG considers that the only difference in inclusion criteria that could be adjusted for by excluding some NEURO-TTRansform patients would be related to KPS score; patients with scores between 51 and 59% were eligible within NEURO-TTRansform but not in HELIOS-A and exclusion of these patients would be appropriate to improve overlap. The company clarified that only one patient with A KPS score in this range was included in the eplontersen group for the ITCs against vutrisiran. Based on there only being a single patient that could have been excluded to improve overlap, as well as feedback from the EAG's clinical expert that the differences in KPS criteria between trials were not important, the EAG does not consider this likely to have a major impact on results. As noted in Section 3.1, the two trials also differ with regards to baseline NIS inclusion, but given the range is wider in HELIOS-A than NEURO-TTRansform, this is not something that can be accounted for given IPD to exclude the patients from HELIOS-A are not available. This is an unresolvable difference between the two trials in terms of overlap but it was a difference that the EAG's clinical expert considered to be minor.

The EAG considers that appropriate methods have been used to identify PFs and TEMs for inclusion in the adjusted ITCs. It agrees with the company's decision to retain all variables identified by its clinical experts despite some not being significant when analyses within NEURO-TTRansform and NEURO-TTR were performed. The EAG asked its clinical expert whether region would be an additional variable worth accounting for but it was not identified as one that was important. The EAG agrees that it is likely that the impact of region would be captured through other factors included in the adjustments such as age, race, disease stage and type of mutation. However, the EAG's clinical expert did identify the following additional variables that would be useful to adjust for in all analyses, which the EAG requested be explored as part of CQ A1:

- Early-onset disease with V50M mutation;
- Baseline mNIS+7 score (included in the adjustment for all outcomes, not just the mNIS+7 analysis as in the company's original MAICs);
- Baseline NIS score;
- N-terminal pro b-type natriuretic peptide (NT-proBNP) levels.

In response to CQ A1, the company provided results of additional MAICs for certain outcomes incorporating most of the variables requested by the EAG. The only exception was baseline NIS score and the EAG accepts the company's rationale for omitting this from the updated MAICs (NIS is a subset of mNIS+7 and adjustment for both may not be appropriate). Similarly, to include early-onset

disease with V50M mutation in the adjustment, the overall V50M mutation (vs non-V50M mutation) was dropped from the original analyses, which the EAG considers to be reasonable.

Given that unanchored analyses have been performed, which are associated with considerable uncertainty, it is important that all potential PFs and TEMs are included in the adjustment.[3] For this reason, the EAG has a preference for analyses that include the most PFs and TEMs. Based on the EAG's clinical expert feedback and EAG review of the balance of variables between eplontersen and vutrisiran groups in Tables 3 to 16 of the CQ response, the EAG considers analyses provided in response to CQ A1 to be the most appropriate for decision-making as these include additional factors considered to be important in terms of prognosis and are generally less imbalanced. However, the level of adjustment does not have a large impact on conclusions drawn from the results.

The EAG considers that overlap for the two studies is reasonable as the ESS remains at least half of the analysed unadjusted eplontersen population for all of the company's original analyses, with ESS not hugely different across the analyses with different levels of adjustment, including when additional factors were included as requested in CQ A1. The EAG requested a distribution of patient weightings be provided for each MAIC (CQ A10) and considered these to be reasonable, with no extreme weights noted.

The adjustments appear to have been successful for all analyses as all variables adjusted for appear to be well-balanced between eplontersen and vutrisiran arms for analyses in the original CS and CQ response. While some additional variables reported in both studies were not adjusted for, the EAG considers that MAICs with adjustment for the most important variables have been provided by the company in response to CQ A1 and the EAG is satisfied that any residual imbalances are minor and should not impact outcomes substantially.

For reasons discussed above, the EAG has a general preference for MAICs provided in response to CQ A1, which include adjustment for early-onset V50M mutation, baseline mNIS+7 and NT-proBNP levels, compared to original reference MAICs presented by the company in the CS. However, for mNIS+7 and Norfolk QoL outcomes, the EAG also has a preference for week 85 observed data to be used rather than week 66 extrapolated data for eplontersen (see Section 4.3.2.3); given versions of the observed week 85 analyses with the additional adjustments outlined in CQ A1 were not available to the EAG, and because the use of week 85 data appears to have a larger impact on results than the

additional MAIC adjustments do, the EAG has a preference for the week 85 observed data analyses with adjustment for variables in the company's original reference MAICs for these outcomes. Similarly, the EAG has a preference for the original treatment discontinuation MAIC rather than the version with additional adjustment provided in response to CQ A1 as the EAG considers the new analyses include incorrect data for HELIOS-A (see Section 4.3.3.6 for more details). A breakdown of the EAG's preferred MAIC for each outcome is presented in Section 4.3.3.

4.3.2.3 Analysis decisions

The company made a number of decisions about analyses in attempts to best align NEURO-TTRansform IPD with the published, aggregate data for HELIOS-A. While the EAG acknowledges the rationale for most of these, it does not necessarily agree that they are the best option in terms of reducing bias. For one of these analysis decisions the EAG requested that scenario analyses be provided using alternative approaches to assess the impact on results. Decisions made by the company are summarised in Table 20 of Appendix 10.4 and discussed in more detail in the paragraphs that follow.

The mNIS+7 versions used in NEURO-TTRansform and HELIOS-A were different and the company describes its efforts to align the two before ITC analyses in response to CQ A8. The EAG considers that most of the differences have been accounted for either through rescoring of NEURO-TTRansform data or excluding additional domains used in NEURO-TTRansform but agrees that it is not possible to account for the difference in how autonomic dysfunction was assessed (heart rate with deep breathing assessed using a neurological test in NEURO-TTRansform vs postural blood pressure assessed by a neurologist). Given the autonomic component of the two assessments is the smallest component in both versions, it is possible that any residual differences are small but the EAG considers ITCs for mNIS+7 to be associated with increased uncertainty compared to other outcomes due to this lack of complete overlap between studies.

To analyse serum TTR levels, steady-state serum TTR levels were estimated. The steady-state period was defined for eplontersen as pre-dose measurements taken from week 49 onwards. In its response to CQ A9 the company states that these time-points were selected to align with the steady-state period covered in HELIOS-A (as outlined in the Statistical Analysis Plan for this trial), which involved pre-dose measurements taken between months 6 and 18; as week 49 is the first pre-dose measurement available for eplontersen between 6 and 18 months, this was the first measurement included within the steady-state period.[24] Furthermore, the company suggests on page 57 of the CS

that half-life data for eplontersen and the relationship between half-life and steady-state also support the use of data from week 49 onwards. The EAG is satisfied with the rationale provided by the company and considers this to be in line with the steady-state period used in HELIOS-A for vutrisiran.

The EAG identified a number of additional potential limitations in terms of the comparability of serum TTR outcomes between studies:

1. Various assays are available to measure serum TTR and it is unclear if those used in the two trials were comparable. The LLOD can vary between assays and if one trial used an assay with a lower limit than the other, it may be able to detect greater knockdown vs baseline than the other in the same patient. Given details of the assay used in the HELIOS-A study do not appear to be publicly available, the EAG agrees that this remains an area of uncertainty that cannot be commented on further. However, the EAG does not completely agree with the company's suggestion that change from baseline values would be unaffected by any difference in LLOD, as TTR levels will be lower at follow-up compared to baseline and any difference in the LLOD between assays may affect comparative results;
2. A correction factor was applied to eplontersen serum TTR data to account for differences between electrochemiluminescence (ECL) and immunoturbidimetry-based methods used in NEURO-TTRansform (eplontersen) and NEURO-TTR (external placebo).[5] In response to part d of CQ A9, the company notes that this correction factor was included in the ITCs for serum TTR in the comparisons against vutrisiran. While the EAG questions the need for this given an enzyme-linked immunosorbent assay (ELISA) was used in HELIOS-A (rather than the exact immunoturbidometric method used in NEURO-TTR), it does not consider this to be a major issue for serum TTR results presented as percentage change from baseline (the EAG's preferred format for serum TTR results) given the correction factor will have been applied to baseline and follow-up results and percentage change from baseline results should be similar regardless of whether or not a correction factor is applied;
3. The per-protocol population was analysed in HELIOS-A, whereas for NEURO-TTRansform the randomised set (all randomised patients) was used (see response to CQ A5).[5, 6] While a per-protocol population analysis for TTR was available from the CSR of NEURO-TTRansform (Table 2.61), the definition of the per-protocol population is substantially different between NEURO-TTRansform and HELIOS-A and it is, therefore, not possible to assess whether and to what extent this could impact comparative estimates obtained from ITCs.[15] This also means

that the population that eplontersen data was adjusted to in this MAIC differs slightly to the population that data was available for in terms of this outcome from HELIOS-A. Given only n=2 patients from the vutrisiran arm of HELIOS-A were excluded from the per-protocol population,[25] the EAG considers the potential impact of this difference on the results of the MAIC for this outcome to be minimal.

For the company's original analyses of mNIS+7, Norfolk QoL-DN, AEs and discontinuation, the company opted not to use week 85 data for eplontersen in the ITCs:

- For mNIS+7 and Norfolk QoL-DN, the company extrapolated week 66 data to obtain data at week 80 in order to align with the time-point from HELIOS-A. This was originally said to be because there was no external placebo group data from NEURO-TTR at week 85 meaning there were no mixed effects models with repeated measures (MMRM) results from the NEURO-TTRansform study at this time-point;
    - In response to part e of CQ A6 the company notes that it does not consider this to be a major limitation in terms of using observed week 85 data.
    - The EAG considers that extrapolation of week 66 data to week 80 introduces unnecessary uncertainty into the ITCs for these two outcomes given observed week 85 data is available and is fairly close to the time-point outcomes are reported at for HELIOS-A (~80 weeks).
    - There are some differences in point estimates between MAICs using extrapolated and observed data, which are more notable than the differences seen with additional variables included in the adjustments in response to CQ A1 (see Section 4.3.3).
    - Therefore, the EAG has a preference for MAICs that have used observed week 85 data for these outcomes, although this is at the expense of the additional adjustments outlined in CQ A1 (see Section 4.3.2.2) as versions using observed week 85 data with this additional adjustment were not available to the EAG. Furthermore, MAICs for the new mBMI outcome provided in response to CQ A2 have been performed using extrapolated week 66 data only, which represents a limitation of this analysis (see Section 4.3.3.4);

- For AEs and discontinuation, week 66 data for eplontersen has been included in the ITCs rather than week 85 data. While the EAG's clinical expert considered that most of these

events will occur earlier after treatment initiation and should be captured by the week 66 data-cut, additional events did occur by week 85 in NEURO-TTRansform. The EAG did not prioritise this as part of the clarification stage but has explored differences in AEs and discontinuation at week 85 (and any potential impact this may have on ITC results) in Section 4.3.4.1.

Relating to the company's approach to missing data in the ITCs, multiple imputation appears to have been used for eplontersen, whereas MMRM with implicit imputation were used for these outcomes at 18 months in HELIOS-A. While it is possible that these differences could impact comparative estimates, given that both of these are missing at random (MAR) approaches, the EAG considers it unlikely that this would be substantial. Furthermore, the EAG reviewed the results of sensitivity analyses using multiple imputation and compared them to MMRM results without multiple imputation for serum TTR, mNIS+7 and Norfolk QoL-DN in the CSR for NEURO-TTRansform and is satisfied that the method used does not have a notable impact on eplontersen results and should not, therefore, be a large concern in terms of impact on results vs vutrisiran obtained from the ITCs.[15]

4.3.3 *Results of the company's indirect treatment comparisons*

The results of the ITCs comparing eplontersen against vutrisiran are presented in the subsections that follow. The EAG presents its preferred analyses for each outcome in this section. The EAG has focused on the results of MAICs rather than STCs (see Section 4.3.2.1). The EAG's preferred MAICs for each outcome are summarised in Table 5 below. The rationale for the EAG's preference and the remaining limitations of these MAICs are discussed in Sections 4.3.2.2 and 4.3.2.3.

Table 5. Details of the EAG's preferred MAICs for each outcome

Outcome	Source of EAG-preferred MAIC	Time-point used/data extrapolation	Variables included in adjustment	ESS	Comment
Serum TTR percentage change from baseline at steady-state	Response to CQ A1 (Table 1)	Week 85 no extrapolation	Age, sex (male), race (white), prior treatment, early onset V50 mutation, cardiac involvement, FAP stage (stage I), baseline serum TTR, baseline mNIS+7, baseline NT-proBNP (>3000 ng/L)	[redacted]	Use of week 85 data with EAG-preferred variable adjustment.
mNIS+7 change from baseline score	Response to CQ A7 (Table 17 – using week 85 data)	Week 85 no extrapolation	Age, sex (male), race (white), prior treatment, V50M mutation, cardiac involvement, FAP stage (stage I), mNIS+7 at baseline	[redacted]	Use of week 85 data preferred but not adjusted for additional variables outlined in CQ A1.
Norfolk QoL-DN change from baseline score	Response to CQ A7 (Table 17 – using week 85 data)	Week 85 no extrapolation	Age, sex (male), race (white), prior treatment, V50M mutation, cardiac involvement, FAP stage (stage I), Norfolk QoL-DN at baseline	[redacted]	Use of week 85 data preferred but not adjusted for additional variables outlined in CQ A1.
mBMI change from baseline score	Response to CQ A2 (Table 2 – including additional variables from CQ A1)	Week 65 with linear extrapolation to week 80	Age, sex (male), race (white), prior treatment, early onset V50M mutation, cardiac involvement, FAP stage (stage I), baseline mBMI, baseline mNIS+7, baseline NT-proBNP (>3000 ng/L)	[redacted]	No version using week 85 data provided. Version provided involves extrapolation. Adjusted for additional variables requested by the EAG.
10-MWT change from baseline score	Response to CQ A2 (Table 2 – including	Week 81 no extrapolation	Age, sex (male), race (white), prior treatment, early onset V50M mutation, cardiac	[redacted]	Week 81 data used (longest available follow-up for this outcome) with no

	additional variables from CQ A1)		involvement, FAP stage (stage I), baseline 10-MWT, baseline mNIS+7, baseline NT-proBNP (>3000 ng/L)		extrapolation. Adjusted for additional variables requested by the EAG.
R-ODS change from baseline score	Response to CQ A2 (Table 2 – including additional variables from CQ A1)	Week 81 no extrapolation	Age, sex (male), race (white), prior treatment, early onset V50M mutation, cardiac involvement, FAP stage (stage I), baseline R-ODS, baseline mNIS+7, baseline NT-proBNP (>3000 ng/L)	[redacted]	Week 81 data used (longest available follow-up for this outcome) with no extrapolation. Adjusted for additional variables requested by the EAG.
Serious AEs	Response to CQ A1 (Table 1)	Week 66 no extrapolation	Age, sex (male), race (white), prior treatment, early onset V50mutation, cardiac involvement, FAP stage (stage I), baseline mNIS+7, baseline NT-proBNP (>3000 ng/L)	[redacted]	Adjusted for additional variables requested by the EAG but uses week 66 rather than week 85 data for eplontersen.
Severe AEs	Response to CQ A1 (Table 1)	Week 66 no extrapolation			
Treatment discontinuation	Figure 34 of the CS	Week 66 no extrapolation	Age, sex (male), race (white), prior treatment, V50M mutation, cardiac involvement, FAP stage (stage I)	[redacted]	Not adjusted for additional variables requested by the EAG and uses week 66 data rather than week 85 data for eplontersen.

MAICs performed for absolute steady-state serum TTR values at follow-up and absolute change from baseline in steady-state serum TTR values, and responder analyses for mNIS+7 and Norfolk QoL-DN outcomes, are not covered in this table as the alternative analyses that are covered in this table were considered to be the most useful analyses for each of the outcomes.

Abbreviations: 10-MWT, 10-metre walk test; CQ, clarification question; CS, company submission; EAG, External Assessment Group; FAP, Familial Amyloid Polyneuropathy; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; mNIS+7, Modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro b-type natriuretic peptide; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin.

In the company's original submission, discussion of the ITC results focuses on the fact that 95% confidence intervals (CIs) are not consistent with statistically significant differences for most analyses, with the company suggesting that this allows a conclusion of similar efficacy and safety between eplontersen and vutrisiran. However, given these are ITCs between two different studies rather than a within-trial comparison that has been powered to demonstrate non-inferiority, for example, the EAG considers that conclusions based on CIs crossing the line of null effect are

inappropriate. Instead, the EAG considers it important to take into account the direction of the point estimate when interpreting results. Although these point estimates are associated with uncertainty based on the CIs, this may be due to the limited data available rather than there not being a genuine difference between treatments.

Furthermore, the EAG considers the use of minimum clinically important differences (MCIDs) to be useful in terms of deciding whether the differences identified through ITCs for continuous outcomes are likely to be clinically meaningful. The EAG identified values that it considers could be useful in terms of interpreting results and while they may not be a perfect match to the population and/or outcome measure, it considers them to be more useful than having no thresholds to consider at all. The EAG identified values for mNIS+7, Norfolk QoL-DN and 10-metre walk test (10-MWT) from the patisiran highly specialised technology NICE appraisal (HST10), the vutrisiran NICE cost-comparison evaluation (CCE; TA868) and/or a secondary publication related to the NEURO-TTR trial.[1, 26, 27] The value for percentage change in serum TTR identified by the EAG was based on the non-inferiority threshold used in the regulatory trial for vutrisiran (HELIOS-A) in terms of making comparisons between vutrisiran and patisiran.[6] In response to CQ A13, the company also provided additional values that could be used as MCIDs, specifically to evaluate a difference between two interventions, for mNIS+7, Norfolk QoL-DN and mBMI based on an [redacted], but stated that given the fatal consequences of ATTRv-PN if untreated, any halting of progression is widely accepted as being clinically meaningful.

All potential MCIDs identified are summarised in Table 21 of Appendix 10.4. The EAG acknowledges that most of the values identified refer to changes from baseline, rather than the difference between two interventions, but considers them useful in the absence of any other thresholds.

The EAG notes that the thresholds identified vary widely across sources which is likely to be the result of different sources of data used to estimate MCIDs (for example, analyses based on different trials), different methodologies used (for example, anchor-based vs distribution-based methods) and variation within the same methodology (for example, different anchor outcomes used or different distribution-based estimates such as standard deviation [SD] vs standard error of the mean [SEM]). This variation in MCID estimates is acknowledged in the literature and is not an issue specific to this area.[28-31] It has been suggested that anchor- and distribution-based estimates should be considered alongside one another, with clinical opinion also used when interpreting these thresholds.[29, 31] Therefore, the EAG has followed this approach by considering whether conclusions would change

across the identified thresholds for each outcome, with clinical expert feedback also sought to determine which thresholds were clinically meaningful.

4.3.3.1 Steady-state serum TTR levels

The EAG focuses on results analysed as percentage change from baseline (rather than absolute or absolute change from baseline measures) given a potential MCID was identified for this measure and the EAG's clinical expert stated that it is often used in clinical practice. Furthermore, the impact of the correction factor mentioned in Section 4.3.2.3 is likely to be limited when percentage change from baseline results are considered.

Results from the EAG's preferred MAIC (see Table 5 for a description) are presented in Figure 2 below. Based on the point estimate, results are slightly in favour of eplontersen with a slightly larger reduction vs baseline with this treatment. However, there is uncertainty based on the width of the 95% CI, which also crosses 0.0. Considering the MCID of 10 percentage points proposed by the EAG (see Appendix 10.4), the EAG notes that the point estimate and upper and lower confidence limits are not above this threshold in either direction. Therefore, the EAG is satisfied that there is unlikely to be a clinically important difference between the two treatments for this outcome. These results are consistent with the original results provided by the company, including reference and alternative MAICs (Figure 20 of the CS). While some limitations associated with the serum TTR analyses remain (see Section 4.3.2.3), the EAG considers these to be minor or unresolvable uncertainties, with the size and direction of bias not possible to ascertain.

Figure 2. Results of the EAG's preferred MAIC for percentage change from baseline in serum TTR levels – eplontersen vs vutrisiran

Abbreviations: CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; SE, standard error; TTR, transthyretin.

4.3.3.2 Modified Neuropathy Impairment Score +7

Results discussed here are for the change from baseline in mNIS+7 composite score. The EAG has not included responder analyses presented in the CS for this outcome given the definition used to

define responders (any negative change vs baseline) was not considered clinically useful by the EAG's clinical expert.

Results from the EAG's preferred MAIC (see Table 5 for a description) are presented in Figure 3 below. Based on the point estimate, results are slightly in favour of eplontersen given lower scores on mNIS+7 indicate less dysfunction. However, the EAG notes that this is a very small difference and the point estimate does not exceed any of the MCIDs identified for this outcome (see Appendix 10.4). While there may be uncertainty given the 95% CI does cross some of the identified MCIDs in Appendix 10.4, it does not cross the threshold considered by the EAG's clinical expert to be more likely to reflect a clinically meaningful difference (12.2-point threshold; the EAG's clinical expert considered the 2-point threshold cited in prior NICE appraisals to be an extremely small difference that would not be considered clinically important). Therefore, the EAG considers that the point estimate and 95% CI from this MAIC are consistent in suggesting no clinically important difference between eplontersen and vutrisiran for mNIS+7.

Limitations of this MAIC remain given a version of the week 85 analysis with additional adjustment was not available to the EAG (see Sections 4.3.2.2 and 4.3.2.3) but the EAG does not consider further adjustment in this analysis would change the results to the extent that its conclusion would change with regards to clinically important differences. Furthermore, it should be noted that it was not possible to completely align the two mNIS+7 versions used in the ITCs for this outcome, meaning the results for this outcome are associated with increased uncertainty. The possible impact of this on results is unclear but likely to be small given the domain that could not be aligned was the smallest domain of mNIS+7 (see Section 4.3.2.3).

The results of the EAG's preferred MAIC differ slightly from the original reference MAIC performed by the company (which involved extrapolation of week 66 data to week 80 rather than using observed week 85 data) in that the point estimate of the latter favoured vutrisiran by ~[redacted] (Figure 1 of an addendum to the submission provided following CQs). The impact of the additional adjustment (requested by the EAG as part of CQ A1) on the results of the company's original MAIC using extrapolation of week 66 data to week 80 was marginally less notable (point estimate of [redacted] with vs without additional adjustment, respectively), which is why the EAG's preference was to use the analysis with observed week 85 data even without the additional adjustments outlined in CQ A1 given this approach was considered to be more appropriate than extrapolating data (see Sections 4.3.2.2 and 4.3.2.3).

Figure 3. Results of the EAG's preferred MAIC for change from baseline in mNIS+7 – eplontersen vs vutrisiran

Abbreviations: CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; mNIS+7, Modified Neuropathy Impairment Score +7; SE, standard error.

4.3.3.3 Norfolk Quality of Life Questionnaire – Diabetic Neuropathy

Results discussed here are for the change from baseline in Norfolk QoL-DN score. The EAG has not included responder analyses presented in the CS for this outcome given the definition used to define responders (any negative change vs baseline) was not considered clinically useful by the EAG's clinical expert.

Results from the EAG's preferred MAIC (see Table 5 for a description) are presented in Figure 4 below. Based on the point estimate, results are slightly in favour of eplontersen given lower scores indicate better quality of life for this outcome. However, the difference based on the point estimate is extremely small and uncertainty exists given the width of the 95% CI, which crosses 0.0. The point estimate for the difference between treatments does not exceed any of the MCIDs reported in Table 21 of Appendix 10.4, although the 95% CIs cross some of the thresholds. Based on the very small difference indicated by the point estimate of this MAIC, the EAG is satisfied that there is unlikely to be a clinically important difference between the two treatments for this outcome.

The EAG considers it important to note that results from the company's original MAICs for this outcome (using extrapolated week 66 data rather than observed week 85 data; Figure 26 of the CS) are notably different in terms of the point estimate, with a larger benefit of eplontersen being suggested originally, which was statistically significant (point estimate [redacted] vs [redacted] in original vs EAG-preferred MAICs, respectively). The impact of the additional adjustment (requested by the EAG as part of CQ A1) on the results of the company's original MAIC using extrapolation of week 66 data to week 80 was less notable (point estimate of [redacted] with vs without additional adjustment, respectively), which is why the EAG's preference was to use the analysis with observed week 85 data even without the additional adjustments outlined in CQ A1 (see Sections 4.3.2.2 and 4.3.2.3).

Limitations of the EAG's preferred MAIC remain given a version of the week 85 analysis with additional adjustment was not available to the EAG (see Sections 4.3.2.2 and 4.3.2.3) but the EAG does not consider further adjustment in this analysis would change the results to the extent that its conclusion would change with regards to clinically important differences.

Figure 4. Results of the EAG's preferred MAIC for change from baseline in Norfolk QoL-DN – eplontersen vs vutrisiran

[redacted]

Abbreviations: CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SE, standard error.

4.3.3.4 Modified body mass index

In response to CQ A2, the company performed MAICs for mBMI, which were requested by the EAG based on clinical expert feedback that it is an important outcome in patients with ATTRv-PN.

Results from the EAG's preferred MAIC (see Table 5 for a description) are presented in Figure 5 below. Based on the point estimate, results are slightly in favour of vutrisiran given higher scores indicate a better outcome in terms of mBMI. However, uncertainty exists given the width of the 95% CI, which also crosses 0.0. Of the two MCIDs identified for mBMI (detailed in Table 21 of Appendix 10.4), the point estimate only exceeds one of these (threshold of 9.8 points based on improvement from baseline). However, the EAG's clinical expert did not consider a 10-point difference to be clinically meaningful and noted that even a difference of ~50 points would be considered to be small. Based on a point estimate from the EAG's preferred MAIC of -[redacted] in favour of vutrisiran, the EAG considers it possible that there is a slight benefit of vutrisiran compared to eplontersen for this outcome. However, this is associated with considerable uncertainty and the difference may not be considered clinically meaningful.

It should be noted that the results presented above are based on the extrapolation of week 65 data rather than use of observed data at week 85 for eplontersen. For reasons described in Section 4.3.2.3, the EAG would have preferred that week 85 observed data was used instead, which would be in line with the EAG's preference for avoiding extrapolation of mNIS+7 and Norfolk QoL-DN

outcomes. The EAG cannot rule out the possibility that results for mBMI may favour vutrisiran slightly more if the week 85 observed data had been used but it considers it unlikely that it would change results to the extent that conclusions around clinical importance would be altered (results from Table 2.116 of the CSR suggest that change from baseline in mBMI [redacted] between week 65 and week 85, but the difference was only [redacted]).

Figure 5. Results of the EAG's preferred MAIC for change from baseline in mBMI – eplontersen vs vutrisiran

Abbreviations: CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; SE, standard error.

4.3.3.5 Other clinical efficacy outcomes

The company also provided MAICs for 10-MWT and R-ODS in response to CQ A2. Higher scores on 10-MWT and R-ODS indicate more favourable outcomes. The range of scores of R-ODS is 0 to 48.

Results from the EAG's preferred MAICs (see Table 5 for a description) for these two outcomes are presented in Figure 6 and Figure 7 below. Based on the point estimates, results are slightly in favour of vutrisiran for the 10-MWT but slightly in favour of eplontersen for R-ODS. However, the point estimates for both outcomes represent extremely small differences and uncertainty exists given the width of the 95% CIs, which also cross 0.0. The difference based on the point estimate is not larger than the lowest identified MCID for 10-MWT (see Table 21 of Appendix 10.4) and no MCIDs were identified for R-ODS. The EAG is satisfied that no clinically important differences are likely to exist between eplontersen and vutrisiran based on these MAICs.

The company confirmed to the EAG that these MAICs were performed using week 81 observed data with no extrapolation performed, which is in line with the EAG's preference for mNIS+7 and Norfolk QoL-DN regarding avoiding the use of extrapolation. These analyses also included the additional adjustment requested as part of CQ A1 for other outcomes.

Figure 6. Results of the EAG's preferred MAIC for change from baseline in 10-MWT – eplontersen vs vutrisiran

[redacted]

Abbreviations: 10-MWT, 10-metre walk test; CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; Norfolk QoL-DN, SE, standard error.

Figure 7. Results of the EAG's preferred MAIC for change from baseline in R-ODS – eplontersen vs vutrisiran

[redacted]

Abbreviations: CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; R-ODS, Rasch-built Overall Disability Scale; SE, standard error.

4.3.3.6 Adverse events and treatment discontinuation

The company performed ITCs for AEs and treatment discontinuation, with the AE analyses focusing on serious and severe AEs. In addition to ITCs, the EAG has explored these outcomes in more detail in Section 4.3.4.1 below, but notes this is based on naïve comparisons which are associated with additional limitations.

As well as providing versions with additional variables adjusted for in response to CQ A1, for treatment discontinuation the company also provided "corrected" analyses given it stated it had analysed an incorrect number of events for HELIOS-A originally (see response to CQ B3). However, the EAG considers the number of discontinuation events analysed originally (n=5 rather than n=3) was correct based on Figure 1 of the HELIOS-A publication.[6] Use of n=3 events reflects the number of treatment discontinuations as a result of AEs rather than all-cause treatment discontinuation. Therefore, a version with the correct data analysed for HELIOS-A *and* with the additional adjustments requested as part of CQ A1 are not available to the EAG for treatment discontinuation. Given Table 20 of the response to CQ B3 suggests only a limited impact of the additional adjustment

on the point estimate, the EAG prefers the analysis using the correct data for HELIOS-A with reduced adjustment (Figure 34 of the CS, presented below in Figure 10).

Results from the EAG's preferred MAICs (see Table 5 for a description) for these outcomes are presented in Figure 8, Figure 9 and Figure 10 below. Based on the point estimates, results for AEs suggest reduced events with eplontersen and results for treatment discontinuation suggest reduced events with vutrisiran. However, uncertainty exists for all three outcomes given the width of the 95% CIs, which also cross 1.0. The EAG is satisfied that, based on point estimates from these MAICs, AEs for eplontersen are unlikely to be worse compared to vutrisiran. For treatment discontinuation, while this appears to be increased for eplontersen, the EAG notes that there is only a small difference in the absolute number of patients that discontinued treatment (n=5 patients discontinuing vutrisiran at week 78 vs n=[redacted] patients discontinuing eplontersen at week 85) and may not be an important difference, as discussed in Section 4.3.4.1. Based on these considerations, the EAG considers it unlikely that there are any large differences in favour of vutrisiran in terms of treatment discontinuation. Therefore, the EAG concludes that it may be reasonable to assume that severe AEs, serious AEs and treatment discontinuation are similar between eplontersen and vutrisiran.

While the results of these MAICs are limited in that week 66 rather than week 85 data were analysed for eplontersen, as discussed in Section 4.3.4.1, the EAG is not concerned that use of week 85 data would change the results of MAICs to the extent that the EAG's conclusions about similarity between treatments would change and the EAG has already considered the difference between absolute number of discontinuations at week 85 for eplontersen compared to vutrisiran in its decision about similarity for this outcome in the preceding paragraph.

Figure 8. Results of the EAG's preferred MAIC for serious AEs – eplontersen vs vutrisiran

[redacted]

Abbreviations: AEs, adverse events; CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; SE, standard error.

Figure 9. Results of the EAG's preferred MAIC for severe AEs – eplontersen vs vutrisiran

[redacted]

Abbreviations: AEs, adverse events; CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; SE, standard error.

Figure 10. Results of the EAG's preferred MAIC for treatment discontinuation – eplontersen vs vutrisiran

[redacted]

Abbreviations: CI, confidence interval; EAG, External Assessment Group; IV, inverse variance; MAIC, matching-adjusted indirect comparison; SE, standard error.

4.3.4 Additional data considered by the EAG

4.3.4.1 Adverse events and discontinuation

Serious AEs, severe AEs and treatment discontinuation are included in the ITCs performed by the company (Section 4.3.3.4) but the company also provides a more detailed breakdown of AEs for eplontersen and vutrisiran in Section B.3.10 of the CS. The EAG notes that these are naïve comparisons with the limitation that differences in study populations between trials have not been accounted for and should be interpreted with more caution when making comparisons. This includes safety data up to 85 weeks for eplontersen in NEURO-TTRansform and up to week 78 for vutrisiran in HELIOS-A. This differs to the ITCs for these outcomes where week 66 data was used in the analyses for eplontersen.

Comparison to vutrisiran

A breakdown of events for eplontersen and vutrisiran in their respective studies is presented in Table 6 below. Overall, while there were some events that occurred slightly more often in one of the treatment groups compared to the other, they appear to be broadly similar, particularly considering there are differences in terms of population that have not been accounted for and that time-points data is available up to differs slightly. The most notable differences were:

- A higher proportion of patients discontinuing the study drug due to treatment emergent AEs (TEAEs) for eplontersen (6% vs 3%), although this was a difference of only n=5 patients. In addition, the definition of this for eplontersen included deaths and it is unclear if the same was true for vutrisiran;
- Serious TEAEs occurred more often for vutrisiran than for eplontersen (26% vs 19%), although this was again a difference of only n=5 patients;
- Injection site reactions (specifically mentioned in the Summary of Product Characteristics [SmPC] for eplontersen) were higher for eplontersen compared to vutrisiran (9% vs 4%; 13 patients vs 5 patients);[4] however, most of these events for eplontersen were mild based on Table 4.11 of the CSR.[15] All events for vutrisiran were described as being mild and transient.

For specific events occurring in ≥10% of patients in either eplontersen or vutrisiran groups, some occurred more frequently with eplontersen, while others were more common in the vutrisiran group. For the former, most events were mild events but there were [redacted] and [redacted] for eplontersen. None of these serious events were considered to be related to the study drug, whereas n=2 of the serious AEs observed in HELIOS-A for vutrisiran were considered to be related to study drug.

A comparison in terms of AEs of special interest (AESIs) and other adverse events of interest (OAEIs) as defined in NEURO-TTRansform was not possible as this was not reported in HELIOS-A for vutrisiran; however, the EAG notes that the proportion of patients with OAEIs for eplontersen ([redacted]) was [redacted] compared to both the small inotersen group included in NEURO-TTRansform ([redacted]) and the external placebo group from NEURO-TTR ([redacted]; Table 60 of the CSR).[15] Similar was observed for AESIs ([redacted] for eplontersen) when compared to the inotersen group from NEURO-TTRansform ([redacted]), but AESIs were [redacted] for eplontersen compared to the external placebo group ([redacted]; Table 60 of the CS).[15]

Vitamin A deficiency was also not reported for vutrisiran; the EAG considers it would have been captured in the trial given vitamin A supplementation is recommended for both drugs to reduce the risk of deficiency. Therefore, it likely occurred less often than for eplontersen as only those AEs occurring in ≥10% of patients are reported in the HELIOS-A publication.[6] However, given that [redacted] [redacted] of the vitamin A deficiency events in NEURO-TTRansform were classed as mild events ([redacted]) and that supplementation with vitamin A is recommended

for both treatments, the EAG is not concerned that there are likely to be important differences in terms of this event that need to be captured via economic modelling.

The EAG notes that immunogenicity (mentioned in the SmPCs for eplontersen and vutrisiran) appears to be [redacted] for eplontersen compared to vutrisiran, with [redacted] of eplontersen patients testing positive for anti-drug antibodies (ADAs) after an 84-week treatment period compared to 3.3% of vutrisiran patients from HELIOS-A after 78 weeks of treatment.[4, 6, 15, 16] Most events were also [redacted] for eplontersen, while events in HELIOS-A for vutrisiran were described as being low in titre and transient with no evidence of an effect on clinical efficacy, safety, or pharmacokinetic (PK) or pharmacodynamic (PD) profiles of vutrisiran. The CSR for NEURO-TTRansform [redacted], which the EAG considers to be a reasonable conclusion, with median titre values across follow-up [redacted], [redacted] than that observed for inotersen ADAs in the same trial (median values above [redacted]; Figure 3.27 of the CSR).[15] The EAG broadly agrees with the company's conclusion that [redacted] of eplontersen based on data provided in CSR tables but notes that the presence of ADAs against eplontersen [redacted]. However, the EAG is not concerned that [redacted] these groups will impact on conclusions made about the similarity to vutrisiran as:

- The analysed data for eplontersen includes patients with and without eplontersen ADA-positivity, meaning any impact on efficacy or safety outcomes should be captured in the trial data used to compare against vutrisiran;
- The median titre of ADAs against eplontersen appears to [redacted] up to week 85, suggesting that the impact of ADA-positivity on outcomes [redacted] over time (and beyond the observed data for this trial), although it is not possible to be sure about this without longer follow-up data. [redacted]

The EAG concludes that while there may be slight differences in terms of the frequency of specific AEs observed for eplontersen and vutrisiran in their respective clinical trials, it does not have concerns that there are likely to be any large differences that need to be captured as part of an

economic model. Proportions with serious and severe AEs are very similar across the treatment groups and no serious events related to study drug were identified for eplontersen. The EAG reviewed AE data for the extension phase of NEURO-TTRansform up to the [redacted] data cut-off and did not identify any additional concerns.

Table 6. Summary of TEAEs through end of treatment for eplontersen and vutrisiran - adapted from Tables 36 and 37 of the CS and Tables 60 and 4.11 of the CSR

Incidence, n (%)	NEURO-TTRansform	HELIOS-A
	Eplontersen (n=144) – week 85+	Vutrisiran (n=122) – week 78
Any TEAE	141 (97.9%)	119 (97.5%)
TEAE related to study drug	[redacted]	NR
TEAE leading to study drug discontinuation (including death for eplontersen)	8 (5.6%)	3 (2.5%)
Severe TEAEs	20 (14%)	19 (15.6%)
Serious TEAEs	27 (19%)	32 (26.2%)
Serious TEAE related to study drug	0 (0.0%)	2 (1.6%)
Injection site reaction	13 (9%)	5 (4.0%)
Death	3 (2%)	2 (1.6%)
Death due to study drug	0 (0.0%)	0 (0.0%)
AESI*	[redacted]	NR
OAEI†	[redacted]	NR
AEs occurring in ≥10% patients in eplontersen OR vutrisiran groups		
COVID-19	48 (33.3%)	NR
Diarrhoea	28 (19.4%)	17 (13.9%)
Urinary tract infection	28 (19.4%)	16 (13.1%)
Vitamin A deficiency	17 (11.8%)	NR
Nausea	16 (11.1%)	12 (9.8%)
Fall	[redacted]	22 (18.0%)
Pain in extremity	[redacted]	18 (14.8%)

Peripheral oedema	[redacted]	16 (13.1%)
Arthralgia	[redacted]	13 (10.7%)
Dizziness	[redacted]	13 (10.7%)
Additional AEs of interest‡		
Injection site reactions (as above)	13 (9%)	5 (4.0%)
Immunogenicity	[redacted]	4 (3.3%)
Vitamin A deficiency (as above)	17 (11.8%)	NR
Vomiting	[redacted]	9 (7.4%)

*AESI were defined in NEURO-TTRansform as ocular adverse events potentially related to vitamin A deficiency, thrombocytopenia and glomerulonephritis; †OAEI were defined in NEURO-TTRansform as coagulation abnormalities, renal impairment, abnormal liver function, AEs at the injection site, flu-like symptoms, central nervous system disorders, haemorrhages, cardiac disorders, or reduced thyroxine; ‡The EAG has included AEs mentioned in the SmPC of vutrisiran and/or eplontersen or those increased in ADA-positive group for eplontersen patients in NEURO-TTRansform as additional events here;

Some additional AE data for vutrisiran were obtained from the data provided in the CS as part of NICE TA868.

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; AESI, adverse events of special interest; CS, company submission; CSR, clinical study report; NICE, National Institute for Health and Care Excellence; NR, not reported; OAEI, other adverse events of interest; SmPC, Summary of Product Characteristics; TA, technology appraisal; TEAEs, treatment-emergent adverse events;.

Comparison of week 85 data to week 66 used in ITCs

The EAG notes that week 85 data from NEURO-TTRansform is not used in the ITCs that have been performed to compare serious AEs, severe AEs and treatment discontinuation between eplontersen and vutrisiran in Section 4.3.3.4 and has instead used data up to week 66.

The EAG reviewed the differences in event frequencies for eplontersen between the two data-points and notes the following:

- Discontinuation at week 66 was ~[redacted]% for eplontersen and at week 85 was [redacted] % (Table 12 of the CSR). This is compared to 4.1% for vutrisiran at week 78 of HELIOS-A. The company's MAIC analyses (see Section 4.3.3.6) suggest that, following adjustments in terms of population, treatment discontinuation is higher for eplontersen compared to vutrisiran, although 95% CIs cross the line of null effect. Had week 85 data been analysed, the EAG considers it likely that this [redacted], although it is unclear what the impact on the [redacted] would be. However, the EAG notes that this is based on [redacted] patients vs 5 patients discontinuing treatment, which

may be considered relatively few events particularly with week 85 for eplontersen being a slightly longer follow-up point than week 78 for vutrisiran;

- For serious AEs, [redacted] % eplontersen patients had serious AEs up to week 66 compared to 26.2% for vutrisiran in HELIOS-A (Table 59 of the CSR). Serious AEs at week 85 for eplontersen are [redacted] compared to week 66 with [redacted] % of patients having serious AEs (Table 59 of the CSR). Results from the company's original MAICs [redacted], although [redacted]. The EAG considers that use of the week 85 rather than week 66 data may [redacted] of eplontersen slightly over vutrisiran but results would likely still show a [redacted] eplontersen, with uncertainty based on [redacted]. The EAG could not locate equivalent data to compare severe AEs between week 66 and week 85 for eplontersen but considers a similar effect as observed for serious AEs is likely to be present.

Based on the points listed above, and the EAG's conclusion that there are not likely to be any important differences in AEs between treatments based on a naïve comparison of AE frequencies under the "comparison to vutrisiran" subheading above (where week 85 data for eplontersen is considered), the EAG is not concerned that use of the week 85 data would change the conclusions of ITCs presented in Section 4.3.3.4.

4.4 Conclusions of the clinical effectiveness section

The SLR process described by the company to identify evidence on the efficacy and safety of eplontersen and its relevant comparators (vutrisiran; see Section 3.3) in the treatment of ATTRv-PN was reasonable and while some concerns are noted, the EAG is not concerned that any relevant studies have been missed (Section 4.1).

Key evidence for eplontersen came from the NEURO-TTRansform study; this study included an eplontersen group and a small inotersen group, with the placebo group from a separate study used to make comparisons against placebo. The EAG has covered these results briefly in Section 4.2.2 and Appendix 10.3, but considers them to be of limited use given the limitations associated with the comparisons against external placebo and because there is no direct comparison against vutrisiran.

There is some concern that the NEURO-TTRansform study lacks applicability to the UK population in terms of mutation type, age and PN stage; however, similar is observed for the HELIOS-A study for vutrisiran and, based on clinical expert feedback, the EAG is satisfied that the relative efficacy and

safety of eplontersen vs vutrisiran (and conclusions about the similarity of treatments made based on ITCs in Section 4.3.3) would not be expected to differ across different populations given these factors have been accounted for in the ITC adjustments (Section 3.1).

NEURO-TTRansform and HELIOS-A studies for eplontersen and vutrisiran, respectively, are considered to be at a similar risk of bias, with the main concern for both being that they are open-label (Section 4.2.1).

Given the lack of direct evidence comparing eplontersen with vutrisiran, ITCs in the form of MAICs and STCs were performed by the company for various outcomes. The EAG had a slight preference for MAICs (Section 4.3.2.1) and has focused on MAIC results in this report (Section 4.3.3). These MAICs are unanchored, which are generally associated with additional uncertainty given the requirement to adjust for all PFs and TEMs (Section 3.3).

Given the MAICs are unanchored, the EAG has a general preference for the MAICs adjusted for additional variables requested as part of CQ A1; however, it was not possible for the EAG to use these for mNIS+7, Norfolk QoL-DN and treatment discontinuation outcomes given additional issues identified for these outcomes were considered more important to address and the company did not supply versions of the analyses with these issues addressed and with the additional adjustments (Sections 4.3.2.2, 4.3.2.3 and 4.3.3).

ITCs performed by the company covered most of the outcomes in the final NICE scope. While overall survival (OS) cardiac function and the effect of amyloid deposits in other organs and tissues (including the eye) in the NICE final scope were not covered by ITCs, the EAG notes that OS and the effect in other organs and tissues were also not covered in the vutrisiran NICE CCE and that data are either not available for eplontersen or would be associated with substantial limitations (Section 3.4).

Of the outcomes that have been included in ITCs, the degree of reduction in serum TTR levels is considered by the EAG's clinical expert to be the key pharmacological determinant of clinical response to treatment, with additional measures such as mNIS+7 and Norfolk QoL-DN providing useful additional information in terms of impact on physical function and quality of life in the ATTRv-PN population (Section 3.4).

MAICs appear to have been performed using appropriate methodology and are in line with NICE DSU guidance (Section 4.3.2.1).

The EAG does not agree with the company's broad conclusion that a lack of statistically significant differences from MAICs indicates that eplontersen and vutrisiran can be considered to be similar in terms of efficacy and safety. Instead, the EAG has based its conclusions about similarity on the position of point estimates relative to MCIDs identified from the literature in combination with clinical expert feedback on clinically meaningful differences for continuous outcomes. For dichotomous outcomes, the EAG has considered the direction of the point estimate alongside a more detailed naïve review of events occurring in the two different studies (Section 4.3.3).

While there are limitations associated with the EAG's preferred MAICs for certain outcomes, the EAG considers it unlikely that resolution of these would have a large impact on the results of the MAICs and lead to its conclusions about clinical similarity changing (see Sections 4.3.2.2, 4.3.2.3 and 4.3.3). These limitations include:

- Lack of additional adjustment for mNIS+7, Norfolk QoL-DN and treatment discontinuation outcomes;
- It was not possible to completely align the two versions of mNIS+7 used in the two trials;
- Uncertainty in how comparable the LLOD for serum TTR assays used in the two trials was and a difference in the population analysed for serum TTR levels between trials;
- Use of extrapolated week 65 data for the mBMI outcome as opposed to using observed week 85 data for eplontersen;
- Use of week 66 rather than week 85 data for eplontersen in the MAICs for serious AEs, severe AEs and treatment discontinuation.

Overall, based on its preferred MAICs the EAG concludes that it is unlikely that there are clinically important differences for any of the outcomes included in ITCs as part of this submission. While some point estimates favour eplontersen and others favour vutrisiran, the EAG is satisfied that these differences are unlikely to be clinically meaningful when MCIDs and clinical expert feedback are considered together. While the point estimate for mBMI favours vutrisiran and is above one of the MCID thresholds identified, based on the EAG's clinical expert feedback for this outcome, and the fact that point estimates for most other outcomes do not favour vutrisiran and indicate only very small differences that are not above any of the identified MCIDs for continuous outcomes, the EAG considers it reasonable to conclude that the two treatments are likely to be similar when considering outcomes as a whole. Similarly, the EAG is not concerned about the apparent increased discontinuation for eplontersen from the ITCs given the absolute difference in the number of

patients discontinuing between treatments may be considered small. A summary of these results and the EAG's conclusions are presented in Table 1 and details of the EAG's preferred MAICs for each outcome are presented in Table 5.

5 Summary of the EAG's critique of cost comparison evidence submitted

The company's base case results are reported in Table 7. These results reflect the patient access scheme (PAS) discount for eplontersen and the list price for vutrisiran, which result in eplontersen being cost saving when compared to vutrisiran. An additional PAS discount is available for vutrisiran and is not considered in these results but is included in the External Assessment Group (EAG)'s confidential appendix.

Several parameters and assumptions have been varied by the company in scenario analyses, the results of which are outlined in Section 6.1.1. In each scenario eplontersen was found to be cost saving compared to vutrisiran.

Table 7. Company's base case results

Interventions	Total Costs (£)	Incremental costs (£)
Eplontersen	[redacted]	-
Vutrisiran	£1,641,648	[redacted]

5.1 EAG comment on the company's review of cost effectiveness evidence

The company performed a systematic literature review (SLR) to identify published health-related quality of life (HRQoL) and cost and resource studies to inform the cost-comparison evaluation (CCE) of eplontersen, which is intended for the treatment of adult patients with stage 1 or stage 2 polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv-PN) in this evaluation. The company did not conduct an SLR to identify cost-effectiveness evidence as this is not prerequisite for CCEs.

As outlined in Section 4.1, database searches were conducted in July 2022 with the most recent update to the searches performed in October 2023. A summary of the EAG's assessment of the company's economic SLR is presented in Table 8.

Table 8. Systematic literature review summary

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	No cost effectiveness search conducted.	Appendix D.1	Appendix D.1	**Appropriate.** Databases included; MEDLINE, EMBASE, Cochrane Library, HTAD and NHS EED.
Inclusion/ exclusion criteria		Appendix D.2	Appendix D.2	**Appropriate**. No exclusions were made based on interventions or comparators.
Screening		Appendix D.2	Appendix D.2	**Appropriate**. PRISMA flow diagram provided.
Data extraction		Appendix D.2	Appendix D.2	**Appropriate.**
Quality assessment of included studies		Appendix D.3	Appendix D.3	**Appropriate.** York CRD checklist used but only for RCTs.

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; HTAD, Health Technology Assessment Database; NHS EED, NHS Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Of the studies identified in the SLR, none were deemed relevant to include in the submission. Of the final records extracted, 76% did not report any drug cost data and the remaining 24% reported cost and healthcare resource use information for treatments other than eplontersen and vutrisiran. The company did not report the HRQoL results of the SLR, however, given that a HRQoL SLR is not required for a CCE the EAG does not consider the omission impactful to the evaluation.

5.2 Summary and critique of company's submitted economic evaluation by the EAG

5.2.1 NICE reference case checklist

Table 9 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the National Institute for Health and Care Excellence (NICE) reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 3.

Table 9. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The company considers the direct treatment effects of eplontersen and vutrisiran in the cost-comparison analysis.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company undertook a cost-comparison analysis to compare eplontersen to vutrisiran.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The base case time horizon in the model was five years as this was considered long enough by the company to reflect all important differences in costs between technologies.
Synthesis of evidence on health effects	Based on systematic review	Health effects were not considered in the cost-comparison analysis.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with the cost-comparison approach, health-related quality of life was not considered by the model.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs have not been discounted in the company's base case as according to the NICE cost-comparison submitting guide the discounting of costs may not be required.

Abbreviations: EAG, External Assessment Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALY, quality adjusted life year

5.2.2 Perspective, time horizon and discounting

The cost comparison model submitted by the company evaluated the costs associated with treating ATTRv-PN patients with eplontersen and vutrisiran from a UK NHS and Personal Social Services (PSS) perspective. The model cycle length was one month, aligning with the treatment cycle for eplontersen, with a base-case time horizon of five years. This was considered by the company long enough to demonstrate the differences in costs given that all treatment costs are fixed over time and treatment durations are assumed to be equal between the technologies. Alternative time horizons of one, two and 10 years were explored by the company in scenario analyses.

The company did not include discounting for time preferences in the model.

5.2.2.1 EAG critique

The EAG considers that the perspective of the model is appropriate as is the cycle length and time horizon. While the EAG notes that the time horizon does not capture costs over a lifetime horizon, as the only difference in modelling assumption between the technologies are costs, and the difference in costs is fixed over time, the EAG considers that the key differences in costs are captured appropriately using the company's preferred time horizon.

While no discontinuing has been included in the model, the EAG considers that time preferences are applicable to the evaluation and that a 3.5% discounting factor should be applied. As such, a 3.5% discounting factor is included in the EAG base case.

5.2.3 Treatment discontinuation

Time to treatment discontinuation (TTD) was included in the base-case analysis and was calculated for eplontersen using time on treatment patient data up to week 85 from the NEURO-TTRansform individual patient data (IPD). The data was extrapolated to the model time horizon using standard parametric models and fit to time-to-event data. Bayesian Information Criterion (BIC) and Akaike information criteria (AIC) estimators were used to evaluate the models, with the exponential curve resulting in the lowest BIC value by 2.5 points and within 0.5 points of the lowest AIC value. After being validated by the company's clinical experts, the exponential curve was selected for the model base-case.

As only the total number of patients who had discontinued vutrisiran treatment by the end of the HELIOS-A trial was known and not TTD, an odds ratio was calculated using the end of study patient

discontinuation data for HELIOS-A and week 66 data for NEURO-TTRansform, which showed no significant difference in end of study discontinuation (see Sections 4.3.2.3, 4.3.3.6 and 4.3.4.1). As such, the company assumed TTD to be equal between eplontersen and vutrisiran and applied the NEURO-TTRansform TTD curves to both technologies in the model. On treatment discontinuation, patients were assumed to receive best supportive care (BSC).

5.2.3.1 EAG critique

In the absence of TTD data from HELIOS-A, the EAG considers that the approach taken by the company is appropriate and utilises the most relevant data available. Additionally, the EAG's clinical experts considered it reasonable to assume that TTD would not differ significantly between treatments.

5.2.4 Resource use and costs

Drug acquisition and administrations costs were included in the model, the details of each are given in the following subsections. Adverse event (AE) costs were also considered but not included in the base case, which the EAG considers reasonable given the EAG's conclusions regarding the company's indirect treatment comparisons (ITCs) for AEs as discussed in Section 4.3.3.6. These costs are therefore not evaluated further.

5.2.4.1 Drug acquisition

The administrations and acquisition costs for eplontersen and vutrisiran are outlined in Table 10 below. A simple PAS of [redacted] is applied to the acquisition cost of eplontersen, leading to a reduction in cost from the list price of [redacted] per month/dose to [redacted].

Table 10. Acquisition costs of the intervention and comparator technologies per patient – reproduced from Table 39 of the CS.

Treatment	Dose per administration (mg)	Vial size (mg)	Cost per unit	Annual cost	Source
Eplontersen	45	45	[redacted]	[redacted]	Proposed simple PAS, AstraZeneca
Vutrisiran	25	25	£95,862.36	£383,449.44	Published list price, BNF[32]

Abbreviations: BNF, British National Formulary; CS, company submission; PAS, patient access scheme

Concomitant vitamin A supplements are assumed equal across both treatments and are therefore excluded from the analysis. Costs associated with BSC are assumed to be zero and are also assumed to be equal across both treatment arms.

As a confidential PAS discount is available for vutrisiran, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case. Please refer to Appendix 10.6 for details on the source of the confidential price for each treatment.

5.2.4.1.1 EAG critique

The EAG considers that the eplontersen and vutrisiran acquisition costs and sources are appropriate, noting that the annual acquisition cost for the treatments are [redacted] when considering the list prices [redacted].

Additionally, vutrisiran costs in the model were applied monthly, aligning with the model cycle length, with a third of the cost being applied every month instead of the list price every three months. As a scenario the EAG requested that the company cost vutrisiran and its administration every three months in line with its administration in clinical practice. The scenario led to an increase in the cost difference with the results reported in Section 6.1.1.

5.2.4.2 Administration

A summary of the administration types and their associated costs are outlined in Table 11. As described, it is assumed in the model that both eplontersen and vutrisiran patients will receive their first treatment administration at the National Amyloidosis Centre (NAC), after which, subsequent administrations for eplontersen will be self-administered or administered by a care giver at home and vutrisiran treatments will be administered by a health care professional (HCP) during a home visit.

Table 11. Location of cost of administration for each treatment – reproduced from Table 40 of the CS.

	Eplontersen	Vutrisiran
Route and frequency of administration	SC QM	SC Q3M
Administration location and cost for first administration	Location: Assumed to be at the NAC Cost: £119.00 Rationale: NHS reference costs 21/22 – HRG code: N10AF[33]	Location: At the NAC Cost: £119.00 Rationale: NHS reference costs 21/22 – HRG code: N10AF[33]
Administration location and cost for subsequent administrations	Location: Self-administered or administered by a caregiver at home Cost: £0.00 Rationale: Assumption and validated by clinical experts	Location: Homecare - administered by a nurse at the patient's home Cost: £33.00 Rationale: Band 4 nurse wage: PSSRU 2022[4] (Assuming 1 hour nurse time, in line with TA868) [34]
Yearly administration costs	£119.00 (first year) £0.00 (subsequent years)	£218.00 (first year) £132.00 (subsequent years)

Abbreviations: CS, company submission; HRG, Healthcare Resource Group; NAC, National Amyloidosis Centre; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; QM, every month; Q3M, every three months; SC, subcutaneous.

5.2.4.2.1 EAG critique

The EAG considers that the company's approach to calculating treatment administration costs is appropriate, with the EAG's clinical expert agreeing that first administrations would be carried out in the NAC for both treatments. Conversely, the EAG's clinical expert additionally stated that many eplontersen patients may not be able to self-administer treatment due to symptom progression or may prefer a HCP to administer treatment. As such, the EAG requested that the company conduct a scenario assessing a range of proportions of eplontersen patients who require a HCP for subsequent treatment administrations. The company conducted the scenario, assuming separately that 5%, 10% and 15% of eplontersen patients would require a HCP for treatment administration. All scenarios had a negligible impact to the overall cost of providing eplontersen, with the 15% scenario assumption leading to a [redacted] in cost difference between technologies. The EAG additionally notes that the difference in administration costs between eplontersen and vutrisiran composites [redacted] of the total difference in costs ([redacted]), further supporting that the cost difference between technologies is robust to administration cost parameter uncertainty.

Given the invasive nature of subcutaneous (SC) administrations, the EAG requested that the company discussed the HRQoL and convenience implications of the difference in administration frequencies between the health technologies, with eplontersen requiring monthly administration compared to every three months with vutrisiran. In response, the company outlined that HRQoL data were collected as part of the NEURO-TTRansform trial with eplontersen demonstrating significant improvements in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score compared to comparators with lower infusion frequencies. The company concluded that any administration-related HRQoL decrement would inherently be captured in the assessment of HRQoL and any attempt to include an additional administration-related disutility would results in double counting. The company additionally considered that if a disutility was included, vutrisiran may be associated with greater administration disutility due to the need for a HCP to administer treatment and the implications this has on the flexibilities of patients' lives.

The EAG considers that given the domains of the Norfolk QoL-DN, which are specific to the development of neuropathic pain and symptoms, the instrument is likely insensitive to measuring HRQoL changes from treatment administrations. Crucially, even if a disutility was measured between treatments, it would not be possible to disentangle any impact of the injection frequency alone on outcomes. As such the EAG considers that SC administration may be impactful to HRQoL, and therefore eplontersen may lead to a greater decrement in HRQoL compared to vutrisiran given the difference in administration frequencies however the difference in utility is likely small. Therefore, the EAG considers a CCE is appropriate for comparing the health technologies but notes that the difference in administration frequency may influence patient choice between treatments.

6 Company and EAG cost comparison results

The company's base case results are provided in Table 12. As a probabilistic sensitivity analysis is not required for a cost comparison evaluation (CCE) according to National Institute for Health and Care Excellence (NICE) guidelines, only deterministic results were calculated using the cost-comparison model and are reported. As noted in Section 5.1, a patient access scheme (PAS) discount is available for eplontersen and is reflected in the total cost. A further set of results incorporating the vutrisiran PAS discount is provided by the External Assessment Group (EAG) in the confidential appendix.

6.1 Company base case results

Table 12. Company's base case results

Interventions	Total Costs (£)	Incremental costs (£)
Eplontersen	[redacted]	-
Vutrisiran	£1,641,648	[redacted]

Note: negative incremental costs indicate eplontersen is cost saving.

6.1.1 Company's scenario and sensitivity analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters including several analyses requested by the EAG at the clarification stage. These scenarios are presented in Table 13, with eplontersen remaining cost saving across all scenarios. Results incorporating the PAS for vutrisiran are provided by the EAG in the confidential appendix.

Table 13. Scenario analysis results

	Total cost		Incremental cost
	Eplontersen	Vutrisiran	Eplontersen vs vutrisiran
Base-case	[redacted]	[redacted]	[redacted]
1-year time horizon	[redacted]	[redacted]	[redacted]
2-year time horizon	[redacted]	[redacted]	[redacted]
10-year time horizon	[redacted]	[redacted]	[redacted]
Inclusion of serious adverse events	[redacted]	[redacted]	[redacted]
Excluding TTD	[redacted]	[redacted]	[redacted]
Eplontersen HCP administration - 5%	[redacted]	[redacted]	[redacted]
Eplontersen HCP administration - 10%	[redacted]	[redacted]	[redacted]
Eplontersen HCP administration - 15%	[redacted]	[redacted]	[redacted]
Discount rate - 3.5%	[redacted]	[redacted]	[redacted]

Cost of vutrisiran applied every third cycle	[redacted]	[redacted]	[redacted]

Note: negative incremental costs indicate eplontersen is cost saving.
Abbreviations: HCP, Health Care Provider; TTD, Time to treatment discontinuation; vs, versus.

The company conducted a one-way sensitivity analysis (OWSA) to explore parameter uncertainty related to treatment administration costs. Parameters were varied to their upper and lower values, allowing parameter cost difference sensitivity to be inferred. Figure 11 details that the cost difference was most sensitive to the vutrisiran subsequent treatment administration cost per cycle, however the magnitude of the sensitivity was small, with the cost difference varying by approximately [redacted] over a 5-year period.

Figure 11. OWSA results for eplontersen vs vutrisiran – reproduced from Figure 36 of the CS

[redacted]

Abbreviations: CS, company submission; GBP, Great British Pounds; OWSA, one-way sensitivity analysis

6.2 Additional economic analysis undertaken by the EAG

6.2.1 Model corrections

The EAG identified no errors in the company model that needed correcting.

6.2.2 Exploratory and scenario analyses undertaken by the EAG

No additional scenario analyses were conducted by the EAG.

6.2.3 EAG preferred assumptions

Table 14 presents the EAG's preferred modelling assumptions for comparing eplontersen to vutrisiran for the treatment of adult patients with stage 1 or stage 2 polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv-PN).

Table 14. EAG preferred assumptions

	Results per patient	Eplontersen	Vutrisiran	Incremental cost	Cumulative incremental cost
0	Company base case				
	Total costs (£)	[redacted]	1,641,648	[redacted]	-
1	3.5% discounting factor				
	Total costs (£)	[redacted]	1,541,175	[redacted]	[redacted]
2	Applying the costs of vutrisiran Q3M				
	Total costs (£)	[redacted]	1,650,559	[redacted]	[redacted]

Note: negative incremental costs indicate eplontersen is cost saving.
Abbreviations: EAG, External Assessment Group; Q3M, every three months

6.2.4 EAG's preferred base case results

Table 15 presents the EAG's deterministic base case results. As previously reported, a PAS discount is available for eplontersen and is reflected in the total cost. A further set of results incorporating the vutrisiran PAS discount are provided by the EAG in the confidential appendix.

Table 15. EAG's preferred base case results

Interventions	Total Costs (£)	Incremental costs (£)
Eplontersen	[redacted]	-
Vutrisiran	1,549,541	[redacted]

Abbreviations: External Assessment Group
Note: negative incremental costs indicate eplontersen is cost saving.

6.3 Summary statement

In summary, the EAG considers that the methods used to conduct the CCE are appropriate as are the assumptions made by the company where limited data are available. Overall, the annual acquisition treatment costs are [redacted] between eplontersen and vutrisiran when comparing their list prices, with eplontersen leading to cost savings in treatment administrations given patients are able to self-

administer treatment. As the administration cost difference composites a small proportion of the total difference in costs ([redacted]), even when accounting for not all eplontersen patients being able to self-administer treatment in scenario analyses, the cost difference between technologies is robust.

If we can assume that the eplontersen treatment effect is not inferior to that of vutrisiran (see Section 4.4 for the EAG's clinical conclusions), then the EAG considers that the only key difference between treatments may be the administration frequencies, which may affect HRQoL (although unlikely to a significant extent) but not the cost difference, and may therefore influence patient choice between treatments.

7 Equalities and innovation

The company has not described any equalities or innovation considerations associated with eplontersen in the company submission. Additionally, the External Assessment Group (EAG) is unaware of any equality or innovation considerations.

8 EAG commentary of the robustness of the evidence submitted by the company

While the External Assessment Group (EAG)'s opinion is that none of the issues below would prevent a cost-comparison evaluation (CCE) being considered appropriate, it notes them as limitations or factors to be aware of.

Clinical

There is some concern that the NEURO-TTRansform study lacks applicability to the UK population in terms of mutation type, age and polyneuropathy (PN) stage; however, similar is observed for the HELIOS-A study for vutrisiran and, based on clinical expert feedback, the EAG is satisfied that the relative efficacy and safety of eplontersen vs vutrisiran (and conclusions about the similarity of treatments made based on indirect treatment comparisons [ITCs] in Section 4.3.3) would not be expected to differ across different populations given these factors have been accounted for in the ITC adjustments.

In the absence of direct comparative evidence for eplontersen vs vutrisiran, unanchored ITCs have been performed, with the EAG focusing on the results of unanchored matching-adjusted indirect comparisons (MAICs). While the EAG is content that its preferred MAICs either account for all important variables (including additional variables requested as part of clarification question [CQ] A1) or that further adjustment is unlikely to have a large impact on results, even the most well-performed unanchored MAICs are considered to be associated with uncertainty given the need to adjust for all prognostic factors and treatment effect modifiers, which is considered to be largely unachievable.[3] Therefore, the EAG considers there to be more uncertainty within this CCE compared to the NICE CCE for vutrisiran,[1] which had direct comparative evidence available for the comparator of interest (patisiran) and did not need to rely on unanchored ITCs.

Aside from the use of unanchored MAICs, the EAG notes that various additional limitations exist for different outcomes, as outlined in Sections 4.3.2.3 and 4.3.3 and summarised in Section 4.4. While these represent limitations of the specific analyses, the EAG has concluded that the impact of these issues is unlikely to be large enough to change the EAG's conclusions about the similarity of eplontersen and vutrisiran for each outcome.

Minimum clinically important difference (MCID) thresholds identified by the EAG for continuous outcomes varied substantially between sources and within sources where different methods were used to calculate MCIDs. This means there is uncertainty with regards to which MCIDs are most appropriate. However, the EAG considers this may be most important for the modified body mass index (mBMI) outcome given the point estimate from the EAG's preferred MAIC favoured vutrisiran and was higher than one of the MCIDs identified for this outcome (for all other continuous outcomes, point estimates did not favour vutrisiran and indicated only very small differences that were not above any of the identified MCIDs). Due to the uncertainty regarding MCIDs, the EAG has employed clinical expert feedback to aid with the decision about which MCIDs are more useful in terms of indicating clinically meaningful differences.

The EAG's conclusions using MCIDs and clinical expert feedback on these MCIDs are based primarily on the point estimate from the EAG's preferred MAICs and it should be noted that there is uncertainty based on 95% confidence intervals (CIs) for most outcomes given they cross MCIDs in some cases.

Economic

Based on the inclusion of the patient access scheme (PAS) discount for eplontersen and list price for vutrisiran, eplontersen remains cost saving under the company's base case and scenario analyses and the EAG's preferred assumptions. However, a confidential PAS discount is available for vutrisiran and so results that include this discount are presented in a confidential appendix to this report.

9 References

1. National Institute For Health and Care Excellence (NICE). Vutrisiran for treating hereditary transthyretin-related amyloidosis: Technology appraisal guidance [TA868], 2023. Available from: https://www.nice.org.uk/guidance/ta868. Date accessed: Mar 24.
2. National Institute for Health and Care Excellence (NICE). Final scope - Eplontersen for treating polyneuropathy caused by hereditary transthyretin amyloidosis [ID6337]: In development [GID-TA11392], 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11392/documents/final-scope. Date accessed: Mar 24.
3. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE, 2016. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted. Date accessed: Mar 24.
4. AstaZeneca Data on File. Eplontersen: Summary of Product Characteristics (SmPC). 2024.
5. Coelho T, Marques W, Jr., Dasgupta NR, Chao CC, Parman Y, França MC, Jr., et al. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. *Jama* 2023; **330**: 1448-58.
6. Adams D, Tournev IL, Taylor MS, Coelho T, Planté-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* 2023; **30**: 1-9.
7. ClinicalTrials.gov. CARDIO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM), 2024. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04136171. Date accessed: Mar 24.
8. ClinicalTrials.gov. HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy, 2024. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04153149. Date accessed: Mar 24.
9. Ioannou A, Fontana M, Gillmore JD. RNA Targeting and Gene Editing Strategies for Transthyretin Amyloidosis. *BioDrugs* 2023; **37**: 127-42.
10. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Date accessed: Mar 24.
11. AstraZeneca UK Ltd. Data on File. ATTRv-PN NHS England Blueteq data - REF-218954. Feb 2024.
12. National Institute for Health and Care Excellence (NICE). Eplontersen for treating hereditary transthyretin amyloidosis [ID6337]: Response to stakeholder organisation comments on the draft remit and draft scope., 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11392/documents/scope-consultation-comments-and-responses. Date accessed: Feb 24.
13. Obi CA, Mostertz WC, Griffin JM, Judge DP. ATTR Epidemiology, Genetics, and Prognostic Factors. *Methodist Debakey Cardiovasc J* 2022; **18**: 17-26.
14. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *New England Journal of Medicine* 2018; **379**: 22-31.
15. AstraZeneca Data on File. Clinical study report - 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. 2024.
16. European Medicine Agency (EMA). Amvuttra : EPAR - Product Information. Summary of product characteristics. , 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf. Date accessed: Mar 24.

17. Garcia-Pavia P, Grogan M, Kale P, Berk JL, Maurer MS, Conceição I, et al. Impact of vutrisiran on exploratory cardiac parameters in hereditary transthyretin-mediated amyloidosis with polyneuropathy. *European Journal of Heart Failure* 2024; **n/a**.
18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from: www.training.cochrane.org/handbook. Date accessed: Mar 24.
19. Centre for Reviews and Dissemination (CRD) University of York. Systematic Reviews: CRD's guidance for undertaking reviews in health care, 2008. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Date accessed: Mar 24.
20. ClinicalTrial.gov. Evaluate the Safety and Tolerability, as Well as the Pharmacokinetic and Pharmacodynamic Profiles of Single and Multiple Doses of Eplontersen Administered Subcutaneously to Healthy Volunteers and Patients With Hereditary Transthyretin-Mediated Amyloidosis (hATTR). ClinicalTrials.gov identifier: NCT03728634., 2022. Available from: https://clinicaltrials.gov/study/NCT03728634. Date accessed: Mar 24.
21. AstraZeneca Data on File. Clinical study report (interim 2 study report) - An Open-Label, Extension Study to Assess the Long-Term Safety and Efficacy of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. 2024.
22. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. *New England Journal of Medicine* 2018; **379**: 22-31.
23. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang C-C, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *New England Journal of Medicine* 2018; **379**: 11-21.
24. Alnylam® Pharmaceuticals. Statistical Analysis Plan ALN-TTRSC02-002. HELIOS-A: A Phase 3 Global, Randomized, Openlabel Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis) 2019. Available from: https://classic.clinicaltrials.gov/ProvidedDocs/79/NCT03759379/SAP_001.pdf. Date accessed: Apr 24.
25. European Medicines Agency (EMA). Assessment report - Amvuttra Available from: https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf. Date accessed: May 24.
26. National Institute for Health and Care Excellence (NICE). Patisiran for treating hereditary transthyretin amyloidosis: Highly specialised technologies guidance [HST10], 2019. Available from: https://www.nice.org.uk/guidance/hst10/documents/committee-papers. Date accessed: Mar 24.
27. Yarlas A, Lovley A, Brown D, Kosinski M, Vera-Llonch M. 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**: 323-35.
28. Franceschini M, Boffa A, Pignotti E, Andriolo L, Zaffagnini S, Filardo G. The Minimal Clinically Important Difference Changes Greatly Based on the Different Calculation Methods. *Am J Sports Med* 2023; **51**: 1067-73.
29. Hu G, Huang Q, Huang Z, Sun Z. [Methods to determine minimal clinically important difference]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2009; **34**: 1058-62.
30. Mouelhi Y, Jouve E, Castelli C, Gentile S. How is the minimal clinically important difference established in health-related quality of life instruments? Review of anchors and methods. *Health and Quality of Life Outcomes* 2020; **18**: 136.
31. Mishra B, Sudheer P, Agarwal A, Nilima N, Srivastava MV, Vishnu VY. Minimal Clinically Important Difference of Scales Reported in Stroke Trials: A Review. *Brain Sciences* 2024; **14**.
32. National Institute for Health and Care Excellence (NICE). British National Formulary. Vutrisiran. Available from: https://bnf.nice.org.uk/drugs/vutrisiran/medicinal-forms/. Date accessed: Dec 23.

33. NHS England. NHS Reference Costs 2021/2022, 2023. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Date accessed: Dec 23.
34. Personal Social Services Research U. Unit Costs of Health and Social Care 2022. Available at: https://kar.kent.ac.uk/100519/1/Unit%20Costs%20of%20health%20and%20Social%20Care%202022%20%28amended%2013%20July%202023%29.pdf. Last Accessed: December 2023.
35. Csilla T, Oskar N. *Transthyretin in the Evaluation of Health and Disease in Human and Veterinary Medicine.* In: David CG, editor. Pathophysiology. Rijeka: IntechOpen; 2017. p. Ch. 4.
36. Dyck PJB, González-Duarte A, Obici L, Polydefkis M, Wiesman JF, Antonino I, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: From NIS to mNIS + 7. *Journal of the neurological sciences* 2019; **405**: 116424.
37. Peripheral Nerve S. Diabetic polyneuropathy in controlled clinical trials: Consensus report of the peripheral nerve society. *Annals of Neurology* 1995; **38**: 478-82.
38. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful Change and Responsiveness in Common Physical Performance Measures in Older Adults. *Journal of the American Geriatrics Society* 2006; **54**: 743-9.

10 Appendices

10.1 EAG critique of the company's SLR

Table 16. A summary of the EAG's critique of the SLR

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**The EAG considers the sources and dates searched to be comprehensive.** Databases searched: • Original SLR: Embase; MEDLINE; and Cochrane. • SLR update: MEDLINE, including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print; Embase; CDSR; CENTRAL; HTAD; and NHS EED. The EAG notes that in the original SLR, MEDLINE and Embase were searched via Embase.com and for the SLR update they were searched via OVID SP. In addition, it is noted that the searches of Cochrane were conducted via OVID SP for the original SLR and via the Cochrane library (CDSR and CENTRAL) for the SLR update. The EAG is unsure whether switching the interfaces used for searching the different databases in the SLR update would impact retrieval. Conference proceedings (January 2020–October 2023): • International Society of Amyloidosis (ISA), American College of Cardiology (ACC), American Heart Association (AHA), European Society of Cardiology (ESC), World Congress of Cardiology (WCC), World Congress of Neurology (WCN), European Academy of Neurology (EAN), American Neurological Association (ANA), International Society of Pharmacoeconomic Outcomes Research (ISPOR), American Academy of Neurology (AAN). It is noted that AAN was only searched as part of the update search and that the 2022 conference proceeding was unable to be searched due to reported technical issues with the congress link. Additional searches of ClinicalTrials.gov, the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) and European Union Clinical Trials Register (EUCTR) were conducted on 17 October 2023, as part of the SLR update. Any trial records for studies already identified from the database searches were linked to the study and extracted. Bibliographies of all relevant SLRs and (network) meta-analyses (NMAs) identified through the electronic database searches were also manually searched to identify additional studies of relevance.
Search strategies	Appendix D.1.1	**The EAG considers the search strategies used to be broadly appropriate but has some concerns about the altered approach for the most recent**

		update searches and is unsure if validated filters for study design were used. The electronic database searches were performed from database inception to date of the SLR, without any time limit. The electronic database searches were conducted using a combination of MeSH/EMTREE terms, and free-text terms for disease (amyloidosis) with no restriction based on intervention. The searches of MEDLINE and Embase also included search terms for study design (RCTs, interventional non-RCTs and observational studies). All free-text terms were limited to abstracts and titles. The terms used to limit by study design in the searches of MEDLINE and Embase appear reasonable but there is no information as to whether validated search filters were used and where they were obtained from. As highlighted above, the EAG notes that different interfaces were used for the original searches of the electronic databases compared to the update searches (Embase.com and OVID SP, etc.). In addition, the search strategy was updated for the SLR update and the rationale reported for this was that, ”the search strategy was updated to be more comprehensive and to align with the updated eligibility criteria”. The updated search strategies were used to re-search all databases between 2012 and 2022 to capture any records previously missed in the original SLR and the new search terms were then used from 2022 to date of search. The EAG is unsure if the change in search interfaces between the original and updated SLRs would have impacted on the results of the SLRs but the EAG is not aware of any key studies being missed.
Inclusion criteria	Appendix D.1.2 (Table 14)	**The EAG considers that no studies of relevance to this CCE have been inappropriately excluded.** The eligibility criteria matched the population outlined in the NICE final scope (adults [≥18 years] with a diagnosis of ATTRv).[2] Criteria for the intervention and comparator were wider than that specified in the NICE scope as the SLR inclusion criteria were “systemic therapy” whereas the final scope included eplontersen, vutrisiran, patisiran and inotersen. However, the company reported that vutrisiran is the only relevant comparator to eplontersen. Therefore, only studies investigating eplontersen or vutrisiran were considered relevant to this submission and prioritised following full-text review. The EAG considers this to be reasonable (please see 3.3 for further EAG critique on comparators). The list of outcomes in Table 14 of Appendix D of the CS are broadly in keeping with the NICE final scope with the exception of effects of amyloid deposits in other organs and tissues (including the eye) that was listed in the scope but not explicitly specified as an outcome for the company’s SLRs (please see Section 3.4 for EAG critique on outcomes). In addition, it is noted that the inclusion criteria were altered for the SLR update to also include 10-metre walk test and Rasch-built overall disability scale as outcomes of interest. The impact of this on the results of the SLR is unclear but these were not outcomes that were included in the ITCs against vutrisiran. The EAG notes that included publications in the SLRs were also limited to English language. Reference lists of all records excluded at full text review

		and following the restriction based on intervention and comparators were provided in Appendix D.
Screening	Appendix D.1.2	**The EAG considers the methods for screening to be robust.** Results from all databases were de-duplicated prior to screening, and the search results from the SLR update were de-duplicated against the original SLR library. Title and abstract, and full-text screening were both performed independently by two reviewers, with disagreements between reviewers resolved by a third reviewer. A PRISMA diagram is provided in Figure 1 of the CS appendices to show the inclusion and exclusion of studies throughout the screening and it is noted that the narrowing of the intervention and comparators to those relevant to the NICE scope is shown in the final box of the PRISMA diagram (resulting in the final inclusion of 23 publications relating to three studies).
Data extraction	Appendix D.1.2	**The EAG considers methods for data extraction to be appropriate.** Data were extracted by a single reviewer into a pre-specified data extraction grid and the extracted data were verified by a second reviewer. Data were extracted from full-text publications, where available and references to other publications within a study were traced to original sources, where appropriate. If a full-text journal publication was not available, then the source used (e.g. abstract or poster) was noted.
Tool for quality assessment of included study or studies	Appendix D.1.2	**The EAG agrees with the company's choice of quality assessment tool of RCTs.** Study quality for the included RCTs was assessed using the quality assessment tool developed by the University of York CRD, as recommended by NICE.

Abbreviations: ATTRv, hereditary transthyretin amyloidosis; CCE, cost-comparison evaluation; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Controlled Register of Trials; CS, company submission; CRD, Centre for Reviews and Dissemination; EAG, External Assessment Group; HTAD, HTAD: Health Technology Assessment Database; ITC, indirect treatment comparison; MeSH, Medical Subject Headings; NHS EED, NHS Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review.

10.2 EAG's quality assessment of NEURO-TTRansform and HELIOS-A

Table 17. A summary of the EAG's critique of the design, conduct and analysis of the NEURO-TTRansform and HELIOS-A trials

Aspect of trial design or conduct	NEURO-TTRansform[5]	HELIOS-A[6]
Randomisation	**Appropriate** Randomised 6:1 to receive eplontersen or inotersen using interactive voice/web response system in block sizes of 7.	**Appropriate** Randomised 3:1 to receive vutrisiran or patisiran using interactive response system. Stratified by TTR genotype (V30

	Does not appear to have stratified for any characteristics at randomisation. However, attempts to mirror the NEURO-TTR trial in terms of proportion with FAP stage 1 and 2 is mentioned in the protocol but no further details provided.	vs non-V30) and baseline NIS score (<50 vs ≥50).
Concealment of treatment allocation	**Appropriate** An interactive third-party system was used for randomisation. While there is not a clear statement to support this, this means it is likely that the randomised allocation sequence was concealed from study investigators/recruiters when deciding if patients met eligibility criteria for the trial. If this concealment was not in place, there is a risk of selection bias in terms of which patients are ultimately included in the trial. The company's critique describes this domain as at moderate risk of bias based on the open-label nature of the trial; however, the EAG notes that concealment of treatment allocation refers to concealment of the randomisation schedule prior to inclusion of a patient in the trial and not the actual treatment each patient has been assigned to following randomisation.	**Appropriate** An interactive third-party system was used for randomisation. The description of the process suggests that the randomisation schedule was not revealed to the investigators/recruiters prior to eligibility of the patient for the trial being confirmed, which is appropriate to reduce the risk of selection bias. The company's critique describes this domain as at moderate risk of bias based on the open-label nature of the trial; however, the EAG notes that concealment of treatment allocation refers to concealment of the randomisation schedule prior to inclusion of a patient in the trial and not the actual treatment each patient has been assigned to following randomisation.
Eligibility criteria	**Appropriate** The EAG's clinical expert had no major concerns about the inclusion and exclusion criteria for this trial. The EAG considers the trial population to reflect that outlined in the NICE final scope well (see Section 3.1).	**Appropriate** Inclusion and exclusion criteria for HELIOS-A were very similar to those for NEURO-TTRansform, which the EAG's clinical expert considered to be reasonable. The EAG considers the trial population to reflect that outlined in the NICE final scope well (see Section 3.1).
	Differences between the two trials in terms of eligibility criteria are considered to be minor by the EAG and its clinical expert (see Section 3.1).	
Blinding	**Risk of bias** Study is open-label with patients and investigators not being blinded to treatment assignment. This is likely to introduce bias that would not be present in a blinded study. Outcome assessors did not appear to be blinded to treatment assignment either, although blinded central review for mNIS+7 was mentioned.	**Risk of bias** Study is open-label with patients and investigators not being blinded to treatment assignment. This is likely to introduce bias that would not be present in a blinded study. Outcome assessors did not appear to be blinded to treatment assignment either. The outcome of serum TTR may be less affected by this bias unless treatment is

	The outcome of serum TTR may be less affected by this bias unless treatment is altered based on knowledge of intervention given it is a largely objective measure. The same could apply for mNIS+7 but there may be more variability across assessors for this outcome, which could still be impacted by knowledge of the intervention.	altered based on knowledge of intervention given it is a largely objective measure. The same could apply for mNIS+7 but there may be more variability across assessors for this outcome, which could still be impacted by knowledge of the intervention.
Baseline characteristics	**Some larger differences for eplontersen vs inotersen and vs external placebo** Baseline characteristics for eplontersen and inotersen groups within NEURO-TTRansform are fairly well-balanced considering the large difference in sample sizes between groups (n=144 vs n=24), although there are some larger differences that may be of concern (for example, baseline mNIS+7 score and V50M mutation). Differences against the external placebo group from NEURO-TTR are also noted at baseline; while analyses vs placebo accounted for some of these as covariates, this did not include all variables that were imbalanced. However, the EAG notes that the comparisons to inotersen and placebo are not relevant to this appraisal in terms of concluding whether eplontersen is similar to vutrisiran. See Table 10 of the CS for a comparison of baseline characteristics across NEURO-TTRansform and NEURO-TTR treatment arms. There is some concern about the applicability of the trial population to the UK population, as described in Section 3.1.	**Some larger differences for vutrisiran vs patisiran and vs external placebo** Baseline characteristics for vutrisiran and patisiran groups within HELIOS-A are fairly well-balanced considering the large difference in sample sizes between groups (n=122 vs n=42), although there are some larger differences that may be of concern (for example, previous tetramer stabiliser use). Differences against the external placebo group from APOLLO are also noted at baseline; while analyses vs placebo accounted for some of these as covariates, this did not include all variables that were imbalanced. However, the EAG notes that the comparisons to patisiran and placebo are not relevant to this appraisal in terms of concluding whether eplontersen is similar to vutrisiran. See Table 1 of the HELIOS-A publication for a comparison of baseline characteristics across HELIOS-A and APOLLO treatment arms. There is some concern about the applicability of the trial population to the UK population, as described in Section 3.1.
	Differences in many baseline characteristics between eplontersen and vutrisiran studies have been accounted for via adjustments in ITCs, as discussed in Section 4.3.2.2.	
Dropouts	**Lower dropout for eplontersen compared to inotersen and external placebo but small numerical differences** Based on Figure 4 of the CS, discontinuation at week 66 in the eplontersen arm of NEURO-TTRansform was 5.6% (8/144), whereas it was higher	**Lower dropout for vutrisiran compared to patisiran and external placebo but small numerical differences between vutrisiran and patisiran** At 18 months, discontinuation in the vutrisiran arm was 4.1% (5/122) and for patisiran was 9.5% (4/42).

	for inotersen at 16.7% (4/24). The proportion discontinued was also lower for eplontersen compared to 66-week data for the external placebo group, with 13.3% discontinued (8/60). The numbers discontinuing are fairly similar for each group despite percentages differing slightly.	Discontinuation at 18 months for the external placebo arm from APOLLO was much higher at 37.7% (29/77). Differences between vutrisiran and patisiran are numerically small despite percentages differing slightly.
	Discontinuation in the two trials appears to be broadly similar, although the time-point assessed at is slightly longer in the HELIOS-A trial. Discontinuation was assessed as an outcome in ITCs, with results presented in Section 4.3.3.4, and naïve comparisons are discussed in Section 4.3.4.1.	
Statistical analysis		
Sample size and power	**No concerns** Sample size estimated based on data from NEURO-TTR trial. Power calculations assumed that percent reduction from baseline in serum TTR would be 80%. Approximately 140 patients were planned to be enrolled to provide 108 evaluable patients, assuming a 10% dropout rate. With 52 evaluable placebo patients from NEURO-TTR, a sample size of 108 in the eplontersen arm of NEURO-TTRansform would provide the following statistical power for comparisons between eplontersen-treated patients and the external placebo group from NEURO-TTR: • ≥95% power to detect a difference of 70.3% in serum TTR CFB; • ≥90% power to detect a 19.6-point difference in mNIS+7 CFB; • ≥80% power to detect a 10.7-point difference in Norfolk QoL-DN CFB.	**No concerns** Sample size of ~160 patients was selected to provide >90% power to establish superiority of vutrisiran over external placebo for the co-primary end-points (mNIS+7 and Norfolk QoL-DN) using a 0.05 significance level at month 9. This was based on a mean change of: • 0 for vutrisiran against the observed mean change of 15 for the external placebo group for mNIS+7; • -4 points for vutrisiran against the observed mean of 11.5 in the external placebo group for Norfolk QoL-DN.
Analysis for estimate of effect	**Some concerns given ITT not used for most outcomes and some differences between arms not accounted for in adjustment** Efficacy analyses were not reported in the ITT population and the FAS population was instead used, defined as those randomised with at least one injection of study drug and with baseline and at least one post-baseline assessment of mNIS+7 and Norfolk QoL-DN. This led to the exclusion of 3 patients	**Some concerns given ITT not used for serum TTR outcome and some differences between arms not accounted for in adjustment** Most efficacy and safety outcomes were analysed in a modified ITT population defined as those randomised who received any amount of study drug. However, serum TTR analysis was performed in the TTR per-protocol population, defined as modified ITT patients with a non-missing TTR

	from the randomised set in the eplontersen arm. These patients are likely to have been excluded as they didn't have either a baseline or single follow-up assessment of mNIS+7 and Norfolk QoL-DN, which could be related to study outcome and represent a risk of bias. AEs and discontinuation were assessed in the safety analysis set, which included all n=144 patients that received at least one dose of study drug. To ensure balance between eplontersen and the external placebo group, propensity score weighting was performed to balance the groups in terms of V50M TTR mutation, previous stabiliser treatment and disease stage. While this would account for some differences between eplontersen and external placebo arms, the EAG does not consider all have been addressed (for example, race, age and patients with clinical diagnosis of ATTRv-CM are also imbalanced at baseline).	assessment at baseline and ≥1 trough TTR assessment with adequate treatment compliance between months 6 and 18). All 122 randomised vutrisiran patients appear to have met the inclusion criteria for the modified ITT population, with n=120 included in the TTR per-protocol population is not provided.[25] Although exclusion of these patients would be due to missing TTR data or lack of compliance, which could be related to the outcome of individual patients, given this applied to only two vutrisiran patients the EAG considers it unlikely that a large amount of bias would be introduced. To ensure balance between vutrisiran and the external placebo group, adjustments using covariates in analyses were performed account for differences between groups in terms of baseline value of the outcome, V50M TTR mutation and age of disease onset (and baseline NIS for outcomes other than mNIS+7). While this would account for some differences between vutrisiran and external placebo arms, the EAG does not consider all have been addressed (for example, proportion of males, prior stabiliser use, PND score and proportion within the cardiac subpopulation are also imbalanced at baseline).
Handling of missing data	**Appropriate** MMRM analyses were used for continuous outcomes up to week 66, which treats missing data as missing at random. All available post-baseline assessments up to week 66 were utilised. Missing data were not explicitly imputed. It is unclear whether the missing at random assumption is appropriate but various alternative analyses were performed (multiple imputation assuming missing at random, multiple imputation assuming copy increments from reference, multiple imputation assuming jump to reference, which was associated with limited impact on the results of the analyses for all applicable outcomes.	**Appropriate** MMRM analyses were used for continuous outcomes up to 18 months, which treats missing data as missing at random. Different methods of analysis including non-missing at random approaches appear to have been explored but results do not appear to be publicly available. It is unclear whether the missing at random assumption is appropriate but the EAG notes the same approach (MMRM) was used for NEURO-TTRansform.
Outcome assessment	**Appropriate**	**Appropriate**

	The EAG considers the outcomes assessed to be appropriate and cover those in the NICE final scope, with the exception of certain outcomes as discussed in Section 3.4. The primary efficacy outcomes were serum TTR percentage reduction and change from baseline in mNIS+7$_{Ionis}$ and Norfolk QoL-DN. These are recognised assessments but as already noted, blinding to treatment assignment was not maintained.	The EAG considers the outcomes assessed to be appropriate and cover those in the NICE final scope, with the exception of certain outcomes as discussed in Section 3.4. The primary efficacy outcomes were change from baseline in mNIS+7$_{Alnylam}$ and Norfolk QoL-DN. These are recognised assessments but as already noted, blinding to treatment assignment was not maintained.

Abbreviations: AEs, adverse events; ATTRv-CM, hereditary transthyretin amyloidosis with cardiomyopathy; CFB, change from baseline; CS, company submission; EAG, External Assessment Group; FAP, Familial Amyloidosis Polyneuropathy; FAS, full analysis set; ITC, indirect treatment comparison; ITT, intention to treat; MMRM, mixed effects models with repeated measures; NICE, National Institute for Health and Care Excellence; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability; TTR, transthyretin.

10.3 Results from NEURO-TTRansform compared to external placebo

While the External Assessment Group (EAG) does not consider the comparisons against external placebo to be relevant in deciding whether or not eplontersen is similar to vutrisiran in terms of outcomes, it has presented results against the external placebo group here given they were the focus of the main publication.[5] It should be noted that these do not represent observed data for the eplontersen arm as analyses have included adjustment to external placebo. Observed data for eplontersen is presented in Section 4.2.2.

Baseline characteristics for eplontersen and external placebo groups can be found in Table 10 of the company submission (CS). As noted by the EAG in Section 4.2.1 and Appendix 10.1, while some adjustment against the external placebo group is performed, this may not resolve all differences at baseline between the two arms, meaning results could be associated with some bias, and the study was open-label, which could also introduce bias. Limitations in terms of the applicability of the NEURO-TTRansform population to the population seen in UK practice are described in Section 3.1.

10.3.1 Primary efficacy outcomes

A description of these outcomes is provided in Section 4.2.2.1. Regarding serum transthyretin (TTR), different assays were used in NEURO-TTRansform and NEURO-TTR (external placebo), meaning adjustments to serum TTR concentrations from NEURO-TTR were made in order to allow for cross-assay comparisons; no further details about this were identified by the EAG in the clinical study report (CSR) but the EAG acknowledges that the company has data for both trials and details on the

two assays so should be able to adjust these appropriately to improve comparability. It may, however, still be associated with some uncertainty.

Week 65/66 results demonstrate statistically significant benefits of eplontersen for all three primary efficacy outcomes compared to the external placebo group at week 65/66, with results at this time-point generally improving relative to external placebo compared to the 35-week interim analyses. Results for these three outcomes are summarised in Table 18 below.

Reductions in serum TTR appeared to occur in the eplontersen group from the first assessment around week 5, with levels reducing further until around week 35, after which levels are more stable/reductions are smaller. This is demonstrated in Figure 12 below; while TTR levels in placebo also fall slightly compared to baseline, which may be unexpected on first consideration, the company notes that this may be explained by reducing nutritional status (demonstrated by modified body mass index [mBMI] reductions for external placebo in Appendix 10.3.2) which has been associated with declining TTR concentrations.[35]

For modified Neuropathy Impairment Score +7 (mNIS+7), scores in the eplontersen group remained fairly stable compared to baseline, whereas the score in the external placebo group increased indicating disease progression. The impact on individual components of the mNIS+7 are also presented in Figure 7 of the CS; results show that eplontersen had a beneficial effect for most domains compared to external placebo, although the impact on some domains was very small and 95% confidence intervals (CIs) crossed the line of null effect for two domains. For Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN), eplontersen patients experienced an improvement in score overall while patients from the external placebo group had scores that worsened at follow-up.

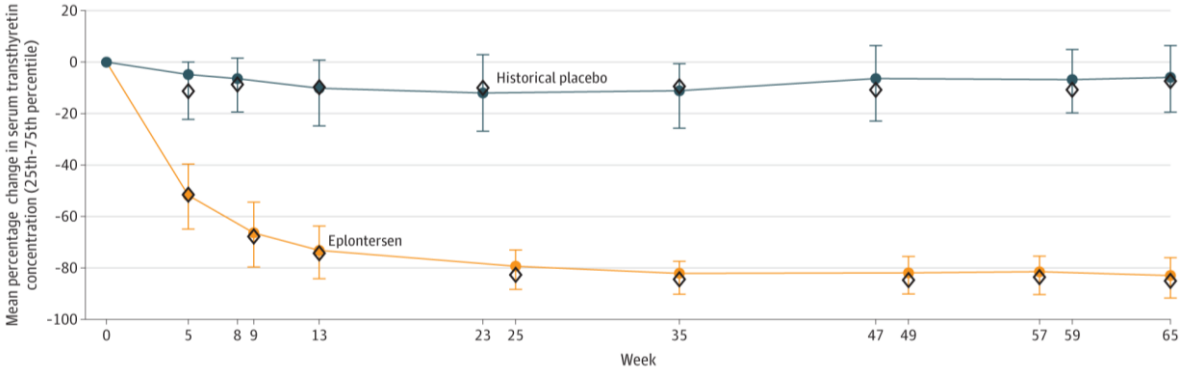
Table 18. Eplontersen vs external placebo – NEURO-TTRansform week 65/66 results – LSM change from baseline in serum TTR, mNIS+7 and Norfolk QoL-DN* - adapted from Tables 13, 15 and 17 of the CS

Parameter	Serum TTR (percentage CFB)		mNIS+7		Norfolk QoL-DN	
	Eplontersen (n=141)	External placebo (n=59)	Eplontersen (n=141)	External placebo (n=59)	Eplontersen (n=141)	External placebo (n=59)
n†	135	51	128	52	128	52
LSM change (or percentage change for serum TTR) from baseline LSM, 95% CI	-81.7%, 95% CI: [redacted]	-11.2%, 95% CI: [redacted]	0.3, 95% CI: -4.5 to 5.1	25.1, 95% CI: 20.2 to 29.9	-5.5, 95% CI: -10.0 to -1.0	14.2, 95% CI 9.5 to 19.0
LSM Difference, 95% CI	-70.4%, 95% CI: -75.2 to -65.7%		-24.8, 95% CI: -31.0 to -18.6		-19.7, 95% CI -25.6 to -13.8	
p-value	<0.001		<0.001		<0.001	

*Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. Analyses were at week 65 for serum TTR and week 66 for mNIS+7 and Norfolk QoL-DN; †number of patients with non-missing data at the time-point.

Abbreviations: CFB, change from baseline; CI, confidence interval; CS, company submission; LSM, least squares mean; MMRM, mixed effects models with repeated measures; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; TTR, transthyretin.

Figure 12. Percentage change in serum TTR concentration to week 65 – NEURO-TTRansform eplontersen and external placebo – reproduced from Figure 5 of the CS



.

Abbreviations: CS, company submission; TTR, transthyretin

10.3.2 Secondary efficacy outcomes

A description of these outcomes is provided in Section 4.2.2.2. As summarised in Table 19 below, week 65 results demonstrated that eplontersen was statistically superior to external placebo in terms of the impact on polyneuropathy disability (PND) score and mBMI. Additional results for 36-item short form questionnaire – physical component summary (SF-36 PCS) and Neuropathy Symptoms and Change (NSC) questionnaires in Tables 20 and 21 of the CS demonstrated a similar impact on these outcomes at week 65/66.

For PND score, while statistically significant, the numerical difference is very small; most patients remained in the same PND stage at week 65 compared to baseline but there were more patients in the eplontersen group that showed an improvement in PND score ([redacted] compared to the external placebo group [redacted]). The EAG notes that the proportion in the lowest impairment group (PND stage I) also reduced at week 65 for the external placebo group, while it remained the same in the eplontersen group (see Figure 9 of the CS).

For mBMI, while reductions in mBMI compared to baseline were noted in both groups, this deterioration was significantly larger in the external placebo group, suggesting that eplontersen has a beneficial effect on mBMI, an indicator of nutritional status.

Table 19. Eplontersen vs external placebo – NEURO-TTRansform week 65 results – change from baseline in PND and mBMI* - adapted from Tables 18 and 19 of the CS

Parameter	PND score		mBMI	
	Eplontersen (n=141)	External placebo (n=59)	Eplontersen (n=141)	External placebo (n=59)
n†	134	51	130	49
LSM change from baseline LSM, 95% CI	[redacted]	[redacted]	-8.1, 95% CI: -28.6 to 12.4	-90.8, 95% CI: -112.8 to -68.7
LSM Difference, 95% CI	[redacted]		82.7, 95% CI: 54.6 to 110.8	
p-value	<0.05		<0.001	

*Analysis based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V50M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction; †number of patients with non-missing data at the time-point.

Abbreviations: CI, confidence interval; CS, company submission; LSM, least squares mean; mBMI, modified body mass index; MMRM, mixed effects models with repeated measures; PND, polyneuropathy disability.

10.3.3 Subgroups

Results of subgroup analyses for the three primary efficacy endpoints from NEURO-TTRansform are presented in Section B.3.7 of the CS in terms of comparisons between eplontersen and external placebo. The company concludes that at week 65/66, treatment effects for eplontersen vs external placebo were consistent across these prespecified subgroups, which included demographics such as age, sex and region/continent, and disease-related factors such as prior treatment, mutation type and cardiomyopathy diagnosis. The EAG agrees that there do not appear to be any large differences in the treatment effect between different subgroups. The whole study population is used in analyses supporting this appraisal, which the EAG considers to be appropriate, and the EAG's clinical expert did not consider there to be any reason that conclusions about the similarity of eplontersen and vutrisiran would differ for particular subgroups.

10.4 Summary of analysis decisions and EAG critique

Table 20. Summary of analysis methods used by the company with EAG comment

Issue	Outcome(s)	Company approach	Rationale	EAG comment	Scenarios requested	EAG-preferred method
Outcome definitions/scores used						
Different mNIS+7 scores used	mNIS+7 (CFB and responder analyses)	Rescoring of mNIS+7$_{Ionis}$ NSC and HRdb domains conducted to better align with HELIOS-A version but autonomic assessment still differs between studies (HRdb vs postural blood pressure). Sensation domain from mNIS+7$_{Ionis}$ excluded. See company's response to CQ A8.	mNIS+7$_{Ionis}$ and mNIS+7$_{Alnylam}$ not directly comparable; additional domain (sensation) in mNIS+7$_{Ionis}$ and two components scored differently (NSC and autonomic function measure; see Figure 2 of CS appendices). Total score ranges are different (-22 to 346 and 0 to 304, respectively) and require alignment for more reliable comparisons.	Agree that alignment should improve ability to compare this outcome between trials but not possible to completely resolve given differed methods used to assess autonomic impact between studies so residual bias may remain and could impact estimates for eplontersen vs vutrisiran.	N/A	Company's original approach as no alternatives possible with the available data, but limitations may remain as discussed in the text above.
Calculating steady-state serum TTR using trough measures	Serum TTR outcomes	Calculated steady-state serum TTR trough levels based on the approach used in HELIOS-A for vutrisiran (pre-dose serum TTR measurements between months 6 and 18). The first time-point included for eplontersen is	In response to CQ A9, said to have been based on the same period as in HELIOS-A. Also noted on page 57 of the CS that calculations based on a tissue half-life of ~16 weeks for eplontersen and the	Agrees that use of steady-state trough TTR levels would be in line with the approach used for HELIOS-A and considers the rationale provided for the selection of time-points to be included for eplontersen to be reasonable.	N/A	Company's original approach considered reasonable. The EAG is satisfied with the company's approach to calculating steady-state TTR time period.

		at week 49 given this is the first pre-dose serum TTR measurement falling between month 6 and 18.	expectation that steady-state is ~three times greater than the half-life also supports the use of data from week 49 onwards for this outcome.			
Assay used for serum TTR	Serum TTR outcomes	Not mentioned	N/A	Various assays for measuring serum TTR are available and LLOD can differ, meaning ability to detect lower levels of TTR differs. It is unclear if LLOD for assays used in the two trials was comparable as the assay used in HELIOS-A does not appear to be publicly available. In response to CQ A9 the company states that as baseline and follow-up results were measured with the same assay in each trial, change from baseline results should be limited in terms of impact of LLOD. However, the EAG does not agree with this statement given a difference in LLOD is likely to impact only follow-up measurements given baseline TTR levels (before treatment) will be higher and not below the LLOD of the assays. Nonetheless, the EAG considers this to be an unresolvable uncertainty and it is unclear whether any bias is introduced.	N/A	Company's original approach as no alternatives possible with the available data. Considered to be an unresolvable uncertainty and unknown if bias is introduced.

Time-points used						
Week 66 data extrapolated to week 80 used instead of week 85 data from NEURO-TTRansform	mNIS+7 and Norfolk QoL-DN CFB outcomes	Linear extrapolation of week 66 data from NEURO-TTRansform performed to week 80 to align with time-point available for HELIOS-A. Performed scenario analyses with no extrapolation at weeks 66 and 85 to assess the impact on results.	Extrapolation to week 80 chosen to align with the time-point data is available for HELIOS-A study. Week 85 data from NEURO-TTRansform not used initially given data not available at this time-point for the external placebo group and no MMRM results available. However, in response to part e of CQ A6 the company acknowledges that the lack of external placebo group data is not a major concern in terms of ITCs against vutrisiran.	The EAG considers the use of week 85 observed data for eplontersen to be more appropriate for the ITCs than use of extrapolated week 66 data. This is because it adds unnecessary uncertainty considering week 85 data has been observed for eplontersen and does not need to be estimated. While the company appears to accept that there are no major limitations associated with using week 85 observed data in its response to part e of CQ A6, it has still used week 66 extrapolated data for the new mBMI outcome provided in response to CQ A2. Given the impact of using extrapolated vs observed data in the ITCs has a larger impact on point estimates for mNIS+7 and Norfolk QoL-DN outcomes than including additional variables in the adjustment does (see Sections 4.3.2.2 and 4.3.3), the EAG has a preference for ITCs using week 85 observed data despite versions of these MAICs with additional adjustment outlined in CQ A1 not being available for these scenarios.	Version without extrapolation at week 66 and a version with week 85 observed data used (CQs A6 and A7).	Week 85 data given this is the most closely aligned with week 80 data from HELIOS-A without extrapolation being required, which adds to uncertainty. These MAICs are limited in that versions with additional adjustments outlined in CQ A1 were not available to the EAG, but additional adjustment of the original analyses of these outcomes had a limited impact on point estimates (see Sections 4.3.2.2 and 4.3.3) and use of week 85 observed data is considered to be a priority for these outcomes. The same option was not available for the mBMI analyses provided in response to CQ A2 as only versions using

						extrapolated week 66 data have been provided. This is a limitation of the analyses for this outcome and is discussed further in Section 4.3.3.
Week 66 data from NEURO-TTRansform used rather than week 85	Serious AEs, severe AEs and treatment discontinuation	Week 66 data for NEURO-TTRansform compared against week 78 data for HELIOS-A, despite data being available at week 85 for eplontersen.	Not provided and not explored in terms of scenario analyses.	The EAG considers it unusual not to use the longest available follow-up data from NEURO-TTRansform for these outcomes. However, clinical expert feedback to the EAG was that these events are most likely to occur early on (before week 66) and so the use of different time-points is unlikely to have a large impact on comparative estimates. The EAG has explored differences at the longer time-point naively with any potential impact on results discussed in Section 4.3.4.1.	Not prioritised for CQs given clinical expert feedback that most events are likely to occur prior to week 66.	Although unusual, the company's original approach was considered reasonable give it is unlikely to have a large impact on ITC results. The EAG has explored differences at week 85 naively and the potential impact on ITC results is commented on in Section 4.3.4.1.
Approaches to missing data/adjustment						
Missing data for continuous outcomes imputed	mNIS+7, Norfolk QoL-DN, serum TTR, mBMI, 10-MWT and R-ODS outcomes	Said to have imputed missing data using multiple imputation of mean difference in the base case analyses	Said to be in line with methods described in the HELIOS-A statistical analysis plan for the 9-month analyses. Multiple imputation MMRM used by the company said to improve traceability in	While the statistical analysis plan for HELIOS-A describes a multiple imputation approach at the 9-month time-point, this was not the case for the outcomes at 18 months. However, on review of sensitivity analyses in the CSR for NEURO-TTRansform, a multiple imputation	N/A	Although unusual, the company's original approach was considered reasonable given it is unlikely to have a large impact on ITC results.

			the ITCs and likely to yield equivalent results to MMRM with implicit imputation.	approach does not have a large impact on eplontersen results for mNIS+7, Norfolk QoL-DN and serum TTR and is unlikely to have a substantial impact on comparative estimates obtained from ITCs.		
Analysis population						
Per-protocol used in HELIOS-A whereas randomised set used for NEURO-TTRansform data	Serum TTR outcomes	Not mentioned	N/A	Serum TTR was analysed in the per-protocol population of HELIOS-A but the randomised set of NEURO-TTRansform and the definition of the per-protocol population was very different between trials. As a result, the population that eplontersen data was adjusted to in these MAICs differs slightly to the population that data was available for in terms of this outcome from HELIOS-A. Given only n=2 patients were excluded from the per-protocol analyses in HELIOS-A the EAG considers it unlikely that this difference would have a large impact on the results of the MAIC for this outcome.[25]	N/A	Company's original approach as no alternatives possible with the available data. The EAG considers the impact of this difference on the comparative results is likely to be minimal given only n=2 patients were excluded from the per-protocol population of HELIOS-A.[25]

Abbreviations: 10-MWT, 10-metre walk test; AEs, adverse events; CFB, change from baseline; CQ, clarification question; CS, company submission; EAG, External Assessment Group; HRdb, heart rate with deep breathing; ITC, indirect treatment comparison; LLOD, lower limit of detection; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; MMRM, Mixed effects models with repeated measures; mNIS+7, Modified Neuropathy Impairment Score +7; N/A, not applicable; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NSC, Neuropathy Symptoms and Change; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin.

10.5 Minimum clinically important differences identified by the EAG

Table 21. Minimum clinically important difference thresholds identified by the EAG

Outcome	MCID	Source	EAG comment
mNIS+7 (lower scores more favourable)	**Consensus statements**		
	2-point change from baseline	Vutrisiran CCE (TA868) and patisiran HST appraisal (HST10)	The 2-point value is based on a statement from the International Peripheral Nerve Society in terms of the original NIS score rather than mNIS+7. 2 points was considered to be the minimum degree of detectable change by physicians.[27, 36, 37] It has been suggested that this threshold may also be useful for mNIS+7 scores given they have been adapted from NIS, including its mention in NICE appraisals of vutrisiran and patisiran.[1, 26] However, the EAG's clinical expert considered a 2-point change to represent an extremely small change in score and did not consider it would reflect a clinically important change or difference. [redacted]
	Anchor-based estimates		
	[redacted]	[redacted]	[redacted]

	[redacted]		[redacted]
	Distribution-based estimates		
	[redacted]	[redacted]	[redacted]

			[redacted]
	12.2-point change from baseline (worsening)	Secondary analysis of NEURO-TTR	An mNIS+7-specific MCID of 12.2 points was suggested in an analysis of NEURO-TTR data,[27] which was available at the time of the vutrisiran appraisal but not patisiran.[1, 26] The EAG notes this is based on the specific version used in NEURO-TTRansform (mNIS+$_{7Ionis}$) but that it is unlikely to completely apply to data analysed in the ITCs given eplontersen data was adapted to match the mNIS+7 version used in HELIOS-A. This was obtained using distribution-based methods only as no outcomes suitable for anchoring mNIS+7 to were identified in this analysis. The 12.2-point threshold represents the mean of three separate distribution-based estimates that were obtained, including ES, SRM and SEM-based estimates (19.0-, 10.8- and 6.9-point thresholds, respectively). The EAG's clinical expert considered that this threshold was more useful in terms of a clinically important change or difference compared to the 2-point NIS-based threshold.
Norfolk QoL-DN (lower scores more favourable)	**Mixed anchor- and distribution-based estimates**		
	8.8-point change from baseline (worsening)	Vutrisiran CCE (TA868) - secondary analysis of NEURO-TTR	Based on an analysis of NEURO-TTR data,[27] as above for the 12.2-point mNIS+7 threshold. This was cited by the company involved in the vutrisiran CCE as a reasonable threshold to use when assessing differences between interventions.[1]

			Anchor- and distribution-based methods were possible in this publication and the 8.8-point threshold is based on the mean of seven different estimates (four anchor-based and three distribution-based). Anchor-based estimates were obtained using two separate anchor outcomes (SF-36 PCS and SF-36 GH domains) using regression (7.2-point threshold obtained for both) and ROC cut-off (8.5-point threshold obtained for both) approaches. Distribution-based estimates were obtained based on ES (13.8-point threshold), SRM (10.2-point threshold) and SEM 9 (6.4-point threshold).
	Anchor-based estimates		
	[redacted]	[redacted]	[redacted]
	[redacted]		

			[redacted]
	Distribution-based estimates		
	[redacted]	[redacted]	[redacted]

mBMI	**Anchor-based estimates**		
	[redacted]	[redacted]	[redacted]
	Distribution-based estimates		
	[redacted]	[redacted]	[redacted]

10-MWT	**Anchor-based estimates**		
	0.10 m/s decline from baseline	Publication cited in the vutrisiran NICE CCE[1, 38]	MCIDs based on anchor-based methodology were estimated using post-intervention data from an RCT a 3-month program of therapeutic exercise in 100 stroke survivors.10-MWT gait speed was anchored to two separate SF-36 domains (ability to walk one block and ability to climb one set of stairs). Only the MCID based on the first domain is mentioned in the NICE CCE of vutrisiran by the relevant company, which the EAG considers is because the domain based on a flight of stairs is less relevant to 10-MWT. Specifically, the MCIDs calculated were anchored to a decline of one level for the respective SF-36 domain compared to baseline. The EAG notes that this MCID may be more limited than those identified for other outcomes in this table given it did not specifically involve analysis of ATTRv-PN patients and was based on data in stroke survivors.
	Distribution-based estimates		
	Range 0.04 to 0.14 m/s change from baseline	Publication cited in the vutrisiran NICE CCE[1, 38]	MCIDs based on distribution-based methodology were estimated using post-intervention data from two separate studies, including an RCT of a 3-month program of therapeutic exercise in 100 stroke survivors and an RCT of a 3-month home-based strength training intervention in 100 older persons with mild to moderate mobility limitations. Distribution-based approaches included were SEM and effect size, leading to the following MCID estimates: • ES of 0.2, small meaningful change (0.05 and 0.06 m/s for the two studies) • ES of 0.5, moderate meaningful change (0.13 and 0.14 for the two studies) • SEM small meaningful change (0.06 and 0.04 for the two studies)

			These distribution-based estimates are not cited in the NICE CCE appraisal despite being from the same paper as the anchor-based MCID above that was cited.
Percentage change from baseline in serum TTR (lower scores more favourable)	**Non-inferiority threshold from HELIOS-A trial**		
	10% worsening compared to comparator treatment	HELIOS-A study	In HELIOS-A, when comparing impact on serum TTR levels between vutrisiran and patisiran, non-inferiority was defined if the lower limit of the 95% CI for the treatment effect was greater than -10% (i.e. if the lower CI was not consistent with vutrisiran being worse than patisiran by at least 10 percentage points in terms of change from baseline scores).[6] While the EAG notes that the rationale for this threshold used in HELIOS-A is unclear and may not be validated in the literature, given the lack of other available thresholds for decision-making, the EAG has discussed the serum TTR results in the context of this 10% threshold.

Abbreviations: 10-MWT, 10-metre walk test; ATTRv-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; CCE, cost-comparison technology appraisal; CI, confidence interval; EAG, External Assessment Group; ES, effect size; HST, highly specialised technologies evaluation; ITC, indirect treatment comparison; mBMI, modified body mass index; MCID, minimum clinically important difference; mNIS+7, modified Neuropathy Impairment Score +7; NICE, National Institute for Health and Care Excellence; NIS, Neuropathy Impairment Score; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PGIC, Patients' Global Impression of Change; RCT, randomised controlled trial; ROC, receiver-operating characteristic; SD, standard deviation; SEM, standard error of the mean; SF-36, 36-item short form questionnaire; SF-36 GH, 36-item short form questionnaire – general health domain; SF-36 PCS, 36-item short form questionnaire – physical component summary; SRM, standardised response mean; TA, technology appraisal; TTR, transthyretin.

10.6 Price sources for treatments included in the confidential appendix

Table 22. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Eplontersen	Simple PAS
Vutrisiran	Simple PAS

Abbreviations: PAS, Patient Access Scheme.

Single Technology Appraisal

Eplontersen for treating polyneuropathy caused by hereditary transthyretin-related amyloidosis [ID6337]

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 23 May 2024** using the below comments table.

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

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Treatment administration methods

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15 of the EAG report states that eplontersen and vutrisiran differ in their methods of administration (self-administered or administered by a health care professional, respectively).	The statement in brackets should be rephrased to “(flexibility to self-administer, or administration by a healthcare professional if required for eplontersen, and administered by a healthcare professional for vutrisiran)”.	The current phrasing suggests eplontersen is only available as a self-administered treatment. This is inaccurate as [redacted]	The EAG has made the change suggested by the company.

Issue 2 Incorrect reporting of R-ODS indirect comparison outcome

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17 of the EAG report states that the point estimate for the mean difference between vutrisiran and eplontersen in R-ODS CfB is slightly in favour of vutrisiran.	This statement should be corrected to "The point estimate is slightly in favour of eplontersen but the difference is small considering a scale of 0 to 48 for this outcome."	A higher R-ODS score represents a lower degree of disability. As such, a positive point estimate, when the HELIOS-A CfB score is subtracted from the NEURO-TTRansform CfB score, indicates that the outcome is in favour of eplontersen.	The EAG thanks the company for highlighting this and has corrected this statement and related text within the report.

Issue 3 Anticipated marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19 of the EAG report states that MHRA marketing authorisation is anticipated in [redacted].	Marketing authorisation for this indication is anticipated to be granted by the MHRA in [redacted].	To reflect the most recent available estimate which were previously communicated with NICE.	The EAG has updated this as requested by the company.

Issue 4 Ongoing trials for eplontersen and vutrisiran

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20 of the EAG report states that there are ongoing trials of eplontersen and vutrisiran in ATTRv-CM.	This statement should be corrected to "There are ongoing trials of eplontersen (CARDIO-TTRansform; NCT04136171) and vutrisiran (HELIOS-B; NCT04153149) in ATTR-CM, including both ATTRv-CM and ATTRwt-CM".	To ensure that the information reported is factually correct.	The EAG has made the change suggested by the company.

Issue 5 Karnofsky Performance Status inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28, 42 and 45 of the EAG report state that the eligibility criteria for NEURO-TTRansform	Please clarify that a total of two patients in NEURO-TTRansform had a KPS of >50% and <60%, so could not have been eligible	The EAG's current interpretation implies that the differences in KPS could have an unknown impact on the analysis – whereas,	The EAG has added the additional detail provided by the company on page 45 only given the EAG's

and HELIOS-A relating to Karnofsky Performance Status is one of the differences between HELIOS-A and NEURO-TTRansform.	for HELIOS-A. The first patient was a screen-failure and, as such, was never randomised or included in any analyses, ITC or otherwise. The second patient was randomised to eplontersen and included in the ITC as part of the full analysis set, with baseline data available for the reference variables.	in reality, this is likely to have a minimal impact on results given that only one patient was enrolled in NEURO-TTRansform that would not have been enrolled in HELIOS-A. To ensure the conclusions of the EAG's clinical experts are fully justified, it would be helpful to add this clarifying information.	statements on page 28 and 42 already highlight that these were not considered to be important differences.

Issue 6 Vutrisiran self-administration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32 of the EAG report states the option to self-administer vutrisiran may be an option in the future.	Remove the statement "although this may be an option in the future".	This statement is speculative since vutrisiran is not currently available as a self-administered product and, therefore, this should not be considered in the decision-making process.	This is not a factual inaccuracy and is based on feedback from the EAG's clinical expert. The EAG has retained this comment in the report.

Issue 7 Inotersen treatment group

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39 of the EAG report states that, in reference to Week 85 trial data, a small inotersen group was included in	All patients receiving inotersen in NEURO-TTRansform switched to eplontersen at Week 37. Please amend to clarify that "a small inotersen group was included until	To ensure that the information reported is factually correct.	The EAG has added the additional information suggested by the company.

NEURO-TTRansform but was not included in the ITC analyses.	Week 36. Formal comparisons to this group were not included as part of the analyses given that inotersen is not a relevant comparator in this submission."		

Issue 8 Exclusion of patients from ITC analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 44 of the EAG report states that it is unclear how many patients in NEURO-TTRansform were excluded from the ITC analyses for not meeting the HELIOS-A inclusion criteria.	Update this statement to "No patients were excluded from the ITC analyses on the basis of the HELIOS-A inclusion criteria."	To ensure that the information reported is factually correct.	The EAG has updated this statement in line with the information provided by the company.

Issue 9 MAICs with additional adjustment using observed Week 85 data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46, 49 and 68 of the EAG report state that versions of the observed Week 85 analyses with additional adjustment	Please clarify that these analyses were not provided due to an alternative understanding around the wording of the clarification question, and the Company instead provided separate analyses with additional adjustments, and for scenarios without	The Company would like to clarify why the EAG comments regarding the MAICs with additional adjustment requested in CQ A1 were not provided for scenarios using Week 85 data	The EAG has amended the wording around this to avoid implying that week 85 observed data analyses with additional adjustments were explicitly requested. Its

requested by the EAG have not been provided.	Week 85 data. Please also explain that the use of additional adjustments with observed Week 85 data is unlikely to significantly alter estimates.	without extrapolation, as requested in CQ A7. This was due to an alternative understanding around the wording of the question. The Company believed that the EAG were requesting the week 85 without extrapolation for the additional endpoints listed within CQ A1 and not the additional adjustment covariates. As such, in our response to CQ A7c, we provide reasoning for not exploring week 85 data for the additional endpoint rather than focussing on the additional adjustment covariates. However, the Company agrees with the EAG conclusion that the addition of further covariates to the adjustment models for the requested endpoints using Week 85 data is unlikely to alter the estimate substantially.	statements in Section 4.3.3 already acknowledge that additional adjustments to this data are unlikely to have a large impact on estimates of relative effectiveness.

Issue 10 HELIOS-A treatment discontinuations

Description of problem	Description of proposed amendment	Justification for amendment	
Page 47 and 59 of the EAG report states that a version of the ITC for treatment discontinuation with the correct number of discontinuation events and additional adjustment is not available.	Please clarify that the ITC for treatment discontinuation used the number of discontinuations due to AEs in the HELIOS-A trial (n=3) which in line with the data presented in Figure 1 of Adams *et al*. 2022.[1]	We note that the EAG counts the number of discontinuations in the HELIOS-A trials as reported in Figure 1 of Adams *et al.* 2022. The Company cannot be entirely certain about which interpretation is correct, but believes Figure 1 does not agree with the information provided in Table 3 and Supplemental Table 1, of Adams *et al.* 2022, The authors noted that there are a total of n=2 deaths in the vutrisiran arm (Supplemental Table 1) and have stated that "Three (2.5%) patients in the vutrisiran group discontinued treatment, and also stopped study participation, due to AEs by Month 18 (two of which were due to death)." This means that the n=2 deaths occurred among the n=3 patients who discontinued due to AEs. Therefore, counting this as n=5 discontinuations seems to double-	This is not a factual inaccuracy. The EAG agrees that the text concerning adverse events in Adams *et al.* 2022 may introduce confusion about whether any treatment discontinuation events are counted twice. However, the EAG does not consider the text cited by the company to contradict the events outlined in Figure 1 of Adams *et al.* 2022 because: • Figure 1 only reports one discontinuation event related to adverse events, with another two events due to deaths (this captures the three AE-related discontinuations cited in the

		count patients who died. The authors have also stated that "Deaths are reported regardless of treatment-emergent status.[1]	company's statement); • The additional two discontinuation events in Figure 1 are classed as 'physician decision' or 'other', which do not seem to be related to the three events already accounted for by adverse events/death. As this outcome/analysis is not specific to AE-related discontinuations, the EAG considers n=5 events for vutrisiran (as in the EAG's preferred MAIC for this outcome) to be correct.

Issue 11 Per protocol analyses in HELIOS-A

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 of the EAG report states information on the number of patients excluded from the per protocol analyses could not be located.	Of the 122 patients who received vutrisiran in HELIOS-A, 120 patients were included in the per protocol analyses. Please clarify that only two patients were excluded from the per protocol analyses, which confirms that the difference in the definition of per protocol between HELIOS-A and NEURO-TTRansform would have a negligible impact on results.	The number of patients included in the per protocol analysis in HELIOS-A can be found in the Table 29 of the European public assessment report for vutrisiran, and should be referred to in the EAG report to ensure that all relevant information is provided.[2]	The EAG thanks the company for highlighting this information and has updated its report in line with this.

Issue 12 Minimum clinically important differences

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In page 53 of the EAG report, the EAG acknowledges that most of the MCID values identified refer to changes from baseline, rather than the difference between two interventions.	Please change the sentence in the preceding paragraph to “In response to CQ A13, the company also provided additional values that could be used as MCIDs, specifically to evaluate a difference between two interventions, for mNIS+7, Norfolk QoL-DN and mBMI based on an…”	To ensure that the information reported is factually correct; the methodology applied in the manuscript provided to the EAG was specifically designed for analysing the differences between vutrisiran and eplontersen in NEURO-TTRansform.	The EAG has added the information requested by the company.

Issue 13 Responder analysis ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 54–56 of the EAG report state that responder analyses from the company submission have not been presented in the EAG report, as the definition used to define responders was not considered clinically useful by the EAG's clinical expert.	Please clarify that, whilst it should be noted that any negative change may not be considered clinically meaningful, performing responder analyses using this definition represents the most appropriate methodology, since it is not feasible to conduct responder analyses ITCs based on a threshold.	The company agrees that it may not be appropriate to consider any negative changes as clinically meaningful. However, it should be noted that this approach was necessary, given that an ITC cannot be performed on any threshold for which aggregate data is not readily available for the comparator.	This is not a factual inaccuracy and the EAG has not made changes to this statement.

Issue 14 Administration-related disutility

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 77 of the EAG report states that the eplontersen may lead to a greater decrement in HRQOL compared with vutrisiran given the difference in administration frequencies.	Please rephase this sentence to: "As such the EAG considers that the different administration profiles may be impactful to HRQoL; eplontersen requires more frequent injections which may impact patients' HRQoL yet vutrisiran administration is more time consuming and has less autonomy which could also impact patients' HRQoL.	If considering a disutility which may be associated with the increased administration frequency for eplontersen, a disutility associated with the more time-consuming and less independent administration of vutrisiran, should also be described. Whilst the Company	This is not a factual inaccuracy and the EAG has not made changes to this statement. As described in the EAG report, according to the EAG's clinical experts the infringement on patient

	Overall, any differences in utility are likely to be minimal.”	firmly believes that the inclusion of an additional disutility associated with the self-administration of eplontersen to be inappropriate, any consideration of such a disutility for eplontersen should be matched with a disutility associated with vutrisiran administration. Please see the Company response to CQ B2 for further detail on why an administration-related disutility should not be considered.	autonomy is minimal when treated with vutrisiran; it is likely that eplontersen patients will similarly require assisted treatment administration. Therefore, the EAG considers administration frequency to be the more critical issue.

Issue 15 HRQoL difference between treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80 of the EAG report states that the EAG considers administration frequencies to be the only key difference between treatments which may affect HRQoL.	Clarify that the administration profiles of vutrisiran and eplontersen differ with regards to administration frequency, length of administration and flexibility of the administration.	It is important to acknowledge that the autonomy and flexibility offered by the self-administration profile of eplontersen is likely to influence patient choice between patients.	This is not a factual inaccuracy and the EAG has not made changes to this statement. With respect to costs and HRQoL, administration frequency is directly relevant

			and so has only been included.

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20 of the EAG report states "The company deemed vutrisiran to be the only relevant comparator for this appraisal based on clinical expert feedback; the EAG's clinical expert agreed with this conclusion given the vast majority of NHS patients (>95%) with ATTRv-PN are **currently receiving,** with most of those remaining on inotersen or patisiran likely doing so due to patient preference rather than a specific clinical reason."	"The company deemed vutrisiran to be the only relevant comparator for this appraisal based on clinical expert feedback; the EAG's clinical expert agreed with this conclusion given the vast majority of NHS patients (>95%) with ATTRv-PN are **currently receiving vutrisiran**, with most of those remaining on inotersen or patisiran likely doing so due to patient preference rather than a specific clinical reason."	Amend sentence to include missing word.	The EAG thanks the company for highlighting this and has amended the error.
Page 23 of the EAG report states "Based on feedback received from the EAG's clinical expert, the EAG the inclusion of vutrisiran as the only comparator is reasonable."	Please re-phrase this to: "Based on feedback received from the EAG's clinical expert, the EAG **agrees that** the inclusion of vutrisiran as the only comparator is reasonable."	Update the spelling of the typographical error to ensure correct spelling.	The EAG thanks the company for highlighting this and has amended the error.

Page 29 of the EAG report states the following: “Furthermore, these additional observations could also be linked to the fact that the same mutation has been observed to present differently in different populations; for example, most patients in the UK that do have the V50M mutation usually present with late onset disease including cardiomyopathy, whereas this mutation in countries such as Portugal typically leads to presentation at a much earlier age and **rarely causes**.”	Please clarify which characteristic should be referred to at the end of this sentence.	Amend sentence to ensure description is presented correctly.	The EAG thanks the company for highlighting this and has amended the error.
Page 30 of the report states “Given that eplontersen baseline characteristics and results from NEURO-TTRansform are adjusted to the HELIOS-A study population as part of the ITCs, the applicability of this trial to the UK population was also explored.”	Please clarify whether “eplontersen baseline characteristics” should be updated to “mean baseline characteristics of patients in the eplontersen arm of the NEURO-TTRansform trial”.	Update the phrasing of the sentence to ensure it refers to the correct patient population.	The EAG has rephrased this to “baseline characteristics and results from the eplontersen arm of NEURO-TTRansform”.

Page 55 of the EAG report states that the results of the company's original MAIC using extrapolation of week 66 data to week 80 was marginally less notable (point estimate of [redacted] with vs without additional adjustment, respectively).	Please update the point estimates to "[redacted]" with adjustment and "[redacted]" without additional adjustment.	To ensure that the information reported is factually correct.	This is not a factual inaccuracy. In response to clarification, the company provided the EAG with an addendum that was said to correct for an "error in its results for the Modified Neuropathy Impairment Score+7 (mNIS+7) with re-scoring at Week 85, where some patients were not being re-scaled correctly and still had the Ionis version mNIS+7 composite score in the indirect treatment comparison (ITC). Corrected results for Week 85 were provided to NICE 17 April. On further investigation this issue also impacts results at Week 66." The figures cited by the EAG in this sentence refer to Figure 1 and Table 2 of this addendum, which correspond to updates of the initial analysis included in the CS and the scenario with additional adjustment provided in response to CQ A1.

Page 60 of the EAG report contains a typo in the name HELIOS-A (“**HELISO-A**”)	Correct spelling of “**HELISO-A**” to “**HELIOS-A**”.	Update the spelling of the typographical error to ensure correct spelling.	The EAG thanks the company for highlighting this and has amended the error.
Page 64 (Table 6) of the EAG report states that 114 participants from the eplontersen arm of NEURO-TTRansform experienced any TEAE.	Please update this value to “141”.	To ensure that the information reported is factually correct.	The EAG thanks the company for highlighting this and has amended the error.
Page 68 of the EAG report state “the EAG considers **is** unlikely that resolution of these would have a large impact on the results of the MAICs”.	Correct typo “**is**” to “**it**”.	Update the spelling of the typographical error to ensure correct spelling.	The EAG thanks the company for highlighting this and has amended the error.
The EAG report, on pages 14, 76, and 81, uses the word “composites” where “comprises” would be more appropriate. For example, on page 14, the report states that “the cost difference due to administration costs comprises a small proportion of the total cost difference between treatments, which is driven by acquisition costs.” Similar usage is found on pages 76 and 81.	Change “**composites**” to “**comprises**” throughout.	Update the spelling of the typographical error to ensure correct spelling.	The EAG considers this is not a typographical error and composites is more appropriate language given the context of the passages.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 30, Section 3.2	The phrase "[redacted]" is marked as confidential but this is unnecessary, since it does not include any confidential information.	Vitamin A supplementation at ~2500 to 3000 IU (but not exceeding this) is also advised in the draft SmPC for patients receiving eplontersen; in the draft SmPC.	The EAG has updated the confidential marking as requested.
Page 31, Section 3.2	Some information from the draft SmPC is not considered to be confidential, this includes information about prescribing and administering eplontersen, but is marked as confidential in the report: The draft SmPC states that treatment should be [redacted]. It also describes the drug as a pre-filled pen that can be used for self-administration. It explains that the first injection by the patient or caregiver should be performed [redacted]	The draft SmPC states that treatment should be prescribed and supervised by a treating physician knowledgeable in the management of patients with amyloidosis. It also describes the drug as a pre-filled pen that can be used for self-administration. It explains that the first injection by the patient or caregiver should be performed under the guidance of an appropriately qualified healthcare professional, with training in the subcutaneous administration provided to patients and/or caregivers. Requirements for the appropriate storage and temperature of the drug before administration are also provided in the draft SmPC.	The EAG has updated the confidential marking as requested.

	[redacted]. Requirements for the appropriate storage and temperature of the drug before administration are also provided in the draft SmPC.		
Page 40, Table 3	The mNIS+7 CfB data for Week 85 is only presented in the CSR and is not publicly available.	[redacted]	The EAG thanks the company for highlighting this and has amended the error.
Page 76, Section 5.2.4.2.1	The % of total difference in costs should be marked as confidential since a back calculation using this value, and publicly available data, allows for a crude estimate of the confidential PAS for eplontersen.	The EAG additionally notes that the difference in administration costs between eplontersen and vutrisiran composites [redacted] of the total difference in costs (£[redacted] of £[redacted]), further supporting that the cost difference between technologies is robust to administration cost parameter uncertainty.	The EAG thanks the company for highlighting this and has amended the error.
Page 81, Section 6.3	The % of total difference in costs should be marked as confidential since a back calculation using this value, and publicly available data, allows for a crude estimate of the confidential PAS for eplontersen.	As the administration cost difference composites a small proportion of the total difference in costs ([redacted]), even when accounting for not all eplontersen patients being able to self-administer treatment in scenario analyses, the cost difference between technologies is robust.	The EAG thanks the company for highlighting this and has amended the error.
Page 97, Table 18	The 95% CI presented for the serum TTR LSM change for eplontersen is not publicly available and remains confidential.	[redacted]	The EAG notes that this information was not marked as confidential in the submission but

			has updated the marking as requested.
Page 97, Table 18	The 95% CI presented for the serum TTR LSM change for the external placebo is not publicly available and remains confidential.	[redacted]	The EAG notes that this information was not marked as confidential in the submission but has updated the marking as requested.

References

1. 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 2023;30:18-26.
2. EMA. Amvuttra (vutrisiran): European public assessment report. 2022.