NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

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   - Joint submission Association of British Neurologists and British Peripheral Nerve Society - endorsed by clinical expert Dr Alexander Rosser
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   - NHS England

5. **Expert personal perspectives** from:
   - Professor P Hawkins – clinical expert (condition only), nominated by Alnylam Pharmaceuticals
   - Mr V Nicholas – patient expert, nominated by Amyloidosis Research Consortium UK
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   - Mr Eric Low – patient expert, nominated by Amyloidosis Research Consortium UK

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

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Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279] **Pre-meeting briefing**

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

– the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
– the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG after the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key abbreviations			
AE	Adverse event	mNIS+7	Modified Neuropathy Impairment Score +7
AGNSS	Advisory Group for National Specialised Services	NAC	National Amyloidosis Centre
BSC	Best supportive care	NIS+7	Neuropathy Impairment Score +7
CEAC	Cost-effectiveness acceptability curve	Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
CHMP	Committee for Medicinal Products for Human Use	NT-proBNP	N-terminal pro b-type natriuretic peptide
ERG	Evidence Review Group	PAS	Patient Access Scheme
EQ-5D-5L	EuroQol 5-Dimensions, Five Level Questionnaire	pg/mL	nanogram/millilitre
hATTR	Hereditary transthyretin-related	PSA	Probabilistic sensitivity analysis
HR	Hazard ratio	QALY	Quality-adjusted life year
HRQoL	Health-related quality of life	SAE	Serious adverse event
ICER	Incremental cost-effectiveness ratio	TTR	transthyretin
mITT	Modified intention-to-treat	WTP	Willingness-to-pay

Disease background

Hereditary transthyretin-related (hATTR) amyloidosis

- Autosomal dominant inherited disorder caused by mutations in the transthyretin (TTR) gene
- Leads to production of abnormal TTR protein by the liver, which accumulates as deposits in the tissues of the body (amyloidosis) mostly in the peripheral nervous system or in tissues of the heart
- Ultra-rare condition
  - Currently 150* cases of hATTR amyloidosis in the UK, 112* in England
- A spectrum of clinical manifestations of hATTR amyloidosis:
  - polyneuropathy
  - cardiomyopathy
  - polyneuropathy and cardiomyopathy (manifest in most people)
- Common genetic mutations include Val122Il (39%), Thr60Ala (25%) and Val30Met (17%)
  - Val30Met mutation is associated with higher survival rate
  - Val122Ile mutation is associated with primary cardiomyopathy
- Reduced life expectancy to 3 to 15 years from onset of symptoms
  - median survival is 4.02 years in the UK (Gillmore *et al.* 2017)
  - people typically die from heart failure or complications of autonomic neuropathy resulting in wasting

* Data from the National Amyloidosis Centre (NAC)

Disease background

hATTR amyloidosis

hATTR is a systemic disorder with diverse clinical presentations and varying degrees of rapidly progression:

Neurological symptoms	Cardiac symptoms
• Peripheral neuropathy: sensory abnormalities in extremities, motor weakness, cachexia, and loss of ambulation • Autonomic dysfunction: low blood pressure when standing up, impotence, severe gastro intestinal (GI) symptoms, bladder dysfunction with recurrent urinary tract infections, cardiac arrhythmias • Progress to death due to GI symptoms, malnutrition and wasting	• Progressive thickening of the ventricular walls, interventricular septum, and cardiomyopathy, resulting in heart failure • Heart failure progress rapidly: substantial worsening of ability to walk, cardiac function • Progress to death

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Source: section 6.1.2 p.34 of the company submission

Classification of hATTR amyloidosis

No staging or disability scoring system covers all aspects of the disease; several scoring systems are available for classifying the disease:

- familial amyloidotic polyneuropathy (FAP) staging system (Coutinho) based on peripheral and autonomic neuropathy disability (used in licence for patisiran)
- polyneuropathy disability (PND) score
- Gillmore *et al.* 2017 staging system for cardiomyopathy (based on biomarkers NTpro-BNP* and estimated glomerular filtration rate)

PND	PND state description	FAP	FAP stage description
0	No impairment	0	No symptoms
I	Sensory disturbances, preserved walking capability	I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II	Impaired walking capability but ability to walk without a stick or crutches	II	Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
IIIA	Walking only with the help of one stick or crutch		
IIIB	Walking with the help of two sticks or crutches		
IV	Confined to a wheelchair or bedridden	III	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

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*NT-proBNP is a cardiac biomarker which Gillmore used to define a staging system for cardiac transthyretin amyloidosis using a cut-off 3000 pg/mL; high NT-proBNP indicates greater cardiac involvement

Source: Table 13 p.74 of the ERG report

Current treatment options

- No available pharmacologic disease-modifying treatment options in the UK
- Available treatment options aim at symptom management supportive care including pain management, nutritional and mobility support and mitigation of the effects of the disease on other organs
- Other pharmacological treatments may be used for treating hATTR
  - Tafamidis is not available in England due to a negative AGNSS recommendation
  - Diflunisal is used off-label, but not suitable for many patients due to being contraindicated in patients with severe heart failure, GI bleeding, or hepatic or renal failure
- Liver transplant rarely performed for hATTR amyloidosis in the UK because outcomes are poor in patients with cardiac involvement

Patisiran (Onpattro)

Alnylam

Marketing authorisation	Indicated for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
Mechanism of action	Ribonucleic acid interference agent that suppresses the production of transthyretin by the liver (including abnormal transthyretin) and thus reduce the accumulation of amyloid deposits in the tissues and organs
Administration & dose	• Intravenous infusion • Recommended dose: 0.3 mg/kg once every 3 weeks, for lifetime • No dose adjustments required
List price and PAS discount	• List price: £7,676 per 10 mg (5 mL) vial; [redacted] per patient per administration (mean of [redacted] vials per administration) • Simple discount PAS approved; included in economic analyses

ERG note there is no explicit information on treatment discontinuation in SPC and the company states that *"It is expected that patients will be treated with patisiran for the duration of their lives, subject to the clinical judgement of the treating physician."*

PAS: patient access scheme; SPC: summary of product characteristics

Decision problem (1/2)

	NICE final scope	Company submission	ERG comments
Population	People with hATTR amyloidosis	• Adults with hATTR amyloidosis with polyneuropathy • No evidence presented for patients with predominantly cardiac forms of hATTR in the absence of polyneuropathy	Population aligned with indication and APOLLO trial although 1 patient in the placebo group had FAP stage 3 disease at baseline
Intervention	Patisiran	As per scope	
Comparator	Established clinical management without patisiran	Best supportive care (BSC)	Company did not define a standardised BSC regimen, hence there might be variations in the care delivered between participating centres

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Source: Table 2 p.20 of the ERG report

Decision problem (2/2)

	NICE final scope	Company submission	ERG comments
Outcomes	• Neurological impairment • Symptoms of polyneuropathy • Cardiac function • Autonomic function (including the effects on the GI system and postural hypotension) • Weight loss • Effects of amyloid deposits in other organs and tissues (including eye) • Serum transthyretin • Motor function • Mortality • AE of treatment • HRQoL (for patients and carers)	Effects of amyloid deposits in other organs and tissues (including the eye), and HRQoL for carers not included	None

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AE: adverse events; HRQoL: health-related quality of life; GI: gastrointestinal

Clinical experts (1/3)

- Condition
  - hATTR is a rare, progressive, devastating and dignity-removing disease that leads to death within 7-10 years
  - Patients presenting with cardiac involvement have a worse prognosis (survival is around 4-5 years) than those presenting with a peripheral neuropathy
- Epidemiology
  - About 30 new cases each year. Most patients are based in England but around 5-10 patients are from Scotland, Northern Ireland or Ireland.
  - Mid estimated prevalence of hATTR (Schmidt *et al*., 2018) is 97. More than 50% are expected to receive treatment
- New technologies
  - Inhibition of the production of amyloid precursor proteins, transthyretin (TTR); would be seen as a “giant leap”
  - Aim to slow or (ideally) stop progression, enable gradual improvement and recovery, and thereby improve mobility and prevent disability; would be given in addition to current supportive care

Clinical experts (2/3)

  - Discontinuation of treatment should be considered when there is evidence of intolerance or lack of efficacy (for example over 12 months or more)
  - Patients are most likely to benefit from the new technologies if they are diagnosed early (stage 1); patients in stage 3 disease (unable to walk) may benefit from treatment (although not possible to assess in trials)

- Outcomes
  - mNIS+7 (measuring neurology impairment) is a sophisticated outcome to assess motor strength, reflexes, sensation, nerve conduction and postural blood pressure
  - Clinically significant outcome is maintenance of ability to walk, and without greater walking aids
  - Clinical benefits of patisiran are reflected in quality of life and clinical metrics; autonomic* benefits (associated to knock-down production of TTR) are difficult to quantify and will be associated with reduction or disease progression
- Service delivery
  - UK patients with hATTR amyloidosis are assessed (for overall clinical status, neuropathy progression and cardiac involvement) and followed up for 6 months at NAC; additional neurological measurements are assessed at the National Hospital for Neurology, UCLH
  - Patisiran will be first administered to patients at NAC and then at home (Alnylam plan to provide a home infusion service)

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NAC: National Amyloidosis Centre

Clinical experts (3/3)

- Current treatment options are limited:
  - tafamidis is not available in the UK
  - diflunisal is often used off-license but has little impact on the progression of the disease and can cause side effects
  - liver transplantation is used in very few patients (high costs, limited by the availability of donor organs)
- No guidelines exist to support clinical practice; there is no defined pathway of care

Impact of hATTR amyloidosis (1/3)

Amyloidosis Research Consortium (ARC) UK survey 2018

The hATTR Patient and Carer Survey conducted by ARC UK included 101 patients and 51 carers who provided information about their experiences (14 patients from UK)

- hATTR has a very high burden on patients, the multi-systemic nature of the disease affects all aspects of life
  - Sensory, motor and autonomic deficits, and in some patients, cardiac involvement, these translate into numerous effects on daily living, including:
- Mobility problems: “I was an avid runner, having completed 22 marathons. Now I walk slowly with the help of a cane.”
- Chronic pain: “It hurts all the way up to my belt.”
- Loss of manual dexterity: “Difficult to do things (buttons, zips, earrings). Dropping things, turning pages in a book. So many things that require tactile sense.”
- Diarrhoea: “I’m afraid to eat out of home away from bathroom. Diarrhoea comes on suddenly.”
- Insomnia: “If I cannot sleep, I steadily decline in all aspects.”
- Neuropathy in hands: “I can’t cook anymore as I’ll burn myself and not even notice”.
- Mental functioning: “Other things I can live with, even the constipation and diarrhoea.”

Impact of hATTR amyloidosis (2/3)

ARC UK survey 2018

- The disease also has a considerable impact on patients work or professional lives
- Patients reported that one of the most challenging aspects of having the disease is losing independence and becoming dependent on other family members
- Many patients have been carers for loved ones and also live with the knowledge that they may pass, or have already passed the disease onto their children

Significant unmet need

- Patients have mixed experiences of symptom and disease management approaches: there is unmet need with regard to efficacy, side-effect burden and convenience/choice
- New treatments specifically for hATTR offer significant hope to patients and their families
- Patients and carers value multiple factors as important for treatment, including efficacy, convenience, risk of side-effects and knowledge of benefits-risks
- Patients are likely to accept risks of side-effects for ‘modest’ gains

Experience with inotersen treatment

- Patients indicated that they considered inotersen to have had a positive effect on managing their disease and minimising their symptoms
- Rated it highly for convenience, an injectable treatment that can be self-administered at home

Impact of hATTR amyloidosis (3/3)

ARC UK survey 2018

The disease has a substantial lifelong impact on entire families

- It places a significant burden on family members as they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own in dealing with the realities of the disease
- Family members often become full or part-time unpaid carers with consequences on their work, social and financial situation
- Carers of hATTR patients reported that dealing with gastrointestinal problems (especially diarrhoea), patients' mental functioning and the combination of multiple symptoms are particularly problematic for them in their caring capacity
- As carers they experience the burden of the disease on their own lives and similarly to patients, multiple domains of their lives are affected by hATTR
- Carers reported that they feel exhausted from worry and from taking on an additional burden of household chores, juggling work and informal caring
- There is also a considerable emotional burden: some feel anger or sadness that their life is no longer their own; also reported they were anxious about seeing the patient deteriorate further
- They worried about their children and future generations who could have the disease

Impact of hATTR amyloidosis

Patient expert on the condition (1/2)

- Lack of understanding of hATTR amyloidosis by GPs and hospitals which can cause a lot of anxiety and a delay in treatment
- It has a major impact on patient's and family's life:
  - Patient can no longer do too many physical activities. day-to-day general activities are harder and slower (due to neuropathy and muscle wastage); partner has had to take on all the physical house chores and most of the running of the family
  - Patient usually loses employment, then hobbies, then social life, then the ability to self-care
  - Effect on bowel movements is the worst: very difficult to control diarrhoeas, can result in weight loss and incontinence, need to be careful on what to eat and have quick access to toilets, often lead to social isolation and travel restriction. Seriously disturb rest when occurs at night
  - Patient became emotional about things and get frustrated by the simplest problem
  - Psychologically devastating: some patients are aware of what to expect as they have seen their relatives with the disease progressed and died
  - Profound concern about children: it is possible and even likely, that they will develop the disease at some point in their lives. There are also situations where more than one patient is affected in one family, which makes the situation extremely difficult for the carers

Impact of hATTR amyloidosis

Patient expert on the condition (2/2)

- Living with disease is painful, depressing and disabling:
  - Neurogenic pain feels like suddenly being stabbed, with very short-duration intense pain and long-lasting aches. Can feel like burning, like being scalded. Does not show for. Usually starts by the feet and then progress proximally.
  - Numbness due to neuropathy starts in feet with a sensory ataxia due to loss of proprioception. It gets difficult to just stand up and balance, resulting in movements that make the patient look like he/she is drunk.
  - Eyes are often involved with glaucoma, vitreous opacification and loss of sight as a result. Being blind and having numb hands is a devastating combination, completely disabling
  - Autonomic dysfunction include hypotension, feeling fainting, digestive, sexual (including impotence), and urinary (frequent urinary infections) symptoms
  - Weakness and muscle atrophy causes difficulty, first walking, then using the hands. The weakness progresses proximally and in advanced stages, even breathing is difficult
  - Cardiac involvement often start with tiredness and shortness of breath. Affects walking distance and later ability to self-care. Often palpitations and arrhythmias require a pacemaker
  - Advanced stages develop central nervous degeneration, with headaches and progressive dementia, patient is in pain, unable to walk or stand, unable to use his or her hands, unable to self-care, with diarrhoea, with pressure ulcers and blind, results in a situation worse than death

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Impact of hATTR amyloidosis

Patient experts about patisiran

- “Dream come true” to have an effective treatment with very minimal side effects. If started early, it allows for a normal quality of life; it is described as “revolutionary” or “magic”
- “We expected that patisiran may stop progression of the disease […] now seeing that patients are recovering functions they had lost, particularly the digestive system and muscle strength. This recovery seems to continue in time, and patients that have been on the drug for several years (since trial phase II) show an amazing improvement”
- “The next generation will no longer have to suffer with this debilitating disease”
- “Patisiran will have a major impact on our lives. It will ease the disabilities that come with this disease and halt its progression
- Only disadvantage is where the treatment is taken and the time and cost to get there: “Patisiran is easy but takes about 3 hours. The main problem is the time and cost needed to get to the NAC in London. This takes place every 3 weeks. Also someone has to travel with me just in case I need support after the treatment.”

Clinical effectiveness evidence

Company submission section C

Clinical trial evidence

	APOLLO	Phase 2		GLOBAL OLE
Design	Phase 3	Phase 2 (dose escalation 0.01 to 0.3mg/kg), open-label	Phase 2 open-label extension (OLE)	Phase 3 open-label extension (OLE)
N	225 (2 from UK)	29 (0 from UK)	27 (0 from UK)	211 (1 from UK)
Intervention	Patisiran (n=148)	Patisiran	Patisiran	Patisiran
Comparator	Placebo (n=77)	None	None	None
Duration	18 months	8.3 months	24 months	12 months* (ongoing; completed July 2019)
Inclusion	hATTR amyloidosis adults with polyneuropathy	hATTR amyloidosis adults with mild-to-moderate neuropathy	Phase 2 patients (who tolerated 2 doses; cardiac subgroup)	APOLLO (n=186) and Phase 2 OLE (n=25) patients
Outcomes	**1º** Effect on neurologic impairment (mNIS+7) **2º** Quality of life (Norfolk QoL-DN), disability, ambulation, nutritional status (mBMI), grip strength, autonomic symptoms, cardiac involvement (incl NT-proBNP), serum TTR levels, EQ-5D-5L, nerve fibre density in skin biopsies	**1º** Safety and tolerability of multiple doses **2º** Pharmacodynamic effect of patisiran on serum total TTR protein levels	**1º** Safety and tolerability **2º** mNIS+7; NIS, HRQoL, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fibre density in skin biopsies, cardiac involvement, serum TTR levels	Long-term efficacy and safety

FAP: Familial Amyloidotic Polyneuropathy; hATTR; Hereditary transthyretin-related; mBMI: modified body mass index; mNIS+7: modified neurologic impairment score; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; OLE: open-label extension; PND: Polyneuropathy Disability; QoL: quality of life; TTR: transthyretin

*Global OLE is ongoing and currently have data for the first 12 months (interim data cut-off); patients may receive patisiran to up to 5 years (including time on APOLLO and Phase 2 OLE)

Endpoint definition: mNIS+7 and Norfolk QoL-DN

mNIS+7

- A composite neurological impairment score with 2 composite scores (maximum of 304 points in total)
  - neuropathy impairment score
  - modified +7 score - large and small fibre sensory tests
- A decrease in mNIS+7 score indicates an improvement in neurological impairment; a difference of 2 points is a clinically important difference in mNIS+7 (company)
- mNIS+7 was specifically modified from NIS+7 to better characterise and quantify sensation anywhere on the body, autonomic function, and nerve conduction changes that are typical in hATTR with Stage 1 and Stage 2 polyneuropathy
- Modifications aimed at ensuring the tests remain sensitive to change with disease progression

Norfolk QoL-DN

- A patient-reported measure validated in patients with hATTR with polyneuropathy
- Designed to capture the impact of neuropathy on quality of life, consisting of:
  - 35 questions across 5 domains, scores range: -4 to 135
  - 5 domains : physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy
- A decrease in Norfolk QoL-DN total score indicates an improvement of quality of life; No minimal clinically important difference for Norfolk QoL-DN is reported in the literature (company), however there is evidence that this measure can clearly distinguish between FAP stages

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mNIS+7: modified NIS+7; NIS: neuropathy impairment; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy

Patient baseline characteristics

	APOLLO		Phase 2	Phase 2 OLE	Global OLE
Arm	Patisiran (n=148)	Placebo (n=77)	Patisiran (n=29)	Patisiran (n=27)	Patisiran (n=211)
Median age	62	63	mean: 56	64.0	65
Male, %	74	75	69	67	74
Mean NIS+7	80.9	74.6	-	53.0	77
Cardiac subpopulation, %	61	47	-	41	-
PND score, %					
0	-	-	-	-	0.5
I	24	26	-	56	23
II	29	30	-	33	28
IIIA	28	29	-	7	20
IIIB	19	14	-	4	21
IV	0	1	-	-	8
FAP stage, %					
0	0	0	-	-	
I	45	48	86	89	44
II	55	51	14	11	49
III	0	1	-	-	8
Mutation, %					
Val30Met	38	52	76	20	46.4
non-Val30Met	62	48	24	7	54

Source: Reproduced from Table 4 p. 32 of ERG report

ERG critique on clinical trial designs

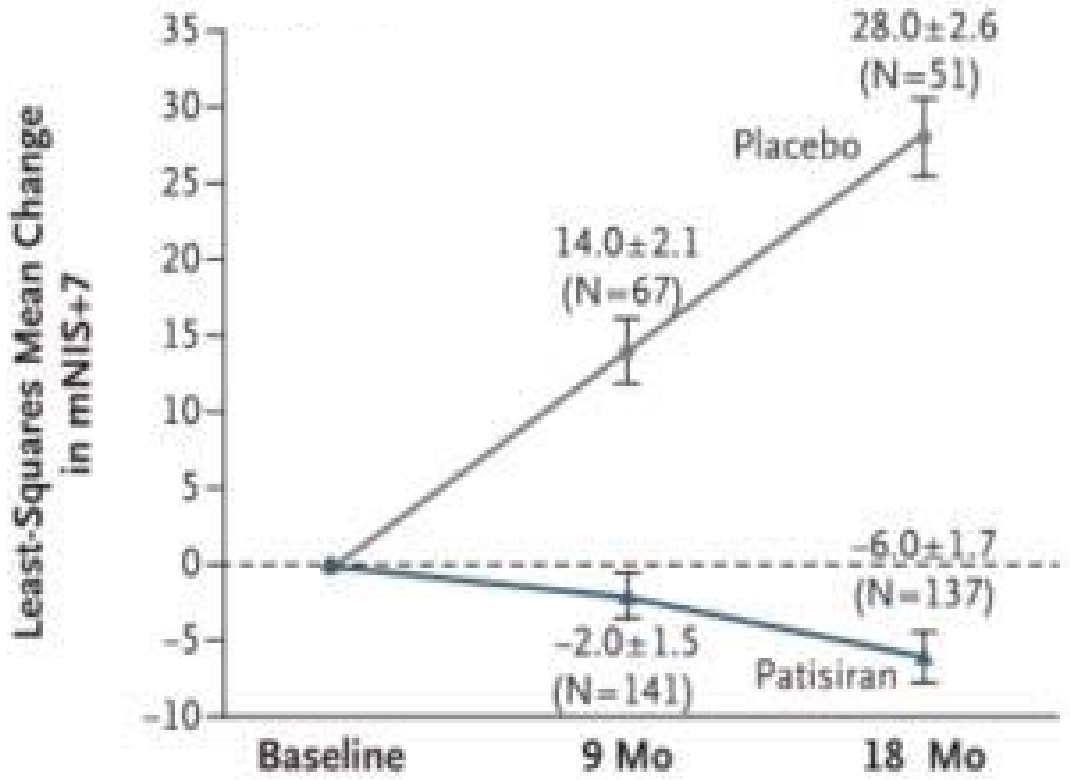
Theme	ERG comments
Phase 2 and Phase 2 OLE study quality	• No formal overall assessment of risk of bias was conducted; therefore the impact of the study quality on the results is unclear • Phase 2 and Phase 2 OLE are at a moderate risk of bias • Global OLE may be at high risk of bias

Uncertainty on reliability of APOLLO clinical evidence	• Patients in trials are consistent with patients seen in clinical practice in England
	• Moderate risk of bias in APOLLO:
	  • More patisiran-treated patients (61%) met the criteria for cardiac involvement than placebo-treated patients (47%); which is interpreted (by the company) as patisiran-treated patients having a worse prognosis overall, on average
	  • Unexpected imbalances in drop-outs between groups with more placebo-treated patients (38%) discontinuing treatment and withdrew from the study compared with patisiran-treated patients (7%)

Outcome (Change from baseline of mNIS+7)	Various issues are associated with measuring change from baseline (rather than adjusting for baseline using covariance): regression to the mean may be strong, post-treatment value must be linearly related to the pre-treatment value, result should not be baseline-dependent
Subgroup analyses	The possibility of heterogeneous treatment effects could not be ruled out because the company did not perform formal interaction test to account for patient characteristics that may be correlated with the subgroup

Clinical results: mNIS + 7

APOLLO



Patisiran vs placebo

- 9 months: -16.0; p<0.001
- 18 months: -34.0; p<0.001

Clinically important difference: 2 points (company)

- Change from baseline in mNIS+7 is significantly lower in patisiran group than in placebo group, at 9 and 18 months
- Treatment effect was significant for
  - all subgroups* (including cardiac and genotype)
  - all components of mNIS+7

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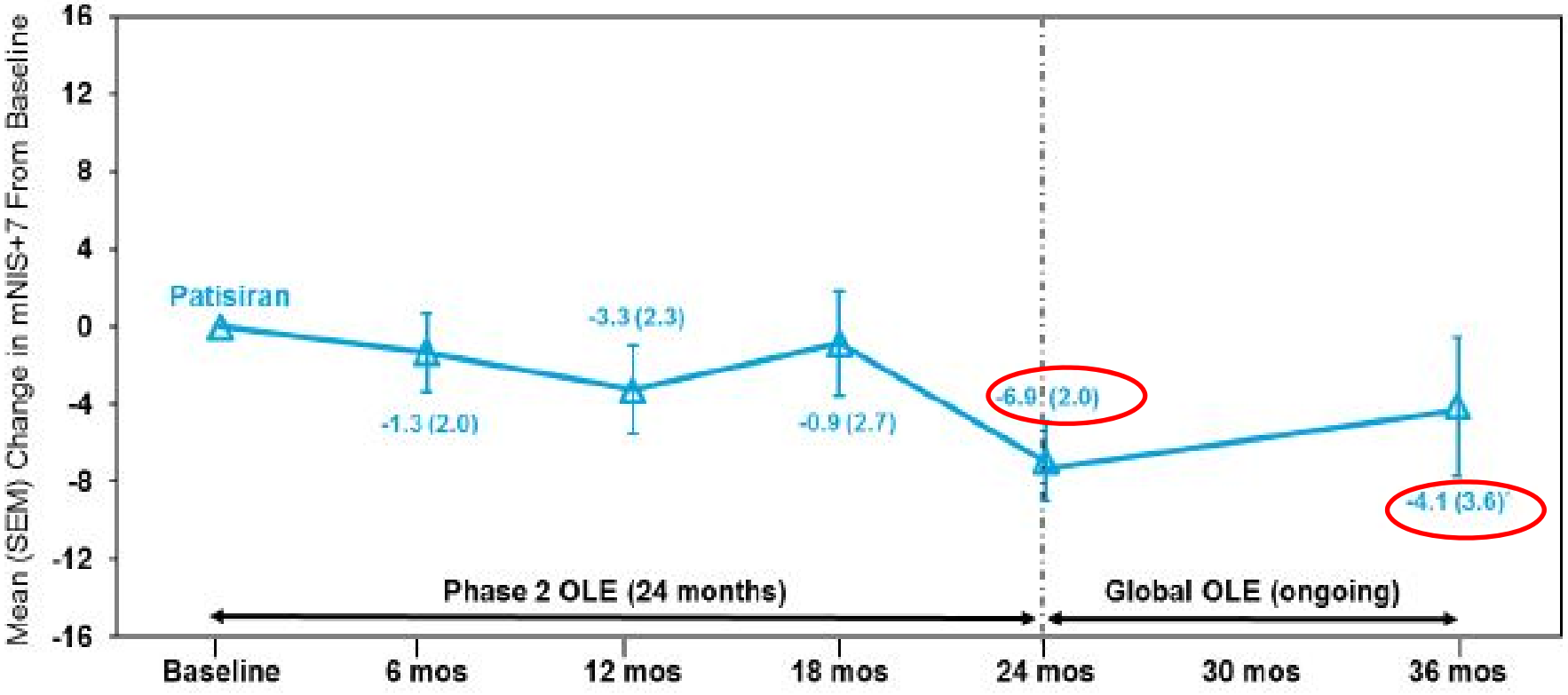
Source: Figure 6 p. 83 of company submission

Clinical results: mNIS + 7

Phase 2 OLE and Global OLE



- **Phase 2 OLE:** mean change from baseline to 24 months was -6.9 (n=26); 74% of patients had no change or an improvement in mNIS+7 at 24 months relative to baseline
- **Global OLE:** mean change from baseline at 36 months was -4.1

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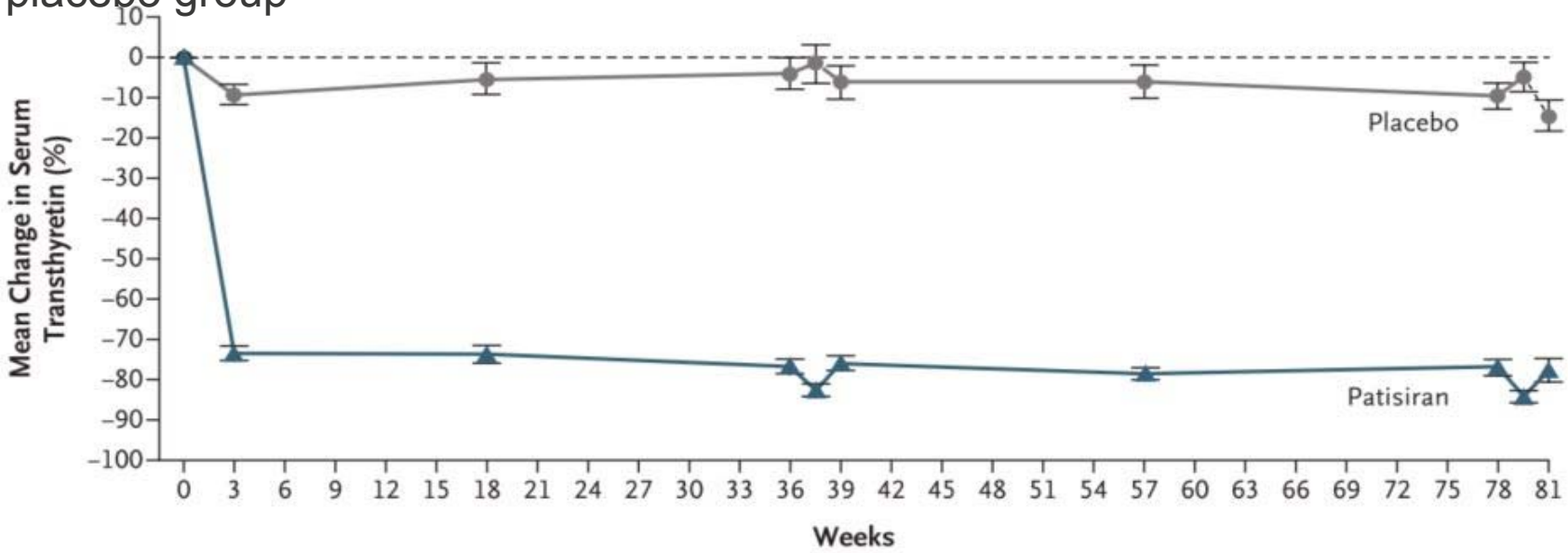
Source: Figure 17 p. 96 of company submission3

Clinical results: Mean serum TTR knockdown
APOLLO, Phase 2 and Phase 2 OLE

- **APOLLO (18 months)**: mean TTR knockdown was 87.8% in the patisiran group and 5.7% in the placebo group



- **Phase 2 dose escalation study:** significant reduction in mean serum TTR levels from baseline at nadir after the first (83.8%) and second (86.7%) dose of patisiran, among patients treated with the 0.3mg/kg Q3W dose
- **Phase 2 OLE (24 months):** mean serum TTR knockdown was 82%
- Clinically important difference (company): TTR reduction of ≥80% is predicted to lead to halting or reversal of neuropathy progression, as indicated by stabilisation or improvement in mNIS+7 from baseline (Polydefkis *et al.* 2018)

Clinical results: cardiac outcomes

APOLLO

- Cardiac subpopulations (61% patisiran; 47% BSC): cardiac outcomes were shown to be improved in most measures in patisiran group compared with placebo at 18 months:
  - Left ventricular (LV) wall thickness (difference between patisiran and BSC 0.9mm, p=0.02),
  - LV end-diastolic volume (difference between patisiran and BSC not reported),
  - global longitudinal strain (difference between patisiran and BSC 1.37%, *p*=0.02),
  - interventricular septum wall thickness (relative treatment effect not reported),
  - posterior wall thickness (relative treatment effect not reported),
  - relative wall thickness (0.05, *p*=0.0168),
  - cardiac output (0.38L/min, *p*=0.044)
- Non-cardiac subpopulation and mITT* overall population: results were broadly similar

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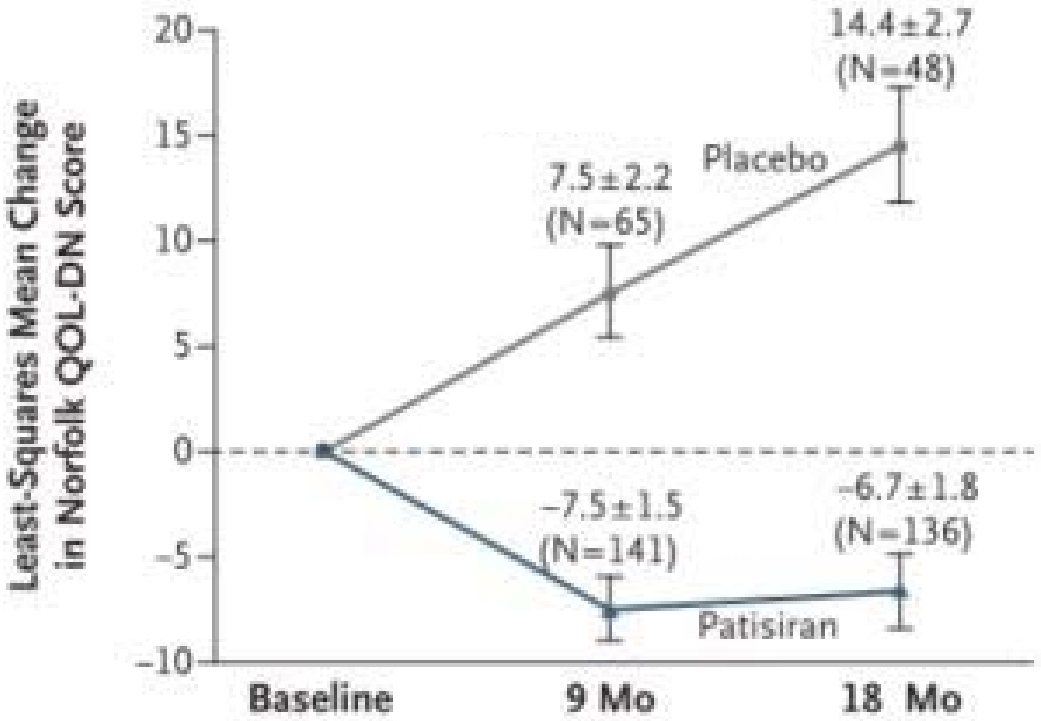
*mITT population in APOLLO consists of all patients randomised, who received at least one dose of patisiran

Clinical results: Norfolk QoL-DN

APOLLO



Patisiran vs. placebo:
18 months: -21.1; p<0.001

No minimal clinically important differences is reported in the literature (company)

- Significant difference in change from baseline at 18 months in favour of patisiran:
  - patients in the placebo group worsened,
  - patients in the patisiran group slightly improved

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Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy

Clinical results: EQ-5D-5L

APOLLO and Phase 2

- **APOLLO:**
  - Difference patisiran group to the placebo group:
    - At 9 months: 0.09 points, (95% CI: 0.05, 0.14)
    - At 18 months: 0.20 points, (95% CI: 0.15, 0.25)
  - Change from baseline to 18 months
    - Patisiran: 0.01
    - Placebo: -0.20

- **Phase 2 OLE:**
  - Mean EQ-5D score
    - At 24 months: 0.76 points
  - Mean change from baseline to 24 months :
    - Patisiran: -0.01 point

Adverse events (AEs)

- Safety data collected from APOLLO, Phase 2 dose escalation and Global OLE
- Almost all patients experienced AEs, in similar proportions (in both arms) for severe and serious AEs
- Fewer patients receiving patisiran discontinued or withdrew treatment due to an AE compared with patients receiving placebo (7% vs 38%)
- Diarrhoea was the only serious AE that was reported in ≥2% more patients in the patisiran group than in the placebo group (5.4% vs. 1.3%).
- 13 deaths were reported in APOLLO (n=7/148 [4.7%] in the patisiran group; n=6/77 [7.8%] in the placebo group), none of which were considered to be related to patisiran.

Adverse events (AEs)

	APOLLO		Phase 2 OLE	Global OLE
Treatment group	Patisiran (n=148) n (%)	Placebo (n=77) n (%)	Patisiran (n=25) n (%)	Total (n=211) n (%)
Treatment duration	**18 months**		**Up to 48 months**	
Any AE	143 (97)	75 (97)	25 (100)	189 (90)
TRAE	73 (49)	30 (39)	7 (28)	59 (28)
Severe AE	42 (28)	28 (36)	3 (12)	38 (18)
Severe TRAE	3 (2)	2 (3)	0	2 (1)
Serious AE	54 (36)	31 (40)	6 (24)	55 (26)
Serious TRAE	2 (4)	0	0	2 (1)
AE leading to withdrawal	7 (5)	11 (14)	0	16 (8)
Death	7 (5)	6 (8)	0	11 (5)

TRAE: treatment-related adverse events

Source: Section 9.7.2 and Table C9 p 107 of company submission

Key issues for consideration

Clinical evidence

- Is APOLLO generalisable to clinical practice in the England?

- Does the committee consider the clinical trials capture
  - benefits that are important to patients?
  - different aspects of the disease?

- Does the committee consider patisiran clinically effective?

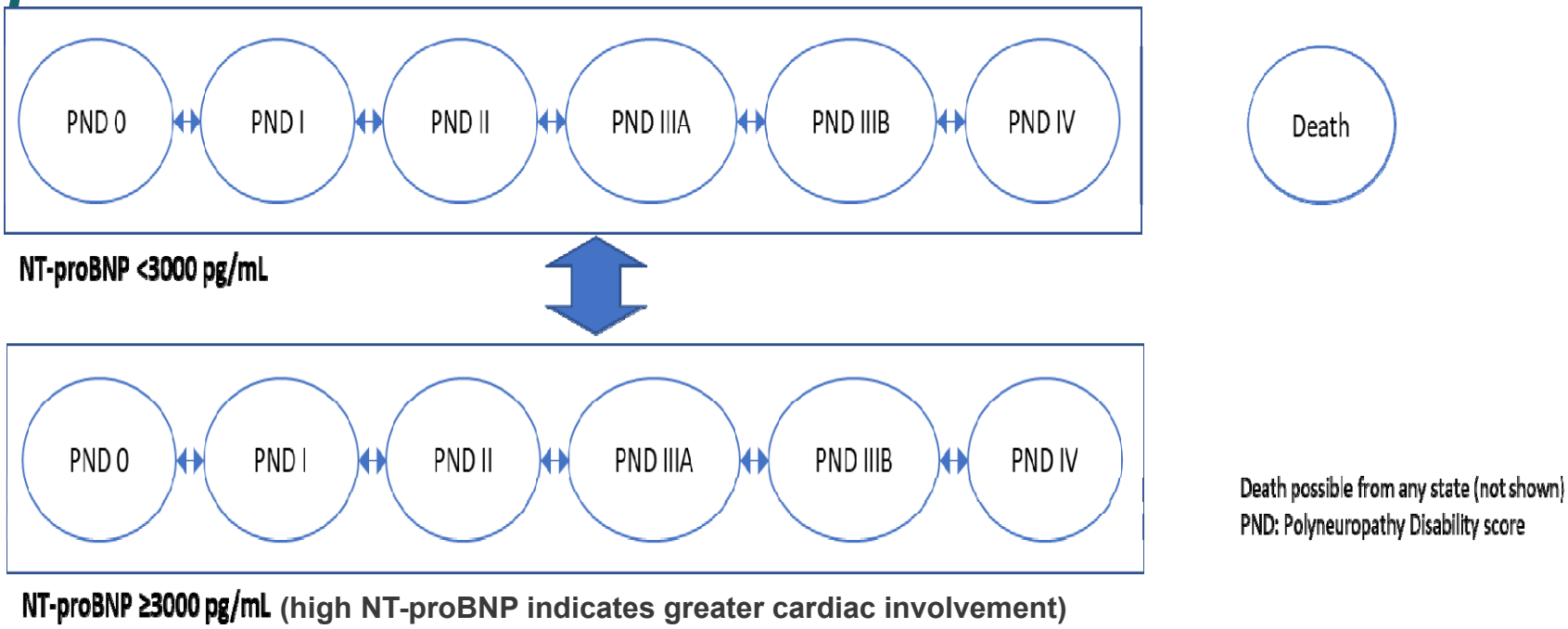
- What is the committee's view on the safety and tolerability profile?

Cost effectiveness evidence

Company submission section D

Company model structure

Description



- Markov model compares patisiran + best supportive care (BSC) vs. BSC
- 12 alive health states defined by a combination of polyneuropathy (PND score) and cardiac involvement (NT-proBNP)
- 40 years cycle length (lifetime), 6 month cycle
- 3.5% discount for costs; 1.5% discount for outcomes
- NHS/PSS perspective

NICE

Source: Figure 26 p 137 of company submission

Company model structure

Overview and key assumptions

- **Disease pathway** modelled through 12 alive health states:
  - Polyneuropathy – PND
  - Cardiac involvement – NT-proBNP
- **Progression of disease** captured through transitions between health states
  - Observed period (0–18 months), based on APOLLO
  - Extrapolation period (beyond 18 months), based on observed period (patisiran) or calculated according to PND and NT-proBNP (BSC)
- **Mortality** calculated by applying hazard ratios to general population mortality risk, for each health state
  - Increasing mortality risk associated with increasing neuropathy and cardiac involvement
- **Quality of life**
  - Starting utility scores allocated to each health state
  - Patisiran: utility increases over time, at a constant rate, up to a cap
  - BSC: utility decreases over time, at a constant rate, down to a cap

Model heath states based on PND score & NT-proBNP

- The company explained that the health states were not based on mNIS+7 score (primary outcome in APOLLO) as it was not possible to establish cut-offs and no data was available to correlate with mortality
- Thus, they based their heath states on PND and NT-proBNP scores because it reflects the natural history of the disease:
  - Strong correlation between PND scores and hATTR amyloidosis progression and severity of neuropathy
  - NT-proBNP is a biomarker used to assess the cardiac involvement (Gillmore *et al.* 2017)
  - PND scores associated with death (Surh e*t al.* 1994)

NICE

Source: Section 12.1.4 of company submission; section 5.3.3 . 13 of ERG report

PND score state descriptions and corresponding FAP stages

PND score	PND state description	Corresponding FAP stage
0	No impairment	Not included in staging system
I	Sensory disturbances but preserved walking capability	Stage I
II	Impaired walking capability but ability to walk without a stick or crutches	Stage II
IIIA	Walking only with the help of one stick or crutch	Stage II
IIIB	Walking with the help of two sticks or crutches	Stage II
IV	Confined to a wheelchair or bedridden	Stage III

Adult patients with hATTR amyloidosis with Stage 1 or 2 polyneuropathy *(as per marketing authorisation)*

- APOLLO included 1 patient with PND IV/FAP Stage III (placebo arm) and 0 patient with Stage 0 disease (in either patisiran or placebo arm)

NICE

Source: Table 13 p 70 of ERG report

ERG critique of model structure

Limitations	ERG justification

Model structure based on PND and NT-proBNP might not be the most appropriate	• Reasonable but FAP staging could be more appropriate
	  • PND only reflects mobility impairment, does not capture autonomic dysfunction symptoms and might not be sensitive over short period of time seen in trial
	  • Conversely, the company reported that PND provides more granular assessment of the disease than FAP
	• Large number of modelled health states creates challenges for estimating transitions
	• Additional concerns about the modelled link between health states and mortality and utility

Cycle length of 6 months	• Cycle length (6 months) differs from trial follow-up period (18 months) - creates challenges for calculation of transitions; observed data relating to 0-9 months and 9-18 months could have been used • ERG was unclear if there was sufficient justification for this cycle length given these challenges

Starting and stopping rules

	Clinical practice (SPC)	Economic model
Start of treatment	Adult patients with hATTR amyloidosis with Stage 1 or 2 polyneuropathy (FAP stage I and II, equivalent to PND score I, II, IIIa, IIIb)	• All patients with hATTR amyloidosis with polyneuropathy are eligible to start patisiran, irrespective of NT-proBNP level or PND score (excluding PND 0). • APOLLO includes 1 placebo-treated patient with FAP Stage 3/PND IV
Stop of treatment	No explicit definition	No "response-based" stopping rules: a discontinuation curve is applied and all patients are assumed to receive patisiran indefinitely (patients who transition to PND IV may still benefit from patisiran)

ERG comments:

- Clinical advisors note that discontinuing patisiran would only be considered if no TTR knockdown was evident; however this could not be directly incorporated to the company's model as TTR trajectory is not modelled
- Patisiran is indicated for FAP stage 1 and 2 therefore starting in stage 3 is not appropriate. This may imply that treatment should stop when moving to stage 3/PND IV
- A single transition matrix was applied, with no adjustment for discontinuation, such that the treatment effect remained constant even though increasing numbers of people discontinued

NICE

Source: section 5.3.3 p.111 of ERG report

Starting state distribution

- Patients can enter the model in any alive health state (except for PND 0) based on baseline distribution of PND scores (APOLLO) * probability of initial NT-proBNP is > 3,000pg/mL
- **ERG** note using that the company applied a equal probability of initial NT-proBNP is > 3,000pg/mL ([redacted]) Across PND states which they consider unnecessary
- At clarification, the company submitted the probabilities of high NT-proBNP by PND state (from APOLLO)

	Probability of initial NT-proBNP (company's model)		Probability of initial NT-proBNP (clarification)	
PND score	NT-proBNP <3,000pg/mL	NT-proBNP ≥3,000pg/mL	NT-proBNP <3,000pg/mL	NT-proBNP ≥3,000pg/mL
0	[redacted]	[redacted]	[redacted]	[redacted]
I	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]

- In their preferred analysis, the ERG used the probability from the clarification and excluded the 1 patient who was in FAP Stage 3/ PND IV

Transition probabilities

Company's approach used 2 transitions matrices

	OBSERVED period (baseline to 18 months)	EXTRAPOLATED period (beyond 18 months)
Patisiran	• Transition matrices were calculated directly using the APOLLO data (18-month data, converted to 6-month cycles using "traditional method") • Inclusion of "non-informative prior distribution" between alive states assuming implying an equal probability of transitioning between health states of 0.083 (patients can move to an improved state)	Same transition matrix as observed period applied
BSC		Patients can either stay in current health state or progress to next worst health state during each cycle. Transition matrices calculated from: 1. PND score: probability of PND decline at 18 months, adjusted to 6-month cycles 2. NT-proBNP level: probability of transition from low to high NT-proBNP over 18 months, based on "gamma function method" NB. No prior distribution included, so patients could not move to an improved or worsened by more than 1 state

ERG critique on transition probabilities

Limitations	ERG justification
"Non-informative" prior (used in observed period) can be unrealistic	Parameter estimates based on "non-informative" priors are unlikely to represent reasonable beliefs when the sample data are limited
BSC transition matrices (used in extrapolated period) are assumed to be restricted	• Model assumes BSC-treated patients cannot transition to an improved or worsened by more than 1 state • This is a strong assumption, but likely to be uncertain
Traditional matrix adjustment method produces bias in favour if BSC	• Method used to convert 18-month data to 6-month cycles is inappropriate when there are more than 2 heath states • produces a small bias in favour of BSC; however other methods are also imperfect • If the model was defined by FAP stage (rather than PND), the issue would still remain, although lessened
Unsure about gamma parametric curve	The company's gamma function method leads to all surviving patients treated with BSC develop NT-proBNP involvement after around 5 years; the ERG is unsure whether the company intended to implement the gamma function approach or how it should be interpreted

NICE

Source: Section 5.3.3 p. 115-116 of ERG report

Mortality risk

- Mortality risk modelled using a series of hazard ratios (HRs) :
  - Mortality risk assumed to increase with advancing PND score and for patients with NT-proBNP score > 3,000pg/mL
  - HRs extracted from literature:
    - Effect of cardiac involvement (NT-probBNP): Gillmore *et al* 2017
    - Effect of neuropathy (PND): Suhr *et al* 1994
  - Following multiple assumptions, HRs were calculated and applied in each heath state:

	NT-proBNP <3000 pg/mL	NT-proBNP ≥3000 pg/mL
PND 0-II	•Defined as "Low-risk group" •HR=2.01 over the mortality of the general UK population *General population * 2.01*	HR=2.04 vs corresponding PND state *General population * 4.12 ….*5.35 ….*19.49 respectively*
PND III	HR=1.30 over the low-risk group *General population * 2.62*	
PND IV	HR=4.73 over the low-risk group *General population * 9.53*	

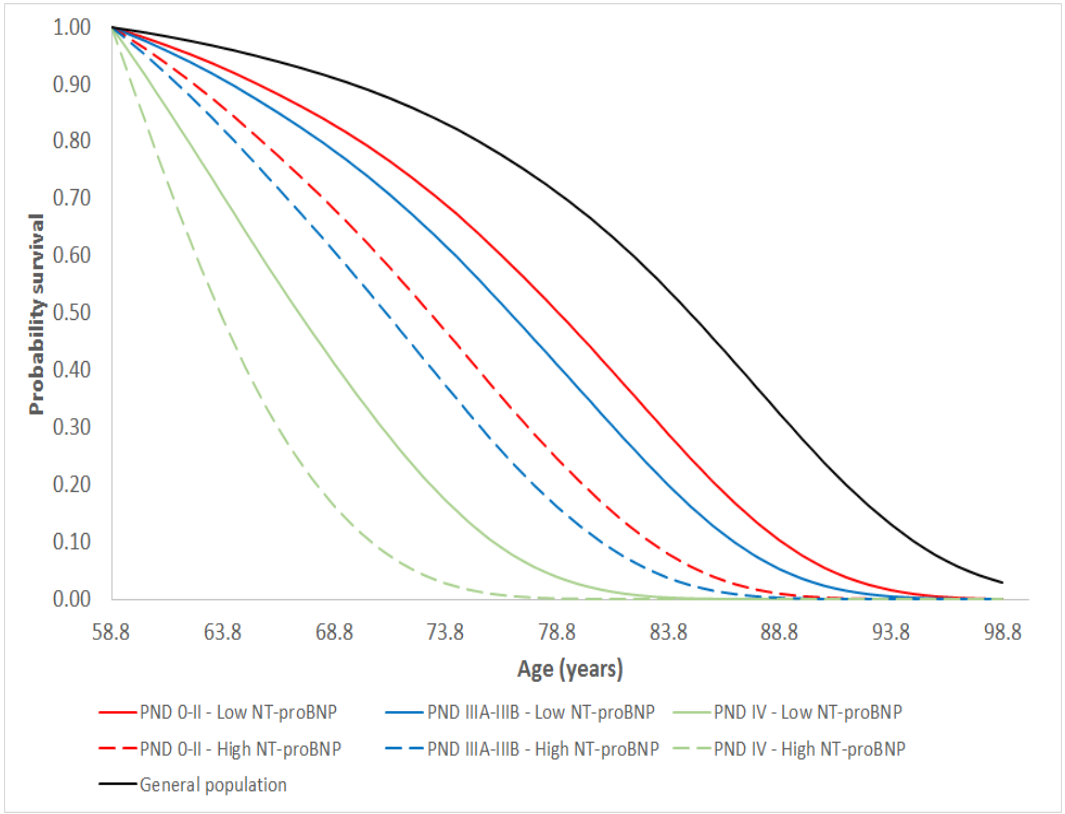
HR: hazard ratio; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability

NICE

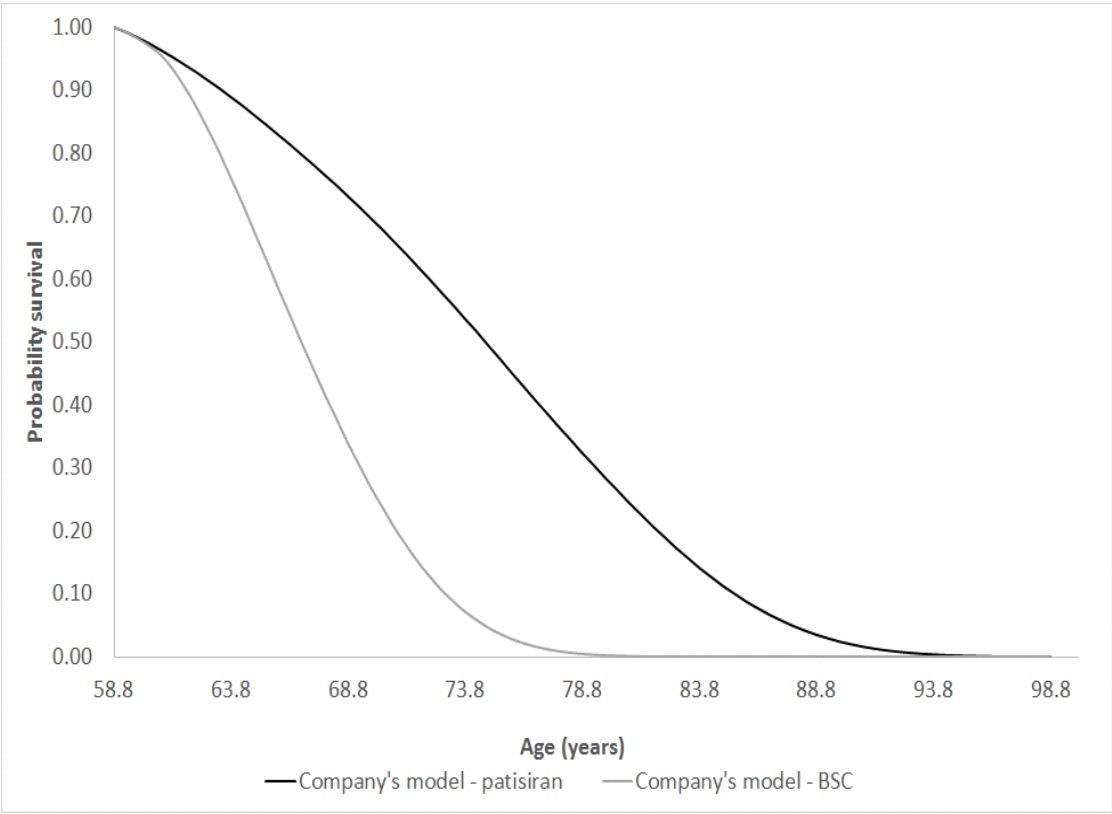
Source: Table D4 p 147 of company submission

Mortality risk – Overall survival (OS) prediction

OS by PND and NT-proBNP scores



OS prediction for patisiran and BSC



Source: Figure 9 p 85 of ERG report (generated by ERG)

ERG critique on mortality risk

Limitations	ERG justification
General method	• Company's approach is largely based on external data; no consideration was given to plausible underlying hazard functions or to supplementing the observed data with experts' beliefs to estimate parameters

Suhr study might not be relevant	• Target population is not clearly defined; no information on patient characteristics
	• Concerns with survival analysis
	  • Time 0 is assumed to be the onset of symptoms, which does not match APOLLO
	  • Censored observations not taken into account (although only 13/27 patients died in the study)
	  • No information on number of deaths by PND stage
	  • Mean survival is derived by weighing means in each PND score according to sample size (rather than number of events)
	  • Hazard rates are estimated from mean values assuming an underlying exponential distribution for the time to death without any justification
	  • Weighted average of HRs might not be relevant for the target population
	• ERG believe the company's approach is convoluted, circular and uncertain

Health-related quality of life (HRQoL)

Company ‘s approach

Each health state starts with a given utility, which then either increases or decreases each month for the patisiran/BSC arm, up to or down to a cap

- Model includes utilities from APOLLO (EQ-5D-5L mapped to EQ-5D-3L)
- A Maximum and minimum utility cap was applied to avoid “ceiling effects”
- Additional cap to ensure utilities do not exceed general population (Kind et al. 1999)

Monthly utility changes were taken from a regression analysis

- Company’s regression analysis assumed PND score & treatment by time as significant covariates

Applied a caregiver disutility of 0.01 in PND IV health state (Alzheimer’s, AGNSS tafamidis report)

HRQoL

ERG critique on company's approach

ERG comments:

- Regression is unreliable: omission of time, treatment and cardiac involvement as covariates
- Application of ceiling effects is a result of statistically poor model which lead to unrealistic utilities
  - utility increases or plateaus as patients age
  - Patisiran: patients with PND II are assumed to have the same HRQoL as a patient with asymptomatic disease (PND 0) over time
  - BSC: patients with PND 0 are assumed to suffer considerable reductions in HRQoL

[redacted]

HRQoL

Company base case and ERG scenario utilities

ERG identified 3 sources of utilities based on FAP stage (Stewart et al., Tafamadis AGNSS report, ICER evaluation report*) and 1 for general population (Ara *et al*., 2010) which they explore in their scenario analyses

			Mean	Maximum cap (patisiran)*	Minimum cap (BSC)*
APOLLO (used in the company's model)	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
Stewart et al (used in ERG scenario analysis)	Val30Met mutation	FAP 1	0.7	-	-
		FAP 2	0.44	-	-
		FAP 3	0.1	-	-
	Other mutations	FAP 1	0.68	-	-
		FAP 2	0.4	-	-
		FAP 3	0.05	-	-

**The CS includes a transcription error relating to the maximum and minimum utility values. The table presents the values which are used in the company's model rather than the incorrect values presented in the CS*

Resource use

Items	Value/description	Source
Patisiran costs • Acquisition* • Administration (in hospital; per infusion) • Premedication (IV dexamethasone and H1/H2 blockers, paracetamol)	• [redacted] per patient (list price) • £301 • £13.89	Company NHS National prices and tariff 2016-17 eMIT 2018, MIMS
BSC cost	£0	Company
Health state costs (per cycle and one-off; increase by health state with increasing severity)	(i) per-cycle polyneuropathy: [redacted] (ii) per-cycle cardiomyopathy: [redacted] (iii) one-off polyneuropathy: [redacted] Patisiran: costs reduced by [redacted] (polyneuropathy) and [redacted] (cardiomyopathy)	Delphi panel
Serious AEs (per event; events with frequency ≥ 2% [APOLLO])	Range: £503 (atrioventricular block) – £1,123 (urinary tract infection)	NHS Reference Costs 2016-17
End-of-life	£5,765.76	NICE TA 451

**Per 6 months; function of cost per vial, body weight distribution, number of administrations and RDI (effective compliance; estimated at 0.97 [APOLLO*

- **ERG comments**
  - Limitation of Delphi: does not yield a probability distribution representing uncertainty about parameters and therefore is unlikely to reflect the true expected cost and uncertainty
  - AEs assumed to occur at a constant rate; however would be expected to be attenuated over time, and inconsistent with assumption of discontinuation of patisiran over time
  - Homecare costs are not included (although patisiran is proposed to be given via homecare after initial treatment at NAC)
  - Errors in cost calculations: repeated application of 'one-off' costs, double-counting of 'one-off' costs, and administration and premedication costs not adjusted by compliance

Discount rate

- The company's base case analysis applies differential discount rates of 1.5% for health outcomes and 3.5% for costs. The company believes
  - Patisiran meets most of the criteria established by NICE for the consideration of a 1.5% discount rate on health effects because has shown a high level of safety and effectiveness over the long term and has demonstrated the ability to halt or reverse disease progression and improve HRQoL
  - the requirement that health benefits must be sustained over at least 30 years would unfairly penalise patients with hATTR amyloidosis as they are often older and therefore would have had an additional life expectancy less than 30 years even in the absence of this disease.
- **ERG note** this approach is inappropriate because
  - NICE Reference Case (and non-reference case) does not support the use of differential discount rates
  - Only some patients are close to death and not all have severely impaired HRQoL (as shown by modelled OS and utilities)
  - Lack of evidence to show that patisiran can improve patients' HRQoL or survival beyond 18-months
  - The expected survival for a matched cohort in UK general population is less than 30 years
  - Proposed arguments for differential discounting could be made for any appraisal

Company's base case

PAS price

	Total costs (£)	Total QALYs		Inc. costs (£)	Inc. QALYs		Cost per QALY gained (£/QALY)
		undisc.	disc*.		undisc.	disc*.	
Probabilistic							
Patisiran	[redacted]	NR	8.42	[redacted]	NR	8.11	[redacted]
BSC	[redacted]	NR	0.31	-	-		-
Deterministic							
Patisiran	[redacted]	9.86	8.52	[redacted]	9.73	8.30	[redacted]
BSC	[redacted]	0.13	0.22	-	-		-

BSC – best supportive care; inc – incremental; QALY - quality-adjusted life years

*based on discount rates of 1.5% for health outcomes and 3.5% for costs

ERG conducted the probabilistic analysis because the company didn't present it

NICE

Source: Table 25 p 95 of ERG report

Probabilistic sensitivity analysis

PAS price

- The probability that patisiran produces more net benefit than BSC at willingness-to-pay (WTP) thresholds <£100,000 per QALY gained is approximately [redacted].
- At WTP thresholds of £200,000 per QALY gained and £300,000 per QALY gained, the probability that patisiran is optimal is approximately [redacted] and [redacted], respectively.

NICE

Source: Figure 11 p.95 of ERG report

Deterministic sensitivity analysis

PAS price

NICE

Source: Figure 12 p.96 of ERG report

Company scenario analyses

PAS price

Scenario	Inc. QALYs (undisc.)	Inc. QALYs (disc.*)	Inc. costs	ICER (per QALY gained)
Company base case (deterministic)	*9.73*	*8.30*	[redacted]	[redacted]
Scenario 1A – pessimistic imputation of missing transition data (all patients with missing data progress to next worst state) rather than no imputation	8.62	7.36	[redacted]	[redacted]
Scenario 1B – optimistic imputation of missing transition data (all patients with missing data regress to next best state)* rather than no imputation	10.51	8.94	[redacted]	[redacted]
Scenario 2 – no utility max/min cap	12.58	10.61	[redacted]	[redacted]
Scenario 3 – exponential time on treatment function implies that N patients that continue to receive patisiran decrease (rather than log-normal function)	9.73	8.30	[redacted]	[redacted]
Scenario 4 –mortality is assumed to be only caused by cardiomyopathy (rather than a combination of PND and cardiomyopathy)	13.35	11.17	[redacted]	[redacted]

*based on discount rates of 1.5% for health outcomes and 3.5% for costs

NICE * *The results for this scenario appear to be incorrect in the CS*

Source: Table 26 p.98 of ERG report

ERG exploratory analyses

- ERG presented a preferred exploratory analysis:
  - Correction or errors and conceptual issues: administration and premedication costs down-weighted by compliance, one-off costs removed, treatment discontinuation removed
  - Equal discount rates: 3.5%
  - Recalculated starting state distribution: including probability of NT-proBNP≥3000pg/ml by PND state, excluding patient with FAP stage 3
  - General population utility cap from Ara and Brazier (instead of Kind et al)
  - Adjusted mortality calculation: mortality effect of cardiac involvement (NT-proBNP) using HR from Gillmore *et al* was removed for low NT-proBNP states

- ERG also presented additional exploratory scenarios based on its preferred analysis
  - Utilities: change in utility over time removed, utility values from Stewart et al, utility decrement for NT-proBNP≥3000pg/ml
  - Resource use: resource use reduction with patisiran halved, removed
  - Transitions: no change in NT-proBNP over time

- ERG notes that its probabilistic analysis corrects some concerns regarding the company's PSA, but considerable uncertainties remain

ERG preferred analysis

PAS price

Option	QALYs (disc.)	Costs	Inc. QALYs (disc.)	Inc. costs	ICER (per QALY gained)
Company's base case					
Patisiran	*8.52*	[redacted]	*8.30*	[redacted]	[redacted]
BSC	*0.22*	[redacted]	*-*	*-*	*-*
(1) Correction of minor errors (applied in subsequent analyses)					
Patisiran	8.52	[redacted]	8.30	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(2) Equal 3.5% discount rates applied					
Patisiran	7.14	[redacted]	6.82	[redacted]	[redacted]
BSC	0.32	[redacted]	-	-	-
(3) Recalculation of starting state distribution and removal of patient with FAP 3					
Patisiran	8.53	[redacted]	8.31	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-

ERG preferred analysis

PAS price

Option	QALYs (disc.)	Costs	Inc. QALYs (disc.)	Inc. costs	ICER (per QALY gained)
Company's base case					
Patisiran	*8.52*	[redacted]	*8.30*	[redacted]	[redacted]
BSC	*0.22*	[redacted]	-	-	-
(4) Use of general population cap from Ara et Brazier (rather than Kind et al.)					
Patisiran	8.54	[redacted]	8.32	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(5) Mortality effect from Gilmore t al was removed for low NT-proBNP states					
Patisiran	8.52	[redacted]	8.30	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(6) ERG-preferred analysis (deterministic, analyses 1-5 combined)					
Patisiran	7.17	[redacted]	6.85	[redacted]	[redacted]
BSC	0.32	[redacted]	-	-	-

ERG exploratory analysis

PAS price

Option	QALYs (disc.)	Costs	Inc. QALYs (disc.)	Inc. costs	ICER (per QALY gained)
(6) ERG-preferred analysis					[redacted]
(7) Change of utility over time is removed (removal of [redacted] and [redacted], per month)					
Patisiran	5.58	[redacted]	3.87	[redacted]	[redacted]
BSC	1.71	[redacted]	-	-	-
(8a) Utility values from Stewart et al - Val30Met mutation (rather than APOLLO)					
Patisiran	5.75	[redacted]	3.51	[redacted]	[redacted]
BSC	2.25	[redacted]	-	-	-
(8b) Utility values from Stewart et al - other mutations (rather than APOLLO)					
Patisiran	5.36	[redacted]	3.41	[redacted]	[redacted]
BSC	1.95	[redacted]	-	-	-
(9) Utilities: lower utility assumed for high NT-proBNP states (rather than similar irrespective of high or low NT-proBNP states)					
Patisiran	7.08	[redacted]	6.73	[redacted]	[redacted]
BSC	0.35	[redacted]	-	-	-

NICE

Source: Table 34 p. 126 of ERG report

ERG's exploratory analysis

PAS price

Option	QALYs (disc.)	Costs	Inc. QALYs (disc.)	Inc. costs	ICER (per QALY gained)
(6) ERG-preferred analysis					[redacted]
(10a) Resource use: patisiran relative reduction of 50%					
Patisiran	7.17	[redacted]	6.85	[redacted]	[redacted]
BSC	0.32	[redacted]	-	-	-
(10b) Resource use: patisiran relative reduction removed (0%)					
Patisiran	7.17	[redacted]	6.85	[redacted]	[redacted]
BSC	0.32	[redacted]	-	-	-
(11) Mortality risks: removal of PND-related mortality (HR = 1)					
Patisiran	7.96	[redacted]	8.99	[redacted]	[redacted]
BSC	-1.03	[redacted]	-	-	-
(12) Mortality risks: zero change in NT-proBNP					
Patisiran	7.17	[redacted]	7.30	[redacted]	[redacted]
BSC	-0.12	[redacted]	-	-	-

NICE

Source: Table 34 p. 126 of ERG report

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incr QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr)
Greater than or equal to 30	3

QALY gain undiscounted

Deterministic analyses			QALY gain undiscounted	QALY gain discounted	ICER (per QALY gained)
Company	Base case		*8.30*	*9.73*	[redacted]
	Scenarios with QALY gain >10	1B	10.51	8.94	[redacted]
		2	12.58	10.61	[redacted]
		4	13.35	11.17	[redacted]
ERG	Base case		9.76	6.85	[redacted]
	Scenario (11) with highest QALY gain		13.70	8.99	[redacted]

Budget impact
PAS price

- Budget impact is based on 100 patients eligible for patisiran
  - Expected uptake of [redacted] per year (included patients who wish to participate in clinical trials, defer treatment or receive alternate treatment)

	Year 1	Year 2	Year 3	Year 4	Year 5
Annual cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- ERG believes the budget impact of patisiran likely to be underestimated:
  - Stage distribution may not be representative of clinical practice (as APOLLO restricted to PND ≤3b)
  - Level of uptake will be higher than the estimates predicted by the company
  - Cost estimates do not take into account the scenario in which patisiran is delivered through the proposed homecare service
  - Unclear whether the budget impact estimates include PAS price

NICE

* From the company submission, numbers identified by NAC

NHS England comments

- No published guideline for this condition
- National Amyloid Centre at the Royal Free hospital in London is the recognised centre for diagnostic evaluation of patients suspected of amyloid-forming conditions
- Pathway for ongoing care and treatment of patients with an established diagnosis is less well defined
- Some patients may be under the care of local neurologists or other specialists
- The availability of disease modifying treatment is likely to improve the definition and clarity of pathways for ongoing care
- If recommended, extra resource use will be in monitoring the effects of treatments
  - Increased outpatient attendance and costs of investigations or imaging
- There will a small requirement for staff training

Equality

- Most common genetic variants of hATTR amyloidosis in England (V122I and T60A) are more prevalent in people with African–Caribbean and Irish family origins
- hATTR amyloidosis typically affects older people
  - Cost-effectiveness methods may penalise older patients: criterion for using 1.5% discount rate of health benefits sustained over 30 years would disadvantage people with a shorter life expectancy
- hATTR amyloidosis is a chronic and disabling condition

Innovation

The company considers patisiran is an innovative treatment because:

- It is a step-change in the management of hATTR amyloidosis
- It is first ever licensed siRNA, thus its mechanism of action is distinct from all previous treatments for hATTR amyloidosis
- There is a unmet need for treatment for hATTR amyloidosis
- It has been awarded with ‘Promising Innovative Medicine’ designation by Medicines and Healthcare products Regulatory Agency (January 2018)

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key issues for consideration

Cost-effectiveness evidence

- What is the committee's view of the structure and assumptions in the economic model?
  - Model structure, disease progression and health state transitions
  - Mortality: effects of PND and cardiomyopathy
  - Utilities: assumed change over time, source of estimates
  - Other assumptions
- What is the appropriate discount rate (3.5% or 1.5%) for costs and health benefits?
- What is the most plausible ICER?
- What QALY weighting should be used in decision-making?
- What factors affecting the guidance need to be taken into account?
  - Equalities issues?
  - Additional factors?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Version: 4 September 2018

Submitted by: Dr. Anant Murthy
VP, Market Access & Policy EU & Canada

Alnylam Pharmaceuticals

Contents

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

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Glossary of terms

Term	Definition
6MWT	6-minute walk test
10MWT	10-metre walk test
ADL	Activities of daily living
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BP	Blood pressure
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CI	Confidence interval
CM	Cardiomyopathy
CMAP	Compound muscle action potential
CMT	Charcot-Marie-Tooth
CNS	Central nervous system
COMPASS-31	Composite autonomic symptom score-31
DPD	^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid
EAMS	Early Access to Medicines Scheme
ECG	Echocardiogram
EPAR	European Public Assessment Report
EQ-5D	EuroQol Five Dimension
EQ-5D-5L	EuroQol Five Dimension, Five Level Questionnaire
EQ-VAS	EuroQoL visual analogue scale
FAP	Familial amyloidotic polyneuropathy
FAC	Familial amyloidotic cardiomyopathy
GI	Gastrointestinal
hATTR	Hereditary transthyretin-mediated amyloidosis
HCRU	Health-care resource utilisation
HRQoL	Health-related quality of life
IRR	Infusion-related reaction
ITT	Intent-to-treat
LLN	Lower limit of normal
LNP	Lipid nanoparticle
LS	Least square
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVF	Left ventricular failure
MAUI	Multi-attribute utility instrument
mBMI	Modified body mass index
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent-to-treat

Term	Definition
MMRM	Mixed model repeat measurement
mNIS+7	Modified Neuropathy Impairment Score +7
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NAC	National Amyloidosis Centre
NCS ∑5	Nerve conduction studies
NHS	National Health Service
NHNN	The National Hospital for Neurology and Neurosurgery
NICE	National Institute for Health and Care Excellence
NIS+7	Neuropathy Impairment Score +7
NIS-LL	Neuropathy Impairment Score of the Lower Limb
NIS-W	Neuropathy Impairment Score-Weakness
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
OLT	Orthotopic liver transplant
PIM	Promising Innovative Medicine
PN	Polyneuropathy
PND	Polyneuropathy disability
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QoL	Quality of life
QST	Quantitative Sensation Testing
RCT	Randomised controlled trial
RDI	Relative dose intensity
RNAi	Ribonucleic acid interference
R-ODS	Rasch-built Overall Disability Scale
SE	Standard error
siRNA	Small interfering ribonucleic acid
SLR	Systematic literature review
SNAP	Sensory nerve action potential
SPC	Summary of Product Characteristics
S ST QSTing	Smart Somatotopic Quantitative Sensation Testing
T_4	Thyroxine
ToT	Time-on-treatment
TTR	Transthyretin
TUDCA	Taurousodeoxycholic acid
UK	United Kingdom
USA	United States of America
US	United States

Term	Definition
wtATTR	Wild-type transthyretin-mediated amyloidosis
WTP	Willingness-to-pay

Executive Summary

Overview of the proposed technology

Parisian (Onpattro®) is the first Committee for Medicinal Products for Human Use (CHMP)-approved medication in the ribonucleic acid interference (RNAi) therapeutic class, recognised as one of the most promising and rapidly advancing frontiers in biology and drug discovery. The discovery of RNAi was awarded the 2006 Nobel Prize in Physiology or Medicine.[1] Alnylam has specifically engineered patisiran to treat hereditary transthyretin (TTR)-mediated (hATTR) amyloidosis, a progressive, life-threatening, ultra-rare disease in which amyloid deposits in multiple organs and tissues trigger a range of chronically disabling symptoms.[2-9] Patisiran directly targets the cause of hATTR amyloidosis by blocking liver production of dysfunctional TTR, leading to a reduction of damaging amyloid deposition throughout the body, potentially allowing the body to recover.[10,11] Patisiran has demonstrated the ability to significantly reduce symptoms, reverse disease progression, and improve health-related quality of life (HRQoL) in a wide range of patients with hATTR amyloidosis.[11] Patisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.[12] The positive opinion from the CHMP was published on 27 July 2018 under the EMA's accelerated assessment procedure which is reserved for medicines expected to offer therapeutic innovation and that are of major public health interest.[13] European Commission (EC) approval is anticipated in September 2018. Patisiran has received the designation of Promising Innovative Medicine (PIM) from the Medicines and Healthcare products Regulatory Agency (MHRA).[14] Alnylam Pharmaceuticals has established an Early Access to Medicines Scheme (EAMS) for eligible hATTR amyloidosis patients, with the MHRA announcing its EAMS Scientific Opinion on August 3rd 2018.[15]

Nature of the condition

Disease background

hATTR amyloidosis is an ultra-rare disease; according to the National Amyloidosis Centre (NAC), in 2018 there are only 150 diagnosed patients with hATTR amyloidosis in the UK, of whom an estimated 112 live in England.[8,9,16]

hATTR amyloidosis affects multiple systems in the body and results in rapidly progressive and debilitating damage to sensory, motor, and autonomic nerves (neuropathy), and to the heart (cardiomyopathy).[2,6] Accumulation of amyloid deposits leads to severe and worsening disability, increasing morbidity, devastating impairment

of the health-related quality of life (HRQoL) of patients and their caregivers, and ultimately death.[2,6,11,17]

While patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients will proceed to manifest symptoms of both over the course of the disease.[6,18-20] Although a genotype-phenotype correlation has been reported for hATTR amyloidosis, with some TTR mutations presenting more commonly with polyneuropathy and others with cardiomyopathy, a mixed manifestation is reported in the UK hATTR amyloidosis population, highlighting the importance of treating both polyneuropathy and cardiomyopathy.[7,16,20,21]

Morbidity, mortality, and HRQoL

Following the onset of symptoms, patients with hATTR amyloidosis typically die within 3 to 15 years depending on the underlying TTR mutation and clinical manifestation.[21,25,43,51] The median survival for hATTR amyloidosis patients with cardiac involvement is 3–5 years after diagnosis.[7,20] Based on calculations using data for UK hATTR amyloidosis patients reported by Gillmore et al. 2017, the median overall survival in the UK is 4.02 years.[7] Death generally results from cardiac involvement or wasting.[7,22,23]

In the absence of effective disease-modifying therapy—none of which were available in UK clinical practice at the time of writing—patients' lives are marked by chronically debilitating symptoms that increasingly impair their ability to live their daily lives.[24] Patients with neurologic manifestations may experience progressive muscle atrophy and resulting weakness in both the lower and upper body.[2,23] Impaired balance often leads to difficulty walking, eventually leaving patients dependent on walking aids or wheelchairs.[2,5] Constant pain may make it difficult to sleep at night or remain active during the day.[5,17,23] Loss of sensation can lead to thermal burns or joint injury to the lower limbs.[23,25] Patients often lose the ability to perform such basic tasks as holding utensils or dressing themselves.[24]

Autonomic dysfunction can cause dizziness and/or fainting, which may result in serious injury and/or hospitalisation for the patient.[26] Bouts of constipation, diarrhoea and faecal incontinence may be so severe that patients are afraid to leave their homes in case they lose bowel control in public.[17,27] Additionally, gastrointestinal symptoms may affect patients' nutritional status and lower their body mass index.[23,27] Once they lose enough body mass, the condition becomes known as wasting which is marked by a drastic loss of body tissue.[23]

Cardiac manifestations of hATTR amyloidosis include shortness of breath and fatigue, which can also severely limit patients' physical functioning including the ability to participate in exercise—including walking—or other activities.[26,28]

The progressive nature of hATTR amyloidosis,[2] combined with the lack of effective treatments, causes strong feelings of fear, frustration and anxiety as reported by UK patients.[17,29] These feelings may lead to depression and suicidal thoughts due to the hopelessness of the condition and the fear of being a burden.[17] hATTR amyloidosis affects all aspects of the patient's life. For example, in a recent survey by the Amyloidosis Research Consortium (ARC), on a scale between 0 (no impact) and 10 (extreme impact), patients rated the following aspects of their lives as ≥8 or higher (i.e., highly impacted): work and professional life (50%), physical health (40%), social and family relationships (32%), emotional and financial wellbeing (29% and 25%, respectively).[29]

The wide-ranging burden of hATTR amyloidosis on activities of daily living and productivity in patients, caregivers, and the healthcare system is revealed by baseline data from the pivotal, phase 3, patisiran randomised controlled trial (RCT) APOLLO, in which the Rasch-built Overall Disability Scale (R-ODS) was used to measure activity and social functioning in patients.[24] The study enrolled adult hATTR amyloidosis patients who were in polyneuropathy disability score (PND) I–IIIB which is an accepted, widely-used and discrete measure of disease evolution and severity (an amendment to the study protocol excluded late-stage patients in PND IV at the screening/baseline visit). At baseline, more than half of patients were not able to perform a complex task such as dancing (59%), standing for a long period (63%) or running (76%).[24] A substantial percentage of patients even had difficulty reading a book (27%) or eating (30%). Most patients were unable to work (69%), and many were hospitalised overnight (28%) or visited the Emergency Department (23%).[24] Caregivers were also negatively impacted, with 15% of patients reporting their caregivers were not able to work and an additional 12% of patients reporting that their caregivers were limited to part-time employment. Caregivers who were able to work averaged 3 weeks of lost work over the period of a year.[24]

Current treatment options

At the time of writing, there are no licensed pharmacological treatment options available in the UK to safely and effectively improve neurologic impairment and cardiomyopathy experienced by patients with hATTR amyloidosis. Orthotopic liver transplant is very rarely performed for hATTR amyloidosis in the UK because

outcomes are poor in patients with cardiac involvement, which is a common presentation of the disease in the UK.

A crucial unmet need exists in the UK for novel therapies that address the multi-systemic nature of hATTR amyloidosis and can safely and effectively halt and/or reverse disease progression, avoiding irreversible functional deficits and disability in these vulnerable patients.

Impact of the new technology

Patisiran represents a step-change in the management of this disease; however, it is not expected the technology will require significant changes to the way current services are organised or delivered. Alnylam Pharmaceuticals UK has worked with a broad range of relevant stakeholders, including the NAC, the National Hospital for Neurology and Neurosurgery, clinicians in regional hospitals, NHS England, Patient Advocacy Groups and NICE to define the pathway by which patients will receive patisiran. Several meetings have been held with all relevant stakeholders under the guidance of NICE's Office for Market Access (OMA). A second multi-stakeholder engagement meeting organised by the OMA was held in July 2018 to discuss the most appropriate service model for the introduction of patisiran. Initiation, treatment and management of patisiran patients will be undertaken by one expert centre (the NAC) and will support targeted and parsimonious use of patisiran by world renowned disease area experts.

The introduction of patisiran in the UK is expected to reduce the burden of hATTR amyloidosis on patients, caregivers, and society. Evidence supportive of this expectation was provided by APOLLO, the largest trial of hATTR amyloidosis to-date. The trial included patients with a broad range of genotypes including those most common in the UK. Results from the trial demonstrated a significant reduction in disease symptoms and disability, improvement in health-related quality of life (HRQoL), nutritional status, strength, and ambulation in as little as 9 months compared to baseline in patients treated with patisiran.[11]

The value of patisiran is supported by the following main pillars:[10,11]

Patisiran directly addresses the underlying cause of the disease through rapid and substantial TTR knockdown

Patisiran treatment substantially reduces serum levels of TTR (median TTR knockdown: 81%)—the cause of hATTR amyloidosis—and the reduction was similar across age, sex, or genotype.[11]

Patisiran improves neurological impairment with meaningful benefit seen as early as 9 months after the start of treatment

Patisiran met the primary endpoint in APOLLO: the mean change from baseline in mNIS+7 at 18 months was significantly lower in the patisiran group (least-square mean [LSM]±standard error [SE]: -6.0±1.7 points) than in the placebo group (LSM±SE: 28.0±2.6 points; LSM difference between groups ± SE: -34.0±3.0; p<0.001).[11] The mNIS+7 is a composite measure of motor, sensory, and autonomic polyneuropathy.[30] The change in neuropathy was robust in the patisiran group: 56% percent of patients in the patisiran arm showed an improvement in terms of reduced neuropathic impairment (change from baseline in mNIS+7 <0 points) at 18 months as compared to 4% of placebo patients (odds ratio [OR]: 39.9, 95%CI: 11.0, 144.4; p<0.001) and the effect of patisiran on mNIS+7 was seen as early as 9 months (LSM difference between groups: -14.70 points, 95% CI: -19.44, -9.96).[10,11]

Patisiran improves patients HRQoL

A significantly higher percentage of patients treated with patisiran experienced improved HRQoL at 18 months relative to baseline than in the placebo group: 51% of patients achieved an improvement [<0 point increase from baseline at 18 months] in the Norfolk quality of life – diabetic neuropathy (QoL-DN) scale compared with 10% in the placebo group.[11] At 18 months the LSM±SE change from baseline was -6.7±1.8 points with patisiran and 14.4±2.7 points with placebo (LSM difference between groups ± SE: -21.1±3.1 points; p<0.001) and the treatment benefit on quality of life was seen as early as 9 months (LSM difference between groups: -15.0 points, 95% CI: -19.8, -10.2).[10,11] Treatment with patisiran led to an improvement in the Norfolk QoL-DN domains previously identified as most relevant to patients, which included physical functioning/large nerve fibre, symptoms, and autonomic neuropathy.[31] These data reveal that the relief from physical symptoms experienced by patients treated with patisiran is a key driver of improved HRQoL, resulting in higher-quality daily life.

Patisiran improves autonomic function, including reducing debilitating gastrointestinal issues compared to baseline at 18 months

Decline of nutritional status (wasting) is a contributor to death in hATTR amyloidosis patients.[23] At 18 months, patients in the patisiran group had maintained their nutritional status relative to baseline (LSM±SE change from baseline was -3.7±9.6 kg/m^2 × albumin g/L) while the placebo group worsened from baseline (-119.4±14.5 kg/m^2 × albumin g/L).[11] The difference between groups was statistically significant (LSM

difference between groups ± SE: 115.7±16.9 kg/m^2 × albumin g/L; p<0.001) and was observed as early as 3 months.[11]

Patisiran improves cardiac function, addressing the multi-systemic nature of disease

Patisiran produced favourable changes in the cardiac subgroup of patients from APOLLO (patients who exhibited symptoms of cardiac involvement which could not be explained by hypertension or aortic valve disease) including reduction in the cardiac predictor of mortality N-terminal pro b-type natriuretic peptide (NT-proBNP) (the adjusted geometric mean ratio to baseline was 0.89 for the patisiran group and 1.97 for the placebo group; ratio: 0.45; p<0.001) and a significant benefit vs placebo in change from baseline to 18 months for left ventricle (LV) wall thickness and longitudinal strain (p=0.02, for both endpoints).[11]

Patisiran improves function, and reduces disability, offering meaningful benefit to patients' daily lives

Patients treated with patisiran had significantly improved strength and motor function (as assessed by negative change in the Neuropathy Impairment Score–weakness [NIS-W] a measure of muscle strength) at 18 months relative to baseline.[11] The LSM±SE change from baseline was 0.1±1.3 points for the patisiran group and 17.9±2.0 points in the placebo group (LSM difference between groups ± SE: -17.9±2.3 points; p<0.001).[11]

At 18 months, patients treated with patisiran had significantly faster walking speeds compared to baseline as measured on the 10-metre walking test (10MWT), in contrast to the decline seen in the placebo group.[11] Among older adults, a change in gait speed on the 10MWT of 0.05 m/s is considered a small but clinically meaningful change, and a change of 0.10 m/s represents a substantial meaningful change.[32] In APOLLO, the LSM±SE change from baseline was 0.08±0.02 m/s for the patisiran group and -0.24±0.04 m/s for the placebo group (LSM difference between groups±SE: 0.31±0.04 m/s; p<0.001).[11]

Patients treated with patisiran showed no decline in their ability to perform activities of daily living (e.g., standing, dancing, reading a book) at 18 months relative to baseline as measured by the R-ODS, in contrast to the worsening disability seen in the placebo group.[11] The LSM±SE change from baseline was 0.0±0.6 points for the patisiran group and -8.9±0.9 points in the placebo group (LSM difference between groups±SE change from baseline vs placebo: 9.0±1.0; p<0.001).[11]

The clinical benefits observed with patisiran treatment remained consistent across patient subgroups, which included age, geographic region, disease stage/severity, genetic mutation status, previous TTR stabiliser use, and cardiac involvement.[11]

The frequency of adverse events (AEs), serious AEs and deaths in APOLLO were comparable between the patisiran and placebo arms. Patients treated with patisiran had fewer overall treatment discontinuations (7% vs 38% in the placebo arm).[11] Fewer patients in the patisiran group discontinued treatment due to AEs compared with placebo (5% vs 14%, respectively). No deaths were considered related to patisiran treatment.[11]

APOLLO is the largest trial in hATTR amyloidosis patients to date. The trial included patients with a broad range of genotypes (39) and included patients with the genotypes most common in the UK.[11] As well, 44% of patients in the trial were from Western Europe and, as is representative of the UK population, the majority of patients had cardiac involvement.[10]

The GLOBAL open-label extension (OLE) has enrolled 99% of the patients that completed the APOLLO trial and will provide long-term evidence of the efficacy and safety of patisiran for the treatment of this debilitating and fatal disease.[33]

Impact on the NHS—costs and health effects

Value for money

Alnylam Pharmaceuticals developed a *de novo* Markov cost-effectiveness (CE) model to estimate the impact of treatment with patisiran on hATTR amyloidosis patients in terms of costs and effects (quality-adjusted life-years; QALYs). The model compared best supportive care (BSC) consisting of established clinical management without patisiran vs patisiran with BSC. To ensure alignment with clinical practice in the UK, the model design and assumptions made were developed in consultation with clinical experts at the NAC.

To characterise polyneuropathy health states and to align with the primary outcomes of the APOLLO trial, the model uses PND score as a functional scale that measures polyneuropathy symptoms. While the PND score does not capture the severity of polyneuropathy symptoms exhaustively,[5] it is a discrete scale that reflects the natural history of the disease in which there is a strong link between the rapid progression seen in hATTR amyloidosis patients and PND score.[2]

The cardiomyopathy health states were defined by the NT-proBNP threshold of 3000 pg/mL, demonstrated to be a predictor of short-term survival in patients with ATTR amyloidosis.[7,34,35]

The undiscounted ICER results for patisiran compared with BSC in terms of LYG and QALYs from the NHS/PSS direct medical perspective were [redacted]/LYG and [redacted]/QALY, respectively. The discounted ICER is [redacted]/LYG and [redacted]/QALY.

[redacted]

Budget impact

There are 112 hATTR amyloidosis patients in England. An estimated 65% of hATTR amyloidosis patients in England are eligible for treatment with patisiran based on information received from the NAC. In combination with the 27 newly diagnosed patients expected in 2019, a total of 100 hATTR amyloidosis patients will be eligible for treatment with patisiran in Year 1. The total budget impact in Year 1 would be [redacted]. The total estimated population expected to receive patisiran in Year 5 [redacted]. These estimates do not consider expected VAT benefits to the NHS due to the provision of homecare infusion services that are part of the service delivery model expected for patisiran. Additionally, these estimates do not take into account potential cost offsets due to avoided costs that occur outside of the NHS or PSS (see section E).

Impact of the technology beyond direct health benefits

Patisiran is anticipated to bring important economic benefit outside the NHS in both patient and caregiver productivity and reduction in financial support from external sources. Thus, it is expected that the introduction of patisiran would reduce the expenditure currently incurred by local government programmes outside the NHS.

Conclusions

In the largest trial of hATTR amyloidosis to-date, measuring a comprehensive range of outcomes that reflect the multi-systemic nature of the disease, and in a population representative of the NHS setting, patisiran was shown not only to halt or reverse disease progression, but also to reduce the neuropathy (as measured by mNIS+7) and cardiomyopathy (as measured by NT-proBNP) that are the cardinal manifestations of the disease, with resultant benefits in patient symptoms, disability, ambulatory ability, nutritional status, and overall HRQoL.[10] Patisiran increased the odds of reversing neurological impairment approximately 40-fold compared with placebo.[10] The benefits of patisiran extended to patients with a wide range of disease severity, and were maintained for at least 3 years.[10,33]

Crucially, the management and treatment of patients at one expert centre (National Amyloidosis Centre) will facilitate the parsimonious and targeted use of patisiran by world renowned disease area experts. This will ensure appropriate use of patisiran, in keeping with the nature of highly specialised technologies. Finally, the estimated budget impact of patisiran is expected to be controlled by the limitation of disease management and treatment to one highly specialised commissioned centre and remains well below £20 million in the first 3 years. The introduction of the first approved RNAi for the treatment of an ultra-rare, life-threatening, genetic disease would offer a step-change in treatment.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 summarises the statement of the decision problem.

Table A1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with hereditary transthyretin-related amyloidosis.	Since the NICE scoping, the CHMP has issued its positive opinion with the final indication statement	The population addressed in the submission and the CE model corresponds to final CHMP indication as well as to the population studied in the pivotal registration-enabling APOLLO trial of adult patients with hATTR amyloidosis. This population reflects the presentation prevalent in the UK. The change from the scope merely reflects the final CHMP approved indication which was not yet known at the time of the scoping conclusion.
Intervention	Patisiran	None	N/A
Comparator(s)	Established clinical management without patisiran.	None	N/A
Outcomes	• Neurological impairment • Symptoms of polyneuropathy • Cardiac function • Autonomic function (including the effects on the GI system and postural hypotension) • Weight loss • Effects of amyloid deposits in other organs and tissues (including the eye) • Serum transthyretin • Motor function • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	None	N/A
Subgroups to be considered	None specified	None	N/A
Nature of the condition	• Disease morbidity and patient clinical disability with current	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options		
Cost to the NHS and PSS, and value for money	• Cost effectiveness using incremental cost per quality-adjusted life-year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise.	None	N/A
Special considerations, including issues related to	• Guidance will only be issued in accordance with the marketing	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
equality	authorisation. • Guidance will take into account any Managed Access Arrangements		

CE: cost-effectiveness; GI: gastrointestinal; N/A: not applicable; NHS: National Health Service; PSS: Personal Social Services; RCT: randomised controlled trial.

2 Description of technology under assessment

2.1 Brand name, approved name and therapeutic class

Onpattro (patisiran) is a ribonucleic acid interference (RNAi) therapeutic.

2.2 Mechanism of action of the technology

Patisiran is the first Committee for Medicinal Products for Human Use (CHMP) approved medicine in the RNAi therapeutic class.

RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals.[36] One of the founders of Alnylam was one of the first to show that "small interfering RNAs" (siRNAs) bind to messenger RNAs (mRNAs) and silence disease-causing genes. These discoveries opened the door for application of RNAi as a new therapeutic strategy.[37] RNAi therapeutics allow for the targeting one specific gene at a time.[36] Recognised as one of the most promising and rapidly advancing frontiers in biology and drug discovery, the discovery of RNAi was awarded the 2006 Nobel Prize in Physiology or Medicine.[38] Alnylam's drug discovery platform exclusively focusses on developing siRNA medicines to target the cause of diseases by potently silencing specific mRNAs, with the goal of blocking production of disease-causing proteins.[12]

Patisiran is an siRNA that Alnylam specifically engineered to treat hATTR by targeting a sequence in the mRNA that codes for transthyretin (TTR).[12] Through RNAi, patisiran degrades TTR mRNA in the liver, thus blocking the production of TTR by the liver. In turn, this leads to reduced TTR levels in the bloodstream, thereby reducing the disease-causing accumulation of amyloid deposits in the tissues and organs, potentially allowing the body to recover. To enhance its therapeutic potential, patisiran is formulated as lipid nanoparticles, enabling it to be delivered directly to the liver cells where TTR is produced.[12]

The innovation represented by patisiran has been recognised by the UK Medicines and Healthcare Products Regulatory Agency (MHRA), which has awarded patisiran Promising Innovative Medicine designation.

2.3 Dosing information

Table A2 summarises the dosing information for patisiran.

Table A2. Dosing information of technology being evaluated

Pharmaceutical formulation	
Method of administration	• IV infusion

Doses	• 0.3 mg/kg • For patients ≥100 kg, the recommended dose is 30 mg
Dosing frequency	• The treatment is administered once every 3 weeks
Premedication	• The following premedication should be given on the day of patisiran treatment at least 60 minutes prior to the start of infusion: o Intravenous corticosteroid (dexamethasone 10 mg, or equivalent) o Oral paracetamol (500 mg) o Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent) o Intravenous H2 blocker (ranitidine 50 mg, or equivalent)
Recommendation for supplementation	• Vitamin A supplementation at approximately 2500 IU per day is advised
Average length of a course of treatment	• The diluted solution of patisiran should be administered by IV over approximately 80 minutes
Anticipated average interval between courses of treatments	• 3 weeks
Anticipated number of repeat courses of treatments	• It is expected that patients will be treated with patisiran for the duration of their lives, subject to the clinical judgement of the treating physician.
Dose adjustments	• No dose adjustments necessary

IV: intravenous; TTR: transthyretin.

Source: Patisiran SPC[12]

3 Regulatory information

3.1 Marketing authorisation

The CHMP opinion was published on 27 July 2018. The European Commission (EC) approval is anticipated in September 2018.

3.2 Timeline of availability

It is anticipated that the technology will be launched in the UK shortly after the EC decision.

3.3 Regulatory approval outside the UK

At the time of this submission, patisiran is available only in the USA, where marketing approval was granted on 10 August 2018. The US Food and Drug Administration (FDA) granted 'breakthrough therapy designation' to patisiran.

3.4 Current use in England

Patisiran is currently available under a compassionate use program in the UK. Additionally, the MHRA has granted patisiran a "Promising Innovative Medicine" (PIM) designation and granted a Scientific Opinion under the Early Access to Medicines Scheme (EAMS) on August 3, 2018. Patisiran is available for use under the approved EAMS protocol.

4 Ongoing studies

4.1 Ongoing studies

Patisiran was evaluated in APOLLO (NCT01960348), a phase 3, randomised, double-blind, placebo-controlled, multi-centre study to determine the efficacy and safety of patisiran over 18 months in patients with hATTR amyloidosis with polyneuropathy.[11,39] APOLLO was completed in August 2017.[40] The results of the APOLLO trial were published in the New England Journal of Medicine on 5 July 2018.[11] The APOLLO trial is the largest trial conducted in hATTR amyloidosis patients and demonstrated the safety and efficacy of treatment with patisiran in patients with a wide range of genotypes, with a varying neuropathy severity, including >50% with cardiac manifestations.[11]

The long-term efficacy and safety of patients treated with patisiran will be evaluated in a Global open-label extension (OLE) study. Patients who completed a phase 2 open-label extension (OLE; NCT01961921) or the Phase 3 APOLLO patisiran studies and met the eligibility criteria were able to enrol in the Global OLE (NCT02510261) to continue receiving patisiran for up to 5 years.[41] The Global OLE is ongoing with an estimate completion date of July 2019.[42]

Adult hATTR amyloidosis patients who meet eligibility criteria and have not previously participated in an interventional hATTR amyloidosis clinical trial involving RNAi therapeutics within the last 12 months are eligible to receive patisiran as part of the Expanded Access Protocol (Compassionate Use program; NCT02939820).[43]

Alnylam submitted an application to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) for assessment for inclusion in the Early Access to

Medicines Scheme (EAMS) on 31 May 2018.[15] The MHRA provided its positive Scientific Opinion for EAMS on 2 August 2018.

No additional evidence is anticipated to be released in the next 12 months from the Expanded Access Protocol or the EAMS study.

4.2 Additional assessment in the UK

Patisiran has been assessed by the MHRA and has been granted a Promising Innovative Medicine designation in January 2018. As mentioned above, Alnylam has submitted an application to the MHRA for the EAMS programme which was accepted, with the MHRA issuing its EAMS Scientific Opinion on 2 August.

A submission to the Scottish Medicines Consortium is planned and the date of submission and assessment are to be determined. The timescales for this assessment are not yet known.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

- hATTR amyloidosis is a genetic disease.
- Specific genotypes in the UK are prevalent among the Afro-Caribbean population and the Northern Irish.

- Due to the hereditary nature of the disease, some families may be disproportionately affected.
- A timely HST review would support NICE's commitment to promoting equality.
- Patisiran is effective and safe across all hATTR genotypes as demonstrated in the pivotal RCT APOLLO.

5.1 Equality assessment

A timely HST review would support NICE's commitment to promoting equality. Patisiran targets a hereditary progressive, debilitating and ultimately fatal disease,[3,7,11] for which effective treatment options in the UK do not exist.[44,45] The most common genetic variants associated with hATTR amyloidosis in the UK are TTR V122I, prevalent in Afro-Caribbean people, and TTR T60A, present in many populations with a frequency of up to 1% in one North Western Irish study.[21] Additionally, because hATTR amyloidosis is a hereditary disease, afflicted families bear a disproportionate burden of the disease.

Additionally, hATTR amyloidosis typically affects older patients in the UK, and current approaches to cost-effectiveness methods may penalize older patients. For instance, patients with a healthy life expectancy of less than 30 years would be discriminated against under existing technology appraisal methods when it comes to the discounting of future health benefits. The potential for equality issues when it comes to adult patients has been documented in the literature and is described in more detail in section 12.1.7.

5.2 Equality of technology

Patisiran is effective across all subgroups of patients with hATTR amyloidosis as demonstrated by the pivotal RCT APOLLO. Availability of patisiran would fill an unmet need for patients with hATTR amyloidosis including those disproportionately affected in the UK such as the Afro-Caribbean community and families impacted by the hereditary nature of the disease.

Section B – Nature of the condition

6 Disease morbidity

6.1 Disease overview

- hATTR amyloidosis is an ultra-rare systemic disease.
- hATTR amyloidosis has a diverse clinical presentation, with varying degrees of rapidly progressive and debilitating sensory, motor, and autonomic neuropathy as well as cardiomyopathy.
- Disease progression leads to significant functional disability, high morbidity, and mortality.
- Based on calculations using data for UK hATTR amyloidosis patients reported by Gillmore et al. 2017 the median overall survival was 4.02 years.

6.1.1 Pathophysiology

Hereditary TTR-mediated amyloidosis (hATTR amyloidosis) is an ultra-rare, multi-systemic disease with a heterogeneous clinical presentation resulting in rapidly progressive and debilitating sensory, motor, and autonomic neuropathy as well as cardiomyopathy. Disease progression leads to significant functional disability, high morbidity, and mortality.[3,5] TTR is an enzyme, mainly synthesised in the liver and choroid plexus of the brain, which circulates in the plasma and cerebrospinal fluid.[46,47] The main physiological roles of TTR are the transport of thyroid hormone thyroxine (T_4) and retinol (by binding to retinol binding protein).[46,47]

TTR may misfold and/or misassemble and aggregate to form amyloid fibrils *in vivo*.[48] In TTR amyloidosis, these fibrils are deposited in multiple tissues and organs; primarily in the nerves, heart, gastrointestinal (GI) tract, liver, and kidneys, where their accumulation leads to the characteristic symptoms of the disease.[6]

Historically, two clinical syndromes of hATTR amyloidosis have been described in the literature: hATTR amyloidosis with polyneuropathy (previously named familial amyloidotic polyneuropathy [FAP]) and hATTR amyloidosis with cardiomyopathy (previously named familial amyloidotic cardiomyopathy [FAC]).[6,49] While patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients with hATTR amyloidosis manifest signs and symptoms of both polyneuropathy and cardiomyopathy over the course of their disease (i.e., most

of those presenting primarily with polyneuropathy will proceed to develop cardiomyopathy,[18,19] and vice versa)[20], and therefore it is more appropriate to refer to hATTR as one hereditary disease with a spectrum of clinical manifestations rather than attempt to classify the disease into two distinct syndromes.[6,50] Discussions with UK experts as well recent academic literature suggest that most UK hATTR patients experience both cardiac and neuropathic manifestations of their disease.[16,50]

The hereditary form of transthyretin-mediated amyloidosis (ATTR) amyloidosis is caused by a genetic mutation in the TTR gene. There are over 120 reported TTR mutations,[51] of which at least 80 are confirmed pathogenic mutations.[49] hATTR amyloidosis is an autosomal dominant disease in which carriers of a mutation are born with the circulating variant protein but do not suffer from amyloid deposition or symptomatic disease until adulthood.[25] Development of disease is likely due in part to the biochemistry of aging.[5,52-54]

A genotype-phenotype correlation has been reported for hATTR amyloidosis, with some mutations more commonly presenting with polyneuropathy and others typically presenting with cardiomyopathy (Figure 1). While the presentation can vary by TTR mutation, a mixed phenotype is most commonly reported.[55,56]

A recent retrospective study of genetic diagnosis in ATTR amyloidosis in the UK assessed patients who underwent TTR gene sequencing at the UK National Amyloidosis Centre (NAC) between 1991 and 2016. A total of 3949 patients were sequenced and TTR mutations were found in 675 patients. The most prevalent TTR variants reported in the UK were associated with both cardiac and polyneuropathy manifestations, namely Val122Ile (39%) and Thr60Ala (25%), though Val30Met was also common (17%).[21]

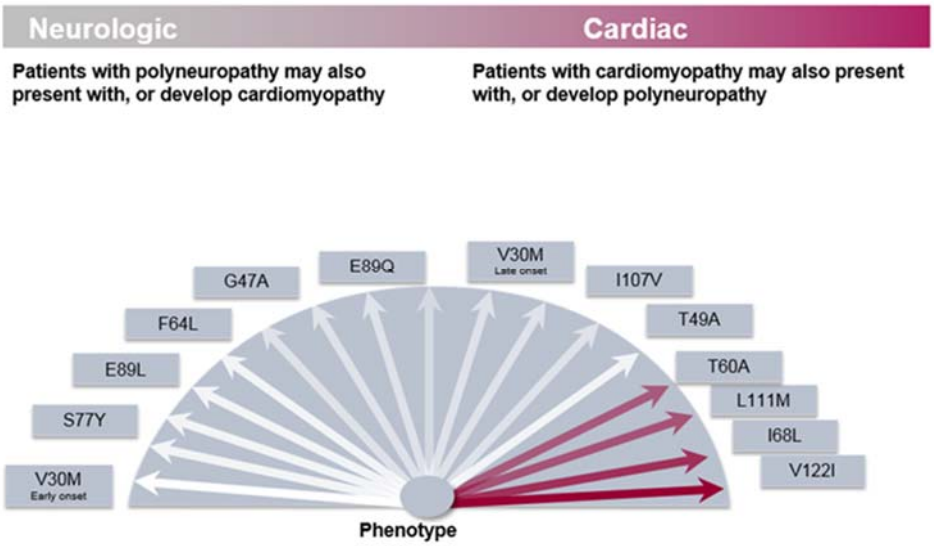


Figure 1. Clinical presentation of common genetic mutations underlying hATTR amyloidosis

hATTR: hereditary transthyretin-mediated amyloidosis; THAOS: Transthyretin Amyloidosis Outcomes Survey.

Sources: Rapezzi et al. 2013;[55] Semigran et al. 2016[56]

6.1.2 Clinical features

hATTR amyloidosis is a multi-systemic disorder with a heterogeneous clinical presentation characterised by multiple symptoms (Figure 2), including autonomic and peripheral neuropathy, cardiac manifestations, and other symptoms affecting the GI system, the eyes, and the central nervous system (CNS).[6,57,58]

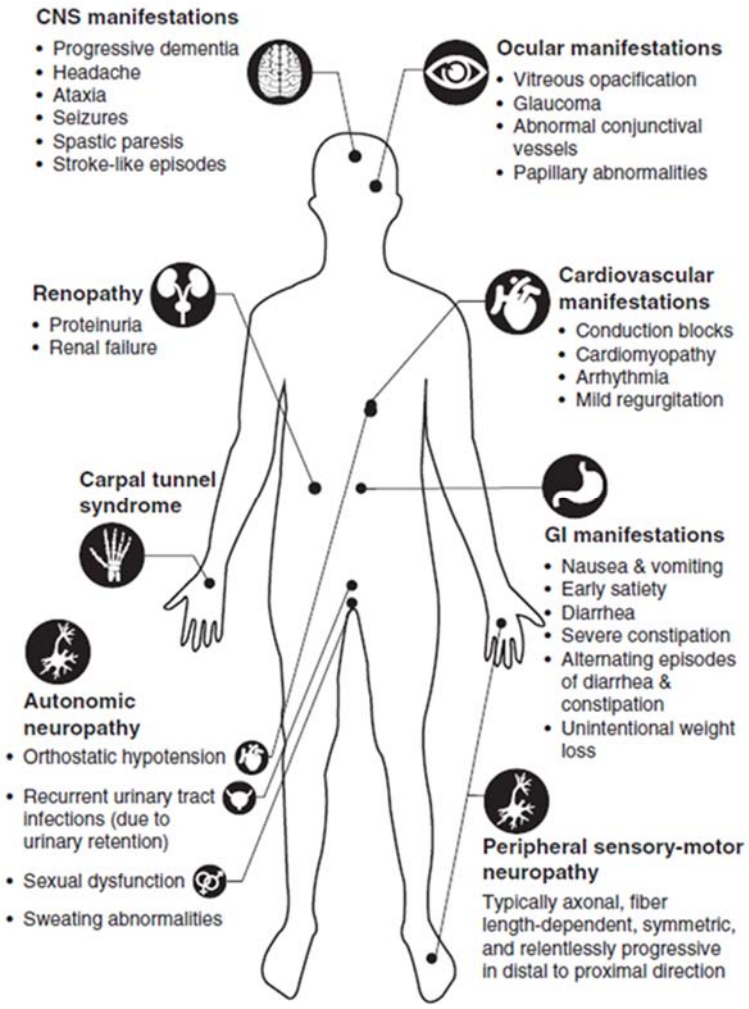


Figure 2. Clinical features of hATTR amyloidosis

CNS: central nervous system; GI: gastrointestinal; hATTR: hereditary transthyretin-mediated amyloidosis.

Source: Conceição et al, 2016[57]

Neurological symptoms

Neuropathy in hATTR amyloidosis results from amyloid-mediated injury to nerve fibres. Peripheral neuropathy usually starts with dysfunction in the small nerves of the extremities and progresses centrally.[25] Sensory abnormalities include painful or non-painful abnormal sensation in the feet and hands; lack of ability to sense temperature is an early symptom.[25] Disease progression eventually leads to motor weakness, decreased pain sensation, generalised weakness, inability to perform activities of daily living, cachexia, and loss of ambulation.[23] In a recent survey of the burden of hATTR amyloidosis on patients and caregivers in the UK, commissioned by Alnylam® Pharmaceuticals and conducted by BresMed (Sheffield, UK), patients from the UK reported that pain, loss of feeling and strength was debilitating and had a

substantial impact on daily life including sleeping, walking, washing, dressing, eating, opening doors, and using the toilet.[17]

Autonomic dysfunction results in debilitating low blood pressure when standing up (orthostatic hypotension), impotence, severe GI symptoms (including early satiety, chronic nausea/vomiting, and both diarrhoea and constipation), bladder dysfunction with recurrent urinary tract infections, as well as cardiac arrhythmias.[5,25,59] Patients and carers reported fear of the patient fainting and falling which could result in serious injury and/or hospitalisation for the patient. As well, the fear has a dramatic effect on the social life and psychological wellbeing of the carer.[17]

Disease progression can be rapid once signs and symptoms begin to manifest and may result in death due to GI complications, which can cause malnutrition and wasting.[26] Renal complications are less frequent, but proteinuria and compromised renal function may arise.[5,6]

Cardiac symptoms

Amyloid deposits may infiltrate any of the cardiovascular organs in the body and affect all processes.[5] Eventually, cardiac infiltration with amyloid causes progressive thickening of the ventricular walls, interventricular septum, and cardiomyopathy, resulting in heart failure.[5,25] As the disease progresses in patients with hATTR amyloidosis, death generally results from cardiac involvement or cachexia.[60]

Patients with symptomatic heart failure experience rapid progression of their amyloid cardiomyopathy, with substantial worsening of ability to walk, cardiac function, New York Heart Association (NYHA) Functional Classification, and health-related quality of life (HRQoL).[49,61]

Scoring systems for hATTR amyloidosis classification

Scoring systems for evaluating hATTR amyloidosis include systems based on the polyneuropathy disability (PND) score and a system based on the stages of peripheral and autonomic neuropathy disability as the disease progresses.[5] Adams et al. 2015 reported a strong association between the rapid progression seen in hATTR amyloidosis patients and the severity of neuropathy as measured by the PND score and FAP stage functional scales of locomotion.[2] Table B1 and Table B2 summarise the two main classification systems for hATTR amyloidosis.

Table B1. Classification of hATTR amyloidosis by PND score

Score	Symptoms
0	No impairment

Score	Symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capability but ability to walk without a stick or crutches
IIIA	Walking only with the help of one stick or crutch
IIIB	Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

hATTR: hereditary transthyretin-mediated amyloidosis; PND: polyneuropathy disability.

Source: Ando et al. 2013[5]

Table B2. Clinical staging of hATTR amyloidosis by FAP stage

Stage	Symptoms
0	No symptoms
I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II	Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
III	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

hATTR: hereditary transthyretin-mediated amyloidosis; FAP: familial amyloidotic polyneuropathy

Source: Ando et al. 2013[5]

6.1.3 Diagnosis

Diagnosis is often challenging given the rarity of the disease in the general population and the complex presentation of the disease with many non-specific clinical features.[6,62,63] Due to cardiac, neurologic, and GI symptoms, patients may consult multiple specialists over the course of several years in search of the correct diagnosis.[3] While a range in time from symptom onset to diagnosis of approximately 1 to 10 years has been reported in Europe and the US, typically, patients remain undiagnosed for 2–3 years after symptom onset.[2,3]

While the literature reporting age at diagnosis in the UK is scare, Sattianayagam et al. 2012 reported the median age at symptom onset for hATTR amyloidosis patients with the underlying Thr60Ala mutation as 63 years (range: 45–78 years).[20] Gillmore et al. 2017 reported the median age at diagnosis for patients with the Val122Ile mutation as 77 years (range: 47–92 years) and 66 years (range: 41–82) years for patients with non-Val122Ile mutations.[7]

In the UK, all patients with suspected or diagnosed ATTR amyloidosis are referred to the NAC.[64] Following presentation with symptoms suggestive of hATTR amyloidosis, patients with a family history may undergo genetic testing to detect the presence of a mutation in the TTR gene.[6]

Other diagnostic tests may be used to identify various aspects of the disease including electrocardiography, echocardiography, and cardiac magnetic resonance imaging for the detection of cardiomyopathy.[6] Quantitative sensory testing (QST) and sudomotor testing may be performed to detect small nerve fibre pathology associated with sensory and autonomic neuropathy, whereas nerve conduction studies can detect large nerve fibre pathology associated with motor neuropathy.[65-67] Tissue biopsy may be used to detect amyloid deposits, but, its use is limited due to the uneven distribution of amyloid fibrils which may yield false-negative results.[5]

6.1.4 Survival

Patients with hATTR amyloidosis face early mortality, usually from heart failure, or complications of autonomic neuropathy resulting in wasting.[20,68]

Several variables present at the time of diagnosis are associated with shorter survival including:[50]

- Higher age
- The presence of Val122Ile or Thr60Ala mutations (the most prevalent variants in the UK)[21]
- Malnutrition leading to weight loss
- Peripheral neuropathy
- Cardiac biomarker levels (NT-proBNP levels ≈ ≥3000 pg/mL)

Following the onset of symptoms, quality of life is severely impacted and the disease proceeds inexorably to death, with a life expectancy limited to 3 to 15 years from symptom onset depending on the TTR mutation and clinical manifestation.[2,6,50,69] The median survival for hATTR amyloidosis patients with cardiac involvement is 3–5 years.[7,20]

Notably, a significant correlation between NT-proBNP and abnormal interventricular septal wall thickness and basal septal strain has been found in hATTR amyloidosis patients, showing it to be a sensitive biomarker for cardiomyopathy for this disease.[70] Elevation of NT-proBNP levels are associated with poor short-term survival in patients with ATTR amyloidosis.[34,35,71]

Consequently, the economic analysis developed for this submission uses NT-proBNP levels to model the impact of cardiomyopathy on the probability of death. Several studies have demonstrated that higher NT-proBNP levels predict decreased survival

in this patient population. Gillmore et al. 2017 proposed a staging system for hATTR patients with cardiomyopathy using the biomarkers NTpro-BNP (cut-off 3000 pg/mL) and estimated glomerular filtration rate (eGFR; cut-off 45 mL/min/1.73m^2).[7] Stage I was defined as NT-proBNP ≤3000 pg/mL and eGFR ≥45 mL/min/1.73m^2, Stage III was defined as NT-proBNP above the cut-off (>3000 pg/mL) and eGFR below the cut-off (<45 mL/min/1.73m^2), and the remainder was classified as Stage II. The study reported that the median survival among hATTR amyloidosis patients with the Val122Ile mutation and NT proBNP values ≤3000 pg/mL NT-proBNP (Stage I; n=89) was 54.4 months (95% CI: 31.1 months, not determinable). Median survival in Stage II patients (n=79) was 28.8 months (95% CI: 23.6, 45.1 months), and in Stage III patients (n=33), 17.7 months (95% CI: 11.5, 22.3 months) ($p<0.006$ for Stage I vs II and $p<0.013$ for Stage II vs III).[7]

For hATTR amyloidosis patients with non-Val122Ile mutations in Stage I (n=70) median survival was 76.7 months (95% CI: 69.0 months, not determinable). Median survival in Stage II patients (n=36) was 54.0 months (95% CI: 28.6, 74.6 months), and in Stage III patients (n=9), 24.1months (95% confidence interval [CI]: 6.3 months, not determinable) ($p<0.02$ for Stage I vs II and $p<0.03$ for Stage II vs III).[7]

Damy et al. 2016 conducted a study of 198 patients with cardiac amyloidosis (including patients with hATTR, wtATTR, and cardiac light-chain amyloidosis), and found that after adjusting for NYHA class, cardiac output, and pericardial effusion, patients in the highest quartile of NT-proBNP level had more than a 17-fold higher risk of death compared with those in the lowest quartile (hazard ratio [HR] 17.46, 95% CI: 2.03, 150.31).[34]

In the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry of patients (Kristen et al. 2017) with hATTR (n=1452) or wtATTR (n=165), the 3-year overall survival (OS) estimate for the three BNP/NT-proBNP quartiles Q1 to Q3 combined was 95.8% ±0.8% and of Q4 was 65.2% ± 3.9%, with a significant difference between the two survival curves ($p<0.001$).[35] After adjusting for age, gender, modified body mass index (mBMI), duration of disease, eGFR, and Val30-Met/non-Val30Met, patients in the highest quartile of NT-proBNP level had a two-fold higher risk of death compared with those in Q1–Q3 combined (threshold 2584 pg/mL; HR for Q1–Q3 vs Q4 of 0.508, 95% CI: 0.278, 0.928).[35]

6.1.5 Specific patient needs addressed

There remains a high unmet medical need for a safe and effective therapy that can be used for the treatment of hATTR amyloidosis to halt or reverse the polyneuropathy and

cardiac manifestations of this disease.[6,50] In the UK, the majority of hATTR patients have no viable treatment, as they are not candidates for orthotopic liver transplant (OLT) and no disease-modifying pharmacological options are available (see Section 8.2.2 for more detail).[44,45,72] Patisiran addresses multiple aspects of hATTR amyloidosis, including sensory, motor, and autonomic neuropathy, as well as cardiomyopathy, by directly targeting the underlying cause of hATTR amyloidosis with rapid and potent reduction of TTR protein.[11] Patisiran reversed neurological and cardiac disease progression and improved HRQoL compared with baseline in the pivotal, phase 3 trial APOLLO (see Section 9.6 for more detail).[11] Patisiran has a favourable safety profile with a low discontinuation rate (see Section 9.7 for more detail).[11]

6.2 Epidemiology

The literature provides very limited prevalence/incidence data for hATTR amyloidosis, due to it being a rare disease with a high degree of endemicity that is not yet well known outside of a few specialty centres.[3,73]

Based on data provided by the NAC, in 2018, the number of patients in the UK with hATTR amyloidosis was 150. Of these, an estimated 112 live in England.[4,9,74]

The incidence of hATTR in England was estimated to be 0.0001%, which was calculated as the average UK incidence from 2012 to 2016 multiplied by the proportion of NAC patients residing in England.[4,9,74] Thus, hATTR amyloidosis meets the criterion for being considered an ultra-orphan indication, namely occurring well below 1000 people in the UK.[75]

6.3 Life expectancy

As reported earlier in Section 6.1.4, the life expectancy of hATTR patients across age and primary clinical manifestation is limited to 3–15 years from symptom onset and from 3–5 years for hATTR amyloidosis patients with cardiomyopathy symptoms.[2,6,7,20,50,69] While the literature on the life expectancy for people with hATTR amyloidosis in England is sparse, based on calculations using data for UK hATTR amyloidosis patients reported by Gillmore et al. 2017,[7] the median overall survival was 4.02 years.

7 Impact of the disease on quality of life

7.1 Impact on quality of life

- hATTR is a rapidly progressive disease that results in chronically debilitating symptoms that increasingly impair patients' ability to live their daily lives.
- The majority of patients from the Amyloidosis Research Consortium (ARC) survey reported symptoms that impact the quality of their daily lives including numbness, and tingling in legs and feet, loss of balance, dizziness, fatigue, difficulty walking, climbing stairs or muscle weakness, diarrhoea, nausea, vomiting, weight loss and loss of appetite, erectile dysfunction, and faecal incontinence.
- The disease affects patients' psychological wellbeing with some reporting severe anxiety and even suicidal thoughts due to the progressive, irreversible disease.
- Symptoms rapidly increase in severity as the disease progresses, resulting in significant disability and increased hospitalisations, absenteeism, and need for additional caregiver support to accomplish daily activities.
- Caregivers are also affected, and report anxiety and frustration related to their role and the wellbeing of their patient.
- Patients treated with patisiran showed significant improvement in physical ability, HRQoL, and on activities of daily living such as walking, standing, dressing themselves, and using utensils.
- Patients treated with patisiran also experienced reduced autonomic dysfunction (e.g., constipation and/or diarrhoea, faecal incontinence), which is a key driver of HRQoL, and maintained nutritional status.

hATTR amyloidosis is a rapidly progressive disease that results in chronically debilitating symptoms and increasing impairment in patients' ability to conduct activities of daily living.[20,24,26,76] Patients experience significant decline in HRQoL as the disease progresses, as was confirmed in the placebo arm of the APOLLO trial as assessed by the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk Qol-DN).[11] hATTR amyloidosis has the greatest impact on HRQoL in patients with both polyneuropathy and cardiomyopathy.[11]

Physical HRQoL

The spectrum of neurologic manifestations includes sensory, motor, and autonomic neuropathy. Progressive muscle atrophy and motor weakness in both lower and upper limbs leads to impaired balance, difficulty walking (which may require the use of walking aids or a wheelchair),[2] as well as to sexual dysfunction.[26] A recent patient survey from the Amyloidosis Research Consortium (ARC) of 101 hATTR amyloidosis patients (including 14 patients from the UK) reported that 74% of patients had difficulty walking, climbing stairs, and experienced muscle weakness. Fifty-two percent of male patients reported experiencing erectile dysfunction.[29]

Neuropathic pain is often worse at night and can lead to pain sensitivity.[5] In a recent survey of the burden of hATTR amyloidosis on patients and caregivers in the US, commissioned by Alnylam® Pharmaceuticals and conducted by Evidera (Boston, US), patients described a substantial impact of neuropathic symptoms on their lives making it difficult to sleep, exercise, and accomplish normal mundane tasks without pain.[17,77] This is supported by the ARC survey in which 86% of patients reported experiencing numbness, tingling or pain in their legs and/or feet.[29] Loss of sensation can lead to thermal burns involving the feet and hands and joint injury to the lower limbs.[23,33] The inability to perform activities of daily living such as holding eating utensils or a drinking glass and difficulty managing buttons and zippers on clothing worsens over the course of the disease.[24]

Autonomic dysfunction is a key driver of HRQoL in hATTR amyloidosis patients.[16,18,27] Autonomic dysfunction results in debilitating orthostatic hypotension and severe GI involvement including alternating bouts of constipation and diarrhoea and faecal incontinence, which can have a serious effect on patients' quality of life.[18,27] For example, patients may experience incapacitating dizziness when waking up and must sit for long period before standing to walk to the bathroom. While waiting to be able to stand they may experience faecal incontinence. Diarrhoea may become continuous in later stages of the disease.[27] Patients from the UK surveyed (commissioned by Alnylam® Pharmaceuticals) reported severe limitations due to bowel and bladder dysfunction. Patients may not know whether they can leave the house and needed to plan access to toilets when away from home. In some patients, bowel and bladder dysfunction were so severe they resulted in involuntary urination or defecation on a regular basis, especially at night leading to sleep deprivation, embarrassment, paranoia, loss of dignity, and emasculation.[17]

Cardiac involvement can cause serious health issues such as rhythm disturbances and myocardial infarction.[26,78] Additionally, symptoms such as fainting, shortness of breath on exertion (which limits patients' activity), fatigue, blurred vision, and dizziness when standing up, pose a substantial burden to patients.[26,78] The associated emotional and psychological burden on patients, their families, and caregivers is significant.[79]

Psychological wellbeing

The UK patient survey (commissioned by Alnylam® Pharmaceuticals) revealed that the deteriorating nature of hATTR, combined with the lack of effective treatments, results in feelings of frustration, fear, anxiety and may lead to depression for both patients and carers.[17] The most frequently mentioned emotions among patients and carers were fear and anxiety, triggered by thoughts of disease progression, death, passing on the gene to children, and whether their partner will be able to cope with the impact of the condition. Three of 33 patients and carers mentioned patients having suicidal thoughts or thinking about assisted suicide, indicating that some patients feel that death may be a better option than living with the advanced disease.[17]

The physical and psychological effects of the disease are reported in the patients' own voices in Table B3.

Table B3. Sample quotations about the impact of hATTR amyloidosis symptoms on patients' lives

Symptom	Impact
Diarrhoea/faecal incontinence	*''So it's embarrassing, you know, sometimes I remember a few times […] I need to the toilet and then I can't find and just only maybe one minute not even one minute I can't hold even one minute and then all my trousers is full so, my sister in law had to find somewhere to buy a trousers and underwear and then I changed in a restaurant toilet and washed it there. You see, sometimes it's embarrassing.' – Patient P*
Shortness of breath	*'… Now, when I physically start to walk I get really tired, my legs ache, get out of breath, that is the thing that really bugs me, is getting out of breath.'* – Patient B
Chronic pain	'*It's like a constant shooting pain that's going down your feet all the time […] it's like having mini electric shocks all the time. […] And in bed as well, it seems to be worse because it keeps me awake at night'* – Patient R
Issues with mobility	*I've lost the strength to control my feet so any time I try and walk my feet just slip, you can't lift it off the ground and then it traps you.'* – Patient D
Fatigue	*'And when I get home, I do only walk […] just first floor, just one. Maybe it was 12 steps, 12 to 14 steps and then I feel very tired. Halfway I have to stop because I'm tired, […] eventually I have to use my hand to help to walk upstairs.'* – Patient P
Diet	*'I've lost so much weight the last weeks. […] Maybe 6 weeks ago, I was down to 7 stone, I was 14 stone then, the doctors weighed me and I was 7.2 […] the nutrients going through my body, I'm just fading away. It's a terrible, terrible disease.' – Patient H*
Psychological	'*Sometimes I think I am bloody awful to live with. Because – as well as getting black days – I get very angry. I get really angry. […] I can get almost violent in that I want to break something. I want to hurt myself…* – Patient S

Source: UK Burden of illness in hATTR amyloidosis patients and carers[80]

Families and carers

Many carers surveyed noted experiencing fatigue, due to the impact of caring for the patient. From the carers' perspective, fatigue often stemmed from disturbed sleep due to various factors including night-time restlessness, the patient's bowel dysfunction, as well as emotional exhaustion and anxiety.[17] Carers also reported frustration at being restricted to the house for hours yet having nothing to do for the patient on occasions when he or she was able to sleep or sit for a period without needing help, yet the carer couldn't leave in case the patient awoke or arose in their absence and fainted or fell.[17]

Activities of daily living

The wide-ranging burden of hATTR amyloidosis on patients, caregivers, and the healthcare system was also revealed by data from the phase 3 APOLLO trial (N=225) of patients with hATTR amyloidosis in various stages of disease, in which the baseline Rasch-built Overall Disability Scale (R-ODS) was used to measure activity and social ability of the participants.[81] Patients were recruited from 46 centres in over 19 countries including the UK.[81] At baseline, patients had difficulty performing activities, even those which are considered low intensity and not very social such as reading a book (27%) or eating (30%).[24] The majority of patients were not able to perform more complex motor tasks such as dancing (59%), standing for a long period (i.e., hours) (63%) or running (76%).[24] Patients experienced worsening disability (on the R-ODS) and ambulation (measured on the 10 metre walk test [10MWT]) from baseline to 18 months, showing increasing disability with disease progression.[11]

As the disease progresses, symptoms rapidly increase in severity, resulting in worsening disability and increasing hospitalisations, and need for additional caregiver support to accomplish daily activities.[24,82,83] During the 1-year period prior to participant enrolment in the APOLLO trial, 28% of patients were hospitalised overnight and approximately 23% used Emergency Department services for disease symptoms.[83] Fifty-three percent of patients required medical equipment to stand or walk.[83] Patients in a later stage of disease had statistically increased overnight hospitalisations at baseline (FAP Stage 1: 17% vs FAP Stage 2: 39%, respectively; p=0.0004).[83] Similarly, late-stage patients required more mobility assistance devices than those in early-stage disease (FAP Stage 2: 89% vs FAP Stage 1: 12%, respectively; p<0.0001).[83] The profound clinical deterioration observed in the placebo group over 18 months, which included marked worsening of polyneuropathy and cardiomyopathy symptoms and the associated deterioration of ambulation, nutritional status, and HRQoL, underscores the

rapid progression of disease in patients with hATTR amyloidosis and the need to intervene with effective treatment early during the disease.[83]

Productivity

Absenteeism is an important issue for patients and families and increases with disease progression. Most patients in APOLLO at baseline reported being unable to work (69%).[24] The inability to work and the need for assistance to live independently were analysed jointly in the APOLLO patient population at baseline and were associated with FAP stage, increasing from 47% of FAP Stage 1 patients to 87% of FAP Stage 2.[24] Twenty-four percent of patients reported receiving government compensation due to disability caused by their illness and this need increased from 18% in FAP Stage 1 to 30% in FAP Stage 2 ($p=0.03$).[24] Caregivers were also impacted financially, with 15% of patients reporting their caregivers were not able to work (from 6% of caregivers for patients in FAP Stage 1 to 22% of those for patients in FAP Stage 2; $p<0.0001$) and an additional 12% of patients reporting that their caregivers were limited to part-time employment.[24] Caregivers who were able to work averaged 3 weeks of lost work over the period of a year.[24] As expected, an increase in social and activity impairment and lost productivity was seen in both patients and caregivers of patients who were in the later stages of the disease.[24]

Additional evidence of the considerable impact of hATTR on patients' and caregivers' ability to work was provided by a US survey of 33 hATTR amyloidosis patients and 18 caregivers which found that unemployment was high in patients with hATTR amyloidosis (range from 42.9% to 71.4%).[82] Additionally, only 33.3% of the caregivers reported working part- or full-time.[82]

The escalating burden of the disease leaves patients progressively unable to function at home and in the workplace. These findings point to a substantial current unmet need for therapeutic options to limit progression of the disease, thereby relieving the burden on patients, caregivers, and society as a whole.

7.2 Impact of the technology

The burden of hATTR on patients, their families, and carers is outlined in detail in Section 7.1.

The introduction of patisiran in the UK is expected to reduce the burden of hATTR on patients, caregivers, and society. Evidence supportive of this expectation was provided by the APOLLO trial, in which a significant reduction in disease symptoms and disability, improvement in HRQoL, nutritional status, strength, and ambulation was seen in patients treated with patisiran relative to those receiving placebo.[11]

Improved physical ability

The primary endpoint in APOLLO was the change from baseline to 18 months in modified Neuropathy Impairment Score +7 (mNIS+7), a comprehensive measure of neurologic impairment that has evolved specifically to assess neurological disease progression in hATTR amyloidosis, and includes an evaluation of motor strength/weakness (e.g., balance, walking with a walking aid),[5] sensation (e.g., pain),[5] reflexes (e.g., ability to dress, use utensils, drink from a glass),[24] nerve conduction (e.g., may result in soreness, weakness, or numbness),[23] and autonomic function (e.g., faecal incontinence)[27] with a numerically higher score indicative of increased disease severity.[11,30] In the patisiran group, 56% of patients showed an improvement of neuropathy (change from baseline in mNIS+7 <0 points) at 18 months as compared to 4% of placebo patients (odds ratio [OR]: 39.9, 95%CI: 11.0, 144.4; p<0.001).[11]

Improved HRQoL

Patients receiving patisiran experienced an improvement in HRQoL relative to baseline (LSM±SE: -6.7±1.8 points), whereas a marked worsening of quality of life occurred in the placebo group (LSM±SE: 14.4±2.7 points; LSM±SE difference between groups: -21.1±3.1 points; 95% CI, −27.2 to −15.0; p<0.001).[11] Notably, patisiran led to an improvement in the Norfolk QoL-DN domains previously identified as being most relevant to patients,[31] including physical functioning/large nerve fibre, symptoms, and autonomic neuropathy.[39] These data reveal that the physical improvements seen in patients treated with patisiran translate to improved HRQoL, meaning that the symptom improvements experienced by patients result in more enjoyable, higher-quality daily life.

Ability to participate in activities of daily living

In addition, patisiran was significantly superior to placebo in terms of multiple aspects of the disease that affect patients' daily living and functioning at home and at work, including:[10,11,24]

- Motor strength (e.g., walking, balance) measured by NIS-W (least square mean [LSM]±SE difference between groups: -17.9±2.3; p<0.001)
- Activities of daily living (e.g., reading a book, using utensils) and social participation (e.g., dancing) measured by R-ODS (LSM±SE difference between groups: 9.0±1.0; p<0.001)
- Ability to walk (walking speed) measured by 10MWT (LSM±SE difference between groups: 0.31±0.04; p<0.001)

- Nutritional status measured by mBMI (LSM±SE difference between groups: 115.7±16.9 kg/m^2 × albumin g/L; p<0.001)
- Autonomic neuropathy symptoms (e.g., faecal incontinence) measured by composite autonomic symptom score-31 (COMPASS-31; LSM±SE difference between groups: -7.5±2.2; p<0.001)

Short- and long-term effects on caregivers and society

These improvements in patient functioning with patisiran would undoubtedly also have a positive effect on family members and carers, who will experience some relief of the burden of care both in the short and long-term. Furthermore, patients with improved mobility and autonomic function may be able to remain productive or return to a level of productivity they once enjoyed in society due to their reduced symptom burden.

Taken together, these results demonstrate that patisiran improves physical characteristics including motor strength, reflexes, and autonomic function in hATTR amyloidosis patients, which should allow them more freedom and autonomy to live a life closer to that of a healthy adult.

8 Extent and nature of current treatment options

- A crucial unmet medical need remains in the UK for novel therapies as there are no available disease-modifying treatment options for patients and current treatment focuses on symptom management (best supportive care; BSC).
- Patisiran represents a step-change in the management of hATTR amyloidosis, filling a considerable previously unmet medical need by targeting the disease aetiology in order to halt or reverse disease progression; patisiran address the multi-systemic nature of hATTR amyloidosis.
- Alnylam has worked with a broad range of stakeholders, including the NAC, the National Hospital for Neurology and Neurosurgery, clinicians in regional hospitals, NHS England, Patient Advocacy Groups and NICE to define the pathway by which patients will receive patisiran.

8.1 Guidelines for hATTR amyloidosis

At the time of this submission, no NICE, NHS England, or other national UK guidance documents on management of hATTR amyloidosis were available.

Relevant clinical practice treatment guidelines, which are anticipated to evolve considerably in the coming years with the introduction of new treatment options, emphasise the importance of an ongoing multidisciplinary approach to managing patients with hATTR amyloidosis.[3] There are no available guidelines that are consistent with the current understanding of the treatment of hATTR amyloidosis as one hereditary disease with a spectrum of clinical manifestations. European guidelines focus on management of the polyneuropathy manifestations of disease and are not reflective of current clinical practice in the UK.[3,5,6]

Ando et al. 2013 published a guideline for the treatment of hATTR in which they propose that from the outset, patients should be treated symptomatically regardless of disease presentation and, if possible, stabilised, since the immediate goal is to alleviate symptoms.[5] The sections relevant to UK clinical practice are outlined in Section 8.2.1.

The NAC provides specialised diagnostic and management advice for amyloidosis patients in England. Most patients require ongoing care from several specialists as supportive treatment of many kinds is vital. Treatment for most patients is delivered by local secondary care facilities with primary care support. Treatment is on an individual, tailored basis.[84]

8.2 Current clinical pathway of care

Current treatment options for hATTR amyloidosis fall under two categories: symptomatic treatment and disease-modifying or stabilising therapy. Symptomatic treatment is more common and a priority to provide immediate relief and improve HRQoL.[5]

However, there are no existing treatment options that safely and effectively improve neurologic impairment or that address cardiomyopathy or other symptomology experienced by patients with hATTR amyloidosis. Patients continue to experience clinically relevant, multi-systemic disease progression despite treatment with existing pharmacotherapy or undergoing OLT. Existing pharmacotherapy options are not approved for use in the UK[45] or not licenced for the treatment of hATTR amyloidosis in the UK or elsewhere and clinical advice suggests OLT is rarely a treatment option in England.[85]

8.2.1 Symptom management (Best Supportive Care)

Table B4 below summarises the main symptomatic therapeutic solutions for hATTR amyloidosis with polyneuropathy, sorted by symptom from Ando et al. 2013.[5] The symptomatic therapeutic solutions outlined below provided the basis for the definition of best supportive care (BSC) in the cost-effectiveness (CE) model presented in this submission and was validated by UK experts at the NAC.[16] No regional differences in best supportive care were assumed for the UK.

Table B4. Treatment for clinical symptoms of hATTR amyloidosis with polyneuropathy

Symptom	Treatment
Arrhythmia	Pacemaker implantation, pharmacotherapy
Cardiac failure	Diuretics, angiotensin converting enzyme inhibitors, blood thinners, heart transplantation
Orthostatic hypotension	Droxidopa, midodrine, amezinium metisulfate, fludrocortisone, plastic stocking, abdominal belt, elevating head
GI disorders (not severe)	Polycarbophil calcium, metoclopramide
Severe diarrhoea	Loperamide
Neuropathic pain	Pregabalin, gabapentin, amitriptyline, duloxetine
Carpal tunnel syndrome	Surgery
Dry mouth	Potassium dihydrogen phosphate, cevimeline
Hypoglycaemia	Glucose loading
Renal failure	Haemodialysis
Urinary incontinence	Distigmine
Anaemia	Erythropoietin, iron
Hypothyroidism	Levothyroxine
Ocular amyloidosis	Vitrectomy, trabeculectomy

GI: gastrointestinal.

Source: Adapted from Ando et al. 2013[5]

Cardiomyopathy symptoms are largely managed with supportive care aimed at alleviation of heart failure symptoms, including restriction of salt intake, diuretics, pacemakers, and arrhythmia management.[5]

8.2.2 Disease specific treatment

<u>Transplantation</u>

Clinical advice suggests OLT is rarely performed in England,[44,85] as outcomes are poor in patients with cardiac involvement,[63,86] which is a common presentation in the UK.[20] In some patients, a worsening of cardiomyopathy can occur after OLT due to an

accumulation of wild-type transthyretin-mediated amyloid fibrils in the muscular tissue of the heart.[63,87] Therefore, OLT is not recommended for patients with cardiac involvement due to the progression of cardiac disease observed post-transplant.[5,60]

OLT is associated with high mortality as well as substantial morbidity due to chronic immunosuppressive medications required to prevent rejection.[5] Transthyretin-mediated amyloidosis patients are more vulnerable to early post-transplant thrombotic complications, in particular hepatic artery thrombosis, which correlates with high morbidity in these patients.[60] Renal function can also deteriorate after OLT, leaving patients requiring dialysis.[88]

As well, OLT does not lead to clinical or functional recovery in patients and although it stops progression of the mutant variant of the disease in approximately two-thirds of patients and increases OS, it does not always lead to a perceived improvement in HRQoL.[22,60]

A retrospective study of the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) found a 5-year survival rate of 79% for patients with the Val30Met mutation vs 56% for patients with non-Val30Met mutations.[89] The considerably lower survival in patients with non-Val30Met mutations further highlights the inadequacy of OLT as a treatment for the majority of UK patients who have non-Val30Met mutations.[20]

Pharmacotherapy

Tafamidis (Vyndaqel®; Pfizer Ltd., United Kingdom) is an oral disease-stabilising agent that kinetically stabilises TTR.[90] In 2012, the Advisory Group for National Specialised Services (AGNSS) recommended that tafamidis not be routinely commissioned nationally in the UK.[45] Therefore tafamidis is not used in clinical practice in the UK. There is limited published evidence of the efficacy of tafamidis in non-Val30Met mutations as the pivotal tafamidis trial studied a patient population with early onset Val30Met mutation.[91]

TTR tetramer stabilisers do not reduce the levels of the pathogenic protein and patients will continue to experience worsening of their neurologic impairment and declining HRQoL over time.[92-94]

Diflunisal is a generic, oral nonsteroidal anti-inflammatory drug (NSAID) that has been demonstrated to bind to and stabilise the TTR tetramer.[72] While used off-label in some countries where available,[3,6,63] diflunisal does not have a licence for the treatment of hATTR amyloidosis in any country. Diflunisal is contraindicated in patients with severe

heart failure, GI bleeding, or hepatic or renal failure.[95] Because patients with hATTR amyloidosis are already at risk of cardiovascular and renal issues due to the disease,[6] many patients may be poor candidates or ineligible for treatment with diflunisal. There are no data on the efficacy or safety of diflunisal in patients with cardiac symptoms.[72]

8.3 Issues with current clinical practice

There remains a crucial unmet medical need in the UK for novel therapies that can safely and effectively address the multi-systemic nature of hATTR amyloidosis, to halt and/or reverse disease progression and thereby avoid irreversible functional deficits and disability.[5,22]

8.4 Proposed pathway of care

Patisiran is the first disease-modifying treatment for adults with hATTR amyloidosis available in the UK. Based on its mechanism of action and the non-clinical and clinical data presented in *Section C – Impact of the new technology*, patisiran is expected to be of significant benefit for UK patients with ATTR amyloidosis.

Alnylam Pharmaceuticals UK has worked with a broad range of relevant stakeholders, including stakeholders from the NAC, the National Hospital for Neurology and Neurosurgery, clinicians in regional hospitals, NHS England, Patient Advocacy Groups (including ARC) and NICE to define and agree on the pathway by which patients will receive patisiran should it receive a licence from the EMA and be approved by NICE. The typical 'patient pathway' by which the majority of patients will receive patisiran, to which all the above stakeholders are aligned, will be:

- An hATTR patient develops neurologic, cardiac or other symptoms and attends their GP who refers them secondary care. Clinicians in secondary care suspect amyloidosis and refer the patient to the NAC.
- A clinician at the NAC investigates the patient (e.g., biopsy, genetic testing, scintigraphy) and confirms the diagnosis of hATTR. The NAC clinician prescribes patisiran and the patient receives their first infusion as soon as possible after diagnosis as a day-case at the NAC.
- The NAC clinician continues to prescribe patisiran and the patient receives two or more further infusions at the NAC as an outpatient (one infusion every 3 weeks).
- After three or more infusions, the NAC clinician decides that the patient is safe for homecare infusion and prescribes patisiran to be infused by a homecare

company approved by the NHS (the decision to move a patient to homecare treatment will be made at the NAC clinician's discretion and a clinician may decide that an individual patient needs more than three infusions to demonstrate suitability). The patient receives home infusion of patisiran, prescribed by the NAC clinician, every 3 weeks on an ongoing basis.

- The NAC clinician continues to see the patient approximately every 6 months to provide specialist advice and input and to monitor response to treatment.

Under this model, a clinician at the NAC will write all prescriptions for patisiran (including the homecare prescriptions) and will be responsible for monitoring patisiran treatment and making all treatment related decisions. Each patient will also likely continue to see a neurologist or cardiologist at their local hospital (as is the current practice), who may be able to help with management of symptoms and also to co-ordinate local care requirements (e.g., for orthotics) but who will not be involved in prescribing or making decisions around patisiran treatment. The NAC will remain as the key national specialist centre for hATTR amyloidosis patients. There may be a small number of patients who would prefer to continue to receive ongoing patisiran infusions at the NAC instead of through homecare. The NAC and NHS England have confirmed to us that patients will be able to choose to do this if they so wish.

This model of care is very similar to that which currently exists today. Today, hATTR amyloidosis patients typically receive regular 'expert' follow-up from a clinician at the NAC and most also continue to see a clinician at their local hospital who may provide symptomatic care.

Alnylam, and the broad range of stakeholders consulted, believe that the model presented remains the best model for both patients and the NHS, for the following reasons:

- Patients will have the benefit of continuing to receive specialist care and expertise from the NAC and will also have the convenience of being able to receive patisiran in their own homes.
- The NHS will benefit from there being a single expert centre that will be able to confirm diagnoses and make appropriate decisions to start and stop treatment. This ensures that all prescribing of patisiran in England takes place in an expert multidisciplinary centre, against consistent standards with appropriate monitoring, data collection and reporting in line with the commissioning policy. It also avoids the need to reorganise how the service currently works or to build a new service. Drug acquisition can all be centralised and administered through

one centre for maximum efficiency. Finally, having a single expert centre driving treatment would facilitate the collection of ongoing observational data to a consistent standard should that be required.

It is possible that a very small minority of patients eligible for patisiran treatment might prefer to receive infusions in a setting other than the NAC or homecare. In such cases alternative arrangements can be made for infusions, as is the standard procedure today for light chain amyloidosis. To ensure the service is reimbursed, the provider should be a nationally commissioned service for comparable conditions, such as peripheral neuropathy.

8.5 Innovation of the technology

Patisiran is the first ever approved siRNA and thus the first drug indicated for any medical condition that utilises the naturally occurring mechanism of RNAi to reduce the expression of mutant mRNA and the corresponding disease-causing protein. The revolutionary nature of RNAi in terms of understanding how genes are expressed and silenced in cells, and its promise for innovative treatments was recognised by the award of the Nobel Prize in Physiology or Medicine in 2006.[1] Alnylam was established to develop RNAi therapeutics into a new class of medicines, and has remained committed to this goal for more than 15 years despite the abandonment of the field by many of the pharmaceutical companies that entered it.[37] Based on this ground-breaking technology, the patisiran mechanism of action is distinct from all previous treatments for hATTR amyloidosis, and is unique in its ability to reduce the level of circulating amyloidogenic protein.[96,97]

As noted in Section 2.2, the UK MHRA has recognised patisiran as an innovation in this area of clear unmet medical need by awarding patisiran a Promising Innovative Medicine designation in January 2018. According to the terms of the programme, the PIM designation is only granted to medicinal products judged to meet all three of the following criteria:[15]

1. The condition is life-threatening or seriously debilitating (with severity justified in terms of mortality and morbidity, with special emphasis on patient HRQoL), and has high unmet medical need, AND
2. The product is likely to offer major advantage over methods currently used in the UK, AND
3. The potential adverse effects of the product are likely to be outweighed by the benefits.

Thus, patisiran has been recognised by the UK regulatory authority to be innovative in its potential to address the high unmet medical need for patients with hATTR amyloidosis.

As no disease-modifying drug options previously existed for patients with hATTR amyloidosis in the UK, patients were condemned to a bleak prognosis in which the disease progressed inexorably towards death, with the available symptomatic treatments so inadequate in advanced stages that some patients considered death preferable to continuing to live with hATTR amyloidosis.[17] As the first disease-modifying drug treatment for hATTR amyloidosis available in the UK, patisiran represents a step-change in the management of hATTR amyloidosis, filling a considerable previously unmet medical need by targeting the disease aetiology in order to retard progression. The potential for patisiran to significantly and substantially improve patient outcomes is supported by findings described in *Section C – Impact of the new technology*.

8.6 Changes to current services

We do not believe that the technology will require significant changes to the way current services are organised or delivered. A description of the clinical pathway model by which patients will receive patisiran is provided in Section 8.4. This model has been discussed and agreed upon by a broad range of stakeholders through one-on-one meetings, an EAMS meeting organised through the NICE Office for Market Access and a multi-stakeholder meeting organised by the NICE Office for Market Access in July 2018. The model builds upon the patient pathway that currently exists in England. In summary, patients are diagnosed at the NAC where they will receive three (or possibly more at the discretion of the clinician) infusions of patisiran. If the NAC clinician believes the patient is suitable, the patient will be referred for NHS-approved homecare and will receive patisiran at home whilst being followed up at the NAC every ~6 months.

Alnylam Pharmaceuticals is working with the NAC and NHS England to 'test' this model for delivering patisiran treatment in patients receiving patisiran as part of EAMS. This should ensure that the model is ready to be rapidly implemented if patisiran receives a license from the EMA and is approved by NICE.

8.7 Additional administration requirements

Supplementation at the recommended daily amount of vitamin A is advised when taking patisiran.[12] To reduce the risk of infusion-related reactions (IRRs), patients should be administered premedications (dexamethasone 10 mg, or equivalent corticosteroid, paracetamol 500 mg, and IV H1 blocker [dexamethasone 10 mg or

equivalent] and IV H2 blocker [ranitidine 50 mg or equivalent]) at least 60 minutes prior to the start of administering patisiran on the day of infusion. For patients who are tolerating their infusions but experiencing side effects due to the corticosteroid premedication, the corticosteroid may be reduced by 2.5-mg increments to a minimum dose of 5 mg of IV dexamethasone or equivalent. Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs.[12]

8.8 Additional facilities, technologies or infrastructure

No additional facilities, technology, or infrastructure are required.

8.9 Tests, investigations, interventions, facilities or technologies no longer needed

A post-hoc analysis of hospitalisation/death data from APOLLO showed an approximate 50% reduction in all-cause hospitalisation/death events caused by SAEs occurring within 28 days of the last patisiran treatment over the entire population of APOLLO (HR: 0.48; range: 0.34, 0.69).[98] A 45% reduction in cardiac related hospitalisation/death was observed in patients treated with patisiran who were part of the cardiac subgroup (HR: 0.54; range: 0.28, 1.01).[98]

Furthermore, a Delphi panel study was conducted on healthcare resource utilisation (HCRU) for the management of polyneuropathy and cardiomyopathy symptoms in hATTR patients. Study methodology and results are described in detail in Section 10.1.10. Based on the mean of the estimates provided by the panellists, it is expected that patisiran will result in a [redacted] and [redacted] decrease in the HCRU for the management of polyneuropathy and cardiomyopathy, respectively, in patients with hATTR amyloidosis at any given PND score and NT-proBNP level.[99]

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

- Patisiran is an effective and safe disease-modifying therapy for patients with hATTR amyloidosis that comprehensively addressing all major aspects of the disease by improving sensory, motor, and autonomic neuropathy, as well as cardiomyopathy.
- Patisiran was shown not only to halt or reverse disease progression, but also to reduce the neuropathy (as measured by mNIS+7) and

cardiomyopathy (as measured by NT-proBNP) that are the cardinal manifestations of the disease.

- Patisiran improved neurologic impairment from baseline in the majority of patients with hATTR amyloidosis: 56% of patients in the patisiran group showed an improvement of neuropathy (change from baseline in mNIS+7 <0 points) at 18 months as compared to 4% of patients from the placebo group (OR of 39.9; 95% CI: 11.0, 144.4; p<0.001).
- Patisiran significantly improved patients' HRQoL, muscle strength, and motor function.
- Patients treated with patisiran showed significantly improved status in their activities of daily living and patients maintained their nutritional status which is a key contributor to mortality in hATTR amyloidosis patients.
- The clinical benefits observed with patisiran were consistent across patient subgroups over time and patisiran produced favourable changes in the cardiac subgroup from APOLLO with lower NT-proBNP levels and improved walking speed (10MWT).
- The safety profile of patisiran was favourable: the frequencies of AEs, SAEs, and deaths in the APOLLO group were comparable with the placebo group and patients treated with patisiran had fewer overall treatment discontinuations than those in the placebo group (7% vs 38%, respectively).
- The APOLLO trial results are relevant to the UK patient population: the trial included genotypes most common in the UK and the majority of patients were from Western Europe. As well, over 50% of APOLLO patients showed signs of neuropathy and cardiomyopathy which is representative of the UK population.

9.1 **Identification of studies**

9.1.1 Published studies

As mentioned in the previous section, historically, hATTR amyloidosis was considered two separate diseases according to the predominant clinical presentation.[6] Now it is recognised as one disease with a wide range of overlap since most patients have both neuropathy and cardiomyopathy symptoms.[6] In order to address this shift in the

definition of hATTR amyloidosis, two comprehensive SLRs were conducted to identify RCTs and observational studies reporting the safety and efficacy of current treatments for adult patients being treated for hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy. The SLRs were conducted in accordance with the requirements of NICE and the Centre for Reviews and Dissemination (CRD) guidance. The detailed search strategy used is listed in Appendix 1.

9.1.2 Unpublished studies

A grey literature search was conducted which included a search for conference abstracts on Embase, searches for ongoing studies in ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), as well as searches for relevant evidence on select regulatory and health technology assessment websites namely, NICE, the Institute of Quality and Efficiency in Health Care (IQWiG), the US Food and Drug Administration (FDA), the European Public Assessment Reports (EPARs), NICE, the Scottish Medicines Consortium (SMC), the All Wales Medicines Strategy Group (AWMSG), and the Canadian Agency for Drugs and Technologies in Health (CADTH).

For the Embase search of conference abstracts and poster presentations (as available), the following meetings were included:

- International Symposium on Amyloidosis
- European Congress on Hereditary ATTR Amyloidosis
- European Society of Cardiology Congress
- American College of Cardiology Annual Meeting
- Congress of the European Academy of Neurology
- American Neurological Association Annual Meeting
- American Academy of Neurology Annual Meeting
- Peripheral Nerve Society Annual Meeting
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and European Meetings

The proceedings of the following conferences (which are not indexed in Embase) were searched manually:

- International Congress on Neuromuscular Diseases
- American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting
- European ATTR Amyloidosis Meeting

In addition, a maximum of five SLR articles were selected and manually searched to validate the study selection and to identify any additional relevant publications.

9.2 Study selection

9.2.1 Published studies

The SLR selection criteria for published studies are summarised in Table C1.

Table C1. Selection criteria used for published studies

	hATTR amyloidosis with polyneuropathy SLR	hATTR amyloidosis with cardiomyopathy SLR
Inclusion criteria		
Population	• Populations or subgroups enrolling at least 80% patients per treatment arm with hATTR amyloidosis with polyneuropathy	• Patients with hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis*
Interventions	• Any treatments	• Any treatments
Comparators	• Any	• Any
Outcomes	• From RCTs: safety and efficacy outcomes, patient-reported outcomes • From single-arm studies: safety and effectiveness outcomes • From observational studies: clinical effectiveness, safety, patient-reported outcomes • From economic studies: costs, cost-effectiveness, and resource use	• From RCTs: safety and efficacy outcomes, patient-reported outcomes • From single-arm studies: safety and effectiveness outcomes • From observational studies: clinical effectiveness, safety, patient-reported outcomes • From economic studies: costs, cost-effectiveness, and resource use
Study design	• RCTs and non-randomised controlled trials • Open-label extensions • Observational studies (prospective, cross-sectional, and retrospective [i.e., chart reviews, registries, surveys, etc.]) of clinical effectiveness and safety • Single-arm trials • Cost-effectiveness, cost-utility, or cost-minimisation studies • Healthcare resource use studies • Utility assessments or patient-reported outcome studies	• RCTs and non-randomised controlled trials • Open-label extensions • Observational studies (prospective, cross-sectional, and retrospective [i.e. chart reviews, registries, surveys, etc.]) of clinical effectiveness and safety • Single-arm trials • Cost-effectiveness, cost-utility, or cost-minimisation studies • Healthcare resource use studies • Utility assessments or patient-reported outcome studies
Language restrictions	None	None
Search dates	Original SLR: 30 May 2017 SLR Update: 10 January 2018	28 January 2018
Exclusion criteria		

	hATTR amyloidosis with polyneuropathy SLR	hATTR amyloidosis with cardiomyopathy SLR
Population	• Not hATTR amyloidosis (such as wtATTR amyloidosis) • hATTR amyloidosis not presenting with predominant polyneuropathy or • hATTR amyloidosis in which polyneuropathy is attributable to another cause • Mixed populations or subgroups with <80% adult hATTR amyloidosis with polyneuropathy • hATTR amyloidosis patients who have undergone OLT	• hATTR amyloidosis patients who have undergone OLT
Interventions	N/A	N/A
Comparators	• Dose-finding clinical trials (i.e., studies in which all treatment arms are different doses of the same agent)	• Dose-finding clinical trials (i.e., studies in which all treatment arms are different doses of the same agent)
Outcomes	• Pharmacodynamic/pharmacokinetic studies or non-clinical studies (such as gene expression or protein expression studies)	• Pharmacodynamic/pharmacokinetic studies or non-clinical studies (such as gene expression or protein expression studies)
Study design	• Letters, literature reviews, expert opinion articles, etc.	• Letters, literature reviews, expert opinion articles, etc.
Language restrictions	• None	• None
Search dates	Original SLR and rescreen: 30 May 2017 SLR Update: 10 January 2018	January 28, 2018

hATTR: hereditary transthyretin-mediated amyloidosis; NA: not applicable; OLT: orthotopic liver transplantation; RCT: randomised, controlled trial; SLR: systematic literature review; wtATTR: wild-type transthyretin-mediated amyloidosis. *May include patients with ATTR with primary cardiomyopathy (hereditary or wild type), hATTR with primary polyneuropathy who also have cardiomyopathy, or ATTR with cardiomyopathy alone (hereditary or wild type).

9.2.2 PRISMA diagrams

The PRISMA diagrams for the two SLRs are shown in Figure 3 and Figure 4.

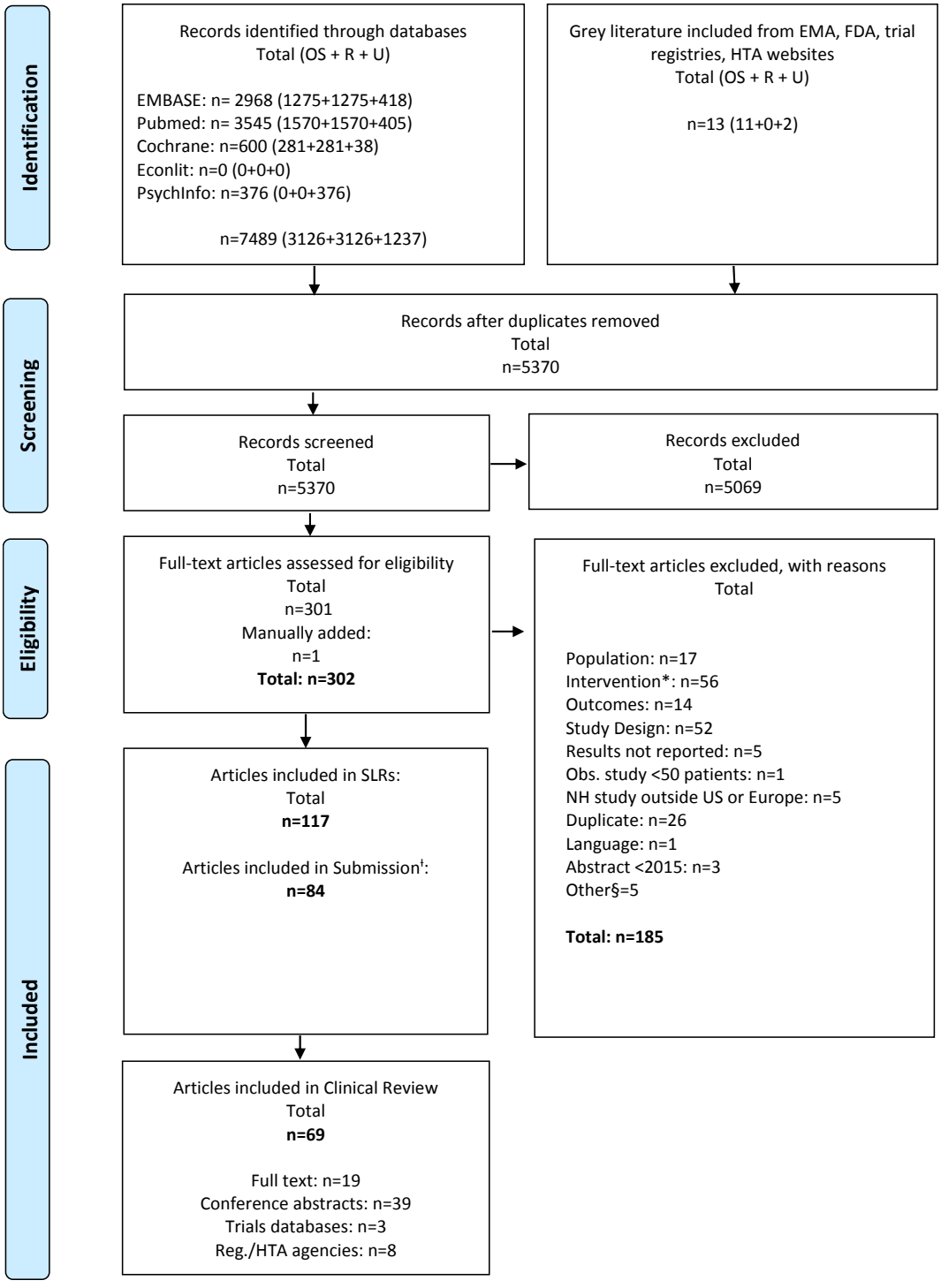


Figure 3. PRISMA flow diagram for clinical evidence in hATTR amyloidosis with polyneuropathy

HRQoL: health-related quality-of-life; HTA: health technology assessment; NH: natural history; OS: original search; R: rescreen; SLR: systematic literature review; Reg.: regulatory; U: update.

*Includes 33 studies in rescreen and 11 studies in update that were related to liver transplant and that were excluded by protocol amendment.

†These totals exclude the natural history studies that were part of the original search.

§2 studies in rescreen and 3 studies in update could not be located.

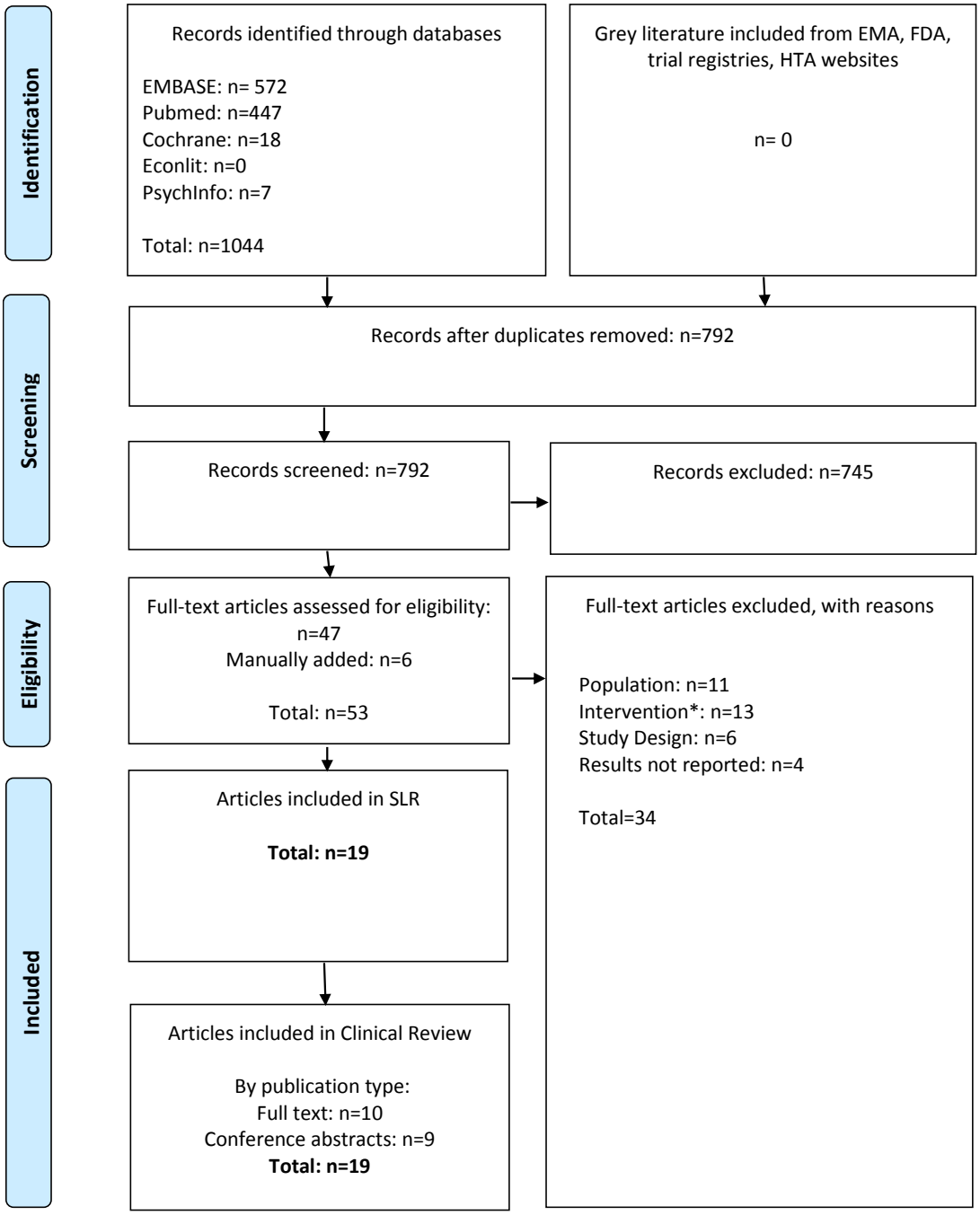


Figure 4. PRISMA flow diagram for clinical evidence in hATTR amyloidosis with cardiomyopathy and wtATTR amyloidosis

EMA: European Medicines Agency; FDA: Food and Drug Administration; HRQoL: health-related quality-of-life; HTA: health technology assessment; Reg.: regulatory; SLR: systematic literature review.

*Includes 4 studies that were related to liver transplant and that were excluded by protocol amendment.

9.2.3 Unpublished studies

The search selection inclusion and exclusion criteria for unpublished studies were the same as the criteria for published studies. These criteria are summarised in Table C1. We have included the grey literature (unpublished) studies in the PRISMA diagrams for each SLR (Figure 3 and Figure 4).

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 SLR results

Table C2 lists the included studies of the SLRs. In the hATTR amyloidosis with polyneuropathy SLR, 69 published studies were identified of which 12 were RCTs and 57 were single-arm interventional, OLE, observational, or retrospective-matched cohort studies. Studies that were identified, but excluded (e.g., interim data or out of scope) are listed in Appendix 1.

Patisiran was evaluated in a phase 3 RCT (APOLLO). While the APOLLO publication identified by the original SLR was a conference abstract presented by Adams et al. in November 2017,[39] on 5 July 2018 full details of the study were published in the New England Journal of Medicine by Adams et al. 2018.[11] One phase 2, single-arm, interventional trial (Suhr et al. 2015),[100] and two OLE studies (phase 2 OLE and Global OLE) were also identified for patisiran. Two abstracts were included from the phase 2 OLE: the final 24-month data cut (Adams et al. 2017)[101], and the cardiac subgroup 24-month data (Adams et al. 2017)[102]. Partisano et al. 2017[33] reported data from the Global OLE which is an ongoing extension of the completed phase 2 OLE and the phase 3 APOLLO trial.

No unique studies from the hATTR amyloidosis with cardiomyopathy SLR were included after duplicates and studies that were out of scope were removed.

All of the non-published studies were excluded and are listed in Appendix 1.

Table C2. List of included published studies from the SLRs

Study code	Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Included/ excluded
P1A-PN-CM	Adams et al. 2017[39]*	APOLLO (NCT01960348)	225 adults aged 18–85 years with diagnosis of hATTR amyloidosis with polyneuropathy. Prior tetramer stabiliser use permitted. Randomised to: Patisiran n=148; Placebo n=77	Patisiran	Placebo	Included
P2A	Suhr et al. 2015[100]	NCT01617967	29 adults ≥18 years with biopsy proven ATTR amyloidosis and mild-to-moderate neuropathy.	Patisiran	None	Included
P3A-PN-CM	Adams et al. 2017[101]*	NCT01961921	27 adults who had previously participated in the phase 2 multi-dose study of patisiran (NCT01617967)	Patisiran	None	Included: Final 24-month data
P3B-PN-CM	Adams et al. 2017[102]*	NCT01961921	Associated abstract to P3A	Patisiran	None	Included: Cardiac subgroup; 24-month data
P4A	Partisano et al. 2017[33]	NCT02510261	27 adults with hATTR amyloidosis with polyneuropathy who participated in the phase 2 OLE (NCT01961921)	Patisiran	None	Included

CM: cardiomyopathy; hATTR: hereditary transthyretin-mediated amyloidosis; OLE: open-label extension; PN: polyneuropathy.

*Duplicate studies that were included in both SLRs were only counted once.

9.3.2 Study exclusion

The reasons for study exclusion from further analysis are summarised in Appendix 1. In the hATTR amyloidosis with polyneuropathy SLR, nine patisiran OLE publications were excluded as they were interim data cuts from the phase 2 OLE study. Seven diflunisal, seven inotersen, and 39 tafamidis studies were excluded as they were outside of the NICE scope. Two additional studies were excluded for interventions that were out of scope (i.e., green tea and taurousodeoxycholic acid [TUDCA]).

In the hATTR amyloidosis with cardiomyopathy SLR, no unique studies remained after removal of those that were out of scope or duplicate studies from the hATTR with polyneuropathy SLR.

None of the non-published studies were included.

9.4 Summary of methodology of included studies

9.4.1 Study design and methodology

Five publications from four of the studies identified in the SLRs are included in this submission. The clinical evidence includes:

- One RCT, one single-arm
- One interventional phase 2 trial,
- Three associated OLE publications (including one in a cardiac subgroup)

APOLLO

The patisiran phase 3 trial APOLLO was an international, multicentre, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy.[11] Eligibility criteria are listed in Table C3. Adult hATTR amyloidosis patients (N=225) were recruited from 46 sites across 19 countries (United States, France, Taiwan, Spain, Japan, Germany, Mexico, Portugal, South Korea, Sweden, Bulgaria, Italy, Canada, Turkey, Cyprus, Brazil, the Netherlands, United Kingdom, and Argentina) and all but two of the study sites were academic hospitals.[81] The patient population included 39 different genotypes (including those most common in the UK), Patients were randomised to receive patisiran (n=148; 0.3 mg/kg every 3 weeks by IV infusion for 18 months) or placebo (normal saline; n=77) (Table C3).[81] The study drug was administered as an IV infusion over 70 minutes (1 mL/min for the first 15 min then 3 mL/min thereafter).[81]

Patients had the option of discontinuing the study drug if they experienced a protocol-defined rapid disease progression at 9 months (defined as ≥24-point increase in mNIS+7) and FAP stage progression relative to baseline and confirmed by an external adjudication committee.[81] Patients who discontinued under those conditions received alternative therapy (in the UK this corresponded to BSC as defined in Section 8.2). All patients who completed the final 18-month assessment were eligible for the OLE study of long-term patisiran treatment.[81]

The 18-month study duration was chosen based on natural history data in hATTR amyloidosis patients and data from the 18-month tafamidis and 24-month diflunisal phase 3 trials, which demonstrated sufficient neuropathy progression in untreated patients over that time frame to allow for detection of a treatment effect.[2,72,81,91]

Patients received the following premedications or equivalent at least 60 minutes before each study-drug infusion: dexamethasone; oral acetaminophen/paracetamol; an H_2 blocker (e.g., ranitidine or famotidine); and an H_1 blocker.[81] The use of tafamidis, diflunisal, doxycycline, taurousodeoxycholic acid (TUDCA), or any investigational agent other than patisiran was prohibited during study participation. These agents may have been used before screening; however, a wash-out period of 14 days for tafamidis, doxycycline, or TUDCA and 3 days for diflunisal was required. Palliative and supportive-care concomitant medication was permitted.[81] Patients were randomised in a 2:1 patisiran: placebo ratio and treatment arms were balanced at study entry for: NIS (5–49 vs 50–130), early-onset Val30Met disease (age < 50 years at onset) vs all other mutations (including late-onset Val30Met), and previous use of tafamidis or diflunisal.[81] Patients and study personnel were blinded to treatment and the details of any patients who discontinued at 9 months due to rapid disease progression remained blinded throughout the study.[81]

The primary objective of the study was to determine the efficacy of patisiran for neuropathy by evaluating the difference between the patisiran and placebo groups in the change from baseline of mNIS+7 score at 18 months. The mNIS+7 used in APOLLO is more robust and comprehensive than tools used in the trials for diflunisal (NIS+7)[72] or other treatments for hATTR amyloidosis including tafamidis (NIS-LL).[81,91] The mNIS+7 used in APOLLO was specifically modified from the original NIS+7 to better characterise and quantify sensation anywhere on the body, autonomic function, and nerve conduction changes associated with hATTR amyloidosis progression.[30] The original NIS+7 was developed for trials with diabetic sensorimotor polyneuropathy and while it adequately assessed weakness and muscle stretch reflexes, it did not capture the loss of sensation, autonomic dysfunction and nerve conduction abnormalities

which are symptoms of hATTR amyloidosis progression.[30] The mNIS+7 incorporates Smart Somatotopic QSTing (S ST QSTing) to assess touch pressure and the loss of heat pain as well as modifications to the autonomic assessment and nerve conduction tests to take into account autonomic test abnormalities and to adequately assess motor and sensory nerve conduction.[30] S ST QSTing provides an improved balance between large and small sensory nerve fibres and measures sensation loss over the entire body rather than only at distal sites.[81]

The mNIS+7 is a 304-point composite measure of neurologic impairment including:[81]

- Neurologic examination of lower limbs, upper limbs, and cranial nerves (NIS-weakness [NIS-W] and reflexes)
- Electrophysiologic measures of small and large nerve fibre function (including nerve conduction studies (NCS) Σ5 of ulnar, peroneal, and tibial compound muscle action potential (CMAP) amplitudes and sural and ulnar sensory nerve action potential (SNAP) amplitudes
- Smart somatotopic quantitative sensory testing (S ST QSTing; including touch pressure and heat pain) at defined locations on the body
- Autonomic function (postural hypotension scored on a grading of function from normal [0 points] to very reduced (2 points)

The secondary objectives were to further demonstrate the clinical benefit of patisiran in terms of HRQoL, motor function, activities of daily living and social participation, nutritional status, and autonomic symptoms by assessing the difference between patisiran-treated and placebo-treated patients on the following measures at 18 months (screened at baseline, 9, and 18 months):[10,11]

- Norfolk QoL-DN questionnaire
- NIS-weakness (NIS-W) score
- R-ODS score
- 10MWT
- mBMI
- COMPASS 31

Efficacy endpoints were assessed using a mixed model for repeated measures and secondary endpoints were analysed in a prespecified hierarchical order to control for the overall type I error.[11] The study was powered for the primary

endpoint,[81] and was not designed to assess between-group differences in mortality.

The main exploratory objectives were to examine the effect of patisiran on cardiac disease manifestations, serum TTR levels, and disease pathophysiology to assess the therapeutic hypothesis that the reduction of circulating amyloidogenic TTR reduces the deposition and promotes the clearance of amyloid fibrils. The following exploratory endpoints were assessed and analysed as the change from baseline to 18 months:[10,11]

- Cardiac function was assessed through echocardiogram and cardiac biomarkers (troponin I and NT-proBNP)
- NIS+7 score
- Grip strength
- EuroQoL-five dimension (EQ-5D-5L) and EuroQoL visual analogue scale (EQ-VAS)
- Assessment of ambulation (PND score and FAP stage)
- Large and small nerve fibre function including nerve conduction studies sum of 5 attributes (NCS Σ5)
- Quantitative sensory testing (QST) by body surface area including touch pressure and heat pain
- Vibration detection threshold, heart rate variability to deep breathing, and postural blood pressure
- Number of patients with rapid disease progression (at 9 months)
- Pathologic evaluation of dermal amyloid burden and sensory and autonomic innervation
- Magnetic resonance neurography
- Pharmacodynamic biomarkers (TTR, retinol binding protein, vitamin A)[81,103]

In addition to the clinical outcomes, serum TTR protein levels were measured at baseline, 9, and 18 months. AEs were assessed throughout the study and graded based on severity and the causal relationship to the study drug or premedication.[81]

A sample size of approximately 200 patients provided 90% power to test a treatment difference of 8.95 points (37.5%) in the mNIS+7 change from baseline with a two-sided

α = 0.05. The populations analysed included modified intent-to-treat (mITT) which included all patients who were randomised and received at least one dose of the study drug and the safety population, which comprised all patients who received at least one dose of patisiran.[81]

Phase 2 trials

Suhr et al. 2015[100] (Appendix 1) was a phase 2, international, multicentre, open-label, multi-dose, dose-escalation trial to evaluate the safety and tolerability of patisiran in adult patients with hATTR amyloidosis (N=29).[100] Patients received doses of patisiran ranging from 0.01 mg/kg to 0.3 mg/kg.[100] Premedication included dexamethasone, paracetamol, and H2 blocker (e.g., ranitidine or famotidine), and H1 blocker (e.g., cetirizine, hydroxyzine, or fexofenadine) to reduce the risk of infusion-related reactions. Patisiran was administered by IV at 3.3 mL/min over 60 min or over 70 min using a micro-dosing regimen (1.1 mL/min for 15 min followed by 3.3 mL/min for the remainder of the dose).[100]

The primary study objective was to evaluate the safety and tolerability of multiple ascending doses of patisiran.[100] Secondary objectives included the assessment of the pharmacodynamic effect of patisiran on serum total TTR protein levels. Serum levels of total TTR protein and wt and mutant TTR protein were separately and specifically measured according to the dosing regimen (Q3W or Q4W for each cohort) between Day 0 and Day 208. Plasma concentration-time profiles were created for TTR siRNA. Safety evaluations included assessment of AEs, ECGs, arterial oxygen saturation using pulse oximetry, vital signs, clinical laboratory safety tests, and physical examinations.[100]

Results from a single-intervention phase 2 OLE of the original single arm study were reported in Adams et al. 2017[101] (final 24-month data; Appendix 1) and Adams et al. 2017 (cardiac subgroup data; Appendix 1).[102] Patients who were treated in the phase 2 study (Suhr et al. 2015)[100] were eligible to roll over into the phase 2 OLE study and receive up to 2 years of dosing at 0.3 mg/kg every 3 weeks (n=27). Clinical endpoints were evaluated every 6 months. The primary objective was to evaluate the safety and tolerability of long-term dosing with patisiran. Secondary objectives included the effect of patisiran on neurologic impairment (mNIS+7 and NIS), HRQoL, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fibre density in skin biopsies, cardiac involvement (assessed in a pre-determined cardiac subgroup) and serum TTR levels.[101] A Global OLE (Partisano et al. 2017; Appendix 1) is ongoing and is assessing the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with

polyneuropathy amyloidosis who participated in the phase 2 OLE or phase 3 APOLLO trial.[33]

Table C3. Summary of methodology for randomised controlled trials – Adams et al. 2017[39] (APOLLO methods from Adams et al. 2017)[81]

Reference:	P1A-PN-CM APOLLO
Study name	APOLLO, NCT01960348 The study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of TTR-Mediated Amyloidosis
Objectives	To evaluate the efficacy and safety of patisiran (ALN-TTR02) in patients with hATTR amyloidosis with polyneuropathy
Location	19 countries and 44 study centres; countries that randomised ≥10 patients were USA, France, Taiwan, Spain, Japan, Germany, Mexico, Portugal, and South Korea
Design	International, multicentre, phase 3, randomised, double-blind, placebo-controlled trial
Duration of study	November 2013 to August 2017, 18-month follow-up
Sample size	N=225 (Patisiran=148, Placebo=77)
Inclusion criteria	• Adults aged 18-85 years with diagnosis of FAP with documented TTR mutation • NIS of 5-130 and a PND score of ≤IIIB • NCS sum of SNAP, tibial CMAP, ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points • Karnofsky performance status requirements ≥60% • ANC ≥1500 cells/mm^3 and platelet count ≥50,000 cells/mm^3 • AST and ALT ≤2.5 ULN, total bilirubin within normal limits, INR ≤2.0 (patients on anticoagulant therapy up to INR ≤3.5 and those with total bilirubin ≤2 ULN were eligible if the elevation was secondary to documented Gilbert's syndrome and the patient had ALT and AST levels within normal ranges) • Serum creatinine of ≤2 ULN • No active hepatitis B or hepatitis C by serology • Negative pregnancy test as appropriate and no breastfeeding; • Birth control: Female and male patients of child-bearing age or with partners of such age agreed to use 2 methods of birth control during the study and for 75 days after the last dose • Willingness to comply with protocol schedule; written informed consent
Exclusion criteria	• Prior liver transplant or planned to undergo liver transplant during the study period • Known cause of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, monoclonal gammopathy, etc.) not related to hATTR amyloidosis • Primary amyloidosis or leptomeningeal amyloidosis • Type I diabetes

	• Type II diabetes for ≥5 years • Vitamin B12 below LLN • Untreated hypo- or hyperthyroidism • Major surgery within the past 3 months or major surgery planned during any point of the study period • Active Hepatitis B or C, or HIV infection • Active infection requiring systemic antiviral or antimicrobial therapy that was not completed prior to first dose of study drug administration • Malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated • NYHA heart failure classification of >2 • Acute coronary syndrome within the past 3 months • Uncontrolled cardiac arrhythmia or unstable angina • Known history of alcohol abuse or daily, heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]) • Investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the investigational drug, whichever was longer • Participated in a clinical study with antisense oligonucleotide (3-month washout period prior to start of APOLLO study drug administration) • Currently taking tafamidis, doxycycline, or TUDAC (14-day washout period prior to start of APOLLO study drug administration) • Currently taking diflunisal (3-day washout period prior to start of APOLLO study drug administration) • Prior severe reaction to liposomal product or a known hypersensitivity to oligonucleotides or any component of patisiran • Unable to take required premedications • Anticipated survival <2 years (opinion of investigator) • Considered unfit • Under legal protection
Method of randomisation	Conducted using an interactive response system; randomised 2:1 to patisiran or placebo, stratified by NIS (5-49 vs 50-130), early-onset Val30Met (<50 years of age at onset) vs all other mutations (including late-onset Val30Met), and previous tetramer stabiliser use (tafamidis or diflunisal) vs no previous tetramer stabiliser use
Method of blinding	Patients and study personnel who monitored patients during infusions and performed clinical assessments were blinded to the study treatment. Unblinded personnel and pharmacists prepared the drug for administration but were not involved in patient management or safety or efficacy assessments. Details of patients who discontinued study drug at 9 months due to rapid disease progression remained blinded throughout the study.

Intervention(s) (n =) and comparator(s) (n =)	Patisiran IV 0.03 mg/kg Q3W (n=148) Placebo sterile normal saline (0.9% NaCl) (n=77)
Baseline differences	≥10% difference in distribution of genotype between groups Val30Met/non-Val30Met, n (%) Patisiran: 56 (37.8) / 92 (62.2) Placebo: 40 (51.9) / 37 (48.1) ≥10% difference in distribution of total cardiac subpopulation between groups, n (%) Patisiran: 90 (60.8) Placebo: 36 (46.8) ≥10% difference in distribution of race between groups Race, Patisiran / Placebo, n (%) Asian: 27 (18.2) / 25 (32.5) Black/African or African American: 4 (2.7) / 1 (1.3) White/Caucasian: 113 (76.4) / 50 (64.9) ≥10% difference in distribution of region between groups Region, Patisiran / Placebo, n (%) North America: 37 (25.0) / 10 (13.0) Western Europe: 62 (41.9) / 36 (46.8) Rest of World: 49 (33.1) / 31 (40.3)
Duration of follow-up, lost to follow-up information	18-month follow-up Treatment discontinuations: Patisiran: n=11 (7.4%) AE: 2.0% Death: 3.4% Progressive disease: 0.7% Physician decision: 0% Protocol deviation: 0.7% Withdrawn by patient 0.7% Placebo: n=29 (37.7%) AE 9.1% Death: 5.2% Progressive disease: 5.2% Physician decision: 2.6% Protocol deviation: 0%

	Withdrawn by patient 15.6% Study Withdrawals: Patisiran: n=10 (6.8%) Placebo: n=22 (28.6%)
Statistical tests	Between-group comparison in mean change from baseline, t-test (p-value) Least-square mean difference from baseline with CIs
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline in neurological impairment assessed with the mNIS+7 at 18 months mNIS+7 total points: 304 Components (maximum points): • NIS-W: Weakness (192) • NIS-R: Reflexes (20) • Quantitative sensory testing by body surface area including touch pressure and heat as pain: (80) • Σ5 nerve conduction studies (10) • Postural blood pressure (2)
Secondary outcomes (including scoring methods and timings of assessments)	All the secondary endpoints were assessed at baseline, Month 9, and Month 18 with the exception of mBMI which was assessed at baseline, Day 84, Day 189, Day 357, Day 462 and Day 546 (which was used as the Month 18 assessment). • Norfolk QoL-DN: 35 questions divided into 5 HRQoL domains. The range of possible total scores is -4 to 136 • NIS-W (Weakness): component of mNIS+7, maximum 192 points • R-ODS: 24 items scored on a scale of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty). A total score will be calculated as the average of all non-missing items multiplied by 24 • 10MWT gait speed: (m/sec) • mBMI: BMI (kg/m^2) × serum albumin concentration (g/dL) • COMPASS-31: total weighted and summed score (range 0-100) based on 6 domains (orthostatic intolerance, vasomotor, secretomotor, GI, bladder, and pupillomotor) Exploratory endpoints: • EQ-5D-5L: 5 HRQoL dimensions are scored on a 5-point Likert scale which are then used to obtain an index value from 0 to 1.0 • NIS+7: 270 total points, components include NIS-W: Weakness (192), NIS-R: Reflexes (20), NIS-S: Sensation (32), Σ7 Nerve tests (26) • Cardiac assessments including: o NT-proBNP (ng/L)

	○ Troponin-I (mg/L) ○ LV wall thickness (cm) ○ LV Mass (g) ○ Longitudinal Strain (%) ○ LV ejection fraction (%) ○ 10MWT gait speed (m/sec) • Grip strength (kg) • Skin biopsies for nerve fibre density and amyloid

AE: adverse event; CI: confidence interval; CM: cardiomyopathy; CMAP: compound muscle action potential; EQ-5D-5L: EuroQol Five Dimension, Five Level Questionnaire; FAP: familial amyloidotic polyneuropathy; GI: gastrointestinal; hATTR amyloidosis: hereditary transthyretin-mediated amyloidosis; HIV: human immunodeficiency virus; INR: international normalised ratio ; IV: intravenous; LLN: lower limit of normal; LV: left ventricular; mBMI: modified body mass index; mNIS: modified Neuropathy Impairment Score; 10MWT: 10-metre walk test; NaCL: sodium chloride; NCS: nerve conduction study; NIS: Neuropathy Impairment Score; NT-proBNP: N-terminal-pro-B-type natriuretic peptide; NYHA: New York Heart Association; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; PN: polyneuropathy; PND: Polyneuropathy Disability Score; Q3W: every 3 weeks; R-ODS: Rasch-built Overall Disability Scale; SNAP: sensory nerve action potential; ULN: upper limit of normal.

Note: One patient in the placebo group had a PND IV score at baseline. This patient enrolled in the study prior to protocol amendment 4.0 which added an inclusion criterion requiring a baseline PND score of ≤IIIB.

Additional sources: Alnylam, data on file (APOLLO CSR)[10]; Alnylam, data on file (APOLLO PROTOCOL)[103]; Clinicaltrials.gov[40]

9.4.2 Sources for studies reported in more than one reference

Details for the APOLLO trial were drawn from a published manuscript and abstracts (presentations), the published trial design and rationale, and the unpublished APOLLO clinical study report and trial protocol.[10,11,24,39,81,83,98,103,104] Data on the patisiran phase 2 OLE (Study ALN-TTR02-003; Adams et al. 2017) were drawn from published abstracts and the clinical study report.[10,101] Data from the cardiac subgroup from the patisiran Study ALN-TTR02-003 phase 2 OLE were reported in Adams et al. 2017.[102] The Global OLE (Study ALN-TTR02-006) comprises patients from APOLLO and Study ALN-TTR02-003.[33]

9.4.3 Baseline characteristics

Table C4 summarised the differences between patient populations and methodology in all included studies.

Table C4. Baseline characteristics for patisiran studies

Baseline characteristic	Study name				
	APOLLO*		Phase 2†	Phase 2 OLE‡	Global OLE§
Study design	RCT		Phase 2, single-arm, interventional	Phase 2 OLE	Global OLE (APOLLO and phase 2 OLE patients)
Population (n)	Patisiran n=148	Placebo n=77	29	27	211
Age, median (range)y	62 (24–83)	63 (34–80)	mean: 56 (15.6)	64.0 (29–77)	65 (26–81)
Male, n (%)	109 (74)	58 (75)	20 (69) -	18 (67)	156 (73.9)-
Median years since diagnosis (range)	1.3 (0.0–21.0)	1.4 (0.0–16.5)	-	-	--
Mean NIS, mean (SD)	60.50 (34.512)	57.02 (32.042)	-	34.8 (range: 4.0–93.4)	64 (range: 0–162)
Mean NIS+7	80.93 (41.507)	74.61 (37.041)	-	53.0 (range: 2.0–122.5)	77 (range: 3–199)-
PND score, n (%)					
0	-	-	-	-	1 (0.5)
I	36 (24)	20 (26)	-	45	49 (23.2)
II	43 (29)	23 (30)	-	9	58 (27.5)
IIIA	41 (28)	22 (29)	-	2	42 (19.9)
IIIB	28 (19)	11 (14)	-	1	45 (21.3)
IV	0	1 (1)	-	-	16 (7.6)
FAP stage, n (%)					
0	0	0	-	-	
I	67 (45)	37 (48)	25 (86.2)	24	92 (43.6)
II	81 (55)	39 (51)	4 (13.8)	3	103 (48.8)
III	0	1 (1)	-	-	16 (7.6)

Mutation, n (%)					
Val30Met	56 (38)	40 (52)	22 (75.9)	20	98 (46.4)
non-Val30Met	92 (62)	37 (48)	7 (24.1)	7	113 (53.6)
Previous stabiliser use, n (%)	78 (53)	41 (53)	Diflunisal: 7 (24.1) Tafamidis: 14 (48.3)	Concurrent use: Diflunisal: 7 Tafamidis: 13 ---- Current use: Diflunisal: 2 Tafamidis: 12	Diflunisal: 3 (1.4) Tafamidis: 13 (6.2)
Cardiac subpopulation, n (%)	90 (60.8)	36 (46.8)	-	11	-

FAP: Familial Amyloidotic Polyneuropathy; NIS: neuropathy impairment score; NIS+7: neuropathy impairment score +7; PND: Polyneuropathy Disability; SD: standard deviation.

Sources:

*Adams et al. 2018;[11] Alnylam data on file (APOLLO [ALN-TTR02-OO4] CSR)[10]

†Suhr et al. 2015;[100]

‡Adams et al. 2017;[101] Adams et al. 2017[102]

§Partisano et al. 2017;[33] Suhr et al. 2018[41]

9.4.4 Subgroup analyses

A pre-specified subgroup analysis of the cardiac subpopulation was performed as part of the patisiran phase 3 APOLLO trial and the phase 2 OLE (Appendix 1).[11,101] As previously mentioned (Section 6.1.1), patients in the UK predominantly carry mutations that are associated with a mixed phenotype, and thus suffer from both polyneuropathy and cardiomyopathy symptoms. As such, the cardiac subpopulation is reflective of the UK population, because polyneuropathy was a key inclusion criterion in these trials and therefore the cardiac subpopulation had both polyneuropathy and cardiomyopathy.

Patients with evidence of cardiac amyloid involvement were well represented in the APOLLO study. The majority of patients in APOLLO (n=90/225 [40%] vs n=36/225 [16%] in the patisiran vs placebo groups, respectively) were included in the cardiac subpopulation analyses. Patients were required to have left ventricular (LV) wall thickness ≥1.3 cm, and cardiac amyloid involvement was ensured by excluding other medical conditions that may contribute to LV wall thickening. An additional 55.6% (n=55/99) of the patients not included in the cardiac subpopulation also had a mean LV wall thickness of ≥1.3 cm but were excluded due to a medical history of hypertension. A total of 181 of the 225 patients in the APOLLO study had a mean LV wall thickness of ≥1.3 cm.[10]

The key cardiac assessments performed in all patients included the evaluation of echocardiogram (ECG), NT-proBNP and troponin 1. The pre-specified cardiac assessments included:[10]

- Change from baseline to 18 months in ECG parameters of cardiac structure (mean LV wall thickness and LV mass), systolic function (longitudinal strain and left ventricular ejection fraction [LVEF]) between the two treatment groups using mixed model repeat measurement (MMRM)
- Change from baseline to 18 months in cardiac biomarkers (NT-proBNP and troponin I) between the two treatment groups using MMRM analysis

Additional post-hoc supportive analyses were performed including:

- Binary analysis of the proportion of patients achieving absolute threshold values or threshold of change from baseline in critical parameters (mean LV wall thickness, longitudinal strain, and NT-proBNP)

Patients in the phase 2 OLE qualified for the cardiac subgroup if baseline echocardiogram showed LV wall thickness of ≥1.3 cm and there was no history of uncontrolled hypertension or aortic valve disease. An ECG was performed every 6 months and serum levels of cardiac biomarkers (NT-proBNP and troponin I) were measured every 3 months.[105]

9.4.5 Patient disposition

APOLLO

Figure 5 shows the CONSORT flow diagram for the APOLLO study. Patients were randomised 2:1 (N=225) to the patisiran arm (n=148) or placebo (n=77).

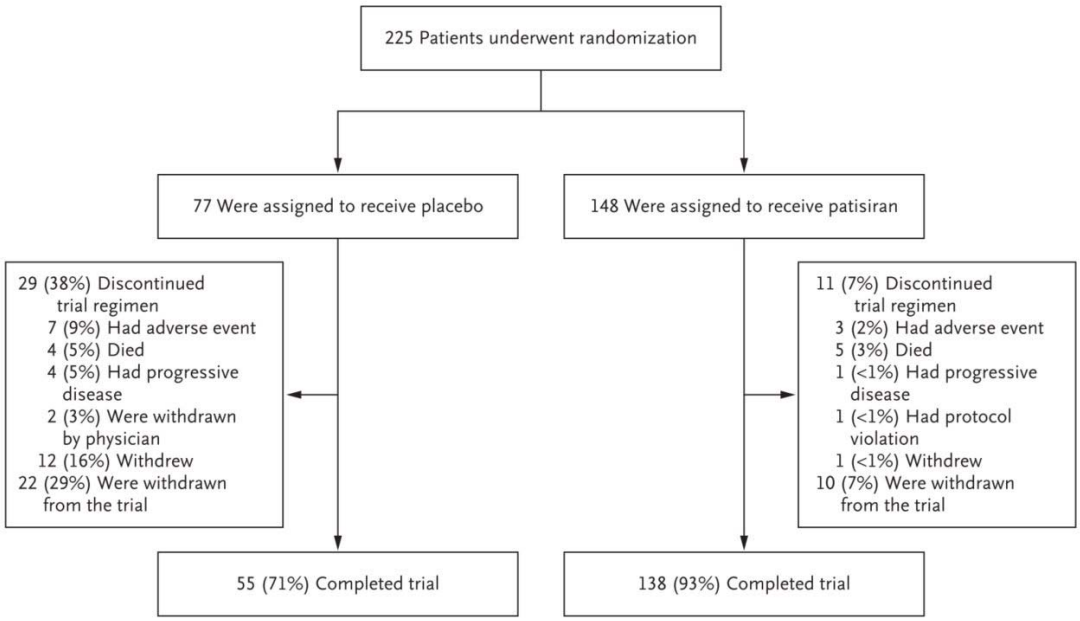


Figure 5. CONSORT flow diagram for APOLLO

AE: adverse event.

Source: Adams et al. 2018[11]

Non-randomised studies

Suhr et al. 2015 enrolled 29 patients of which 26 completed the study.[100] The patisiran phase 2 OLE study enrolled 27.[101] The Global OLE has enrolled 211 patients (eligible patients from APOLLO and the phase 2 OLE).[41]

9.4.6 Discontinuations and loss to follow-up

APOLLO

Of the 148 patients randomised to the patisiran arm in APOLLO, 138 completed treatment and 11 patients discontinued. The reasons for discontinuation included: AEs (n=3), death (n=5), disease progression (n=1), protocol deviation (n=1), and withdrawal of consent (n=1). In contrast 29 patients withdrew from the placebo group, the majority for withdrawal of consent (n=12), AEs (n=7), death (n=4), physician decision (2), or disease progression (n=4).[11]

Non-randomised studies

In the phase 2 dose/escalation study, one patient discontinued due to a protocol amendment, another withdrew due to AE (03 mg/kg every 3 weeks group) and one discontinued due to a protocol violation.[100] In the patisiran phase 2 OLE one patient discontinued at approximately 20 months due to gastroesophageal cancer.[101] No other patient withdrawals were reported in the Global OLE.[33,41]

9.5 Critical appraisal of relevant studies

9.5.1 Quality assessment tables

Quality assessment of all relevant studies identified in the SLR was conducted independently by two researchers, with disagreements resolved by a third researcher. For the APOLLO RCT, the quality assessment table was adapted from the Centre for Reviews and Dissemination (CRD) guidance on undertaking reviews in health care.[106] The non-randomised studies were assessed using an adapted table from the Critical Appraisal Skills Programme: Making sense of a cohort study.[107] The quality assessment analysis for the APOLLO is summarised in Table C5. The quality assessment analyses for the phase 2, phase 2 OLE, and Global OLE trials are summarised in Appendix 1.

Table C5. Critical appraisal of randomised control trials – Adams et al. 2017[39] (APOLLO)

Reference:	P1A-PN-CM	
Study name	APOLLO, NCT01960348	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Conducted using an interactive response system
Was the concealment of treatment allocation adequate?	Yes	Conducted using an interactive response system
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Demographics and clinical characteristics were generally balanced between the patisiran and placebo treatment arms.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients and study personnel who monitored patients during infusions and performed clinical assessments were blinded to the study treatment. Unblinded personnel and pharmacists prepared the drug for administration but were not involved in patient management or safety or efficacy assessments. Details of patients who discontinued study drug at 9 months due to rapid disease progression remained blinded throughout the study.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes, for overall study	A larger proportion of patients withdrew in the placebo group. Data not specifically presented for cardiomyopathy subgroup. No adjustment was made.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Outcomes reported as stated a priori, clearly stated exploratory subgroup analysis performed on cardiac subgroup
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT method used and appropriate. Missing data imputed using pre-specified algorithm where appropriate.

CM: cardiomyopathy; ITT: intent-to-treat; PN: polyneuropathy.

Note: The critical appraisal of the APOLLO study was initially based on the Adams et al. 2017 abstract that was identified from the SLR conducted in January 2018. The appraisal was subsequently revised based on additional information reported by Adams et al. 2018[11] published 5 July 2018.

Additional source: Clinicaltrials.gov[40]

9.6 **Results of the relevant studies**

9.6.1 Results table

APOLLO

The clinical efficacy of patisiran was evaluated in the APOLLO RCT. Table C6 summarises the clinical efficacy outcomes. The endpoints in the APOLLO trial were chosen to measure the effects of patisiran on a broad range of clinically important and patient-relevant outcomes, including the impact of patisiran on neurological and cardiac manifestations, quality of life, disability, functional status, and nutritional status.[81]

The primary endpoint was the difference between patisiran and placebo treatment in the change from baseline at 18 months in mNIS+7, analysed using MMRM method in the mITT population.[11] A decrease from baseline in mNIS+7 is indicative of a reduction in neurologic impairment and suggests improvement of neuropathy, whereas an increase in mNIS+7 suggests worsening of neuropathy.[81]

Patisiran met the primary endpoint in APOLLO: the change from baseline in the mNIS+7 was significantly lower in the patisiran group than in the placebo group. At 18 months, the LSM±SE change in mNIS+7 from baseline was -6.0±1.7 points in the patisiran group and 28.0±2.6 points in the placebo group (LSM±SE difference between groups: -34.0±3.0 points; $p<0.001$; Figure 6).[11] Additional, pre-specified sensitivity analyses on the primary endpoint resulted in a consistent estimate of the treatment effect of patisiran compared to placebo on mNIS+7, confirming the robustness of the primary analysis.[10]

The improvement in neuropathy inpatients from the patisiran group compared to baseline was seen early, and at 9 months the difference between this improvement in neuropathy and the worsening of neuropathy in the placebo group was -15.98 points (LSM; 95% CI: -20.70, -11.27 points).[10,11]

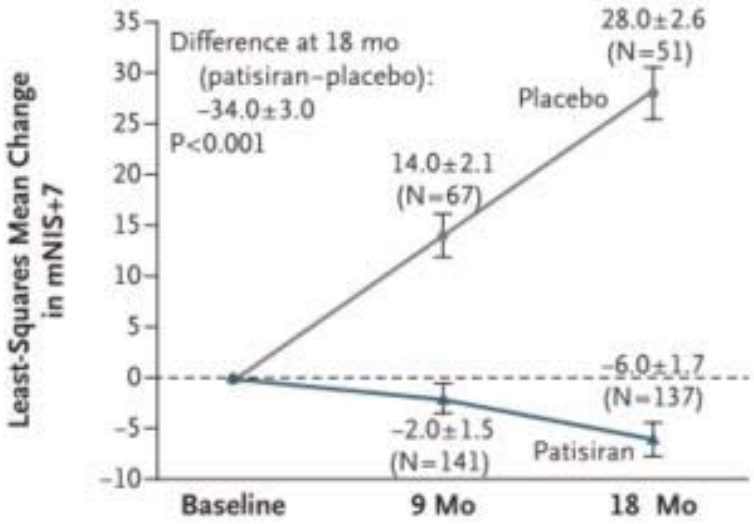


Figure 6 Mean change from baseline in the mNIS +7 in the patisiran and placebo arm

mNIS+7: modified neurologic impairment score +7; SEM: standard error of the mean.

Source: Adams et al. 2018[11]

The robust improvement from baseline on the mNIS+7 with patisiran was present across subgroups, including age, race, underlying mutation, previous stabiliser use, those patients who were in later FAP stage at baseline and the cardiac subpopulation (Figure 7) and the treatment effect was significant for all subgroups and components of the mNIS+7 (Figure 8).[11]

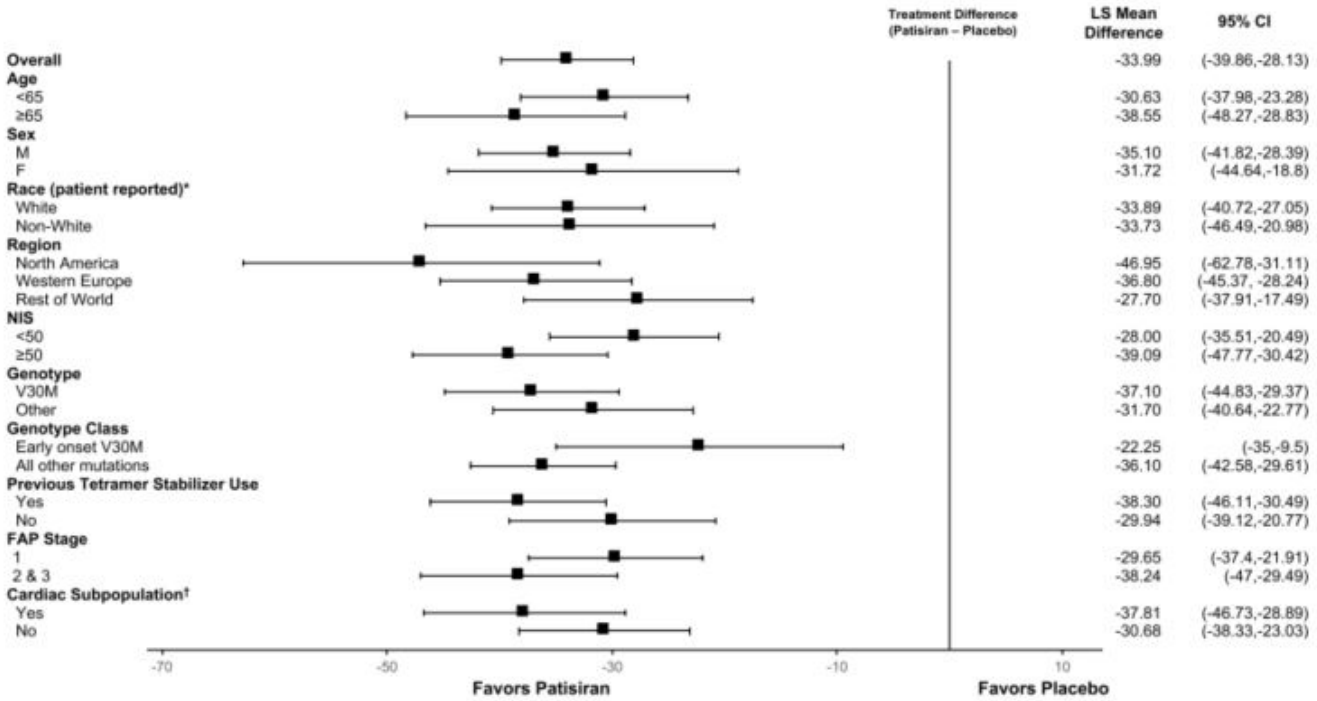


Figure 7. Change from baseline to 18 months on the mNIS+7 in patient subgroups

CI: confidence interval; FAP: familial amyloid polyneuropathy; LS: least squared; mITT: modified intent to treat; mNIS+7: modified neurologic impairment score +7; NIS: neurologic impairment score.

*Race was patient reported, Non-White subgroup: patients who identified themselves as Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or other Pacific Islander, or Other; patients who did not report race or reported more than one race were not counted in either subgroup.

†Cardiac subpopulation: patients with a baseline left ventricular wall thickness of 13 mm or more in the absence of a history of aortic valve disease or hypertension.

Source: Adams et al. 2018[11]

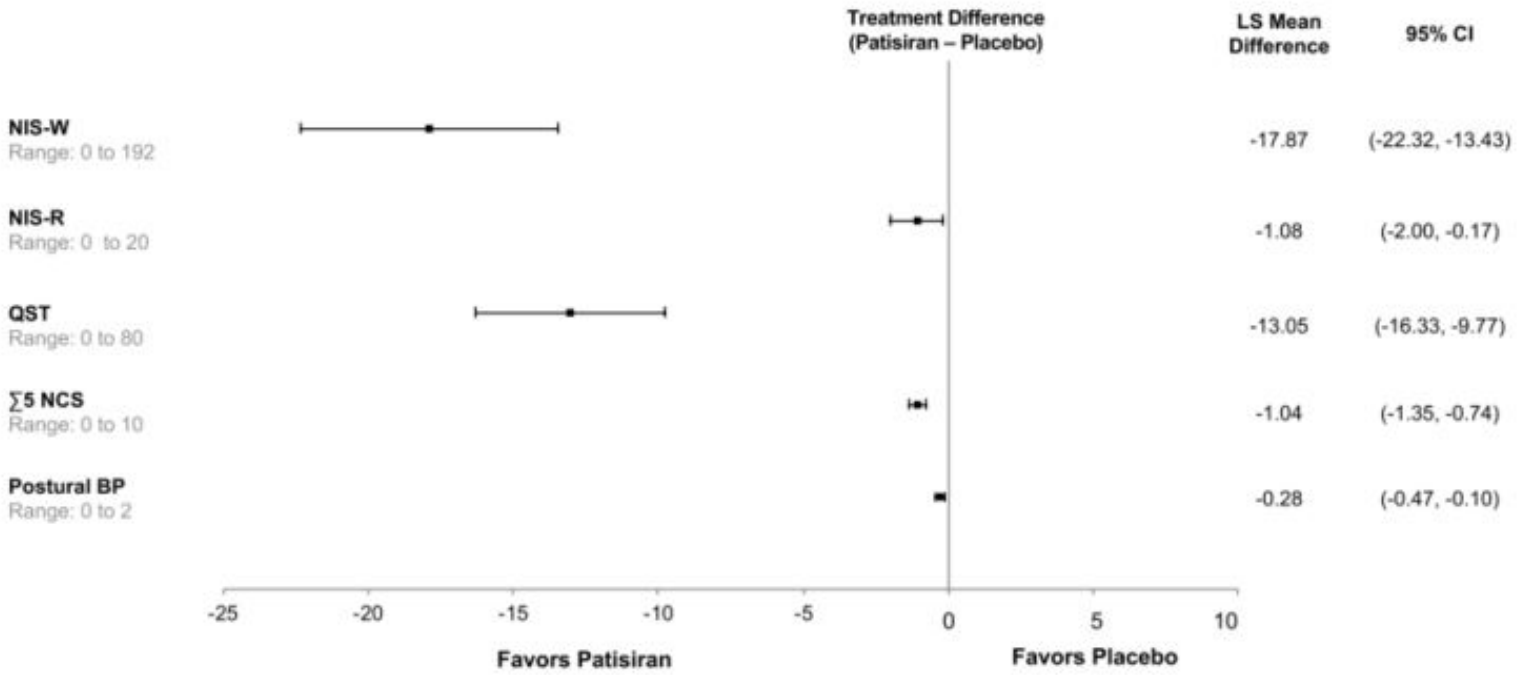


Figure 8. Changes from baseline to 18 months on the mNIS+7 components

BP: blood pressure; CI: confidence interval; LS: least square; mNIS+7: modified neurologic impairment score +7; NCS: Nerve Conduction Studies; NIS-R: neuropathy impairment score-reflexes; NIS-W: neuropathy impairment score-weakness; QST: Quantitative Sensory Testing.

Source: Adams et al. 2018[11]

Patisiran demonstrated consistent benefits in patients with early and progressively advanced neuropathy at baseline compared to placebo (Figure 9).[11]

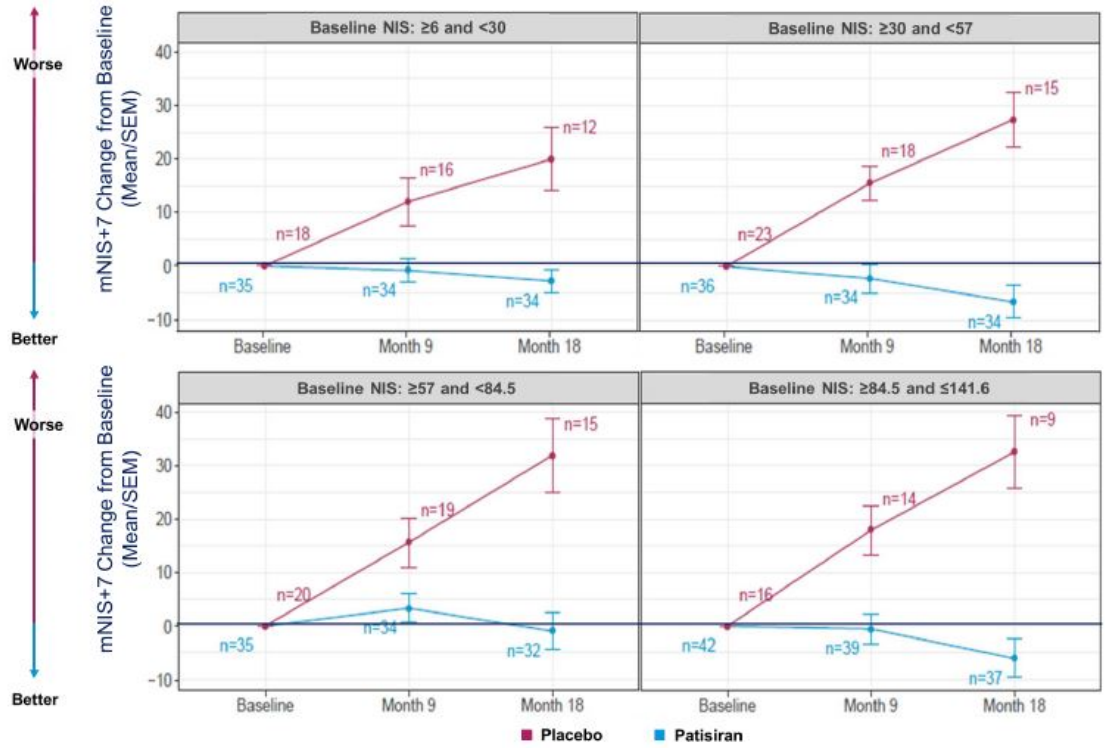


Figure 9. Change in mNIS+7 from baseline in patients with early or advanced neuropathy

mNIS+7: modified neuropathy impairment score +7; NIS: neuropathy impairment score; SEM: standard error of the mean.

Source: Obici et al. 2018[108]

The number of patients with a change from baseline in mNIS+7 of <0 points was evaluated as a prespecified analysis. The majority of patients on patisiran (56%) showed an improvement of neuropathy (change from baseline in mNIS+7 <0 points) at 18 months as compared to 4% of placebo patients (OR of 39.9; 95% CI: 11.0, 144.4; p<0.001; Figure 10).[11]

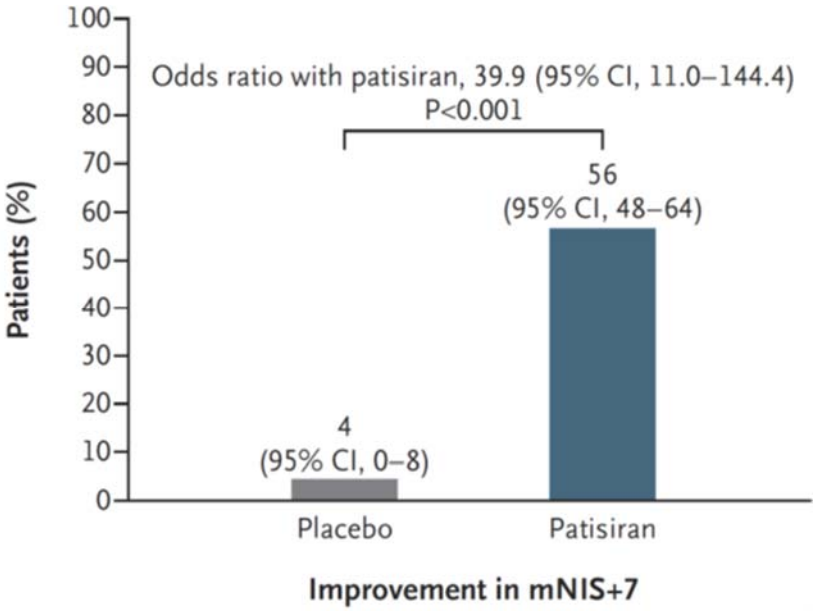


Figure 10. mNIS+7 binary analysis

CI: confidence interval; mNIS+7: modified neuropathy impairment score +7.

Source: Adams et al. 2018[11]

The key secondary endpoint was the difference between patisiran and placebo treatment in the change from baseline to 18 months in the total score of Norfolk QoL-DN questionnaire, which has previously been validated for the assessment of HRQoL in patients with hATTR amyloidosis.[109] The range of scores on this scale is from -4 to 136: a decrease from baseline in Norfolk QoL-DN total score represents improvement in HRQoL, and an increase from baseline in total score represents worsening.[11]

At 18 months, the patisiran group showed improvement in HRQoL from baseline (LSM±SE: -6.7±1.8 points), whereas HRQoL worsened in the placebo group (LSM±SE: 14.4±2.7 points); the difference between groups was statistically significant (LSM±SE: -21.1±3.1 points; 95% CI, −27.2 to −15.0; p<0.001; Figure 11).[11]

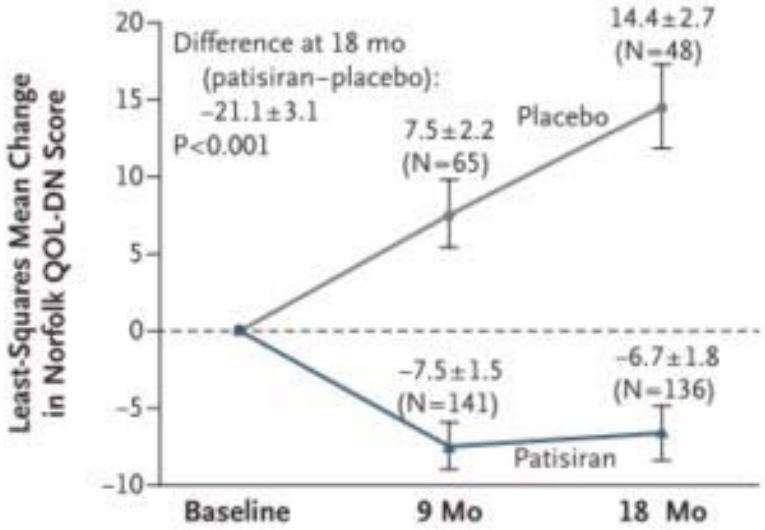


Figure 11. Norfolk QoL-DN change from baseline to 18 months

LS: least square; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; Pati: patisiran; PBO: placebo.

Source: Adams et al. 2018[11]

This improvement in HRQoL with patisiran was seen across almost all subgroups and did not significantly vary by genotype, showing a consistent effect of patisiran in the patient population. Perhaps most importantly, this improvement was robust in the cardiac subgroup and across FAP stages (Figure 12).[11] Within the cardiac subpopulation, patients in the patisiran arm had significantly more favourable change than those in the placebo arm in the overall Norfolk QoL-DN from baseline to 18 months (LSM change: 20.4 vs -2.6; LSM difference between groups: -23.0; $p=1.65x10^{-6}$).[110]

The domain scores for the Norfolk QoL-DN showed significantly more favourable change across all domains for patients treated with patisiran compared with placebo (with the exception of early-onset Val30Met patients, in which the point estimate was consistent with that in other subgroups but the difference did not attain statistical significance due to a wider 95% CI) and on the physical functioning/large fibre, symptoms, and autonomic domains at 18 months relative to baseline (Figure 13).[11]

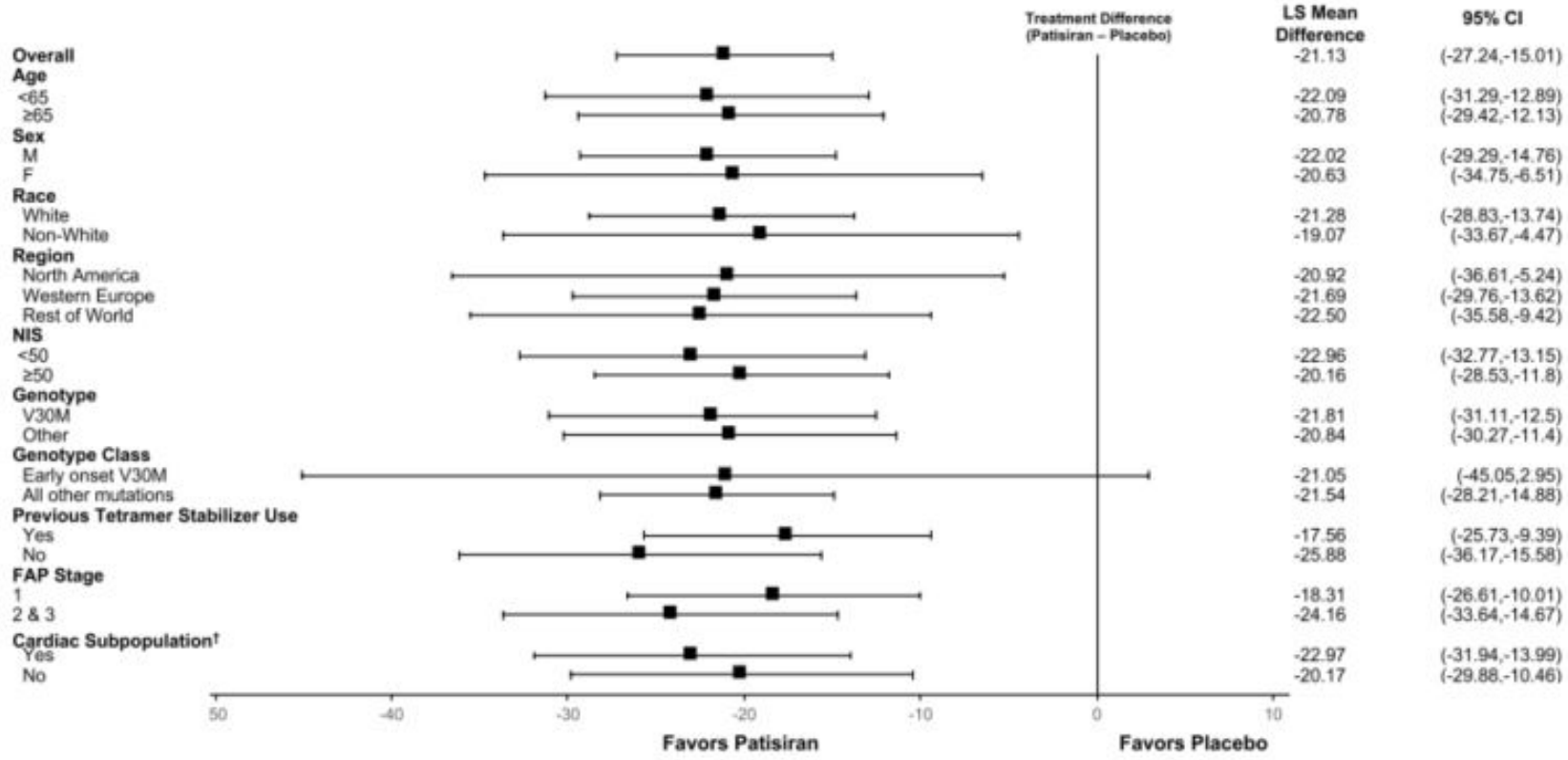


Figure 12. Norfolk QoL-DN change from baseline to 18 months in patient subgroups

CI: confidence interval; FAP: familial amyloidotic polyneuropathy; LS: least square; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; NIS: neuropathy impairment score.

Source: Adams et al. 2018[11]

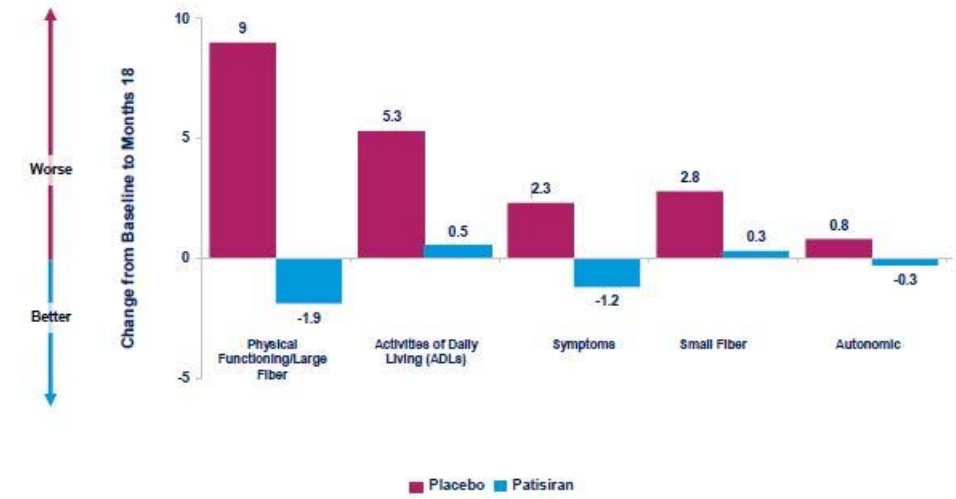


Figure 13. Change from baseline to 18 months in the Norfolk QoL domain scores

ADL: activities of daily living; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy.

Source: Mauermann et al. 2018[111]

A post-hoc binary analysis showed 51% (95% CI: 43, 59) of patients in the patisiran group demonstrated improvement in the Norfolk QoL-DN score at 18 months, compared to 10% (95% CI: 4, 17) in the placebo group (OR 10.0, 95% CI: 4.4, 22.5; p<0.001; Figure 14).[11]

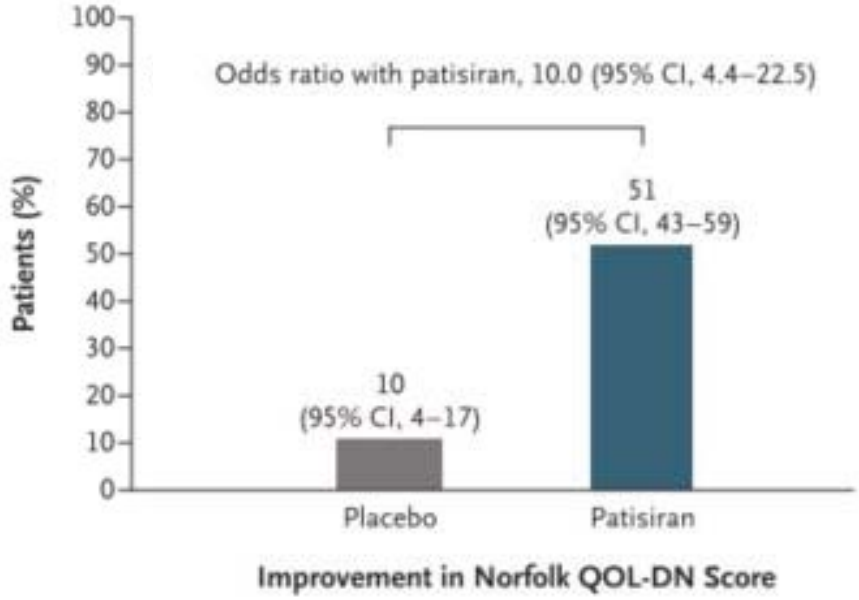


Figure 14. Norfolk-QoL-DN binary analysis

CI: confidence interval; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy.

Source: Adams et al. 2018[11]

All secondary endpoints achieved significant between-group differences in favour of patisiran at 18 months and for most endpoints these differences were seen as early as 9 months (3 months for the mBMI).[11,103]

- Patients treated with patisiran preserved their motor strength as measured on the NIS-W compared to baseline, in contrast with the decline observed in the placebo group. The LSM±SE change from baseline was 0.1±1.3 points for the patisiran group and 17.9±2.0 points in the placebo group (LSM difference between groups±SE: -17.9±2.3 points; p<0.001).[11] As well, the difference in change between groups was seen as early as 9 months after treatment initiation (LSM difference between groups: -7.04 points, 95% CI: -10.33, -3.76).[10] Note that a decrease from baseline represents improved strength.
- The patisiran group showed stabilisation in R-ODS score (a disability score that measures daily and social activity such as holding a book, eating, dancing, standing, and running),[24] representing a statistically significant difference in disability at 18 months for patients in the patisiran group compared to the worsening disability experienced in the placebo group. The LSM±SE change from baseline was 0.0±0.6 points for the patisiran group and -8.9±0.9 points in the placebo group (LSM±SE difference between groups: 9.0±1.0 points; p<0.001).[11] Note that the score range is 0–48 and a lower score indicates increased disability.[81] The difference between the improvement in disability score in the patisiran group and the decline in the placebo group was evident at the earlier 9-month test (LSM difference between groups: 4.3 points, 95% CI: 2.7, 5.8).[10]
- Patients treated with patisiran preserved their gait speed measured on the 10MWT at 18 months compared to the decline observed in patients in the placebo group. The LSM±SE change from baseline was 0.08±0.02 m/s for the patisiran group and -0.24±0.04 m/s in the placebo group (LSM±SE difference between groups: 0.31±0.04 m/s, p<0.001).[11] Note that on the 10MWT a positive change indicates being able to walk faster, and 0.10 m/s represents a substantial meaningful change. The difference in 10MWT change from baseline between the patisiran and placebo groups was seen as early as 9 months (LSM difference between groups: 0.156 m/s, 95% CI: 0.099, 0.213).[10]
- The patisiran group showed a significantly lower decrease compared with the placebo group in nutritional status (as measured by mBMI; increase from baseline suggests improvement in nutritional status which is important for maintaining body weight).[27] At 18 months, patients in the patisiran group had largely

maintained their nutritional status relative to baseline (LSM±SE change from baseline was -3.7±9.6 kg/m^2 × albumin g/L) while the placebo group worsened substantially from baseline (-119.4±14.5 kg/m^2 × albumin g/L).[11] The difference between groups was statistically significant (LSM difference between groups±SE: 115.7±16.9 kg/m^2 × albumin g/L; p<0.001).[11] The change in nutritional status was evidently different between the patisiran and placebo groups as early as 3 months (LSM difference between groups at Day 84: 17.0 kg/m^2 × albumin g/L, 95% CI: -4.1, 38.1).[10]

- At 18 months, the patisiran group showed significantly more favourable changes in autonomic neuropathy symptoms (on the COMPASS-31 which measures autonomic symptoms like diarrhoea, male erectile dysfunction, fainting; scores range from 0 to 100 with higher scores indicating more autonomic symptoms)[112] compared to the placebo group (LSM±SE change from baseline was -5.3±1.3 points for the patisiran group and 2.2±1.9 points for the placebo group; LSM±SE difference between groups: -7.5±2.2 points; p<0.001).[11]

Cardiac exploratory endpoints

Patients with evidence of cardiac amyloid involvement were well represented in this study. The pre-specified cardiac subpopulation comprised 56% the total patients in the patisiran and placebo groups (60.8% vs. 46.8%, respectively).[10] The cardiac subpopulation is defined in detail in section 9.4.4.

Patients treated with patisiran had a significant improvement in mean LV wall thickness, LV end-diastolic volume, and global longitudinal strain compared to placebo at 18 months (Figure 15). Patients in the patisiran group had significantly greater reduction in LV wall thickness from baseline at 18 months (LSM±SE difference from baseline: -1.0±0.2 mm for the patisiran group and -0.1±0.3 mm for the placebo group; LSM±SE difference between groups: -0.9±0.4 mm; p=0.02).[11] Results for global longitudinal strain also favoured patisiran (LSM±SE difference from baseline: 0.08±0.28% for the patisiran group and 1.46±0.48% for the placebo group; LSM±SE difference between groups: -1.37±0.56%; p=0.02).[11]

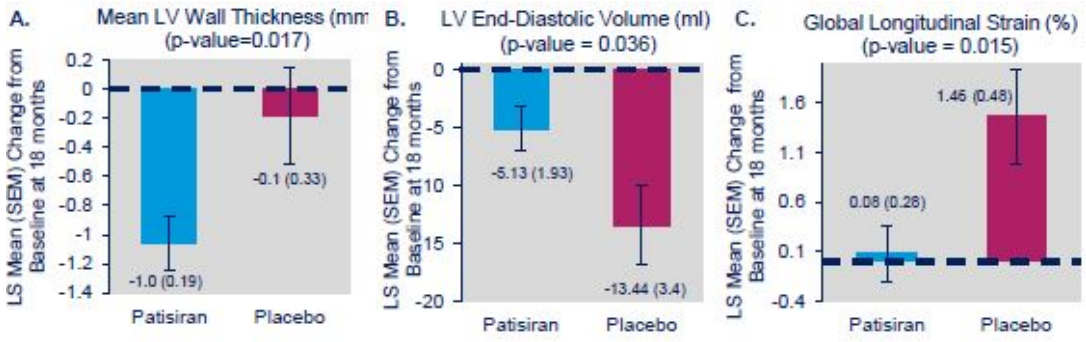


Figure 15. Echocardiographic parameters following 18 months of treatment with patisiran

LS: least square; LV: left ventricular; SEM: standard error of the mean.

Source: Solomon et al. 2018[113]

NT-proBNP levels were decreased in the patisiran group from baseline at 18 months, but increased in the placebo group. The adjusted geometric mean ratio for levels at 18 months compared to baseline was 0.89 in patients treated with patisiran and 1.97 in patients treated with placebo (ratio 0.45; p<0.001) which represented a significant 55% difference in favour of patisiran.[11]

Patients in the cardiac subgroup treated with patisiran demonstrated an increased 10MWT gait speed of 0.35 m/s (95% CI: 0.242, 0.466; $p=7.42x10^{-9}$) compared to placebo.[39,113]

The majority of troponin I values (90.2%) were reported as <0.1 µg/L based on assay sensitivity, and all such values were imputed to 0.1 µg/L for analysis. Accordingly, the lack of precision in troponin I data as collected prohibits an accurate assessment of patisiran treatment effect on troponin I.[10]

Other exploratory endpoints

The mean TTR level at baseline was similar in both the patisiran and placebo-treated patients 196.5 mg/L (range: 52–411 mg/L) and 198.8 (range: 59–320 mg/L), respectively.[10] The reduction (knockdown) in serum TTR levels was rapid and sustained over the period of 18 months in the group of patients treated with patisiran. The median reduction in serum TTR levels during the 18 months was 81% (range: -38 to 95) and was similar across age, sex, and genotype.[11]

The mean max serum TTR reduction (knockdown) from baseline for patisiran over 18 months was 87.8% and the mean (SEM) serum TTR reduction from baseline was 82.6% (1.36) and 84.3% (1.48) at 9 and 18 months, respectively (Figure 16).[10,114] In contrast, in the placebo group, the mean percent reduction was 1.5% and 4.8%, respectively.[10,114] At week 3 (on Day 22 after only one dose of patisiran), the mean

TTR percent reduction in the patisiran-treated group was 73.5% and was maintained over the duration of the study. In contrast, in the placebo group, the mean percent TTR reduction was 9.3% at Day 22. The overall mean percent reduction of TTR over 18 months in the placebo group was 5.7%.[10,114]

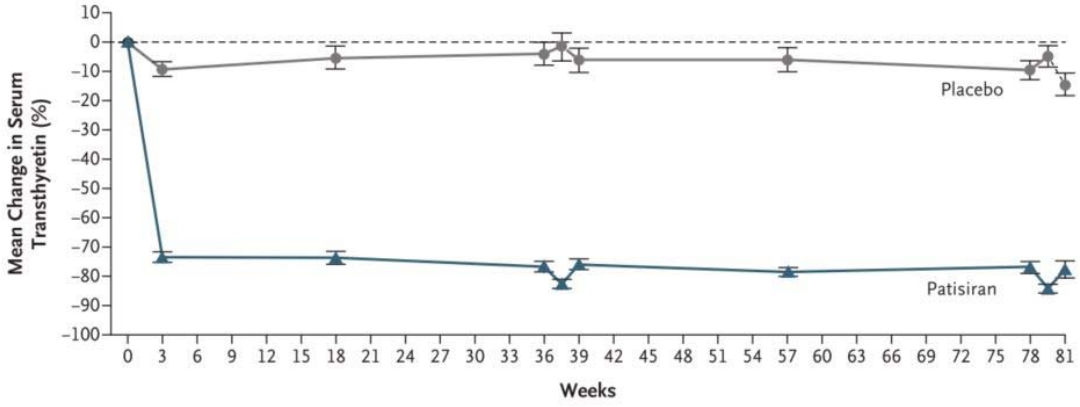


Figure 16. Mean serum TTR knockdown in patients at baseline, 9 and 18 months

Note: Bars indicate standard error. The nadirs seen at 9 and 18 months correspond to the predose and postdose assessments for those time points.

Source: Adams et al. 2018[11]

Additional key exploratory endpoints results (all assessed as change in baseline over time) are reported below:[10,11,104,115116,117]

- A greater proportion of patients in the patisiran group than in the placebo arm had a stable or improved PND score: 73% (108/148) vs 30% (23/77), respectively. Improved PND scores were achieved by 8% (12/148) of patients in the patisiran arm but no patients in the placebo arm. In the patisiran group, improvement in PND score was observed across all baseline severities (PND I through IIIB). Of the patisiran-treated patients who improved, 83% had an improvement from PND IIIA/B to PND I corresponding to improving from requiring a walking aid to being able to walk unassisted. Stable PND scores were seen in 65% (96/148) of patients in the patisiran group and 30% (23/77) in the placebo group. PND score worsened in 20% (30/148) of patients on patisiran vs 42% (32/77) of those on placebo. Among patisiran patients who worsened, most worsened by one PND score (25/30 patients; 83%), while three patients (10%) worsened by two PND score and two patients (7%) worsened by three PND score. In contrast, of the 32 placebo patients who worsened, half (16) worsened by one PND score and the other half worsened by two or more PND scores.

- Improvement in neuropathy (NIS+7) and large fibre function (composite score as the sum of NIS+7 components, NCS Σ5 + VDT + QST-BSA_TP) for patients in the patisiran group compared to the placebo group (LSM difference between groups: -24.14 points; 95% CI: -29.30, -18.98 and -6.80 points; 95% CI: -9.02, -4.59, respectively.
- An improvement in small fibre function for patients was seen in the patisiran group compared to the placebo group (LSM difference between groups: -6.97 points; 95% CI: -9.19, -4.76).
- Overall improvement in quality of life as assessed by EuroQoL-5D (EQ-5D) for patients in the patisiran group compared to the placebo group at 9 and 18 months (LSM difference between groups: 0.09 points; 95% CI: 0.05, 0.14 and 0.20 points; 95% CI: 0.15, 0.25, respectively; $p=1.40x10^{-12}$).
- Overall improvement in the EQ-VAS for patients in the patisiran group compared to the placebo group at 9 and 18 months (LSM difference between groups: 5.4 points; 95% CI: 0.5, 10.3 and 9.5 points; 95% CI: 4.3, 14.8, respectively; p= 0.0004).
- Overall improvement in grip strength for patients in the patisiran group compared to the placebo group at 9 and 18 months (LSM difference between groups: +3.8 kg; 95% CI: 1.9, 5.7 and +7.2 kg; 95% CI: 5.2, 9.2, respectively).
- At Month 18, a greater proportion of patients in the patisiran group had stable or improved FAP stage compared with the placebo group (79.1% and 44.2%, respectively).

Non-randomised studies

Key results from the non-randomised studies supporting the efficacy of patisiran include:

- Phase 2 study (Appendix 1): Significant reduction of serum TTR levels for patients treated with 0.3 mg/kg Q3W after the first and second dose of patisiran ($p<0.001$)[100]
- Phase 2 OLE (Appendix 1): Sustained mean serum TTR knockdown over 24 months (82.06)[101,105]
- Phase 2 OLE (Appendix 1): 74.1% of patients treated with patisiran had a sustained lower mNIS+7 or decrease relative to baseline at 24 months[101]
- Phase 2 OLE (cardiac subgroup; Appendix 1): Sustained decrease (improvement) in mNIS+7 at 24 months for patients with cardiac involvement[102]

- Global OLE (Appendix 1): Patisiran demonstrated maintenance of effect on mNIS+7 over 36 months (Figure 17)[33]
- Phase 2 OLE (Appendix 1): Significant increase (indicating improvement) in the sweat gland nerve fibre density (SGNGD) lower limb measure and mean absolute change from baseline in dermal amyloid content at the 6, 12, 18, and 24-month distal thigh assessments and at 24 months for the SGNFD distal leg measure (Figure 18 and Figure 19, respectively)[101]

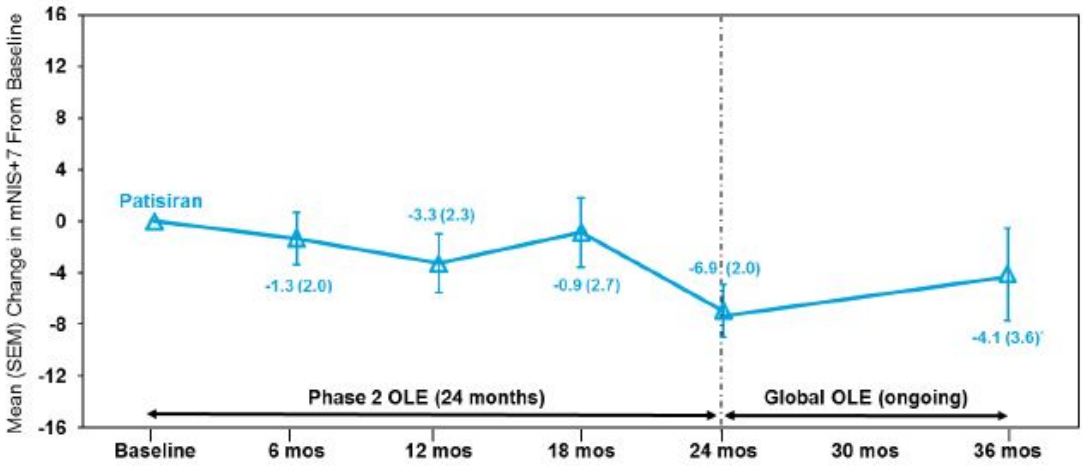


Figure 17 Mean change in mNIS+7 over 36 months

mNIS+7: modified Neuropathy Impairment Score; SEM: standard error of the mean

Source: Partisano et al. 2017[33]

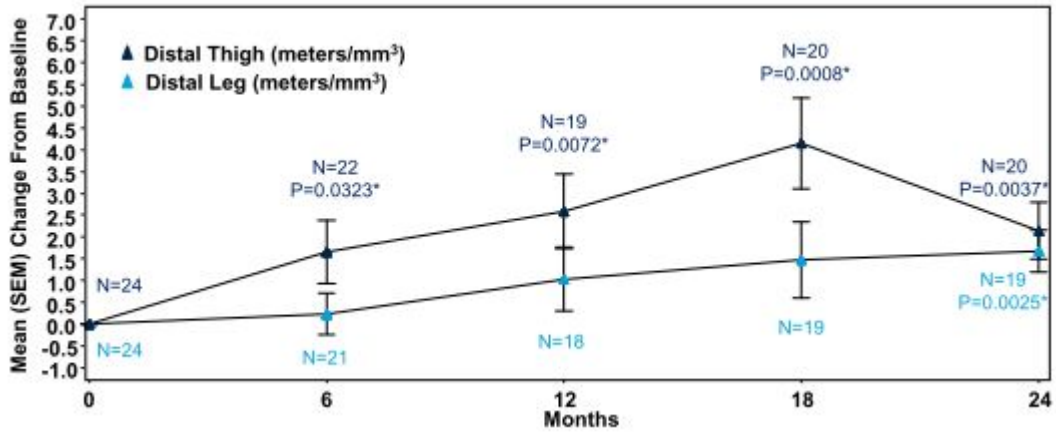


Figure 18 Sweat gland nerve fibre density over 24 months

SEM: standard error of the mean

Source: Adams et al. 2017[101]

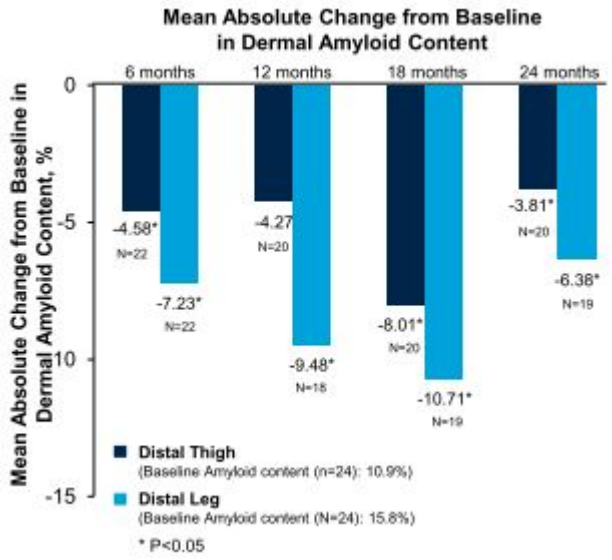


Figure 19 Mean absolute change from baseline in dermal amyloid content over 24 months

Source: Adams et al. 2017[101]

Table C6. Outcomes from published and unpublished studies – Adams et al. 2017[39] (APOLLO)

Reference	P1A-PN-CM				
Study name	APOLLO, NCT01960348				
Size of study groups	Patisiran (n=148) Placebo (n=77)				
Study duration	18 months				
Type of analysis	mITT				
Outcome Name (unit)	**Effect Size**		**Statistical test**		Comments
	Value	**95%CI**	**Type**	**p-value**	
mNIS+7* (range 0-304 points)	-33.99	(-39.86, -28.13)	t-test	$9.26x10^{-24}$	Significant improvement with Patisiran in subgroup analyses regardless of age, sex, race, geographic region, NIS, genotype, previous tetramer use, FAP stage, and cardiac subpopulation
NIS-Weakness* (range 0-192 points)	-17.87	(-22.32, -13.43)	t-test	1.40×10^{-13}	mNIS+7 subcomponent
NIS-Reflexes* (range 0-20 points)	-1.08	(-2.00, -0.17)	NR	NR	mNIS+7 subcomponent
QST* (range 0-80 points)	-13.05	(-16.33, -9.77)	NR	NR	mNIS+7 subcomponent
Σ5 NCS* (range 0-10 points)	-1.04	(-1.35, -0.74)	NR	NR	mNIS+7 subcomponent
Postural BP* (range 0-2 points)	-0.28	(-0.47, -0.10)	NR	NR	mNIS+7 subcomponent
mNIS+7 binary analysis, OR for % patients improved at 18 months (95%CI)	39.9	(11.0, 144.4)	chi^2	$1.82x10^{15}$	
mBMI* (kg/m^2 x albumin g/dL)	115.7	NR	t-test	$8.83x10^{-11}$	
COMPASS-31* (range 0-100 points)	-7.53	NR	t-test	0.0008	
Serum TTR KD, mean % (SEM) change from baseline at 18 months	Patisiran: 84.3% (1.48) Placebo: 4.8% (3.38)	NR	NR	NR	
NT-proBNP* (ng/L)	-370.2	NR	t-test	$7.74x10^{-8}$	Exploratory endpoint, cardiac subgroup Patisiran (n=90) Placebo (n=36)
Troponin-I* (mg/L)	0.004	NR	t-test	0.87	
LV wall thickness* (cm)	-0.093	NR	t-test	0.0173	
LV Mass* (g)	-15.75	NR	t-test	0.15	
Longitudinal Strain* (%)	-1.37	NR	t-test	0.0154	
LV ejection fraction* (%)	0.43	NR	t-test	0.78	
10MWT gait speed* (m/sec)	0.35	NR	t-test	$7.42x10^{-9}$	

Norfolk QoL-DN* (range -4 to 136 points)	-21.1	NR	t-test	$1.10x10^{-10}$	Significant improvement with patisiran in subgroup analyses regardless of age, sex, race, geographic region, NIS, genotype, previous tetramer use, FAP stage, and cardiac subpopulation
Norfolk QoL-DN binary analysis, % patients improved at 18 months (OR)	10.0	(4.4, 22.5)	chi^2	1.95×10^{-10}	
R-ODS* (range 0 to 48 points)	9.0	NR	t-test	$4.07x10^{-16}$	

BMI: body mass index; BP: blood pressure; CI: confidence interval; CM: cardiomyopathy; FAP: familial amyloidotic polyneuropathy; KD: knockdown; LV: left ventricular; mBMI: modified body mass index; mITT: modified intent-to-treat; mNIS: modified Neuropathy Impairment Score; 10- MWT: 10-metre walk test; NCS: nerve conduction studies; NIS: Neuropathy Impairment Score; Norfolk- QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; NR: not reported; NT-proBNP: N-terminal-pro-B-type natriuretic peptide; PN: polyneuropathy; QST: quantitative sensory testing; R-ODS: Rasch-built Overall Disability Scale; SAC: serum albumin concentration; SEM: standard error of the mean; TTR: transthyretin.

* Between-group difference in mean change from baseline at 18 months (Patisiran-Placebo)
Note: The clinical outcomes reported were initially based on the Adams et al. 2017[39] abstract that was identified from the SLR conducted in January 2018. On 5 July 2018 the publication of the APOLLO study (Adams et al. 2018)[11] and the table results were validated against the publication. Only rounding differences were observed.

9.6.2 Population analysed

No analyses other than intention-to-treat were presented.

9.7 **Adverse events**

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Included studies reporting adverse events

Details of the study selection, study methodology, and critical appraisal and results of the studies are reviewed in Section 9.2 through Section 9.6 and in Appendix 1.
Safety data from the RCT APOLLO are presented as well as data on the long-term safety of patisiran treatment from the Global OLE.[11,33,41]

9.7.2 Adverse events reported

The safety and tolerability of patisiran as reported in the APOLLO trial are summarised in Table C7. All safety analyses reported were performed on the safety population (i.e., patients who received at least one dose of the study drug; n=225).[10,11] Overall, the number of AEs and patient deaths were similar in the patisiran and placebo groups. The number of patients with SAEs (36% [n=54/148] patisiran vs 40% [n=31/77] placebo) was comparable between the two groups and the number of patients with an AE leading to discontinuation of the study treatment was lower in the patisiran group than in the placebo group (5% [n=7/148] patisiran vs 14% [n=11/77] placebo).[10,11]

Most patients experienced at least one AE in the patisiran (97% [n=143/148]) and placebo (97% [n=75/77]) groups.[11] Severe AEs were reported in 28% (n=42/148) patients in the patisiran group and 36% (n=28/77) in the placebo group.[11] As expected, a higher proportion of patients in the patisiran group than in the placebo group had AEs related to the study drug (49.3% [n=73/148] vs 39.0% [n=30/77], respectively).[10,115] Few patients had severe study-drug–related AEs in either group (2.0% [n=3/148] and 2.6% [n=2/77] for patisiran and placebo, respectively).[10,115] Overall, 13 deaths were reported in APOLLO (5% [n=7/148] in the patisiran group and 8% [n=6/77] in the placebo group); however, no deaths were considered related to patisiran.[11]

SAE ≥2% in any treatment group

Of the SAEs reported in APOLLO, the only SAE that was reported in ≥2% more patients in the patisiran group than in the placebo group was diarrhoea (5.4% vs 1.3%, respectively).[11]

There were no increases in observed frequency of SAEs for the patisiran (n=148) compared to the placebo group (n=77) by system organ class:[10,39]

- Cardiac disorders: 13.5% (n=20/148) patisiran group; 13.0% (n=10/77) placebo group
- Gastrointestinal disorders: 8.8% (n=13/148) patisiran group; 7.8% (n=6/77) placebo group
- Metabolism and nutrition disorders: 2.7% (n=4/148) patisiran group; 7.8% (n=6/77) placebo group
- Infections and infestations: 5.4% (n=8/148) patisiran group; 11.7% (n=9/77) placebo group
- Renal and urinary disorders: 0.7% (n=1/148) patisiran group; 6.5% (n=5/77) placebo group
- Respiratory, thoracic, and mediastinal disorders: 2.7% (n=4/148) patisiran group; 5.2% (n=4/77) placebo group
- Vascular disorders: 5.4% (n=8/148) patisiran group; 3.9% (n=3/77) placebo group

Treatment related AEs (TRAEs)

The proportion of patients experiencing treatment-related AEs was 49.3% (n=77/148) in the patisiran group and 39.0% (n=30/77) in the placebo group.[10,115] Severe AEs considered related to study drug included unilateral (10.7% [n=1/148]) and radicular pain (1.4% [n=2/148]) in the patisiran group, and glucose present in the urine (1.3% [n=1/77]) and tubulointerstitial nephritis (1.3% [n=1/77]) in the placebo group.[10]

Infusion related reactions (IRR)

The majority of IRRs were mild in severity and decreased over time.[11] Overall, 18.9% (n=28/148) patients in the patisiran group and 9.1% (n=7/77) patients in the placebo group reported at least one IRR.[10,11] There were no severe IRRs and no IRRs were reported as SAEs. A total of eight patients had a total of 17 infusion interruptions (including one discontinuation; 0.7%) due to an IRR in the patisiran group.[10,11] Two patients, received a partial dose (an infusion <160 mL of the planned infusion volume was considered a partial dose) at two of the infusions (one of these patient's subsequently discontinued dosing). For the other remaining 15 times when an infusion

was interrupted for an IRR, the patients received a complete dose. All eight patients had their first interruption of an infusion within the first four infusions and all eight patients had their first IRR within the first two infusions.[10]

Hepatic disorders

As patisiran is directed to the liver, and because nonclinical studies revealed changes in serum liver marker and liver histopathology, the frequency of hepatic events was evaluated by performing an analysis of AEs mapping to the standardised MedDRA query (SMQ) Drug Related Hepatic Disorders.[118] Overall the frequency of hepatic AEs mapping to the SMQ was similar across the treatment groups (5.4% vs 9.1% in the patisiran and placebo group, respectively.[10,115]

Most of the hepatic AEs were mild or moderate in severity and considered not or unlikely related to the study drug. Hepatic AEs considered possibly related to the study drug were hepatic enzyme increased and blood alkaline phosphatase increased in the patisiran group (0.7% [n=1/148] each) and hypoalbuminemia in the placebo group (1.3% [n=1/77]) all of which were mild in severity.[10,115] Hepatic SAEs were reported in three patients in the placebo group (liver function test abnormal, hypoalbuminemia and liver transplant; one patient each) and in one patient in the patisiran group (ascites). All hepatic SAEs were considered unlikely or not related to study drug.[10,115]

Cardiac safety in the mITT population (APOLLO)

Cardiac AEs and SAEs occurred at similar frequencies in both treatment groups in the mITT population. The frequency and causes of deaths between the placebo and patisiran groups were similar and consistent with natural history.[11,113]

In the mITT population (patisiran group, n=148; placebo group, n=77) the following cardiac events were reported:[11,113]

- Cardiac disorders AEs: 28% (n=42/148) patisiran; 36% (n=28/77) placebo
- Cardiac disorders SAEs: 14% (n=20/148) patisiran; 13% (n=10/77) placebo
- Cardiac arrhythmias (high-level group term): 19% (n=28/148) patisiran; 29% (n=22/77) placebo
- Torsades de Pointes SMQ*: 5.4% (n=8/148) patisiran; 18.2% (n=14/77) placebo
- Cardiac Failure SMQ (narrow)†: 9% (n=14/148) patisiran; 10% (n=8/77) placebo
- Deaths: 5% (n=7/148) patisiran; 8% (n=6/148) placebo

*Events were summarised using a standard MedDRA query for events that may be associated with Torsades; it does not mean that these were confirmed events of Torsades. No events of Torsades have been reported.

†Events included in Cardiac Failure SMQ: congestive cardiac failure, acute and chronic cardiac failure, pulmonary oedema, cardiogenic shock, right ventricular failure.

Cardiac subpopulation

A total of 56% (n=126/225) of the patients in APOLLO met the criteria for the cardiac subpopulation, including 60.8% (n=90/148) in the patisiran group and 46.8% (n=36/77) in the placebo group (see section 9.4.4).[10] Overall, the safety profile of patisiran in patients with cardiac involvement was similar to that observed in the study safety population.[39]

The proportion of patients experiencing cardiac disorders system organ class AEs (32.2%; n=29/90 patisiran group, 36.1%; n=13/36 placebo group) and SAEs (14.4%; n=13/90 patisiran group, 11.1%; n=4/36 placebo group) in the cardiac subpopulation was similar across the two treatment groups.[39]

Thirty-one out of 90 patients (34.4%) from the patisiran group and 13 out of 36 (36.1%) patients from the placebo group experienced SAEs, including:[39]

- Cardiac disorders: 14.4% (n=13/90) patisiran group; 11.1% (n=4/36) placebo group
- Cardiac arrhythmias: 18.9% (n=17/90) patisiran group; 30.6% (n=11/36) placebo group
- Torsades de Points: 7.8% (n=7/90) patisiran group; 13.9% (n=5/36) placebo group*

Nine patients in the cardiac subgroup died (5 [5.6%] patisiran group; 4 [11.1%] placebo group).[39]

*Events were summarised using a standard MedDRA query for events that may be associated with Torsades; it does not mean that these were confirmed events of Torsades. No events of Torsades have been reported.

AEs over time

The proportion of patients with AEs, including cardiac, GI, renal, and urinary disorders remained stable over the course of the study for both treatment groups (Table C8). There was no increase of AEs in the infections and infestations category over time. The proportion of patients experiencing infusion-related reactions and the number of

such events decreased over the first 6 months of the study treatment and continued to decrease for the remainder of the study.[10]

Long-term safety of patisiran

The Global OLE is ongoing and data presented are not final. The Global OLE enrolled patients from the Phase 2 OLE and APOLLO. Patients with hATTR amyloidosis who completed the Phase 2 OLE and Phase 3 APOLLO patisiran studies and met eligibility criteria were able to roll over and continue receiving patisiran 0.3 mg/kg IV q3W for up to 5 years.[41] Of the 187 patients from APOLLO eligible to participate in the OLE, 186 (99%) were enrolled.[11]

In the Global OLE study patients were treated with patisiran for an additional 11 or 21 months (APOLLO patisiran and Phase 2 patisiran, respectively) or newly treated for 10 months (APOLLO placebo), representing 211 patient-years and 3,505 doses of patisiran. The safety in patients treated with patisiran for up to 48 months is reported in Table C9.[41]

Table C7. Adverse events across patient groups – Adams et al. 2017[39] (APOLLO)

Reference	P1A-PN-CM		
AE	**Patisiran (n=148) n (% of patients)**	**Placebo (n=77) n (% of patients)**	**Relative risk (95% CI)**
Type of AE			
AE*	143 (96.6)	75 (97.4)	NR
Severe AE	42 (28.4)	28 (36.4)	NR
SAE	54 (36.5)	31 (40.3)	NR
AE leading to discontinuation	7 (4.7)	11 (14.3)	NR
AE leading to study withdrawal	7 (4.7)	9 (11.7)	NR
Death†	7 (4.7)	6 (7.8)	NR
SERIOUS AEs ≥2% IN ANY TREATMENT GROUP			
At least 1 SAE	54 (36.5)	31 (40.3)	NR
Cardiac			
Cardiac failure	3 (2.0)	2 (2.6)	NR
Cardiac failure congestive	3 (2.0)	2 (2.6)	NR
Orthostatic hypotension	3 (2.0)	1 (1.3)	NR
Atrioventricular block complete	3 (2.0)	0	NR
Gastrointestinal			
Diarrhoea	8 (5.4)	1 (1.3)	NR
Dehydration	1 (0.7)	3 (3.9)	NR
Vomiting	1 (0.7)	3 (3.9)	NR
Constipation	0	2 (2.6)	NR
Metabolic			
Hyponatremia	0	2 (2.6)	NR
Hereditary neuropathic amyloidosis	0	2 (2.6)	NR
Respiratory			
Pneumonia	3 (2.0)	3 (3.9)	NR
Pneumonia aspiration	0	2 (2.6)	NR
Renal/genitourinary			
Acute kidney injury	1 (0.7)	4 (5.2)	NR
Urinary tract infection	0	4 (5.2)	NR
CARDIAC SUBPOPULATION	**Patisiran (n=90)**	**Placebo (n=36)**	
Any AE	86 (95.6)	35 (97.2)	NR
Cardiac Disorders	29 (32.2)	13 (36.1)	

Any SAE	31 (34.4)	13 (36.1)	NR
Cardiac Disorders	13 (14.4)	4 (11.1)	
Cardiac Arrhythmias	17 (18.9)	11 (30.6)	NR
Torsades de Pointes	7 (7.8)	5 (13.9)	NR
Deaths	**5 (5.6)**	**4 (11.1)**	NR

AE: adverse event; CI: confidence interval; CM: cardiomyopathy; PN: polyneuropathy; SAE: serious adverse event.
*Majority of AEs were mild or moderate in severity
†No deaths considered to be related to study drug
Note: The clinical safety table from the APOLLO study was initially based on the Adams et al. 2017[39] abstract that was identified from the SLR conducted in January 2018. On 5 July 2018 the publication of the APOLLO study (Adams et al. 2018)[11] and the table results were validated against the publication. Only rounding differences were observed.

Table C8. Adverse events over time in ≥10% of patients in any group by preferred term (safety population)

Preferred term	Number of Patients (%)*/Events†											
	Patisiran 0.3 mg/kg (N=148)						Placebo (N=77)					
Months n (%)	<3 (n=148)	≥3 to <6 (n=145)	≥6 to <9 (n=143)	≥9 to <12 (n=141)	≥12 to <15 (n=141)	≥15 (n=138)	<3 (n=77)	≥3 to <6 (n=75)	≥6 to <9 months (n=67)	≥9 to <12 (n=66)	≥12 to <15 (n=56)	≥15 (n=51)
At Least 1 AE	120 (81.1)/485	97 (66.9)/372	106 (74.1)/358	92 (65.2)/298	96 (68.1)/253	101 (73.2)/312	59 (76.6)/264	62 (82.7)/257	54 (80.6)/211	51 (77.3)/192	40 (71.4)/130	44 (86.3)/177
Diarrhoea	23 (15.5)/33	18 (12.4)/38	18 (12.6)/35	15 (10.6)/27	9 (6.4)/16	13 (9.4)/16	14 (18.2)/24	15 (20.0)/23	9 (13.4)/16	5 (7.6)/13	3 (5.4)/6	7 (13.7)/13
Oedema peripheral	16 (10.8)/19	11 (7.6)/14	13 (9.1)/16	7 (5.0)/7	3 (2.1)/4	9 (6.5)/9	5 (6.5)/5	3 (4.0)/4	5 (7.5)/6	6 (9.1)/6	7 (12.5)/11	3 (5.9)/3
Infusion related reaction	25 (16.9)/65	10 (6.9)/26	8 (5.6)/15	6 (4.3)/19	6 (4.3)/10	4 (2.9)/10	4 (5.2)/15	6 (8.0)/19	5 (7.5)/20	5 (7.6)/16	1 (1.8)/4	1 (2.0)/5
Fall	13 (8.8)/16	9 (6.2)/11	4 (2.8)/4	3 (2.1)/3	3 (2.1)/3	9 (6.5)/10	8 (10.4)/13	7 (9.3)/7	7 (10.4)/8	5 (7.6)/6	2 (3.6)/4	5 (9.8)/5
Constipation	7 (4.7)/7	0	6 (4.2)/7	4 (2.8)/4	5 (3.5)/6	5 (3.6)/5	5 (6.5)/6	2 (2.7)/3	3 (4.5)/4	3 (4.5)/3	2 (3.6)/2	1 (2.0)/1
Nausea	8 (5.4)/11	6 (4.1)/6	5 (3.5)/7	7 (5.0)/12	6 (4.3)/9	5 (3.6)/5	7 (9.1)/8	3 (4.0)/4	6 (9.0)/6	2 (3.0)/3	0	1 (2.0)/1

Preferred term	Number of Patients (%)*/Events†											
	Patisiran 0.3 mg/kg (N=148)						Placebo (N=77)					
Months n (%)	<3 (n=148)	≥3 to <6 (n=145)	≥6 to <9 (n=143)	≥9 to <12 (n=141)	≥12 to <15 (n=141)	≥15 (n=138)	<3 (n=77)	≥3 to <6 (n=75)	≥6 to <9 months (n=67)	≥9 to <12 (n=66)	≥12 to <15 (n=56)	≥15 (n=51)
Dizziness	9 (6.1)/11	4 (2.8)/4	2 (1.4)/2	4 (2.8)/4	2 (1.4)/2	1 (0.7)/1	5 (6.5)/8	4 (5.3)/7	3 (4.5)/6	3 (4.5)/6	1 (1.8)/4	3 (5.9)/6
Urinary tract infection	7 (4.7)/9	6 (4.1)/6	5 (3.5)/6	3 (2.1)/4	6 (4.3)/6	7 (5.1)/9	1 (1.3)/1	8 (10.7)/10	1 (1.5)/2	4 (6.1)/4	2 (3.6)/2	2 (3.9)/4
Fatigue	2 (1.4)/2	7 (4.8)/8	2 (1.4)/2	3 (2.1)/6	3 (2.1)/5	4 (2.9)/4	4 (5.2)/8	3 (4.0)/5	2 (3.0)/2	1 (1.5)/1	1 (1.8)/1	1 (2.0)/1
Headache	4 (2.7)/4	4 (2.8)/4	2 (1.4)/2	3 (2.1)/4	5 (3.5)/6	5 (3.6)/5	5 (6.5)/6	1 (1.3)/1	1 (1.5)/1	1 (1.5)/1	0	1 (2.0)/1
Cough	4 (2.7)/4	3 (2.1)/3	2 (1.4)/2	3 (2.1)/3	2 (1.4)/2	4 (2.9)/4	4 (5.2)/4	4 (5.3)/4	2 (3.0)/2	0	1 (1.8)/1	0
Insomnia	9 (6.1)/15	5 (3.4)/6	1 (0.7)/1	0	0	2 (1.4)/2	3 (3.9)/4	3 (4.0)/5	0	1 (1.5)/1	1 (1.8)/1	1 (2.0)/1
Nasopharyngitis	4 (2.7)/4	3 (2.1)/4	3 (2.1)/4	4 (2.8)/4	5 (3.5)/5	2 (1.4)/5	4 (5.2)/5	1 (1.3)/2	3 (4.5)/3	0	1 (1.8)/1	0
Vomiting	5 (3.4)/6	3 (2.1)/4	3 (2.1)/3	3 (2.1)/3	3 (2.1)/3	2 (1.4)/2	1 (1.3)/1	5 (6.7)/8	2 (3.0)/6	3 (4.5)/12	1 (1.8)/3	0
Asthenia	7 (4.7)/10	6 (4.1)/10	2 (1.4)/2	1 (0.7)/1	2 (1.4)/2	0	3 (3.9)/6	1 (1.3)/1	0	4 (6.1)/5	1 (1.8)/1	2 (3.9)/2
Pain in extremity	2 (1.4)/2	1 (0.7)/1	2 (1.4)/3	2 (1.4)/2	1 (0.7)/1	3 (2.2)/4	2 (2.6)/2	1 (1.3)/4	0	2 (3.0)/3	0	3 (5.9)/3
Muscular weakness	1 (0.7)/2	0	2 (1.4)/3	2 (1.4)/2	1 (0.7)/1	0	6 (7.8)/6	5 (6.7)/6	1 (1.5)/1	2 (3.0)/2	1 (1.8)/1	1 (2.0)/1
Anaemia	3 (2.0)/3	0	0	0	0	0	2 (2.6)/2	2 (2.7)/4	1 (1.5)/1	3 (4.5)/3	0	1 (2.0)/2
Syncope	2 (1.4)/2	1 (0.7)/1	0	0	0	0	1 (1.3)/1	1 (1.3)/1	3 (4.5)/4	1 (1.5)/1	1 (1.8)/1	1 (2.0)/1

*If a patient experienced more than 1 event in a given system organ class (SOC), that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term (PT), that patient is counted only once for that PT. Percentages are based out of the total number of subjects (N) who were on study at the start of the indicated exposure duration category.

†The total number of events for all patients; a patient can be counted more than once if the patient has multiple events.

Source: Alnylam data on file (APOLLO [ALN-TTR02-OO4] CSR)[10]

Table C9. Safety in patients treated with patisiran for up to 48 months

Previous treatment group	APOLLO Placebo n (%)	APOLLO Patisiran n (%)	Phase 2 OLE Patisiran n (%)	Global OLE Total n (%)
AE	45 (91.8)	119 (86.9)	25 (100.0)	189 (89.6)
AE related to study drug	22 (44.9)	30 (21.9)	7 (28.0)	59 (28.0)
Severe AE	16 (32.7)	19 (13.9)	3 (12.0)	38 (18.0)
Severe AE related to study drug	1 (2.0)	1 (0.7)	0	2 (0.9)
SAE	19 (38.8)	30 (21.9)	6 (24.0)	55 (26.1)
SAE related to study drug	2 (4.1)	0	0	2 (0.9)
AE leading to study withdrawal	9 (18.4)	7 (5.1)	0	16 (7.6)
Study drug related AE leading to study withdrawal	1 (2.0)	0	0	1 (0.5)
Death	7 (14.3)	4 (2.9)	0	11 (5.2)

AE: adverse event; OLE: open-label extension; SAE: serious adverse event.

Source: Suhr et al. 2018[41]

9.7.3 Summary of safety profile

The safety profile of patisiran in patients with hATTR amyloidosis has been well characterised in both placebo-controlled and long-term extension studies.[11,33,41,101,102,119]

In the APOLLO trial, the frequencies of AEs, SAEs, and death were comparable between the patisiran and placebo arms. The majority of AEs were considered mild or moderate in severity. Patisiran was associated with fewer overall treatment discontinuations and treatment discontinuations due to AEs compared with placebo.[119] None of the deaths that occurred were considered to be related to the study drug and nearly all eligible APOLLO patients (186/187 [99%]) enrolled in the Global OLE study where they continued to receive patisiran.[41,119]

In the phase 2 OLE (Adams et al. 2017), the majority of AEs were mild or moderate in severity. AEs related to patisiran and occurring in ≥4 patients were infusion-related reactions (IRRs, 22.2%) and flushing (22.2%).[101] In patients who continued treatment to the Global OLE trial, patisiran continued to be well tolerated after 48 months of treatment.[41]

The important identified risk of IRRs can be reduced with premedications and a controlled rate of infusion and appears to diminish over time.[10]

9.8 Evidence synthesis and meta-analysis

When more than one study is available, and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Evidence synthesis

As no comparators were identified in the NICE Decision Problem and only one RCT (APOLLO) was described, evidence synthesis and/or meta-analysis were not appropriate.

9.8.2 Rationale for exclusion

Only one RCT was included in the submission and as no other RCTs or comparators were considered as part of this scope, a qualitative comparison is not possible.

9.9 Interpretation of clinical evidence

9.9.1 Statement of principal findings

Patisiran is an effective and safe disease-modifying therapy for patients with hATTR amyloidosis that has been shown to comprehensively address all major aspects of the disease by improving sensory, motor, and autonomic neuropathy, as well as cardiomyopathy. The value of patisiran in hATTR amyloidosis is supported by the following main pillars:

- Patisiran directly addresses the underlying cause of disease through rapid and substantial TTR knockdown.
- Patisiran improves neurological impairment with meaningful benefit seen as early as 9 months after the start of treatment
- Patisiran improves cardiac function, addressing the multi-systemic nature of disease
- Patisiran improves autonomic function, including reducing debilitating GI issues and orthostatic hypotension compared to baseline at 18 months
- Patisiran improves patients HRQoL,
- Patisiran improves function, and reduces disability, offering meaningful benefit to patients' daily lives

Patisiran is a disease-modifying therapeutic, directly targeting the underlying cause of hATTR amyloidosis via the suppression of TTR protein production by the liver.[6,11,63] The pivotal, phase 3 trial APOLLO reported an 81% median reduction of serum TTR from baseline for patisiran over 18 months.[11] The RNAi mechanism of action of patisiran (based on the Nobel-prize winning technology of RNAi interference)[1] harnesses a naturally occurring and catalytic process to rapidly reduce serum TTR levels.[10]

Patisiran addresses the multi-systemic nature of hATTR amyloidosis, including both neuropathy and the cardiac impairment, as demonstrated by a comprehensive set of endpoints in the APOLLO trial. Neuropathic assessments included sensory, motor, and autonomic neuropathy, as well as disability, HRQoL, nutritional status, grip strength, and ambulation. As cardiac involvement is prevalent in hATTR amyloidosis, cardiac endpoints were evaluated including echocardiographic and NT-proBNP which is a sensitive biomarker for disease severity and survival.[35,39]

Patisiran was shown not only to halt or reverse disease progression, but also to reduce the neuropathy (as measured by mNIS+7) and cardiomyopathy (as measured by NT-

proBNP) that are the cardinal manifestations of the disease, with resultant benefits in patient symptoms, disability, ambulatory ability, nutritional status, and overall HRQoL.[10] The benefits of patisiran extended to patients with a wide range of disease severity, and were maintained for at least 3 years.[10,33] Patisiran increased the odds of reversing neurological impairment approximately 40-fold compared with placebo.[10]

Patisiran met the primary endpoint in the APOLLO trial and demonstrated a significant reduction in neurologic disease progression vs placebo.[11]

- The mNIS+7 scale, a comprehensive measure of sensorimotor and autonomic neuropathy designed specifically for hATTR amyloidosis, was used to assess neurologic impairment in the APOLLO trial; a numerically higher score indicates increased polyneuropathy.[30]
- This endpoint is a composite measure of motor, sensory, and autonomic polyneuropathy including the modified NIS (weakness and reflexes), quantitative sensory testing (QST), nerve conduction studies (NCS), and postural blood pressure, with the score ranging from 0 (no impairment) to 304 points (maximum impairment).
- The mNIS+7 is weighted towards detection of change in motor function (which has the greatest impact on ambulation and activities of daily living) and increases the sensitivity of detecting changes in sensation by testing both small and large nerve sensation (which are also clinically meaningful, as the former can interfere with basic activities such as buttoning a shirt, while the latter can lead to burns and ulcerations on the feet or hands due to sensation loss).[30]
- The primary endpoint of APOLLO, mean change from baseline in mNIS+7 at 18 months, was significantly lower in the patisiran group compared with placebo (mean±SE: −6.0±1.7 vs 28±2.6; p<0.001).[11]
- Patisiran improved neurologic impairment from baseline in the majority of patients with hATTR amyloidosis. The patisiran group showed a trend towards stable and improved PND scores compared with placebo (73% vs 30%, respectively).[11] The placebo group reported more patients who worsened on the PND score (58.2%) than the patisiran group (21.7%).[10]

All secondary endpoints of APOLLO achieved significant between-group differences in favour of patisiran treatment:

- Patisiran was associated with significantly improved HRQoL: The LSM±SE difference between groups was -21.1±3.1 points (p<0.001). 51% of patients

achieved an improvement [<0 point increase from baseline at 18 months] in the Norfolk QoL-DN compared to 10% in the placebo group.[11]

- Patients in the patisiran group showed significantly improved strength and motor function, as assessed by negative change in the NIS-W at 18 months(LSM±SE difference between groups: -17.9±2.3 points; p<0.001).[11]
- Patisiran produced significant improvements in ambulation, as assessed by increased gait speed on the 10MWT (LSM±SE difference between groups: 0.31±0.04 m/sec; p<0.001).[11]
- Patients in the patisiran group showed significant improvements in the R-ODS scale which measures activity and social function and captures the limitations on everyday activity (LSM±SE difference between groups: 9.0±1.0; p<0.001).[11]
- Nutritional status, which is a key contributor to mortality in hATTR amyloidosis[68] was maintained by patisiran at 18 months (LSM±SE difference between groups: 115.7±16.9 kg/m^2 × albumin g/L; p<0.001).[11]
- Autonomic neuropathy symptoms, which contribute to the malnutrition and GI morbidities associated with hATTR amyloidosis, were significantly improved by patisiran treatment at 18 months (LSM±SE difference between groups: −7.5±2.2; p<0.001), per negative change on the COMPASS-31 questionnaire.[11]

Patisiran produces rapid and sustained efficacy in patients with hATTR amyloidosis. In the APOLLO trial, improvements in neurological impairment, HRQoL, and disease burden were maintained through 18 months. Primary and secondary endpoints reported statistically significant improvements as early as 9 months (with the exception of the COMPASS-31 endpoint which trended towards improvement and was statistically significantly improved at 18 months).[11]

Additionally, the clinical benefits observed with patisiran treatment were consistent across patient subgroups (including age, geographic region, disease stage/severity, mutation status, previous TTR stabiliser use, and cardiac involvement). In the cardiac subgroup of patients who exhibited symptoms of cardiac involvement which could not be explained by hypertension or aortic valve disease (stenosis), patisiran produced favourable changes in exploratory cardiac endpoints relative to placebo, including reductions in the cardiac biomarker NT-proBNP, and associated improvement in ambulation (10MWT gait speed).[11] Section 6.1.4 reviews the robust evidence that NT-

proBNP levels of >2500-3000 pg/mL are associated with poor short-term survival in patients with hATTR amyloidosis.[34,71]

The frequency of AEs, SAEs, and deaths in the APOLLO trial were comparable between the patisiran and placebo arms. Fewer patients in the patisiran group discontinued treatment due to AEs compared with placebo (5% vs 14%, respectively).[11] Seven patients from the patisiran group died during the study, however, no deaths were considered related to patisiran treatment.[11]

Patisiran remained generally well tolerated among patients over the long term. Safety results reported that patients treated up to 48 months continued to show a similar safety profile to that seen in the APOLLO study.[41] Patisiran addresses the multi-systemic nature of hATTR amyloidosis and provides improvement across symptoms, providing a safe and effective treatment option for the heavy burden of the disease.

9.9.2 Strengths and limitations

The APOLLO trial is the largest trial of hATTR amyloidosis patients to date. It was a global, randomised, blinded trial that demonstrated the safety and efficacy in patients with 39 different genotypes (including those most common in the UK), over a wide range of neuropathy severity, including patients who only had mild sensory abnormalities as well as those with severe motor, sensory and autonomic abnormalities who required two walking sticks to walk. In addition, echocardiogram, NT-proBNP, gait speed, and NYHA class indicated that on average the majority of these patients had moderately severe cardiac involvement, with clinical manifestations of heart failure at baseline which is relevant to the UK population of hATTR amyloidosis patients.[10,11,20]

Limitations in the evidence base include that patisiran was not evaluated in patients with very early stage, latent neuropathy, and the experience in end-stage patients who are wheelchair-bound or bed-ridden (FAP stage III, PND score IV) is very limited within APOLLO and the Global OLE. More evidence on the use of patisiran in cases of more advanced disease will be accruing in the ongoing Global OLE.

While the randomisation stage of the pivotal RCT APOLLO was limited to 18 months, this duration was sufficient to capture the clinically meaningful treatment effects. The clinical benefit observed in the APOLLO trial was maintained in the OLE, supporting the relevance of the RCT results to long-term treatment with patisiran.

Patients in the placebo arm of APOLLO were not prescribed a BSC regimen specifically based on the recommendations of Ando et al. 2013[5] in alignment with clinical practice in the UK (and used in the CE model developed for this submission). However, no clinically meaningful differences are expected based on this limitation since no medications that could change the disease course were used in APOLLO or as part of the BSC regimen defined by Ando et al. 2013.[5]

9.9.3 Relevance to the scope

The evidence base comprised patients who participated in the RCT APOLLO (Adams et al. 2018),[11] the phase 2 study (Suhr et al 2015),[100] the phase 2 OLE (Adams et al. 2017)[101] and/or the Global OLE (Partisano et al. 2017).[33]

Population

The pivotal APOLLO trial included patients with hATTR amyloidosis and polyneuropathy, and was directly relevant to the patient population in the UK because:[11,20] 1) the trial included patients with the genotypes most common in the UK, 2) the majority of patients in the trial were from Western Europe, and 3) as is representative of the UK population, the majority of patients also had cardiac involvement.[10,20]

Outcomes

The outcomes listed in the NICE scope were measured in the APOLLO trial including neurological impairment and symptoms of polyneuropathy, cardiac function, and autonomic function.[11]

Clinical effectiveness

APOLLO showed very strong evidence of clinical efficacy (Section 9.6) and safety (Section 9.7) for the main population and cardiac subpopulation. The overall magnitude of health benefits to patients and carers reported in the evidence base are likely to be achieved in clinical practice in the UK as the recommended dosage is based on the dosage used in the APOLLO trial.[11]

Impact of the technology beyond direct health benefits

The impact of patisiran beyond direct health benefits is discussed in greater detail in Section 14. The use of patisiran is anticipated to result in significant societal economic benefits due to increased productivity and independence of patients and correspondingly reduced burden on caregivers.[24]

9.9.4 External validity

External validity of the patisiran study results is likely to be high since APOLLO was the largest study in hATTR amyloidosis patients, enrolling a substantial proportion of all patients who have this ultra-rare disease, and the evidence base included:[11]

1. All stages of the disease
2. A broad range of genotypes, including those most relevant to the UK
3. Diverse symptoms reflecting the multi-systemic nature of the disease
4. A range of patient experience with prior therapies

Thus, the study captured the heterogeneity of the patient population encountered in clinical practice.

9.9.5 Criteria for suitability

Not applicable. Patisiran is suitable for all patients indicated.

10 Measurement and valuation of health effects

- hATTR is a progressive and debilitating disease and as such, HRQoL is not assumed to be constant over time, but deteriorates without treatment.
- The EQ-5D-5L utilities in the patisiran arm of APOLLO showed a trend of improving over time within the same PND score while there was an unambiguous trend towards deterioration in the placebo arm.
- Patients in the patisiran group consistently scored better than those in the placebo group of APOLLO across all primary and secondary endpoints by PND score change category including on the Norfolk QoL-DN, R-ODS, 10MWT, and COMPASS-31 scales.

10.1 **Patient experience**

10.1.1 HRQoL in hATTR amyloidosis

A comprehensive discussion of the effects of hATTR amyloidosis on patients' quality of life can be found in Section 7.1. hATTR amyloidosis is a rapidly progressive disease that results in chronically debilitating symptoms, with increasing impairment of patients' ability to conduct activities of daily living.[20,24,26,76] The burden of illness is substantial early on and increases with disease progression.[120]

Because amyloid fibril deposition occurs at multiple sites throughout the body, the clinical presentation of hATTR amyloidosis is multi-systemic and highly variable across patients.[57,121] Consequently, the aspects of hATTR amyloidosis that cause the greatest HRQoL impairment can vary from one patient to another depending on the spectrum of symptoms they experience.

Patients whose predominant symptoms relate to progressive muscle atrophy and weakness in their limbs may experience difficulty walking and inability to perform other activities of daily living such as holding eating utensils or a drinking glass, or managing buttons and zippers.[5,24] Patients in the APOLLO study had difficulty performing daily activities at baseline, including those which are considered low intensity and not very social such as reading a book (27%) or eating (30%).[24] Overall, the majority of patients were not able to perform more complex motor tasks such as dancing (59%), standing for a long period (i.e., hours) (63%), or running (76%).[24]

Symptoms of peripheral sensory neuropathy include painful abnormal sensation in the feet and hands, including the loss of sensation which can lead to thermal burns

involving the feet and hands (due to the inability to register heat) as well as joint injury in the lower, weight-bearing limbs.[5,23,25]

Patients with autonomic neuropathy abnormalities may experience debilitating orthostatic hypotension (low blood pressure when moving from sitting to standing that can cause dizziness, a light-headed feeling, blurry vision and even fainting), incontinence or retention leading to recurrent urinary tract infections, sweating abnormalities, and sexual dysfunction.[23]

Patients who manifest cardiovascular symptoms typically experience breathlessness and fatigue.[122] Cardiovascular manifestations also impair patients' ability to walk.[61] Patients may develop carpal tunnel syndrome as a common clinical manifestation that can precede cardiac manifestations.[122]

GI manifestations may lead to several symptoms including chronic nausea/vomiting especially after eating, alternating episodes of diarrhoea and constipation, early satiety and wasting due to unintentional weight loss, which worsens as the disease progresses (see Figure 20).[23,27]

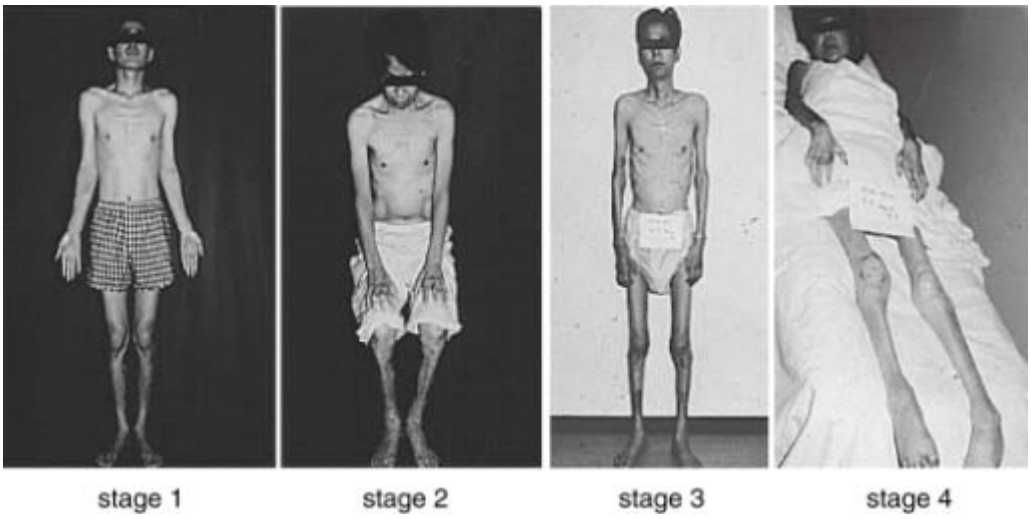


Figure 20. Wasting in hATTR amyloidosis by FAP stage

Source: Araki and Ando 2010[123]

10.1.2 HRQoL change over time

Patients with hATTR amyloidosis experience significant decline in quality of life as the disease progresses, with particularly poor quality of life reported by patients who develop both polyneuropathy and cardiomyopathy symptoms.[39] Symptoms rapidly increase in severity, resulting in significant disability and increased hospitalisations, absenteeism, and need for additional caregiver support to accomplish daily

activities.[24,82,83] The associated emotional and psychological burden on patients, their families, and caregivers is significant.[79]

As the disease progresses, HRQoL impairment worsens (see Figure 11). For example, among patients in the APOLLO study, the number of tasks and activities that ≥50% of patients were unable to perform at baseline was higher in those in more advanced FAP Stage; in FAP Stage 1, the only activity that half or more of patients were unable to do was to run (53%), but by FAP Stage 2, 96% were unable to run, 50% were unable to travel by public transportation, 75% were unable to carry and put down a heavy object, 85% were unable to dance, and 86% were unable to stand for hours.[24] The need for mobility assistance devices increased (89% in FAP Stage 2 vs 12% in FAP stage 1; $p<0.0001$) with disease progression.[83]

The need for hospitalisation increases dramatically with disease progression. At baseline in APOLLO, the percentage of patients with an overnight hospitalisation more than doubled between FAP Stage 1 and FAP Stage 2 (17% vs 39%; $p=0.0004$).[83]

The inability to work and requirement for assistance to live independently worsens with disease progression. In APOLLO, 47% of patients in FAP Stage 1 were unable to work at baseline and this increased to 87% for patients in FAP Stage 2. Similarly, lost workdays numerically increased from 24 to 63 in FAP Stage 1 vs FAP Stage 2 ($p=0.061$) and the need for government compensation increased from 18% to 30%, respectively ($p=0.03$).[24]

HRQoL data derived from clinical trials

10.1.3 HRQoL SLR

Table C10 summarises the HRQoL data derived from the clinical trials presented in Section 9.

Table C10. HRQoL data derived from included clinical trials

Study	Study name NCT Number	Instrument	Method of valuation	Measurement points	Consistency with reference case	Appropriate for CEA	Results with CIs*
Adams et al. 2017 (P1A-PN-CM)[39] Additional results reported from Denoncourt et al. 2016[120]	APOLLO NCT01960348	Norfolk QoL-DN	Total score based on 5 domains of QOL	Baseline Month 9 Month 18	Included in scope	No	Baseline mean: Patisiran: 59.6 Placebo: 55.5 LSM change from baseline (SEM) at 18 months: Patisiran: -6.7 (1.77) Placebo: 14.4 (2.73) Difference: -21.1, p=1.10x10^{-10} Baseline demographics by PND score, mean: PND score I (n=57): 35.51 PND score ≥II (n=167): 65.96
		R-ODS	Total score for overall disability based on 24 items	Baseline Month 9 Month 18		No	Baseline mean: Patisiran: 29.7 Placebo: 29.8 Mean change from baseline at 18 months Patisiran: 0 Placebo: -8.9 Difference: 9.0, p= 4.07x10^{-16} Baseline demographics by PND score, mean: PND score I (n=57): 40.89 PND score ≥II (n=167): 25.88
		EQ-5D-5L	MAUI based on 5 HRQoL dimensions	Baseline 18 months		Yes	This measure was included as an exploratory endpoint and 18-month results have not yet been reported Baseline demographics by PND score, mean: PND score I (n=56): 0.76

							PND score ≥II (n=167): 0.59 EQ-5D-VAS Baseline demographics by PND score, mean: PND score I (n=57): 40.89 PND score ≥II (n=167): 25.88
Adams et al. 2017 (P3B-PN-CM)[101] Additional results reported from Denoncourt et al. 2015[124]	NCT01961921	EQ-5D-5L	MAUI based on 5 HRQoL dimensions	Baseline 24 months	Included in scope	Yes	Baseline mean (range): 0.8 (0.3, 1.0) Mean change from baseline (SEM) for all patients: -0.01 (0.02) EQ-5D-5L mean (SEM): PND score I: 0.8 (0.05) PND score ≥II: 0.7 (0.02) All PND scores: 0.8 (0.03) EQ-5D-VAS mean (SEM): PND score I: 75.2 (4346) PND score ≥II: 60.0 (4.46) All PND scores: 67.9 (3.44)
		R-ODS	Total score for overall disability based on 24 items	Baseline 24 months		No	Baseline mean (range): 38.1 (15.0, 48.0) Mean change from baseline (SEM): -1.8 (0.8)

*CIs were not reported in the available abstracts. Where available range and SEM were reported.
CEA: cost-effectiveness analysis; CI: confidence interval; CM: cardiomyopathy; EQ-5D-5L: EuroQol Five Dimension, Five Level Questionnaire; LS: least square; MAUI: multi-attribute utility instrument; PN: polyneuropathy; QOL-DN: quality of life – diabetic neuropathy; R-ODS: Rasch-built Overall Disability Scale; SF36: 36-Item Short Form Health Survey.

10.1.4 Mapping HRQoL

Utilities used in the model were derived directly from the EQ-5D data in the APOLLO study, using UK tariffs and stratified by PND and NT-proBNP categories in order to assign utilities for the model health states (see Section 10.1.9 for further details). The EQ-5D-5L data were mapped to EQ-5D-3L to derive utility values according to the mapping function developed by van Hout et al. 2012.[125,126]

10.1.5 HRQL studies

As with the search strategies to identify clinical and HRQoL data, SLRs were designed to identify relevant economic evidence in the published literature. As described previously, while the current understanding of hATTR amyloidosis recognises it as one hereditary disease with a spectrum of clinical manifestations, due to the historical concept of two separate diseases, two SLRs were conducted, one for hATTR amyloidosis with polyneuropathy and the other for hATTR amyloidosis with cardiomyopathy.[6] The search strategy is provided in Appendix 1. The results of the SLRs are reported in Figure 21 and Figure 22. The list of studies from the SLRs that are relevant to the final NICE scope are summarised in Table C11. The list of HRQoL studies identified by the SLR that are excluded due to being out of scope are summarised in Appendix 2.

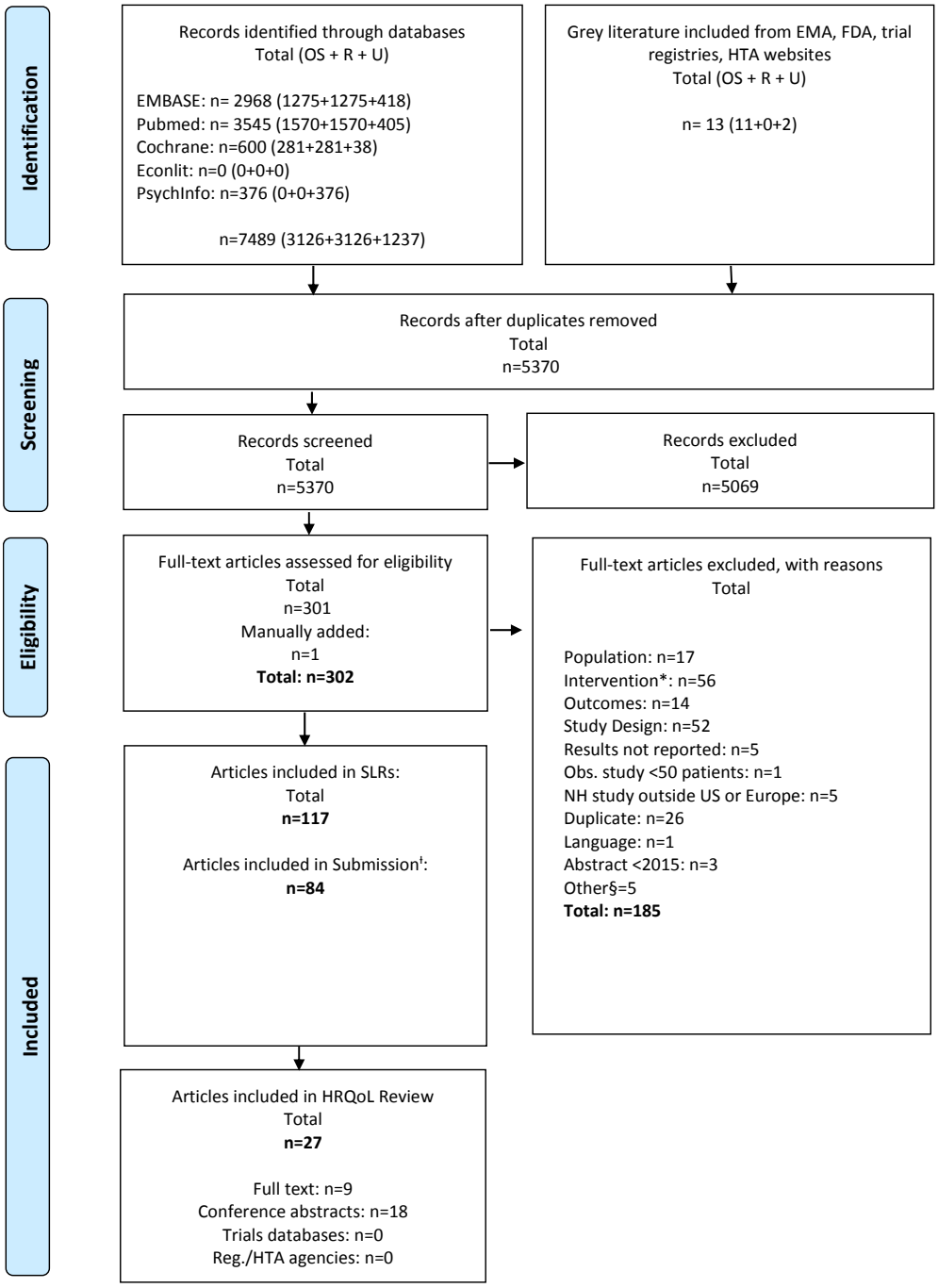


Figure 21. PRISMA flow diagram for HRQoL evidence in hATTR amyloidosis with polyneuropathy

HRQoL: health-related quality-of-life; HTA: health technology assessment; NH: natural history; OS: original search; R: rescreen; Reg.: regulatory; U: update

*Includes 33 studies in rescreen and 12 studies in update that were related to liver transplant and that were excluded by protocol amendment.

§2 studies in rescreen were not available; 1 study in the rescreen and 2 studies in update were abstracts published before 2015 and two studies in update were not available.

†These totals exclude the natural history studies that were part of the original search

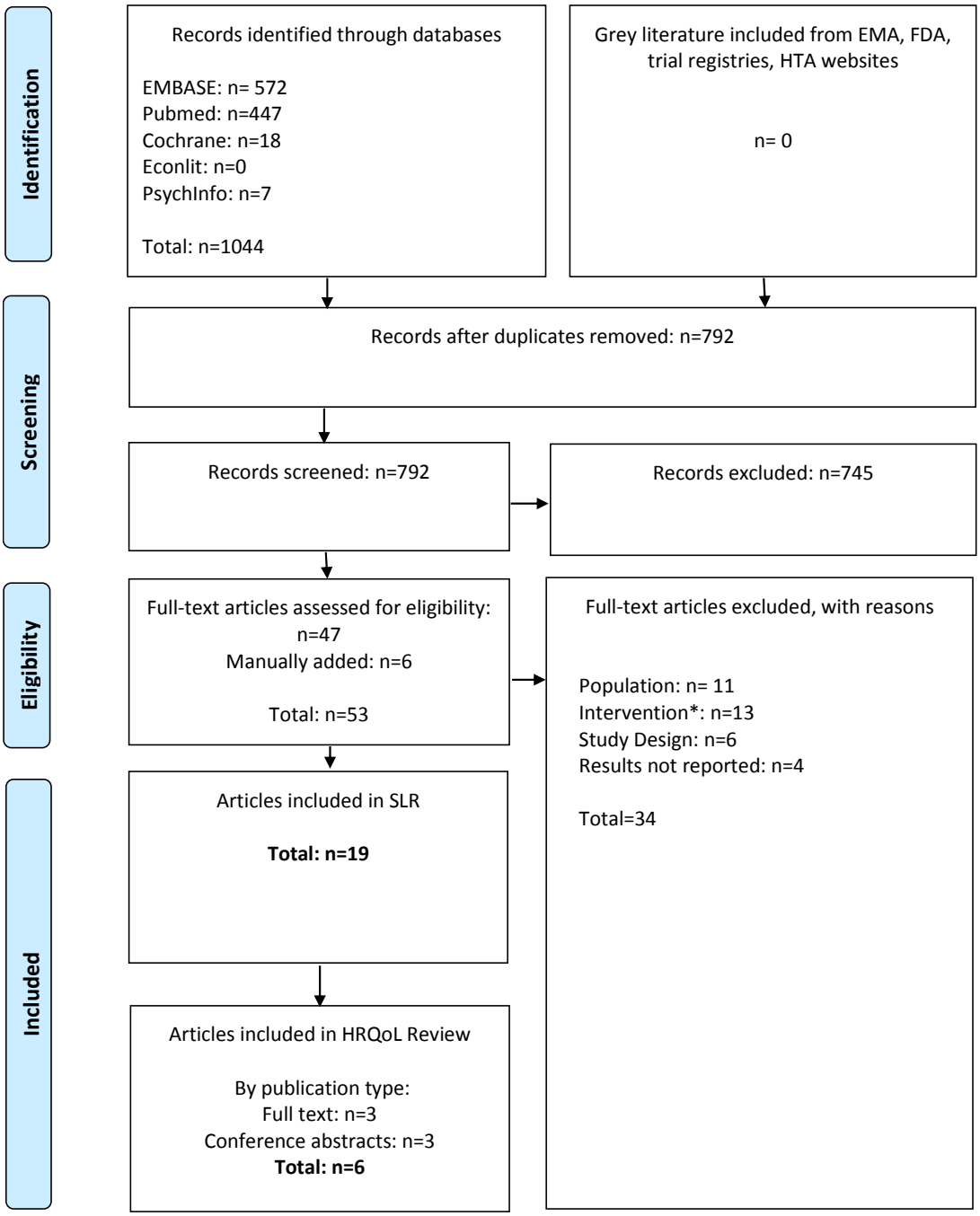


Figure 22. PRISMA flow diagram for HRQoL evidence in hATTR amyloidosis with cardiomyopathy and wtTTR amyloidosis

HRQoL: health-related quality-of-life; HTA: health technology assessment; Reg.: regulatory.
*Includes 4 studies that were related to liver transplant and that were excluded by protocol amendment.

Table C11. List of included HRQoL studies

Study code	Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Included/excluded?
P1A-PN-CM	Adams et al. 2017[39]*	APOLLO (NCT01960348)	225 adults aged 18–85 years with diagnosis of hATTR amyloidosis with polyneuropathy. Prior tetramer stabiliser use permitted. Randomised to: Patisiran n=148; Placebo n=77	Patisiran	Placebo	Included
P3A-PN-CM	Adams et al. 2017[101]*	NCT01961921	27 adults who had previously participated in the phase 2 multi-dose study of patisiran (NCT01617967)	Patisiran	None	Included
P3L - PN-CM	Denoncourt et al. 2015[124]	NCT01961921	27 adults who had previously participated in the phase 2 multi-dose study of patisiran (NCT01617967)	Patisiran	None	Included
P1B-PN-CM	Denoncourt et al. 2016[120]	APOLLO (NCT01960348)	225 adults aged 18–85 years with diagnosis of hATTR amyloidosis with polyneuropathy. Randomised to: Patisiran n=148; Placebo n=77	Patisiran	Placebo	Included

CM: cardiomyopathy; hATTR: hereditary transthyretin amyloidosis; OLE: open-label extension; PN: polyneuropathy.

10.1.6 HRQoL measured from the literature

Details of the studies in which HRQoL data were reported can be found in Table C10.

10.1.7 Key differences in published literature and data used in the model

No other studies were identified that reported utilities by PND score.

10.1.8 Adverse events

Although it is expected that several AEs may have a negative impact on patients' HRQoL, the included published studies provided no data specifically on the relationship between AEs and HRQoL in patients with hATTR amyloidosis. No explicit impact of AEs on HRQoL was modelled, so as to avoid duplicating the reported impact of the AEs. We believe that the potential impact of treatment-specific AEs is already taken into account implicitly in the different set of utilities by treatment arm.

10.1.9 CE model utility inputs

The pivotal, international, phase 3 APOLLO trial measured changes in HRQoL in patients treated with patisiran and those receiving placebo over a period of 18 months. The large population size and broad range of mutation types represented in the study population allowed for the direct capture of HRQoL results appropriate for the CEA of patisiran.[11]

A regression analysis was developed to identify the relationship between HRQoL and the identifiers of health state in the model. A forward selection process was put in place and the following covariates were analysed, along with their interaction terms: PND score (0, I, II, IIIA, IIIB, and IV), NT-proBNP (<3000 pg/mL or ≥3000 pg/mL), treatment arm, and time (in months). The analysis was conducted on the pooled EQ-5D measurements at baseline, 9 and 18 months in both treatment arms. The forward selection process identified PND score and the product of treatment arm by time as significant covariates. Table C12 reports the parameters of the final linear regression model.

A caregiver disutility score of 0.01 associated with the impact on carers was applied to all patients in the PND IV health state.[127]

Table C12. Summary of quality-of-life values for CEA

State	Utility value	SE(*)	Lower value, Upper value	Reference in submission
Parameters of the regression				
PND 0	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND I	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND II	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IIIA	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IIIB	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IV	[redacted]	[redacted]	[redacted]	**APOLLO trial**
Per-month change with patisiran treatment	[redacted]	[redacted]	[redacted]	**APOLLO trial**
Per-month change with BSC treatment	[redacted]	[redacted]	[redacted]	**APOLLO trial**
Patisiran, maximum utility				
PND 0	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND I	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND II	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IIIA	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IIIB	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IV	[redacted]	[redacted]	[redacted]	**APOLLO trial**
BSC, minimum utility				
PND 0	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND I	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND II	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IIIA	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IIIB	[redacted]	[redacted]	[redacted]	**APOLLO trial**
PND IV	[redacted]	[redacted]	[redacted]	**APOLLO trial**
HRQoL other settings				
Caregiver disutility (PND IV)	**0.01**	**0.001**	**0.008, 0.012**	**Tafamidis submission**

AE: adverse events; BSC: best supportive care; CE: cost-effectiveness; HRQoL: health-related quality of life; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability. *When not available in the original sources a standard value of 10% of the mean was considered for the SE

Sources: APOLLO (Adams et al. 2017);[39] Alnylam data on file (APOLLO [ALN-TTR02-OO4] CSR);[10] Tafamidis AGNSS submission.[127]

10.1.10 Validation of CE model inputs:

A Delphi panel was conducted to investigate current use of UK NHS and Personal and Social Services (PSS) resources in hATTR amyloidosis. The research objectives of the panel were to investigate current use of UK NHS and PSS resources in hATTR amyloidosis, specifically with regard to resources used in the management of polyneuropathy-related and cardiomyopathy-related symptomatology (stratified by PND score and NT-proBNP levels [< or ≥3000 pg/mL], respectively), and to investigate the potential impact of patisiran in the use of UK NHS and PSS resources in hATTR amyloidosis.

In collaboration with Alnylam, BresMed identified UK clinical experts within the field of hATTR amyloidosis for the Delphi panel. In total, 25 invitations were sent out to prospective participants with experience of treating adult patients with hATTR amyloidosis in the UK. The number of initial positive responses was 10, and a final total of seven experts participated in this Delphi panel, all of whom completed both rounds of the survey. Participants' background information and the Delphi process methodology are outlined in summarised in Appendix 3.

Costing

In line with the NICE reference case, resources that fall under the control of the NHS and PSS were costed for inclusion in the patisiran CE model.[128] Generic drugs (such as tramadol) were costed using the Commercial Medicines Unit's electronic marketing information tool (eMIT), which considers the cost paid by NHS Trusts[129] for generic drugs. Where generic versions were unavailable, branded drugs were costed using the Monthly Index of Medical Specialities (MIMS).[130] Drug wastage was not considered when costing HCRU. NHS reference costs for 2016/17 and the Personal Social Services Research Unit (PSSRU) costs for 2017 were used to cost procedures, services and healthcare staff. [131,132] One-off resources were costed using PSSRU 2017, where available. However, some resources associated with care and mobility were costed using the websites euromedical.co.uk and completecareshop.co.uk.

Results

The polyneuropathy and cardiomyopathy resources identified and estimates of their use by the NHS and PSS as obtained in the Delphi panel are summarised in Appendix 3. A total of 76 polyneuropathy-related and 28 cardiomyopathy-related healthcare resources were identified and their usage rates quantified by the panel for patients with

a PND score of I–IV. Additionally, panellists identified and estimated the usage rate of four polyneuropathy-related healthcare resources utilised by patients with a PND 0 score who previously scored PND I or higher.

Based on the APOLLO trial results, panellists indicated the extent to which they expected HCRU of patients with hATTR amyloidosis to change if patisiran were introduced. The panellists were asked to not include any resources associated with patisiran administration, and to assume that the patient's PND score and NT-proBNP level remained constant.

Based on the estimates provided by the panellists, total polyneuropathy-related resource use costs were [redacted], and [redacted] per 6 months, for patients at PND 0, I, II, IIIA, IIIB, and IV, respectively. In addition, patients with NT-proBNP levels less than and greater than 3000 pg/mL were found to utilise [redacted] and [redacted] of NHS and PSS resources per 6 months, respectively.

Using the mean of the estimates provided by the panellists, it is expected that patisiran will result in a [redacted] and [redacted] decrease in the HCRU for the management of polyneuropathy and cardiomyopathy, respectively, in patients with hATTR amyloidosis at any given PND score and NT-proBNP level.

Full details of the results can be found in Appendix 3.

10.1.11 Variation in HRQoL by health states

Based on the observed clinical evidence from APOLLO, patients in the patisiran arm have different EQ-5D-5L utilities than patients in the BSC arm within the same PND score.[10] The EQ-5D-5L utilities in the patisiran arm showed a trend of improving over time within the same PND score, while in the placebo arm there was a clear trend towards deterioration.

Patisiran patients consistently scored better than those treated with placebo across all primary and secondary endpoints by PND score change category including the Norfolk QoL-DN, R-ODS, 10MWT, and COMPASS-31. This trend was observed even in the small percentage (20%) of patients who worsened in PND score while treated with patisiran (Figure 23).[10]

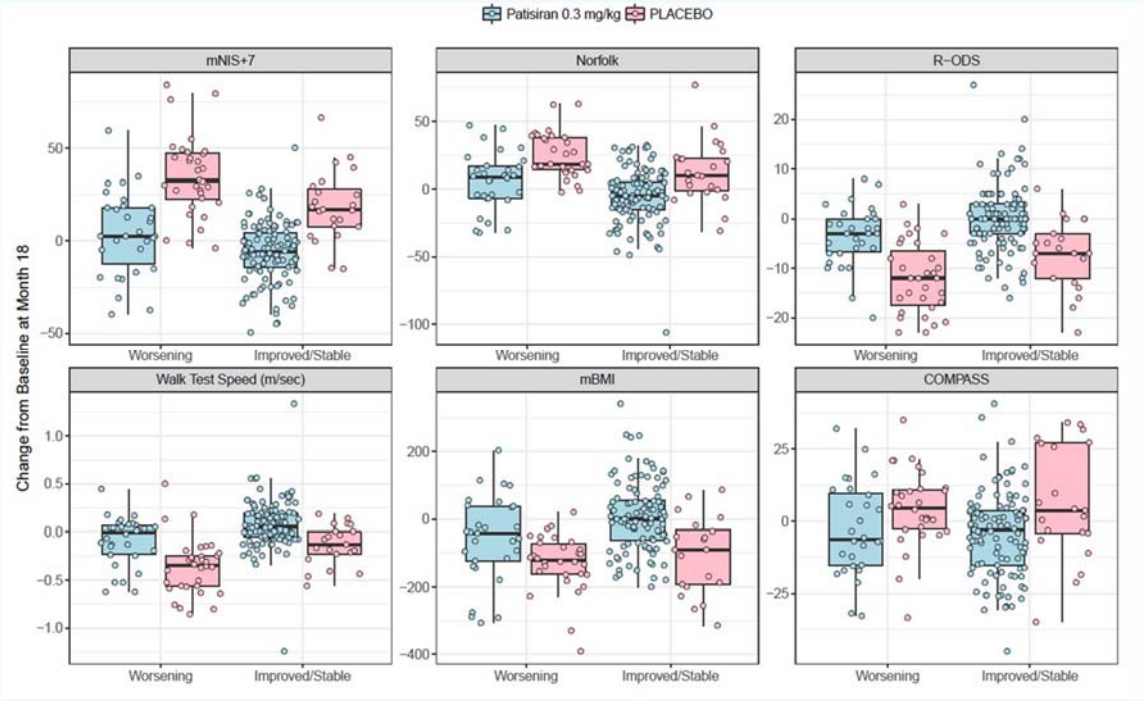


Figure 23. Primary and secondary endpoints by PND score change categories

mNIS+7: modified neuropathy impairment score +7; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; R-ODS: Rasch-built Overall Disability Scale; mBMI: modified body mass index; COMPASS-31: Composite autonomic symptom score-31

The change in HRQoL with disease progression is captured in the CEA by using the utilities at baseline in APOLLO for the first model cycle and subsequently changing them according to the average change by PND score and treatment arm. A linear regression analysis (described in Section 10.1.9) was performed to predict EQ-5D-5L utility scores as a function of several possible covariates. Significant variables marking health states in the model were identified for inclusion in the final model by forward selection. The analysis showed significant association with PND score, treatment arm, time, and the interaction between treatment arm and time. The regression function was implemented in the model to allow the simulation of the trend of utilities over time for each treatment arm and within each PND score.

The model incorporates a PND-score–dependent increase in HRQoL with patisiran, as observed over 18 months in APOLLO. This improvement is maintained over the long term, consistent with findings of the patisiran OLEs. Conversely, the analysis assumes that HRQoL decreases over time approaching zero in patients receiving BSC. Of note, the utility score for PND IV in the placebo arm at 18 months is negative following conversion of the EQ-5D-5L scores with the UK tariff, signifying that the perceived HRQoL of this health state is worse than death. The range of possible utility values

was constrained by the upper (75th percentile) and lower (25th percentile) observed values by treatment arm and PND score in order to avoid ceiling effects.

10.1.12 Health effects from the literature excluded from analysis

No relevant health effects identified in the literature or clinical trials were excluded from analysis.

10.1.13 Baseline HRQoL inputs

The baseline HRQoL in the analysis was measured in the pivotal, international, phase 3 trial APOLLO and used in the model. The health states used in the CE model aligned with the HRQoL events recorded at baseline in APOLLO.

10.1.14 HRQoL over time

As hATTR is a progressive and debilitating disease, HRQoL is not assumed to be constant over time, but is assumed to deteriorate without treatment.[11,24] Data from APOLLO showed that utilities improved over the 18-month study period in patients treated with patisiran and worsened in those receiving placebo (Section 10.1.11).

10.1.15 Amended values from the baseline HRQoL inputs

No values have been amended.

10.1.16 Treatment continuation rules

Patisiran infusion should be discontinued in the case of serious or life-threatening IRR, pregnancy or planned pregnancy, and breastfeeding.[12]

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Health economic SLR

As with the search strategies to identify clinical and HRQoL data, SLRs were designed to identify relevant economic evidence in the published literature. As described previously, while the current understanding of hATTR amyloidosis recognises it as one hereditary disease with a spectrum of clinical manifestations, two SLRs were conducted due to the historical concept of two separate diseases, one for hATTR amyloidosis with polyneuropathy and the other for hATTR amyloidosis with cardiomyopathy.[6] The search strategy is provided in Table C1 and Appendix 1.

11.1.2 Inclusion and exclusion criteria

The selection criteria for economic studies is outlined in Table C1 in Section 9.1.

11.1.3 Published and unpublished studies

Figure 24 and Figure 25 show the PRISMA diagrams for the SLRs of hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy, respectively.

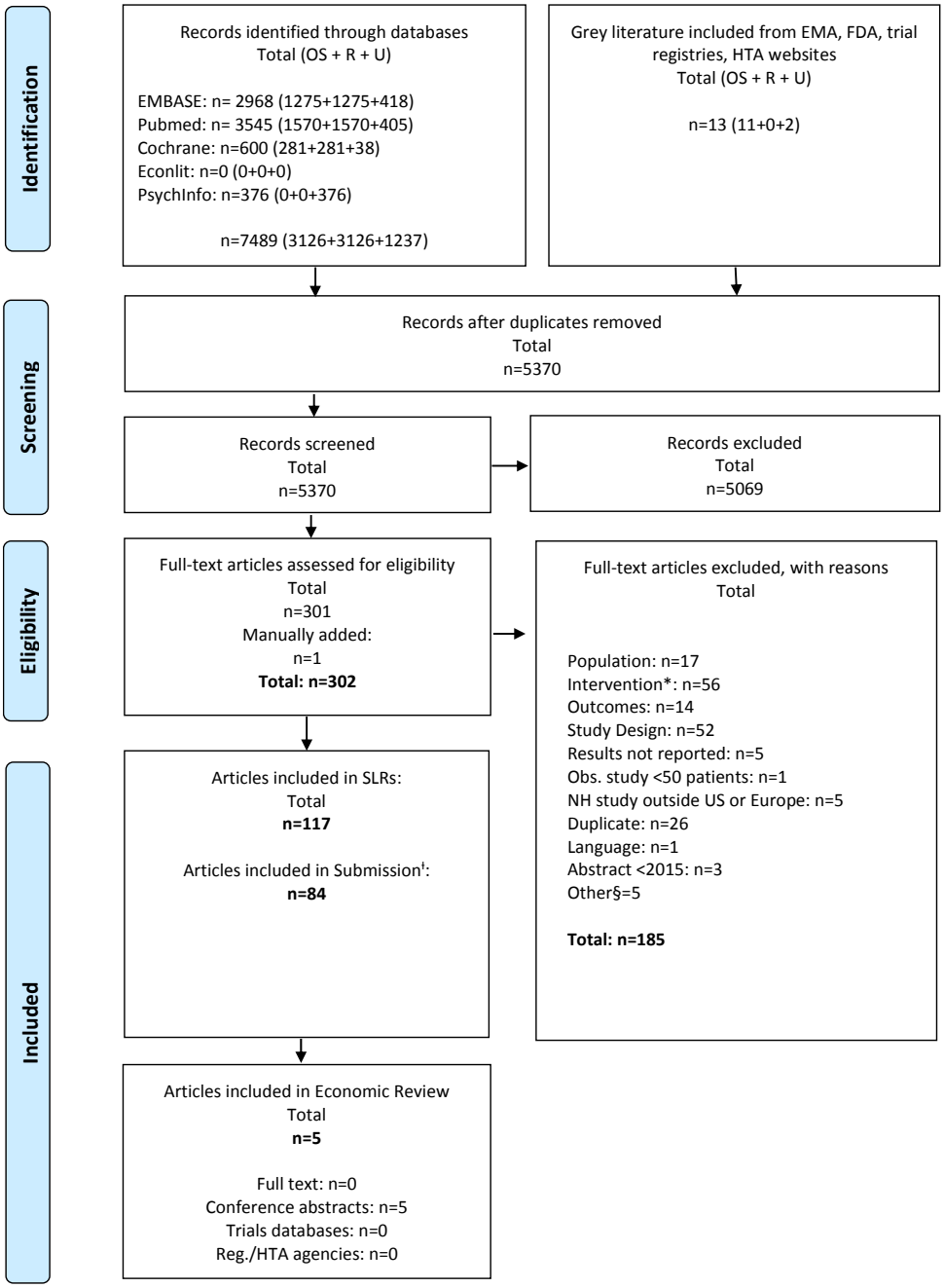


Figure 24. PRISMA flow diagram for economic evidence in hATTR amyloidosis with polyneuropathy

HRQoL: health-related quality-of-life; HTA: health technology assessment; NH: natural history; OS: original search; R: rescreen; Reg.: regulatory; U: update

*Includes 33 studies in rescreen and 12 studies in update that were related to liver transplant and that were excluded by protocol amendment.

§2 studies in rescreen were not available; 1 study in the rescreen and 2 studies in update were abstracts published before 2015 and two studies in update were not available.

†These totals exclude the natural history studies that were part of the original search

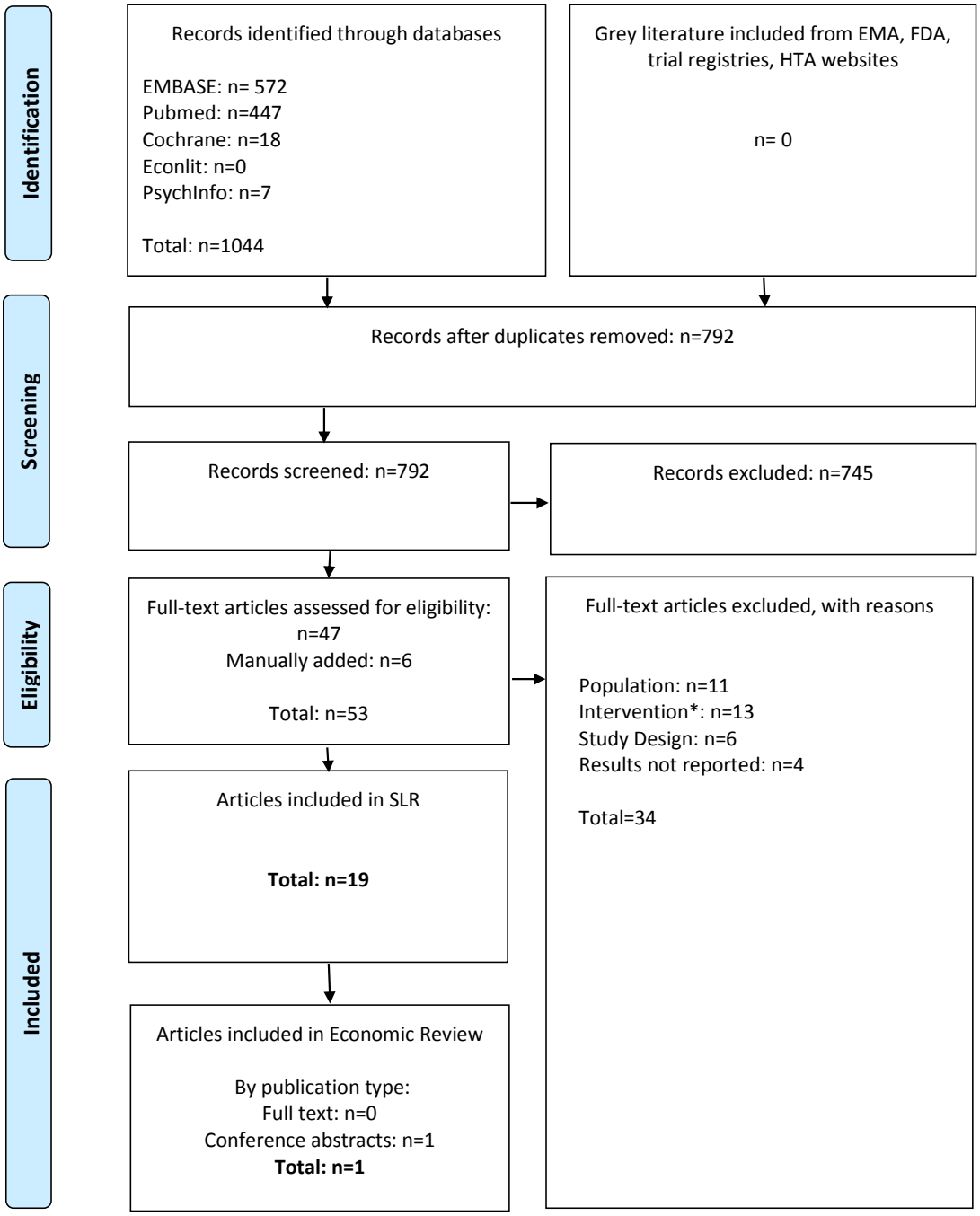


Figure 25. PRISMA flow diagram for economic evidence in hATTR amyloidosis with cardiomyopathy and wtATTR amyloidosis

HRQoL: health-related quality-of-life; HTA: health technology assessment; Reg.: regulatory.

*Includes 4 studies that were related to liver transplant and that were excluded by protocol amendment.

11.2 Description of identified studies

11.2.1 Included studies

No economic studies identified by the SLR were relevant to the submission. All economic evaluations identified by the SLR were excluded from the submission

because costs were not reported, or no interventions were considered, as summarised in Appendix 4.

11.2.2 Quality assessment

No health economic studies identified by the SLR were included in the submission.

12 Economic analysis

Section 12 requires the sponsor to provide information on the *de novo* cost-effectiveness analysis.

The *de novo* cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

- A *de novo* Markov model was developed that incorporated health states defined by the combination of PND score and NT-proBNP level.
- The model used data from the pivotal RCT APOLLO or published natural history data highly relevant to the UK and inputs and assumptions were validated by the NAC.
- The undiscounted ICER for patisiran was [redacted]/QALY and the discounted ICER for patisiran was [redacted]/QALY—[redacted].
- The CEA results for patisiran should be considered in context of the high unmet need in this patient population as no disease-modifying therapy is currently available to treat hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy in the UK.

12.1 Description of the *de novo* cost-effectiveness analysis

12.1.1 Patient groups included in the cost-effectiveness analysis

The CEA considers adult patients with hATTR amyloidosis. Demographic data inputs to the CEA were obtained from the baseline characteristics of the mITT population in the APOLLO trial.

12.1.2 Technology and comparator

Consistent with the NICE scope, which specifies that the comparator should be established clinical management without patisiran, the CEA considers patisiran administered on top of BSC vs BSC alone. This aligns with clinical practice in England where OLT is rarely performed and other pharmacotherapeutic options are not

appropriate or available.[44,45,72] A NICE Scientific Advice Report from 2015 and the AGNSS tafamidis assessment report confirmed the rarity of OLT in England.[127,133] This was also confirmed by clinical experts at the NAC.[16]

12.1.3 Model structure

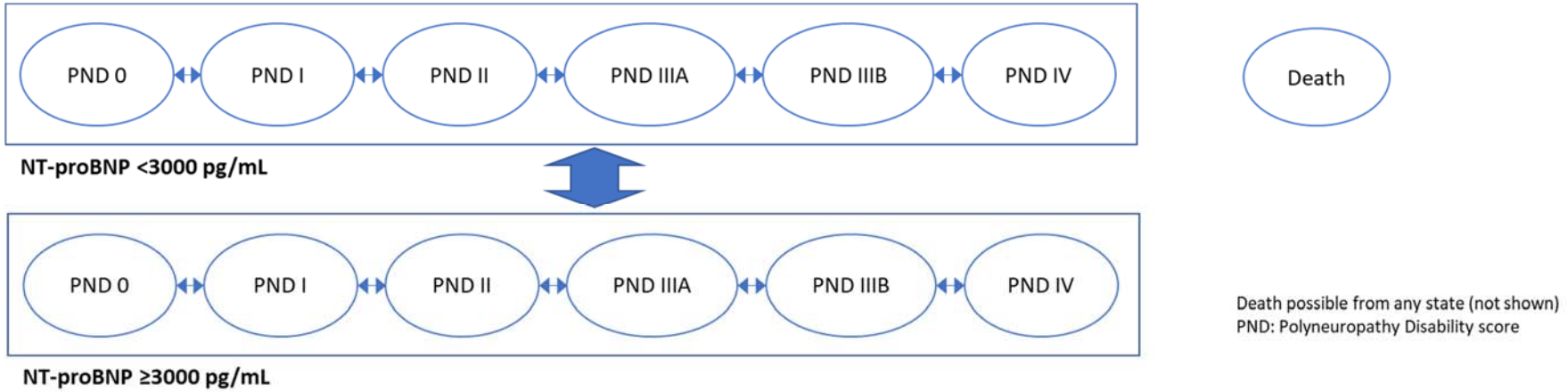
No economic models for patisiran or for other technologies used in UK clinical practice in the indicated population were published at the time of the model development. We therefore developed a *de novo* CE model in conformity with requirements of NICE as expressed in its Guide to the Methods of Technology Appraisal.[128] The CE model for patisiran is found in Appendix 5.

Figure 26 shows the design of the *de novo* Markov model for the CEA for patisiran. The model incorporated health states defined by the combination of PND score (see Section 6.1.2 and 10.1.11) and NT-proBNP (the latter as a binary measure based on the reported threshold of 3000 pg/mL; see Sections 6.1.4, 12.1.4 and 12.1.6 for further information on this measure).[7,71] The combination of PND score, which measures the severity of polyneuropathy symptoms, and NT-proBNP, which measures cardiomyopathy, captures the multi-systemic nature of the disease.[3,5] The efficacy of patisiran and BSC were measured in terms of transition probabilities based on the transitions recorded in the APOLLO trial.[10]

This standard Markov model was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) to assess costs and effects, life-years (LYs) and quality-adjusted life-years (QALYs) of patisiran and BSC in a simulated cohort of hATTR amyloidosis patients. The cohort transitioned across six health states, defined by PND score 0 to IV (see Section 6.1.2). Patients in the PND 0 state by definition are asymptomatic and are therefore not considered in the initial distribution of the model. However, patients entering the model in PND I may improve during the course of the simulation and transition to PND 0. The absence of symptoms in these patients is considered temporary and as such, treatment is continued (Figure 26).

Additionally, the cohort was stratified by NT-proBNP (above or below the threshold of 3000 pg/mL). In total, the model comprised 13 health states, including death, to which patients could transition from any other state.

At the start of the simulation the cohort was distributed by PND score and NT-proBNP according to the baseline distributions in the APOLLO trial (Table D1).[39] At each subsequent cycle, patients moved across PND and NT-proBNP levels based on the transition matrices in the model. The model structure was validated by the NAC (see Section 12.2.5).[16]



CE: cost-effectiveness; PND: polyneuropathy disability; NT-proBNP: N-terminal pro b-type natriuretic peptide

Figure 26. Markov model of the CEA for patisiran

Table D1. Initial patient health states defined by PND score and NT-proBNP value

Clinical measure	Base Case
PND score	
PND I	[redacted]
PND II	[redacted]
PND IIIA	[redacted]
PND IIIB	[redacted]
PND IV	[redacted]
NT-proBNP	
Initial NT-proBNP (pg/mL)	[redacted]
% of patients above 3000 pg/mL	[redacted]

PND: polyneuropathy disability; NT-proBNP: N-terminal pro b-type natriuretic peptide.

Source: Alnylam data on file (APOLLO [ALN-TTR02-OO4] CSR)[10]

12.1.4 Justification of the CE model structure

Basing the model health states on PND score and NT-proBNP levels is relevant in the context of the multi-systemic nature of the disease. PND scores reflect the natural history of the disease in which there is a strong association between the rapid progression seen in hATTR amyloidosis patients and the severity of neuropathy as measured by the PND score.[2]

Notably, the model health states are not based on the mNIS+7 score even though this measure is sensitive to change in polyneuropathy in hATTR amyloidosis (see Section 12.2.2) and was selected as the primary endpoint for APOLLO.[11] As a continuous measure and not an index, it was not possible to establish cut-offs in the range of the mNIS+7 score, making it unsuitable for the discrete definition of the health states in the CE model. As well, data were not available in the published literature to correlate values of mNIS+7 with mortality rates, and a regression analysis to predict mortality on the basis of mNIS+7 scores using the APOLLO data was not feasible due to the limited number of deaths observed in the trial.

Therefore, to characterise polyneuropathy health states, the model uses PND score, a functional scale that measures polyneuropathy symptoms.[5] The PND score was found to be associated with mortality and HRQoL in APOLLO, and was shown to be significantly associated with NIS score by Adams et al. 2015[2] (see Section 12.2.2). While these associations support the appropriateness of using PND score to assign utilities, this method of determining health states is a simplification as the PND score does not fully capture the full range of neuropathy symptoms patients experience including autonomic and sensorimotor dysfunction. This was revealed by the finding that patients in the patisiran arm of APOLLO consistently scored better than patients

in the placebo arm across all primary and secondary endpoints by PND score change category and even within PND score category for the small percentage (20%) of patients who worsened in PND score in the patisiran arm[10] (see Section 10.1.11). Patients treated with patisiran had improved HRQoL compared with patients treated with placebo, even within the same PND score category, and thus in reality utilities may vary within a given PND score.

NT-proBNP has been shown to have a significant correlation with abnormal interventricular septal wall thickness and basal septal strain in hATTR amyloidosis patients, making it a sensitive biomarker of cardiomyopathy for this disease and relevant to assessing patients in clinical practice.[70] As well, poor short-term survival is seen in ATTR amyloidosis patients with elevated NT-proBNP levels (See Section 6.1.4).[34,35,71]

The exclusion of OLT from the CE model structure aligns with the clinical practice in England where it is very rarely performed, as explained in Section 12.1.2.[44,45,72]

12.1.5 List and justification for all assumptions in the model

Table D2 summarises the major assumptions in the CE model for patisiran. The CE model assumptions were validated by clinical experts at the NAC[16] as described in Section 12.2.5.

Table D2. Patisiran CE model assumptions

Assumption	Justification	Reference
PND score is used to define health states related to polyneuropathy	• PND scores reflect the natural history of the disease in which there is a strong association between the rapid progression seen in hATTR amyloidosis patients and the severity of neuropathy[2] • The PND score was shown to be significantly associated with NIS score by Adams et al (2015)[2]	Section 6.1.2 Section 12.2.2
NT-proBNP biomarker is used to assess cardiac involvement in patients with hATTR amyloidosis	• NT-proBNP is a sensitive biomarker of cardiomyopathy for this disease and relevant to assessing patients in clinical practice; the use of NT-proBNP as a sensitive predictor of survival is well documented in the clinical literature[7,35,71]	Section 6.1.4 Section 12.1.4 Section 12.2.1
NT-proBNP is considered as a binary variable as a function of the threshold 3000 pg/mL	• A threshold of approximately 3000 pg/mL was consistently identified in the literature	Section 12.1.6
The same transition matrix for patisiran is used in the extrapolation period	• This assumption is based on similar observed rates on the PND score for patients in the OLE phase 2 studies[105]	Section 12.2.1
Transition matrix for BSC in the extrapolation period is estimated from the PND transitions in APOLLO and the Gamma function method for NT-proBNP	• The relationship reported in Adams et al. 2015[2] demonstrated internal validity to predict PND improvement/worsening from APOLLO	Section 12.2.2
Utilities are different by PND score and by treatment arm	• Directly observed in the APOLLO trial[11] • PND score may not fully capture the range of some neuropathy symptoms such as autonomic and sensorimotor dysfunction	Section 10.1.11
The mean change of utilities by PND and by treatment arm recorded in the APOLLO study is applied in the extrapolation period	• It is clinically reasonable to extrapolate long-term utility decrements with BSC and improved/preserved utilities with patisiran because by all HRQoL measures in APOLLO the patients in the placebo arm had poorer HRQoL, for any given PND score[11] • The application of a “roof” (75th percentile) and “floor” (25th percentile) to this change ensures that the	Section 12.2.1

Assumption	Justification	Reference
	difference in utility between PND scores is preserved	
The relative effects of PND score and NT-proBNP on mortality are assumed as independent and therefore were estimated from different sources.	• Literature on the relationship of PND score and NT-proBNP on mortality are scarce • Citations retrieved through a systematic literature search were reviewed and only one study was identified which reported mortality by PND score (Suhr et al. 1994)[134] • Gillmore et al. 2017 reported the association between NT-proBNP and mortality[7]	Section 12.1.6 Section 12.2.1
The effect of NT-proBNP on mortality was extrapolated from the composite scoring system devised by Gillmore et al. 2017,[7] modified to assume that mortality is exclusively related to NT-proBNP level and no mortality is attributed to the other variable in the scoring system, eGFR (renal function)	• Gillmore et al. 2017[7] was determined to be the study most relevant to the UK condition • This assumption was made in order to simplify the model and was validated by the clinical experts at the NAC[16]	Section 12.2.1

BSC: best supportive care; eGFR: estimated glomerular filtration rate; hATTR: hereditary transthyretin amyloidosis; HRQoL: health-related quality of life; mNIS+7: modified neurological impairment scale; NAC: National Amyloidosis Centre; NT-proBNP: N-terminal pro b-type natriuretic peptide; OLE: open-label extension; PND: polyneuropathy disability.

12.1.6 Model health states

The model health states are designed to capture progression of neuropathy (PND stages) and cardiomyopathy (NT-proBNP) symptoms of hATTR amyloidosis.

The PND score is a functional measure connected with polyneuropathy symptoms which has discrete cut-off points between scores. The PND score has been shown to be associated with HRQoL in APOLLO.[10] As well, the PND score has been shown to be significantly associated with the NIS score by Adams et al. 2015,[2] and with mortality by Suhr et al. 1994.[134]

While it is a reasonable assumption that polyneuropathy could also influence mortality, the literature characterising this relationship is scarce. Citations retrieved through a systematic literature search were reviewed and only one paper that reported survival by PND score (Suhr et al. 1994) was identified.[134] A multivariate analysis using data from APOLLO to model the effect of different degrees of polyneuropathy on survival was planned, but was not conducted due to the low number of deaths in APOLLO.

NT-proBNP was shown to be associated with survival in a number of observational studies, with a threshold of approximately 3000 pg/mL consistently identified as a sensitive cut-off predicting increased mortality.[7,20,71]

12.1.7 Key features of the model not previously reported

Table D3 summarises the additional key features of the model.

Table D3. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon	The time horizon of the simulation corresponds to patient's lifetime, due to the chronic nature of the disease. In model simulation the time limit is set to 40 years, corresponding to 80 model cycles. Extrapolation of clinical inputs is discussed in Section 12.2.1.	NICE Guide to the Methods of Technology Appraisal 2013[128]
Discount rate	Discount rate for costs: 3.5% Discount rate for outcomes: 1.5%	The discount rate for cost is set at 3.5% annually, according to UK NICE reference case. The discount rate for outcomes is set to 1.5% per year, based on the evidence that the treatment effects of patisiran are both substantial in restoring health and sustained over a very long period.	NICE Guide to the Methods of Technology Appraisal 2013[128]
Perspective (NHS/PSS)	The model was constructed from a 3rd-party payer perspective.	In the base-case setting the perspective of the UK NHS is considered, including only direct medical costs.	NICE Guide to the Methods of Technology Appraisal 2013[128]
Cycle length	6 months	The choice of the cycle duration is based on the consideration that within 6 months clinically meaningful events typically occur in this disease. This consideration is supported by the fact that it is common clinical practice to see patients every 6 months.	APOLLO trial[10]

NHS, National Health Service; PSS, Personal Social Services

Differential discount rates

Differential discount rates of 3.5% for costs and 1.5% for health benefits were applied in the base case. Although differential discounting remains controversial, prominent health economists have made a compelling argument that differential discounting of health benefits is the appropriate method for correctly adjusting for the growth in the value of health benefits over time.[135-137]

There is considerable support in the literature for the argument that the value of health is expected to grow over time; put another way, health is considered by society as more valuable over time, and the monetary value of a QALY will increase in future.[136-140] Gravelle and Smith (2001) analysed cost-effectiveness from both a behavioural and social welfare point of view and found that in both cases, the value of health grows with time and that if the focus of decision makers is to maximise social welfare, a discounting scheme must account for this growth.[138]

A CEA with similar discount rates for cost and health benefits may not properly reflect how the value in health effects changes over time.[136,137] When health effects are not

valued in monetary terms (as is the case when health effects are measured in QALYs) an equal discount for costs and benefits risks undervaluing future health benefits.[137] When health effects are measured in QALYs, the growth in the value of health effects is appropriately accounted for by lowering the discount rate for health effects relative to costs. In this case, differential discounting gives more weight to future health effects, reflecting that the value of health effect is expected to grow over time.[135,137,138]

The NICE Guide to the methods of technology appraisal (2013) states that a discount of 1.5% on costs and health effects may be considered for technologies that provide a long-term health benefit, over a very long period of at least 30 years, and which restore people who would otherwise die or have a very severely impaired life to full or near full health.[128]

The high morbidity and mortality of hATTR amyloidosis and the severe impairment of the disease on patients' HRQoL have been established in Section 6 and Section 7, respectively. Patisiran has shown a high level of safety and effectiveness over the long term and has demonstrated the ability to halt or reverse disease progression and improve HRQoL in hATTR amyloidosis patients (Section 9).[11,33] Thus, patisiran for hATTR amyloidosis treatment meets most of the criteria established by NICE for the consideration of a 1.5% discount rate on health effects.

One criterion that should not be applied to patients with hATTR amyloidosis is the 30-year threshold for maintenance of health benefit. O'Mahony and Paulden (2014) have established that the requirement that health benefits must be sustained for at least 30 years can result in discrimination on the basis of age, as a patient with a remaining healthy life expectancy of less than 30 years would be subject to equal discounting, yielding a less favourable ICER.[140] According to the latest statistics, the life expectancy for women and men in England and Wales is 83.08 and 79.46 years, respectively.[8] As such, the requirement that health benefits be sustained over at least 30 years would unfairly penalise patients with hATTR amyloidosis, who, as detailed above in Section 6.3, are often older at diagnosis (median age at baseline in APOLLO was 62 years)[11], and thus would have had an additional life expectancy less than 30 years even in the absence of this disease.

Additional support for the selection of a 1.5% discount rate for health effects in our model is provided by consideration of research by Gravelle and Smith (2001), who proposed that in cases where health only affects income (i.e., the inability to work) the discount rate on health effects should be 3.5% and in cases where health has no effect on income (i.e., in cases where a patient relies entirely on social services or on private

insurance) the appropriate discount would be 1%.[138] Given that many patients with hATTR amyloidosis may be close to or already past retirement at diagnosis, this patient population would fall along the continuum between these two values and therefore a discount of 1.5% on health effects should be considered appropriate.

Given the supporting literature, the age of the hATTR amyloidosis patient population in the UK, and the demonstrated clinical safety and efficacy of patisiran to halt or reverse disease progression and improve patient's HRQoL over the long-term, a discount rate of 1.5% for health benefits is appropriate for the present CEA.

12.2 Clinical parameters and variables

12.2.1 Clinical evidence used in the cost-effectiveness analysis

Citations retrieved through a systematic search of the clinical literature were reviewed to identify studies that correlated PND score and NT-proBNP with survival. Only one paper was found that correlated PND score with survival: Suhr et al. 1994.[134] The study included 27 patients with FAP in Sweden, followed from 1982 to 1993. The study reported a mean survival of approximately 7.4 years in patients in PND I, 5.4 years in PND II, 5.0 years in PND III and 1.4 years in PND IV.[134] Please note that at the time of this study the score PND III was not split into IIIA and IIIB. An HR of 1.30 for mortality of patients in PND III as compared with patients in PND I-II was estimated, assuming an exponential survival function. In the same way, an HR of 4.73 was estimated for patients in PND IV as compared to PND I-II.[134] A multivariate analysis using data from APOLLO to model the effect of different degrees of polyneuropathy on survival was planned, but was not conducted due to the low number of deaths in APOLLO.

The study from Gillmore et al. 2017[7] was determined to be relevant to estimate the correlation between NT-proBNP and survival in the UK context, given that the study comprised a large sample of patients with hATTR amyloidosis enrolled at the NAC (n=201 with the Val122Ile mutation and n=115 with other genotypes). The study proposed a staging system previously described in Section 6.1.4. The stages were significantly associated with long-term survival in the entire cohort (wild-type and hATTR-amyloidosis).[7] The model assumed that the entire effect on mortality was attributed to NT-proBNP and not to the other element of the original scoring system (eGFR). The purpose of the assumption was to simplify the simulation, and it was based on the clinical opinion that cardiac involvement is the main factor driving mortality in hATTR amyloidosis patients. This simplifying assumption was considered acceptable by the NAC.[16] Using the weighted average of the HR for Stage II vs Stage I in the Val122Ile and non-Val122Ile subgroups reported in Gillmore et al. 2017,[7] an

HR of 2.04 was calculated. This HR was applied in the model to characterise the increased mortality for patients who have NT-proBNP ≥3000 pg/mL.

Additionally the study from Gillmore et al. 2017[7] was used to estimate the mortality of the low-risk group among hATTR patients (i.e., those patients who have PND score from 0 to II and NT-proBNP <3000 pg/ml). This information was obtained from the survival of patients with hATTR amyloidosis in Stage I in this study.[7] The median OS in the Val122Ile and non-Val122Ile subgroups of patients in Stage 1 was 5.4 years, which, if an exponential survival function is assumed, corresponds to an estimated mean survival of 7.7 years.[7] This estimated survival was compared with that of a sample of the general UK population with the same starting age and sex ratio as in the hATTR amyloidosis cohort in Gillmore et al. 2017.[7] As the PND score distribution in Gillmore study cohort was not known, it was assumed that the distribution was the same as in the APOLLO study. Based on these considerations, it was estimated that patients in the low-risk group (i.e., with hATTR amyloidosis and no other risk factor as defined by PND score and NT-proBNP) had an HR of death of 2.01 with respect to the general UK population.

The input data used in the model to simulate mortality are summarised in Table D4.

Table D4. Schema of the mortality risks applied in the simulation

	NT-proBNP <3000 pg/mL	NT-proBNP ≥3000 pg/mL
PND 0-II	Low-risk group HR=2.01 over the mortality of the general UK population	HR=2.04 vs patients with NT-proBNP<3000 pg/mL and same PND score
PND III	HR=1.30 over the low-risk group	
PND IV	HR=4.73 over the low-risk group	

HR: hazard ratio; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability.

Transition matrices

The transitions in the first three cycles of the simulation, corresponding to the duration of the APOLLO trial (efficacy period, 18 months), were informed by the actual transitions recorded for this dataset. The numbers of patients moving from PND/NT-proBNP states at baseline (in rows) and reaching other states after 18 months (in columns) are reported in Table D5 and Table D6 for the patisiran and placebo groups, respectively. The transition probabilities included in the model were estimated based on the data in the tables below with the Bayesian method proposed by Briggs et al. 2003,[141] using a Dirichlet distribution with a non-informative prior belief (i.e., a probability of 1% was assigned to every possible transition). Transition probabilities as described were validated by the NAC.[16]

Table D5. Shift table (from baseline to 18 months) for the patisiran group (APOLLO; n=148)[10]

From\To		NT proBNP <3000 pg/mL						NT proBNP ≥3000 pg/mL						Missing	Total
PND score		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV		
NT proBNP <3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
NT proBNP ≥3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
Missing															
Total															

PND: polyneuropathy disability; NT-proBNP: N-terminal pro b-type natriuretic peptide

Table D6. Shift table (from baseline to 18 months) for the placebo (BSC) group (APOLLO; n=77)[10]

From\To		NT proBNP <3000 pg/mL						NT proBNP ≥3000 pg/mL						Missing	Total
PND score		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV		
NT proBNP<3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
NT proBNP≥3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
Missing															
Total															

BSC: best supportive care; PND: polyneuropathy disability; NT-proBNP: N-terminal pro b-type natriuretic peptide.

Time on treatment (ToT)

Extrapolating ToT for patients receiving patisiran was conducted by parametric curve fitting to the patient-level data from APOLLO. The following main parametric functions were assessed for goodness of fit: exponential, Weibull, log-logistic, log-normal, and Gamma. The goodness of the fit of these functions was assessed with the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics (Table D7). The log-logistic function was selected to inform the fraction of patients still on

treatment at each time point in the simulation based on the goodness of fit. Figure 27 shows how the parametric curves compare for the extrapolation of the ToT for patisiran.

Table D7. Goodness of fit

Fit Statistics	AIC	BIC
Exponential	80.151	83.107
Weibull	69.792	75.704
Log-normal	69.463	75.375
Log-logistic	69.776	75.688
Gamma	71.219	80.087

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Figure 27. Extrapolation of the ToT for patisiran

ToT: Time on treatment.

12.2.2 Extrapolation of costs and clinical outcomes: assumptions and justification

The clinical outcomes extrapolated beyond study follow-up for the patisiran and placebo arms discussed in this section were all validated by the clinical experts at the NAC during the meeting described in Section 12.2.5.[16]

Patisiran arm

The APOLLO trial data extended to 18 months. However, the phase 2 OLE (Study ALN-TTR02-003; 24 months for a total treatment period of 36 months), showed rates of improved, stable, or progressive PND scores and change in NT-proBNP levels similar to those recorded in the APOLLO study (Table D8). Therefore, the same transition matrix as was used for the efficacy period was applied to the extrapolation period in the patisiran arm. Beyond the 18 months of the APOLLO trial, the model assumed stabilisation of the disease and the same transitions between PND scores observed in APOLLO were maintained.[16]

Table D8. Comparison of transition rates between PND scores and NT-proBNP levels in the patisiran arm of the APOLLO trial (12 months) and in the OLE phase 2 (Study ALN-TTR02-003)

	APOLLO (results scaled to 12 months)		OLE (Study ALN-TTR02-003)	
	N	% (12 months)	N	%
PND score				
Worsened	30	14.9%	4	16.0%
No change	92	79.1%	20	80.0%
Improved	12	6.0%	1	4.0%
ΔNT-proBNP (pg/mL)	148	-49.9	25	-49.6

OLE: open-label extension; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability.

Source: Gonzalez-Duarte et al. 2018[116]

BSC arm

While no studies were identified that described the natural progression of disease categorised by PND score, citations retrieved through a systematic literature search were reviewed and a study from Adams et al. 2015[2] was identified which reported that the PND score was significantly associated with the mNIS+7 score.[2] The study observed 283 patients with hATTR amyloidosis from four countries (France, Italy, Portugal, and the US) and estimated an mNIS+7 progression rate of 17.8 points per year in untreated patients.[2] The placebo arm of the APOLLO trial reported similar results (a change of 27.96 points on the mNIS+7 in 18 months corresponding to a scaled value of 18.6 points in 12 months). Based on the reported values from Adams et al. 2015,[2] the observed evolution in mNIS+7 in APOLLO was assumed to continue after the initial 18 months. The transition matrix for PND score transitions in the placebo arm was extrapolated based on the observed rates of progression/worsening of PND in the APOLLO study (Table D9).

Table D9. PND score transitions in 18 months from the placebo arm of APOLLO

	Improved	No Change	Worsened
Placebo (BSC)	0.0%	41.8%	58.2%

BSC: best supportive care.

Note: Patients with missing data were excluded from this baseline analysis (n=22)

Source: Alnylam, data on file (APOLLO [ALN-TTR02-OO4] CSR)[10], Gonzalez-Duarte et al. 2018[116]

The literature on the natural history of the evolution of NT-proBNP is scarce. Citations retrieved through a systematic literature search were reviewed and only one paper was identified that described the evolution of NT-proBNP in patients with wtATTR or hATTR (Ruberg & Berk 2012).[61] Ruberg & Berk 2012[49] reported an increase in NT-proBNP of 1816 pg/mL every 6 months in a patient population of hATTR amyloidosis patients with the Val122Ile mutation (n=11) or wtATTR amyloidosis (n=18).[61] These data formed the basis of the transition matrix extrapolation for BSC using the Gamma function for NT-proBNP transitions (see Section 12.2.3). The use of Ruberg & Berk 2012[49] to inform the transition matrix extrapolation beyond 18 months was considered reasonable by the NAC.[16]

12.2.3 Intermediate outcome measures linked to final outcomes

Relationship for NT-proBNP transitions

The following method was developed to allow the simulation of transitions between the states defined by the NT-proBNP threshold of 3000 pg/mL (i.e., above or below), based on the change of the NT-proBNP levels in the same time period.

The parameters of a Gamma distribution were estimated in order to fit the mean NT-proBNP at baseline ([redacted]) and the percentage of patients above the threshold of 3000 pg/mL ([redacted]) in the entire APOLLO population. The Gamma distribution was selected for its characteristic skew that allows only positive values (the log-normal function also presents similar characteristics, but the long tail of the distribution makes it a less appropriate choice).

Once the baseline Gamma distribution was determined, the transition probabilities between the NT-proBNP states were calculated based on the assumption that the final distribution is given by another Gamma function with the mean given by the NT-proBNP change and the same variance as the baseline distribution. This is equivalent to assuming that all the patients in the cohort had the same change in NT-proBNP, namely the mean change. The process can be visualised as a Gamma distribution rigidly shifting as a function of the mean change of NT-proBNP, thereby determining the percent of patients that are above and below the threshold (Figure 28).

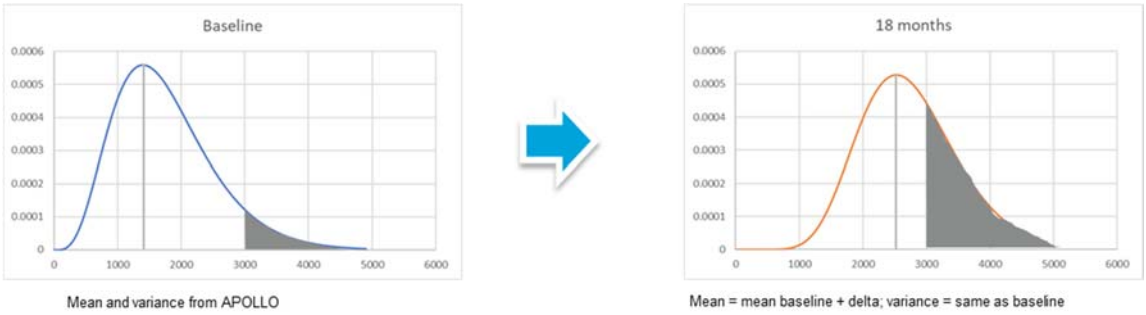


Figure 28. Descriptive representation of the method to estimate transition probabilities between NT-proBNP states, based on the NT-proBNP mean change. The shaded area represents the % of patients with NT-proBNP ≥3000 pg/mL

12.2.4 Adverse events included in the cost- effectiveness analysis

AEs considered in the model include serious events occurring in at least 2% of participants in either treatment arm of the APOLLO study (Table D10).[10] The cumulative incidence recorded in the trial was rescaled to the 6-month duration of the cycle length in the simulation.

Table D10. Incidence of adverse events in the APOLLO study

Preferred Term; number of patients (%)	Placebo (N=77)	Patisiran (N=148)
At least 1 SAE	31 (40.3)	54 (36.5)
Diarrhoea	1 (1.3)	8 (5.4)
Cardiac failure	2 (2.6)	3 (2.0)
Cardiac failure congestive	2 (2.6)	3 (2.0)
Orthostatic hypotension	1 (1.3)	3 (2.0)
Pneumonia	3 (3.9)	3 (2.0)
Atrioventricular block complete	0	3 (2.0)
Acute kidney injury	4 (5.2)	1 (0.7)
Dehydration	3 (3.9)	1 (0.7)
Vomiting	3 (3.9)	1 (0.7)
Urinary tract infection	4 (5.2)	0
Constipation	2 (2.6)	0
Hereditary neuropathic amyloidosis	2 (2.6)	0
Hyponatremia	2 (2.6)	0
Pneumonia aspiration	2 (2.6)	0

Source: Alnylam, data on file (APOLLO [ALN-TTR02-OO4] CSR)[10]

12.2.5 Validation of the clinical model parameters and inputs used in the analysis

On 13 June 2018, Alnylam Pharmaceuticals met with Professor Philip Hawkins, Head/Clinical Director and Professor Julian Gillmore, Professor/Consultant at the NAC

for the purpose of clinically validating the CE model. The NAC provides the diagnosis scoring/staging, monitoring, and advice on the management for patients with amyloidosis (including hATTR amyloidosis) in the UK and thus are considered the highest level of expertise on all aspects of the disease.[142] Table D11 summarises the CE model assumptions and methodology presented to these reviewers, and their responses.

Table D11. Clinical validation of the CE model assumptions and methodology

CE model assumptions/methodology	NAC clinical expert opinion
Overall	
General design of model	Appropriate; noted that model captures the multi-systemic nature of the disease
Health states defined by PND score and NT-proBNP	Appropriate, considering data limitations in hATTR
Use of observed PND transitions in APOLLO	Agree; prefer this decision vs Pfizer's use of Norfolk TQoL score cut-offs to define FAP stages in their tafamidis submission[127]
UK clinical practice	
0% OLT in England	Agree
Cardiomyopathy mortality	
HR for patients with NT-proBNP >3000 pg/mL estimated from HR reported for Stage II patients by Gillmore et al. 2017[7]	Reasonable and appropriate
HR estimate for patients with NT-proBNP >3000 pg/mL estimated as a weighted average of the HR for V122I and other (mixed-genotype) subgroups reported by Gillmore et al. 2017[7]	Agree
Polyneuropathy mortality	
Inclusion of mortality due to polyneuropathy	Agree
Mortality due to polyneuropathy estimated from Suhr et al. 1994[134]	Appropriate, in the absence of other sources
Extrapolation past 18 months	
PND transitions and NT-proBNP evolution for patisiran extrapolated from observed data in APOLLO patisiran arm	Reasonable
mNIS+7 progression for BSC extrapolated from observed data in APOLLO placebo arm	Agree; noted that extrapolated values were supported by data reported by Adams et al. 2015[2]
NT-proBNP evolution for BSC extrapolated from Ruberg & Berk 2012[61]	Appropriate, in the absence of other sources
Face validity	
LY estimates in the BSC arm	The estimated LYs for the BSC arm used in the CE model are within the realm of plausibility; reasonable to say that the model has face validity
HRQoL values by PND score	

CE model assumptions/methodology	NAC clinical expert opinion
Utility values differ within the same PND score for patisiran and BSC	Reasonable to expect different utilities for patisiran and BSC as observed in APOLLO, because PND health states as defined in the model may be capturing autonomic symptoms as well as functional aspects of hATTR, and autonomic symptoms may progress at a different rate than PND score (a functional scale); believe HRQoL is driven mainly by autonomic symptoms (diarrhoea, constipation, wasting)
Extrapolation of utilities after 18 months	
Capping change in utilities in patisiran arm after initial 18 months	Agree
Decrease in utilities for BSC arm capped after 18 months	Conservative assumption because autonomic symptoms could worsen without the patient progressing in PND score; however, consider the assumption to be reasonable

BSC: best supportive care; CE: cost-effectiveness; hATTR: hATTR: hereditary transthyretin amyloidosis; HR: hazard ratio; HRQoL: health-related quality-of-life; LY: life-years; NAC: National Amyloidosis Centre; NT-proBNP: N-terminal pro b-type natriuretic peptide; OLT: orthotopic liver transplant; PND: polyneuropathy disability score; TQoL: total quality of life

12.2.6 Summary of the clinical variables included in the cost-effectiveness analysis

The patient characteristics and clinical variables used in the CE model are summarised in Table D12. The HRQoL inputs to the CE model are summarised in Section 10.1.9.

Table D12. Summary of clinical variables applied in the CE model

Variable	Value	Range*		Distribution	Source
		Lower value	Upper value		
Population characteristics					
Age (years)	58.8	57.25	60.40	Gamma	APOLLO
Males (%)	70.5	56.0	83.2	Beta	APOLLO
Initial disposition					
Distribution in PND score (%)					
PND I	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
PND II	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
PND IIIA	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
PND IIIB	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
PND IV	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
NT-proBNP					
Initial NT-proBNP (pg/mL)	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
% of patients above 3000 pg/mL	[redacted]	[redacted]	[redacted]	[redacted]	APOLLO
Risk of death by PND and NT-proBNP					
HR of death PND IIIA-IIIB vs. PND I-II	1.30	1.04	1.55	Gamma	Suhr et al. 1994
HR of death PND IV vs. PND I-II	4.73	3.81	5.66	Gamma	Suhr et al. 1994
RR PND I and NT-proBNP<3000 pg/mL vs. the general population	2.01	1.62	2.41	Gamma	Gillmore et al. 2017
HR of death NT-proBNP≥3000 pg/mL	2.04	1.64	2.44	Gamma	Gillmore et al. 2017

BSC: best supportive care; CE: cost-effectiveness; CI: confidence interval; HR: hazard ratio; RR: risk ratio; NHS: National Health Service; NT-proBNP: N-terminal pro b-type natriuretic peptide; mNIS+7: modified neurological impairment score +7; SE: standard error.

*The upper and lower values were set based on the 95% CI if available, or calculated using ±1.96 * the SE. If neither of these were available, the values were varied ±10% of the mean.

Sources: Alnylam data on file [APOLLO ALN-TTR02-OO4 CSR]);[10] Data on File;[10] Gillmore et al. 2017;[7] Ruberg & Berk 2012;[49]

12.3 **Resource identification, measurement and valuation**

12.3.1 NHS reference costs

NHS reference costs and PSSRU costs for the clinical management of the condition are listed in Appendix 3.

12.3.2 Resource identification, measurement and valuation studies

The SLRs summarised in Table C1 and Appendix 1 were designed with broad search terms in order to capture any relevant resource data for the NHS in England. No published resource data were identified.

12.3.3 Assessment of the applicability of resource data used in the cost-effectiveness model

A Delphi panel was convened to investigate the current use of UK NHS and PSS resources in hATTR amyloidosis in England, specifically resources used (per 6 months) in the management of patients, stratified by both PND score and NT-proBNP levels, as well as to investigate the wider societal costs associated with the management and care of patients with hATTR amyloidosis, including productivity losses due to early retirement or sick leave of patients and their caregivers. The methods and statistical plan are described in Section 10.1.10. The Delphi panel report including results is available in Appendix 3.

Technology and comparators' costs

12.3.4 Technology list price

The list price for patisiran is £7676.47 per 10 mg/5 mL vial.

12.3.5 If the list price is not used in the *de novo* cost- effectiveness model, provide the alternative price and a justification.

The list price of the technology was used in the base-case CE model. [redacted].

12.3.6 Annual cost of patisiran

<u>Price of patisiran per treatment/patient</u>

The relative dose intensity (RDI) is a measure of the differences between the prescribed dose and what is taken in practice (i.e., capturing skipped doses and dose modifications), hence modelling treatment costs incorporating RDI supports accurate estimation of the cost of treatment. The RDI for patisiran was estimated at 0.97,

calculated as the ratio of the actual cumulative number of doses received by patients in the APOLLO trial (3740 doses) divided by the theoretical number of doses (1 dose every 3 weeks × 18 months × 148 patients).

Administration cost

The administration cost of patisiran was considered comparable with that of a complex IV infusion of a chemotherapy and estimated at £301 per treatment using the NHS reference costs (2016/17; Deliver more complex Parenteral Chemotherapy at first attendance, day case and regular day/night [SB13Z]).[143]

The patient pathway of care service model proposed by Alnylam Pharmaceuticals UK after consultation with an extensive range of clinical stakeholders (including clinicians at the NAC, the National Hospital for Neurology and Neurosurgery, regional hospitals, and NHS England), patient advocacy groups (including the ARC), and NICE, presented in Section 8.4, includes the provision of home infusion for patients who are eligible. However, the number of patients who would be eligible and who would choose to undergo home infusion is not known. Therefore, the model does not include the option for home infusions in the base case; instead, all patients are assumed to be infused at the NAC.

Premedication costs

Each administration of patisiran requires a premedication regimen consisting of IV dexamethasone and H1/H2 blockers along with oral paracetamol/acetaminophen given at least 60 minutes prior to each infusion.[11] The cost associated with this regimen was estimated at £1.60 per treatment.[144]

The costs per treatment per patient associated with the new technology in the CE model are summarised in Table D13.

Table D13. Costs per treatment/patient associated with the technology in the CE model

Items	Value (£)	Source
Price of the technology per treatment/patient	[redacted]	APOLLO
Administration cost	301	NHS 2016/17
Other costs (premedication)	1.60	BNF
Total cost per treatment/patient	[redacted]	Total

CE: cost-effectiveness; N/A: not applicable.

Sources: APOLLO (Adams et al. 2018);[11] British National Formulary;[144] NHS 2016/17.[143]

The estimated administrations of patisiran are 8.7 per 6-month cycle of the model.

12.3.7 Health state costs

The per-cycle and one-off costs listed in Table D14 were determined by the Delphi panel process outlined in Section 10.1.10.

Table D14. List of health states and associated costs in the CE model

Health states	Base-case	Range Lower value, Upper value	Distribution
Per-cycle costs by PND stage (£)			
PND 0	[redacted]	[redacted]	Mix
PND I	[redacted]	[redacted]	Mix
PND II	[redacted]	[redacted]	Mix
PND IIIA	[redacted]	[redacted]	Mix
PND IIIA	[redacted]	[redacted]	Mix
PND IV	[redacted]	[redacted]	Mix
Per-cycle costs due to cardiomyopathy (£)			
NT-proBNP ≤3000 pg/mL	[redacted]	[redacted]	Mix
NT-proBNP >3000 pg/mL	[redacted]	[redacted]	Mix
One-off costs (£)			
PND 0	[redacted]	[redacted]	
PND I	[redacted]	[redacted]	Mix
PND II	[redacted]	[redacted]	Mix
PND IIIA	[redacted]	[redacted]	Mix
PND IIIA	[redacted]	[redacted]	Mix
PND IV	[redacted]	[redacted]	Mix

CE: cost-effectiveness; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability.

12.3.8 Adverse-event costs

Table D15 summarises the list of costs related to the AEs included in the CE model.

Table D15. List of AEs and summary of costs included in the CE model

Unit costs of serious AEs (£)	Base-case	SE	Range	
			Lower value	Upper value
Diarrhoea	916.80	91.68	737.11, 1,096.50	
Cardiac failure	508.72	50.87	409.01, 608.43	
Cardiac failure congestive	553.58	55.36	445.08, 662.08	
Orthostatic hypotension	617.11	61.71	496.16, 738.07	
Pneumonia	819.09	81.91	658.54, 979.63	
Atrioventricular block complete	502.83	50.28	404.27, 601.38	
Acute kidney injury	978.32	97.83	786.57, 1,170.07	
Dehydration	727.25	72.73	584.71, 869.80	
Vomiting	916.80	91.68	737.11, 1,096.50	
Urinary tract infection	1,123.22	112.32	903.07, 1,343.37	
Constipation	916.80	91.68	737.11, 1,096.50	
Hyponatraemia	727.25	72.73	584.71, 869.80	
Pneumonia aspiration	819.09	81.91	658.54, 979.63	

AEs: Adverse events; CE: cost-effectiveness.

Source: NHS Reference Costs (2016/17)

12.3.9 Miscellaneous costs

Additional costs include those for “one-off” mobility aids such as wheelchairs, shower chair, walking aids, kitchen and bathroom adjustments, door openers, rails, ramps, and a homecare bed including a lift are summarised in Table D16.

Table D16. Additional costs

	Unit cost (£)
Electric wheelchair	1,468.00
Manual wheelchair	734.00
Stick	16.00
Crutch	9.89
Walking chair	133.54
Walking frame	63.63
Permobil	1,395.00
Shower chair	108.96
Adjustment, kitchen	5,160.00
Adjustment, bathroom	5,160.00

Door opener	16.82
Rails	37.50
Ramps	341.00
Homecare bed including lift	1,363.79

Sources: PPSRU 2017; www.euromedical.co.uk

To reflect the fact that individuals incur additional resources shortly before death, all patients who die in the model, regardless of treatment option, incur an additional resource use component representing "end of life" care. End-of-life costs are summarised in Table D17.

Table D17. End-of-life costs

			OWSA	
	Base case	SE	Lower value	Upper value
Proportion being treated in hospital (%)	51.5	5.1	41.4	61.5
EOL hospital days	21.50	2.15	17.29	25.71
Cost of palliative care in hospital (£ per day)	463.77	46.38	372.87	554.66
Proportion being treated in hospice (%)	23.1	2.3	18.6	27.6
EOL hospice days	17.40	1.74	13.99	20.81
Cost of community palliative care per day (£)	158.23	15.82	127.21	189.24
End-of-life care cost (£)	5,765.76			

EOL: end of life; OWSA: one-way sensitivity analysis; SE: standard error.

Source: NICE TA 451[145]

12.3.10 Resource savings or redirection of resources

Reductions in HCRU associated with the use of patisiran are detailed in Appendix 3. No additional opportunities for resource savings to the NHS have been identified.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Types of sensitivity analysis that have been carried out in the cost-effectiveness analysis

Deterministic (one-way) and probabilistic sensitivity analyses were conducted on the model base-case parameters. Scenario analyses were conducted in order to further test the uncertainty around specific model inputs and assumptions.

12.4.2 Details of sensitivity analyses

Deterministic (one-way) sensitivity analysis

In order to assess the impact of each of the inputs on the overall result, a univariate analysis was conducted to identify the parameters with greatest influence on the model results. Each parameter selected was set to upper and lower values, holding all other parameters constant, to understand how sensitive the ICER was to changes in the inputs. The upper and lower values for the parameters, as shown in Table D18, were set based on the 95% CI or range of the base-case value if directly available or calculated as ±1.96 x the SE. When neither the 95% CI nor the SE was available, values were varied ±10% of the mean value. For HRQoL utilities resources, upper and lower values in the sensitivity analysis were derived from the 25th and 75th percentile of the values recorded in the APOLLO trial. For HCRU the extremes were calculated considering the minimum and maximum values in the answers from the experts enrolled in the Delphi panel. Discount rates of 0% and 6% were also assessed.

Probabilistic sensitivity analysis

To address the uncertainty in the parameters used within the model, a probabilistic sensitivity analysis (PSA) was implemented. The PSA was performed on the comparison between patisiran and BSC. For all parameters, the distribution used was Beta, Normal, Gamma, or Dirichlet. Mean results were calculated from the 1000 simulations in this analysis. The PSA distributions are summarised in Table D18.

Scenario analyses

Scenario 1A & B

In the CEA, transition probabilities are driven by tables of transitions between health states as recorded in the APOLLO study. In the base-case analysis, missing values were not imputed when deriving transition probabilities for the CE model.

The scenario analyses explored how these missing data affected the results of the transition probabilities. A conservative assumption was tested Scenario 1A, in which

all patients in the patisiran arm for whom PND score and/or NT-proBNP level data were missing, either at baseline or at 18 months, were considered to have progressed to the next (worse) health state while all patients in the placebo arm with missing data improved to the previous (better) health state.

An optimistic assumption was tested in Scenario 1B, where the same patients from the patisiran arm were considered to have improved to the previous (better) health state and those from the placebo arm were considered to have progressed to the next (worse) health state. All other parameters remained the same as in the base case.

Scenario 2

In the CEA, utilities by health state in the patisiran and BSC arm were obtained at each time point from the regression formulas. However, the possible values used in the base-case simulation were capped so that utilities could not exceed a minimum or maximum value provided in each health state by the 25th or 75th percentiles of values recorded in the APOLLO trial or the equivalent utility (by age and sex) of the general UK population.

In Scenario 2, no limits on the value of utilities were considered. In each cycle of the model, the utilities were calculated from the regression formulas without constraint. All other parameters remained the same.

Scenario 3

The parametric survival analysis approach was used in the model to analyse the ToT with patisiran, and for the base-case scenario the log-normal function was selected based on the goodness of fit statistics (see Figure 27). The choice of this function implies that over time, the percentage of patients that continue to receive treatment with patisiran remains stable.

In Scenario 3, an alternative assumption—that the percentage of patients who continue to receive treatment with patisiran decreases over time—was analysed by selecting the exponential function. All other parameters remained the same.

Scenario 4

The base-case analysis estimated mortality from PND score based on data reported by Suhr et al. 1994[134] and by NT-proBNP level as determined from Gillmore et al. 2017.[7]

As discussed previously in Section 12.2.1, Suhr et al. 1994[134] was the only reference identified in the literature that reported mortality by PND score. Although the use of the

mortality data derived from this study was validated by the NAC (see Section 12.2.5), it should be acknowledged that the sample size was relatively low, and thus mortality as a function of PND score remains an important area of uncertainty in the CEA.

In Scenario 4, in order to analyse the uncertainty around the use of the data reporting mortality by PND score, all mortality in the CE model was considered to be due to cardiomyopathy as measured by NT-proBNP levels, in keeping with the clinical profile of patients in the UK whose predominate clinical manifestations involve the heart, even if neuropathic impairment is present. All other parameters remained the same.

12.4.3 Summary of the variables used in the sensitivity analyses

Table D18 summarise the variables used in the one-way deterministic and probabilistic sensitivity analyses.

Table D19 summarises the variables used in the scenario sensitivity analyses.

Table D18. Variables used in one-way deterministic and probabilistic scenario analyses

Variable	Base-case value	Lower value	Upper value	PSA Distribution
General settings				
Discount rate outcomes	1.5%	0.0%	6.0%	-
Discount rate costs	3.5%	0.0%	6.0%	-
Population characteristics				
Initial age (years)	58.80	57.25	60.40	Gamma
Proportion of males	70.5%	56.0%	83.2%	Beta
Initial population distribution				
Distribution by PND state				
PND I	[redacted]	[redacted]	[redacted]	Dirichlet
PND II	[redacted]	[redacted]	[redacted]	Dirichlet
PND IIIA	[redacted]	[redacted]	[redacted]	Dirichlet
PND IIIB	[redacted]	[redacted]	[redacted]	Dirichlet
PND IV	[redacted]	[redacted]	[redacted]	Dirichlet
NT-proBNP				
Initial NT-proBNP (pg/mL)	[redacted]	[redacted]	[redacted]	Gamma
NT-proBNP≥3000 pg/mL	[redacted]	[redacted]	[redacted]	Beta
Effectiveness of treatments				
Delta NT-proBNP BSC extrapolation period (pg/mL every 18 months)	5448.0	4380.2	6515.8	Normal
Risk of death				
RR PND 0–II and NT-proBNP<3000 pg/ml vs general population	2.01	1.62	2.41	Gamma
HR of death NT-proBNP≥3000 pg/mL	2.04	1.64	2.45	Gamma
HR of death PND IIIA–IIIB vs PND I–II	1.30	1.04	1.55	Gamma
HR of death PND IV vs PND I–II	4.73	3.81	5.66	Gamma
HRQoL by PND score				
Parameters of the regression				
PND 0	[redacted]	[redacted]	[redacted]	

Variable	Base-case value	Lower value	Upper value	PSA Distribution
PND I	[redacted]	[redacted]	[redacted]	Normal
PND II	[redacted]	[redacted]	[redacted]	Normal
PND IIIA	[redacted]	[redacted]	[redacted]	Normal
PND IIIB	[redacted]	[redacted]	[redacted]	Normal
PND IV	[redacted]	[redacted]	[redacted]	Normal
Time*patisiran	[redacted]	[redacted]	[redacted]	Normal
Time*BSC	[redacted]	[redacted]	[redacted]	Normal
Maximum utility, patisiran	[redacted]	[redacted]	[redacted]	
PND 0	[redacted]	[redacted]	[redacted]	Normal
PND I	[redacted]	[redacted]	[redacted]	Normal
PND II	[redacted]	[redacted]	[redacted]	Normal
PND IIIA	[redacted]	[redacted]	[redacted]	Normal
PND IIIB	[redacted]	[redacted]	[redacted]	Normal
PND IV	[redacted]	[redacted]	[redacted]	Normal
Minimum utility, BSC	[redacted]	[redacted]	[redacted]	
PND 0	[redacted]	[redacted]	[redacted]	Normal
PND I	[redacted]	[redacted]	[redacted]	Normal
PND II	[redacted]	[redacted]	[redacted]	Normal
PND IIIA	[redacted]	[redacted]	[redacted]	Normal
PND IIIB	[redacted]	[redacted]	[redacted]	Normal
PND IV	[redacted]	[redacted]	[redacted]	Normal
HRQoL other settings				
Disutility on carers (PND IV)	0.010	0.008	0.012	Gamma
Serious AEs ≥2%				
AE incidence per cycle, patisiran				
Diarrhoea	0.018	0.015	0.022	Gamma
Cardiac failure	0.007	0.005	0.008	Gamma
Cardiac failure congestive	0.007	0.005	0.008	Gamma

Variable	Base-case value	Lower value	Upper value	PSA Distribution
Orthostatic hypotension	0.007	0.005	0.008	Gamma
Pneumonia	0.007	0.005	0.008	Gamma
Atrioventricular block complete	0.007	0.005	0.008	Gamma
Acute kidney injury	0.002	0.002	0.003	Gamma
Dehydration	0.002	0.002	0.003	Gamma
Vomiting	0.002	0.002	0.003	Gamma
Urinary tract infection	0.000	0.000	0.000	Gamma
Constipation	0.000	0.000	0.000	Gamma
Hereditary neuropathic amyloidosis	0.000	0.000	0.000	Gamma
Hyponatremia	0.000	0.000	0.000	Gamma
Pneumonia aspiration	0.000	0.000	0.000	Gamma
AE incidence per cycle, BSC				
Diarrhoea	0.004	0.003	0.005	Gamma
Cardiac failure	0.009	0.007	0.010	Gamma
Cardiac failure congestive	0.009	0.007	0.010	Gamma
Orthostatic hypotension	0.004	0.003	0.005	Gamma
Pneumonia	0.013	0.011	0.016	Gamma
Atrioventricular block complete	0.000	0.000	0.000	Gamma
Acute kidney injury	0.018	0.014	0.021	Gamma
Dehydration	0.013	0.011	0.016	Gamma
Vomiting	0.013	0.011	0.016	Gamma
Urinary tract infection	0.018	0.014	0.021	Gamma
Constipation	0.009	0.007	0.010	Gamma
Hereditary neuropathic amyloidosis	0.009	0.007	0.010	Gamma
Hyponatremia	0.009	0.007	0.010	Gamma
Pneumonia aspiration	0.009	0.007	0.010	Gamma
Direct costs				
Time on treatment				

Variable	Base-case value	Lower value	Upper value	PSA Distribution
Time on treatment, intercept	[redacted]	–	–	Normal
Time on treatment scale	[redacted]	–	–	Normal
Administration cost				
Complex IV infusion, per cycle (£)	2,695.89	2,167.50	3,224.29	Gamma
Other costs				
Premedication cost, per cycle (£), patisiran	13.89	11.17	16.62	Gamma
HCRU				
Per cycle costs (£), polyneuropathy-related				
PND 0	[redacted]	[redacted]	[redacted]	Mix
PND I	[redacted]	[redacted]	[redacted]	Mix
PND II	[redacted]	[redacted]	[redacted]	Mix
PND IIIA	[redacted]	[redacted]	[redacted]	Mix
PND IIIB	[redacted]	[redacted]	[redacted]	Mix
PND IV	[redacted]	[redacted]	[redacted]	Mix
Per-cycle costs (£), cardiomyopathy-related				
NT-proBNP<3000	[redacted]	[redacted]	[redacted]	Mix
NT-proBNP≥3000 pg/mL	[redacted]	[redacted]	[redacted]	Mix
One-off costs (£)				
PND 0	[redacted]	[redacted]	[redacted]	Mix
PND I	[redacted]	[redacted]	[redacted]	Mix
PND II	[redacted]	[redacted]	[redacted]	Mix
PND IIIA	[redacted]	[redacted]	[redacted]	Mix
PND IIIB	[redacted]	[redacted]	[redacted]	Mix
PND IV	[redacted]	[redacted]	[redacted]	Mix
Reduction of HCRU with patisiran				
Polyneuropathy-related	[redacted]	[redacted]	[redacted]	Mix
Cardiomyopathy-related	[redacted]	[redacted]	[redacted]	Mix

Variable	Base-case value	Lower value	Upper value	PSA Distribution
Cost of AEs				
Serious AE unit costs (£)				
Diarrhoea	916.80	737.11	1,096.50	Gamma
Cardiac failure	508.72	409.01	608.43	Gamma
Cardiac failure congestive	553.58	445.08	662.08	Gamma
Orthostatic hypotension	617.11	496.16	738.07	Gamma
Pneumonia	819.09	658.54	979.63	Gamma
Atrioventricular block complete	502.83	404.27	601.38	Gamma
Acute kidney injury	978.32	786.57	1,170.07	Gamma
Dehydration	727.25	584.71	869.80	Gamma
Vomiting	916.80	737.11	1,096.50	Gamma
Urinary tract infection	1,123.22	903.07	1,343.37	Gamma
Constipation	916.80	737.11	1,096.50	Gamma
Hyponatremia	727.25	584.71	869.80	Gamma
Pneumonia aspiration	819.09	658.54	979.63	Gamma
End-of-life cost				
EOL, % being treated in hospital	51.5%	41.4%	61.4%	Beta
EOL hospital days	21.50	17.29	25.71	Gamma
Cost of palliative care in hospital (£ per day)	463.77	372.87	554.66	Gamma
EOL, % being treated in hospice	23.1%	18.7%	27.8%	Beta
EOL hospice days	17.40	13.99	20.81	Gamma
Cost of community palliative care per day (£)	158.23	127.21	189.24	Gamma

AE: adverse event; BSC: best supportive care; EOL: end-of-life; HCRU: healthcare resource use; HR: hazard ratio; HRQoL: health-related quality of life; IV: intravenous; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability; RR: risk ratio.

Table D19. Scenario analyses considered in the CEA

Scenario	Base-case analysis	Changes to the model inputs or assumptions
Scenario 1A	Patients from APOLLO with missing data for PND score and/or NT-proBNP level at baseline or at 18 months were not imputed when deriving transition probabilities for the CE model.	Conservative: These patients were considered to have progressed to the next (worse) health state in the patisiran arm and improved to the previous (better) health state in the placebo arm.
Scenario 1B		Optimistic: These patients were considered to have improved to the previous (better) health state in the patisiran arm and progressed to the next (worse) health state in the placebo arm.
Scenario 2	Utilities were capped at the 25th and 75th percentile of the maximum values recorded in APOLLO and could not exceed the equivalent utility (by age and sex) of the general UK population.	No limit to the calculation of utilities by regression formula was considered.
Scenario 3	The log-normal function was selected based on goodness of fit statistics.	The exponential function was selected as the parametric function for ToT with patisiran.
Scenario 4	Mortality from PND score based on data reported by Suhr et al. 1994[134] and by NT-proBNP level as determined from Gillmore et al. 2017[7] were used in the model.	100% of mortality in the model was linked to cardiomyopathy (as measured by NT-proBNP levels).

PND: polyneuropathy disability; NT-proBNP: N-terminal pro b-type natriuretic peptide; ToT: time on treatment.

12.4.4 Parameters omitted from sensitivity analyses

No parameters or variables listed in Table D18 were omitted from the sensitivity analyses.

12.5 **Results of economic analysis**

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life-years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life-years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 Base-case incremental cost-effectiveness analysis

The ICER results for patisiran compared with BSC in terms of LYG and QALYs from the NHS/PSS direct medical perspective, are presented in Table D20. Patisiran compared with BSC yields an undiscounted incremental cost-effectiveness of [redacted]/LYG and an incremental cost-utility of [redacted]/QALY. The discounted ICER is [redacted]/LYG and [redacted]/QALY. [redacted].

Table D20. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Patisiran	[redacted]	15.78	9.86	[redacted]	7.41	9.73	[redacted]
BSC	[redacted]	8.37	0.13				
Discounted (1.5% for benefits, 3.5% for costs)							
Patisiran	[redacted]	13.73	8.52	[redacted]	5.95	8.30	[redacted]
BSC	[redacted]	7.78	0.22				

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year.

12.5.2 Comparison of outcomes from decision problem to clinically important outcomes from the clinical trials

Table D21 reports the APOLLO RCT results at 18 months and 18-month values predicted by the model for the outcomes considered in the CEA. In general, the model estimates were comparable to the trial results, and any discrepancies are too minor to invalidate the overall conclusions of the CEA.

Table D21. Summary of model results compared with clinical data

	Results at 18 months		
Outcome	APOLLO RCT	Model estimate	Difference (model - APOLLO)*
Patisiran PND 0	0.7%	1.7%	0.9%
Patisiran PND I	24.1%	24.5%	0.4%
Patisiran PND II	25.5%	26.1%	0.5%
Patisiran PND IIIA	24.1%	24.4%	0.3%
Patisiran PND IIIB	19.0%	17.6%	-1.3%
Patisiran PND VI	6.6%	5.7%	-0.8%
BSC PND 0	0.0%	2.9%	2.9%
BSC PND I	15.4%	16.9%	1.5%
BSC PND II	19.2%	18.7%	-0.6%
BSC PND IIIA	15.4%	16.9%	1.5%
BSC PND IIIB	34.6%	29.7%	-4.9%
BSC PND VI	15.4%	14.9%	-0.4%
Patisiran NT-proBNP <3000 pg/mL	90.5%	87.2%	-3.3%
Patisiran NT-proBNP ≥3000 pg/mL	9.5%	12.8%	3.3%
BSC NT-proBNP <3000 pg/mL	78.8%	76.0%	-2.8%
BSC NT-proBNP ≥3000 pg/mL	21.2%	24.0%	2.8%
Patisiran death rate†	4.7%	2.6%	-2.2%
BSC death rate†	7.8%	3.0%	-4.8%
Patisiran AE rate‡	17.6%	17.5%	0.0%
BSC AE rate‡	40.3%	40.2%	-0.1%

AE: adverse event; BSC: best supportive care; NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability; RCT: randomised controlled trial.

*Due to rounding, numbers in this column may not be identical to the differences that would be calculated using the values tabulated in the two columns to the left.

†Mortality is based on the natural history literature

‡Serious AEs ≥2% in any Treatment Group

Sources: Alnylam data on file [APOLLO ALN-TTR02-OO4 CSR]);[10] Suhr et al. 1994;[134] Gillmore et al. 2017[7]

PND score was used in the model to define health states related to polyneuropathy including neurological impairment. As shown in Table D21, the distribution of patients by PND score projected by the model at 18 months was generally similar to that observed in APOLLO. The largest discrepancy was the proportion of BSC patients with the severe score of PND IIIB, which the model underestimated by 4.9%; in contrast,

the percentage of patisiran patients in PND IIIB was underestimated by only 1.3%. There was a slight overestimate by the model of the number of patients improving to PND 0, which also disproportionately favoured patients in the BSC arm vs the patisiran arm (model overestimate: 2.9% vs 0.9%, respectively) even though no patients in APOLLO receiving placebo experienced this improvement. This is also not expected to be a plausible improvement for patients on BSC in real-world practice since, unlike patisiran, BSC is not disease-modifying therapy.

For the index of cardiomyopathy, NT-proBNP level, the model slightly overestimated the proportion of patients in the more severe category (≥3000 pg/mL), by 3.3% for BSC and 2.8% for patisiran. Model predictions were even closer to the APOLLO data for the rate of SAEs in both treatment arms.

As mentioned above, the mortality functions used in the model were based on data derived from the natural history literature due to the low number of deaths reported in the APOLLO trial. Despite this difference in sources, there was relatively close agreement between the 18-month mortality predicted by the model and that seen in APOLLO. The model results underestimated mortality by only 2.2% for the patisiran group and by 4.8% for the BSC group. This larger underestimate of mortality for the BSC arm indicates the model may have underestimated the survival benefit of patisiran vs BSC (i.e., was conservative towards patisiran). Further validation of the mortality estimates from the model is provided in Section 12.7.1, including an explanation that the model projects long-term mortality increases, which may compensate for the underestimate at 18 months.

12.5.3 Proportion of the cohort in the health state over time

The Markov traces showing the proportion of the cohort in each health state over time are presented in Figure 29 for the patisiran arm and in Figure 30 for the BSC arm. Table D22 and Table D23 summarise the proportion of the patient cohort across all health states over time for the patisiran arm and BSC arm, respectively.

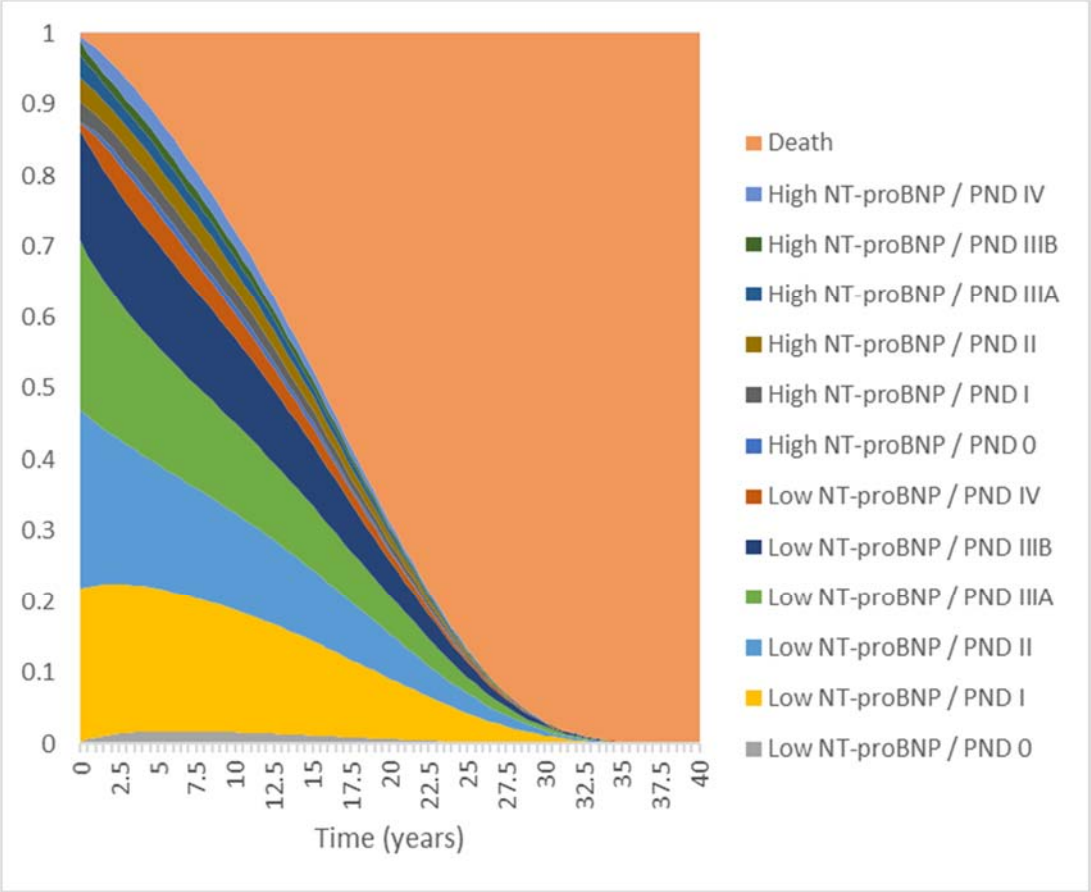


Figure 29. Proportion of the patient cohort across all health states over time (Markov trace) for the patisiran arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; PND: polyneuropathy disability.

Table D22. Proportion of the patient cohort across all health states over time, patisiran arm

		Low NT-proBNP						High NT-proBNP					
Years	Death	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
0	0.00740	0.00000	0.21696	0.25570	0.24366	0.15084	0.00379	0.00000	0.03033	0.03574	0.03400	0.02105	0.00052
0.5	0.01628	0.00426	0.21502	0.24288	0.23114	0.15413	0.01653	0.00190	0.02715	0.03300	0.02941	0.01697	0.01133
1	0.02560	0.00773	0.21345	0.23177	0.22046	0.15544	0.02546	0.00384	0.02544	0.03128	0.02641	0.01527	0.01787
1.5	0.03633	0.01049	0.21192	0.22191	0.21097	0.15550	0.03152	0.00560	0.02459	0.03022	0.02443	0.01475	0.02176
2	0.04723	0.01263	0.21048	0.21325	0.20262	0.15493	0.03565	0.00709	0.02430	0.02967	0.02319	0.01479	0.02418
2.5	0.05913	0.01425	0.20895	0.20547	0.19503	0.15385	0.03829	0.00831	0.02429	0.02941	0.02241	0.01504	0.02558
3	0.07104	0.01547	0.20740	0.19853	0.18820	0.15253	0.04000	0.00926	0.02443	0.02938	0.02195	0.01534	0.02647
3.5	0.08402	0.01636	0.20567	0.19217	0.18185	0.15090	0.04091	0.00999	0.02461	0.02943	0.02165	0.01559	0.02684
4	0.09692	0.01699	0.20388	0.18643	0.17606	0.14914	0.04139	0.01052	0.02480	0.02956	0.02148	0.01578	0.02705
4.5	0.11103	0.01741	0.20186	0.18104	0.17055	0.14711	0.04140	0.01089	0.02491	0.02966	0.02134	0.01587	0.02692
5	0.12499	0.01767	0.19977	0.17608	0.16547	0.14500	0.04123	0.01114	0.02499	0.02976	0.02123	0.01591	0.02676
6	0.15480	0.01782	0.19510	0.16697	0.15603	0.14029	0.04027	0.01133	0.02491	0.02978	0.02095	0.01575	0.02601
7	0.18570	0.01764	0.18996	0.15874	0.14749	0.13519	0.03891	0.01125	0.02457	0.02955	0.02056	0.01540	0.02504
8	0.21786	0.01726	0.18434	0.15108	0.13958	0.12975	0.03728	0.01100	0.02401	0.02906	0.02002	0.01490	0.02386
9	0.25096	0.01673	0.17833	0.14381	0.13214	0.12409	0.03551	0.01063	0.02326	0.02832	0.01935	0.01431	0.02257
10	0.28614	0.01608	0.17176	0.13665	0.12487	0.11808	0.03349	0.01015	0.02233	0.02731	0.01849	0.01362	0.02102
15	0.48384	0.01175	0.13203	0.10009	0.08900	0.08459	0.02209	0.00697	0.01595	0.01944	0.01258	0.00931	0.01238
20	0.69601	0.00681	0.08453	0.06141	0.05273	0.04898	0.01100	0.00358	0.00876	0.01015	0.00617	0.00484	0.00504
25	0.87295	0.00278	0.03970	0.02730	0.02206	0.01962	0.00336	0.00117	0.00320	0.00331	0.00183	0.00161	0.00111
30	0.97072	0.00063	0.01065	0.00676	0.00488	0.00404	0.00046	0.00018	0.00059	0.00049	0.00024	0.00025	0.00010
35	0.99729	0.00006	0.00117	0.00066	0.00040	0.00030	0.00002	0.00001	0.00004	0.00002	0.00001	0.00001	0.00000
40	0.99993	0.00000	0.00004	0.00002	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

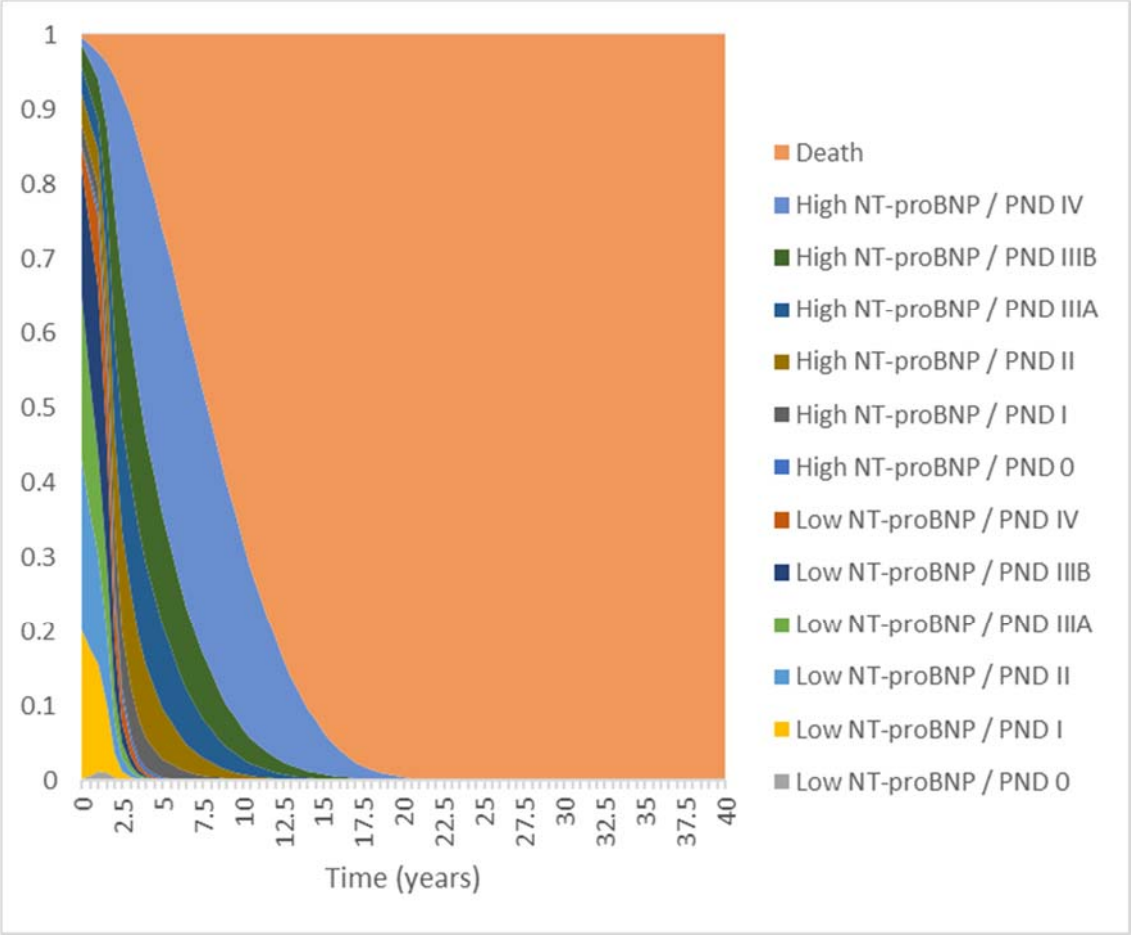


Figure 30. Proportion of the patient cohort across all health states over time for BSC arm

BSC: best supportive care; PND: polyneuropathy disability

Table D23. Proportion of the patient cohort across all health states over time, BSC arm

		Low NT-proBNP						High NT-proBNP					
Years	Death	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
0	0.00740	0.00000	0.21696	0.25570	0.24366	0.15084	0.00379	0.00000	0.03033	0.03574	0.03400	0.02105	0.00052
0.5	0.01772	0.00401	0.18092	0.19829	0.18924	0.19524	0.04766	0.00398	0.02767	0.04247	0.03760	0.03816	0.01705
1	0.02958	0.00903	0.15393	0.15842	0.15025	0.21775	0.07984	0.00896	0.02758	0.04638	0.03926	0.05010	0.02893
1.5	0.04402	0.01413	0.13366	0.13058	0.12238	0.22654	0.10179	0.01398	0.02864	0.04904	0.03990	0.05825	0.03709
2	0.06571	0.00482	0.04726	0.05997	0.05670	0.09124	0.07068	0.01593	0.07971	0.11321	0.10740	0.15881	0.12856
2.5	0.09412	0.00165	0.01668	0.02590	0.02619	0.03757	0.04154	0.01365	0.08208	0.13332	0.13713	0.18660	0.20357
3	0.12548	0.00056	0.00588	0.01076	0.01189	0.01580	0.02262	0.01070	0.07067	0.13107	0.14725	0.18899	0.25833
3.5	0.16164	0.00019	0.00207	0.00434	0.00528	0.00674	0.01176	0.00809	0.05701	0.11893	0.14615	0.18236	0.29544
4	0.19877	0.00007	0.00073	0.00172	0.00229	0.00290	0.00595	0.00602	0.04476	0.10356	0.13889	0.17279	0.32156
4.5	0.24016	0.00002	0.00026	0.00067	0.00098	0.00125	0.00294	0.00445	0.03463	0.08785	0.12796	0.16170	0.33715
5	0.28135	0.00001	0.00009	0.00026	0.00041	0.00054	0.00143	0.00327	0.02662	0.07333	0.11545	0.15009	0.34715
6	0.36873	0.00000	0.00001	0.00004	0.00007	0.00010	0.00033	0.00176	0.01551	0.04932	0.08935	0.12559	0.34921
7	0.45616	0.00000	0.00000	0.00001	0.00001	0.00002	0.00007	0.00094	0.00894	0.03211	0.06577	0.10115	0.33483
8	0.54160	0.00000	0.00000	0.00000	0.00000	0.00000	0.00002	0.00050	0.00510	0.02039	0.04653	0.07840	0.30746
9	0.62188	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00027	0.00289	0.01269	0.03187	0.05864	0.27176
10	0.69755	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00014	0.00162	0.00775	0.02117	0.04234	0.22943
15	0.94196	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00008	0.00051	0.00191	0.00533	0.05021
20	0.99690	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00002	0.00010	0.00034	0.00264
25	0.99997	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00002
30	1.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
40	1.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

12.5.4 QALYs accrued over time

The undiscounted and discounted QALYs accrued over time are summarised in Figure 31 to Figure 38.

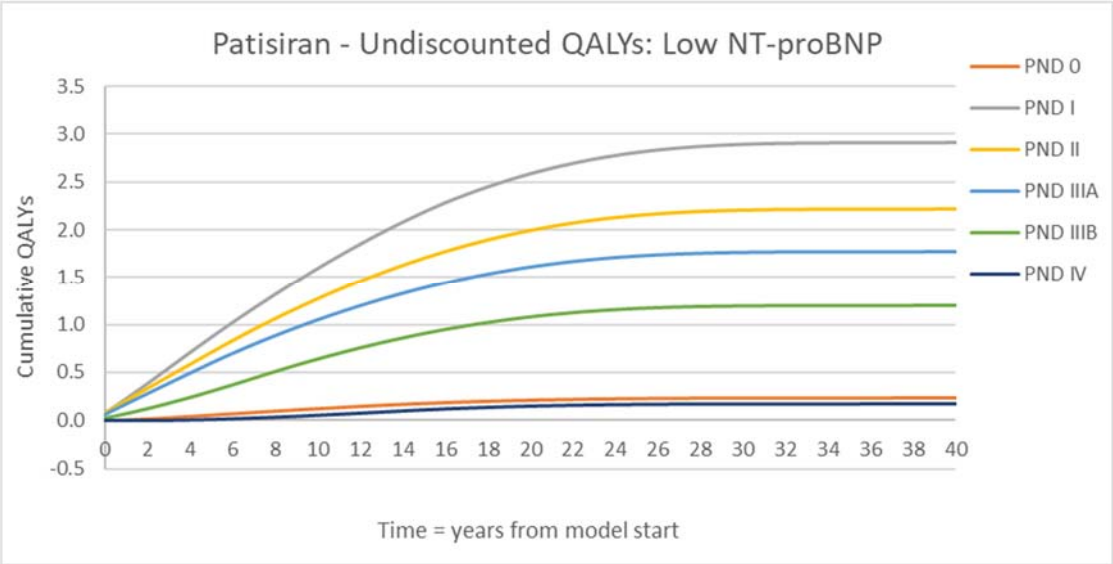


Figure 31. Undiscounted QALYs for low NT-proBNP over time in the patisiran arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

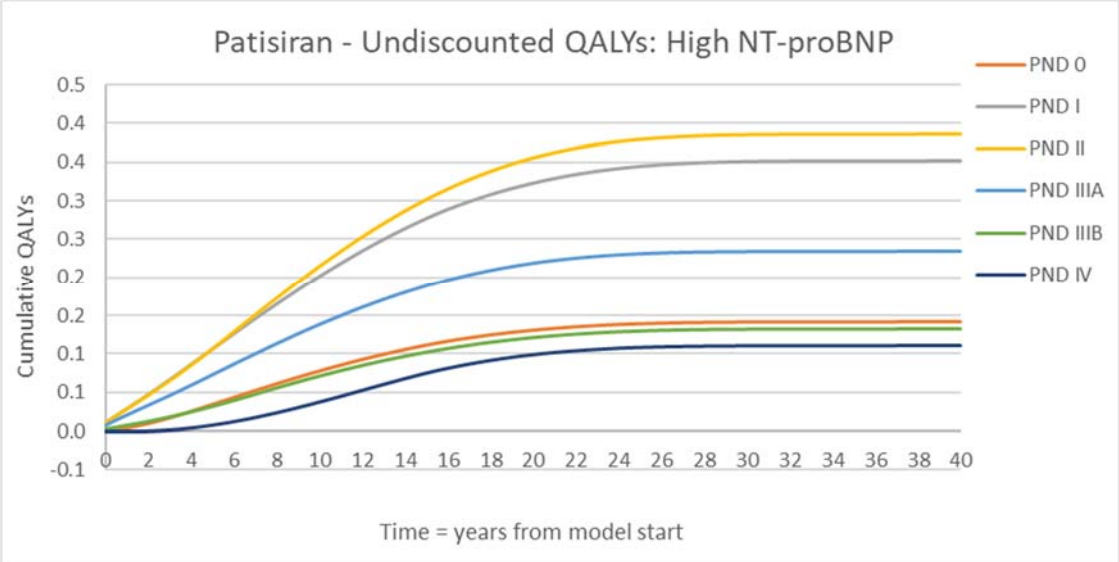


Figure 32. Undiscounted QALYs for high NT-proBNP over time in the patisiran arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

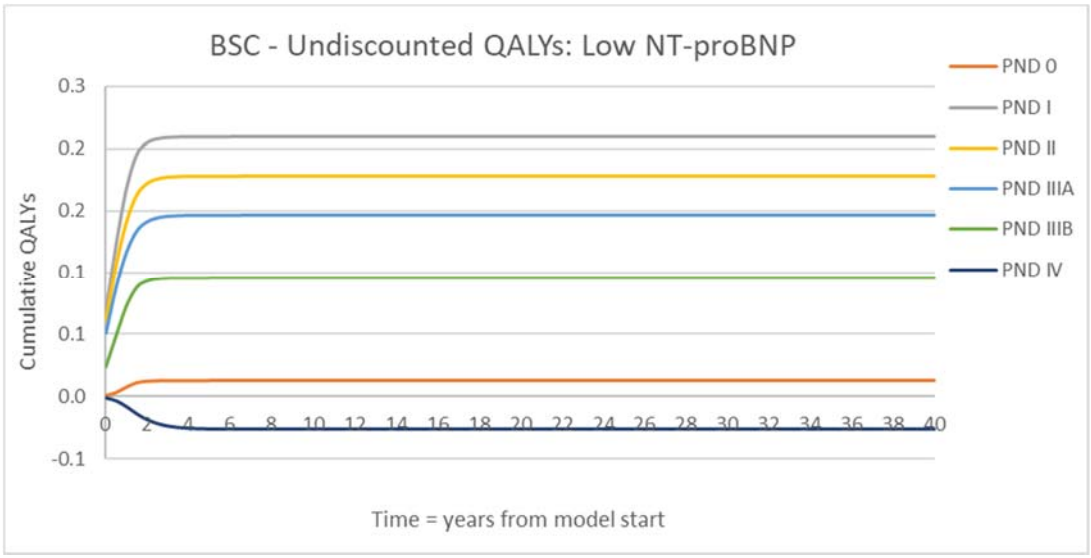


Figure 33. Undiscounted QALYs for low NT-proBNP over time in the BSC arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

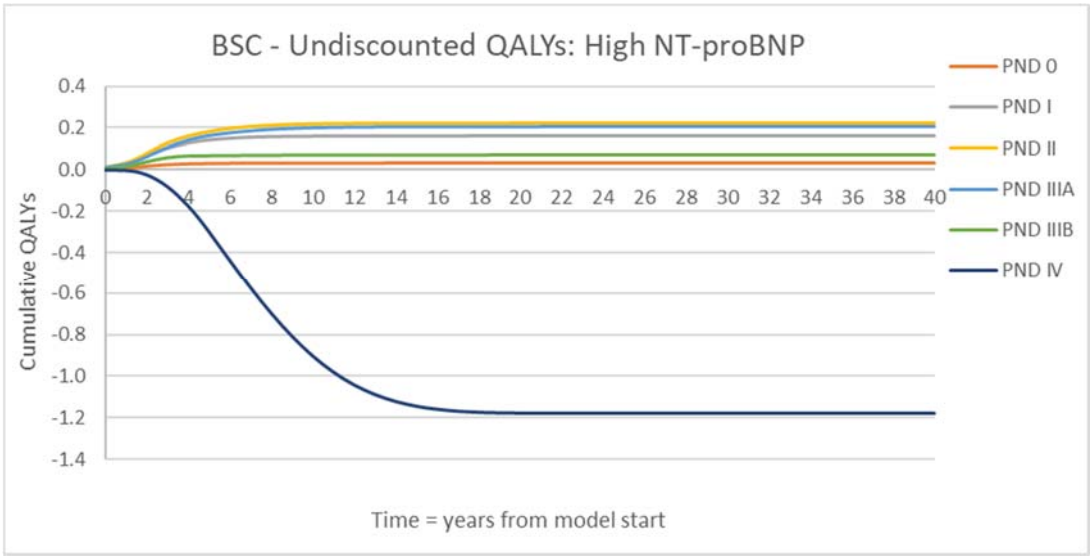


Figure 34. Undiscounted QALYs for high NT-proBNP over time in the BSC arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

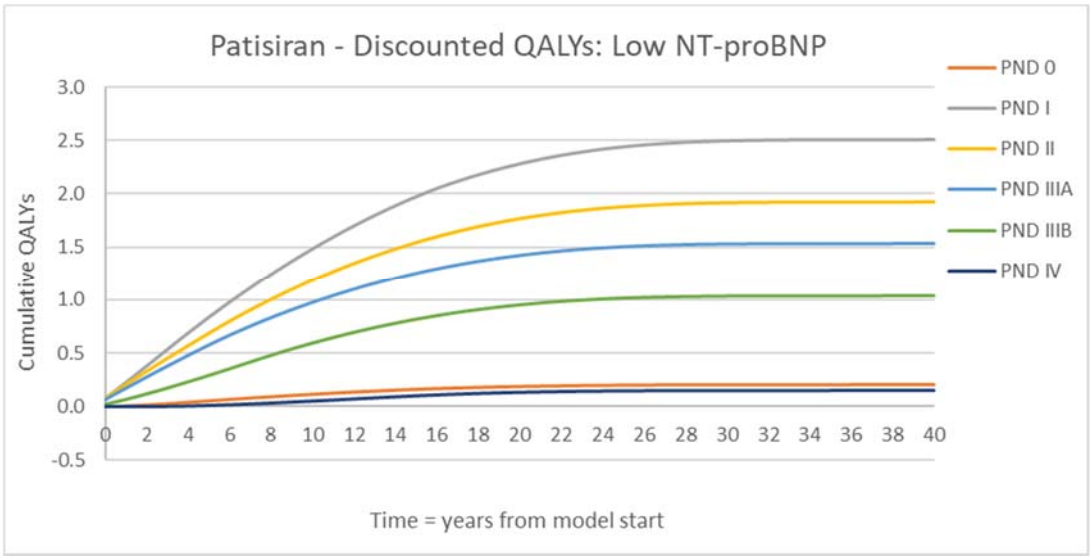


Figure 35. Discounted QALYs for low NT-proBNP over time in the patisiran arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

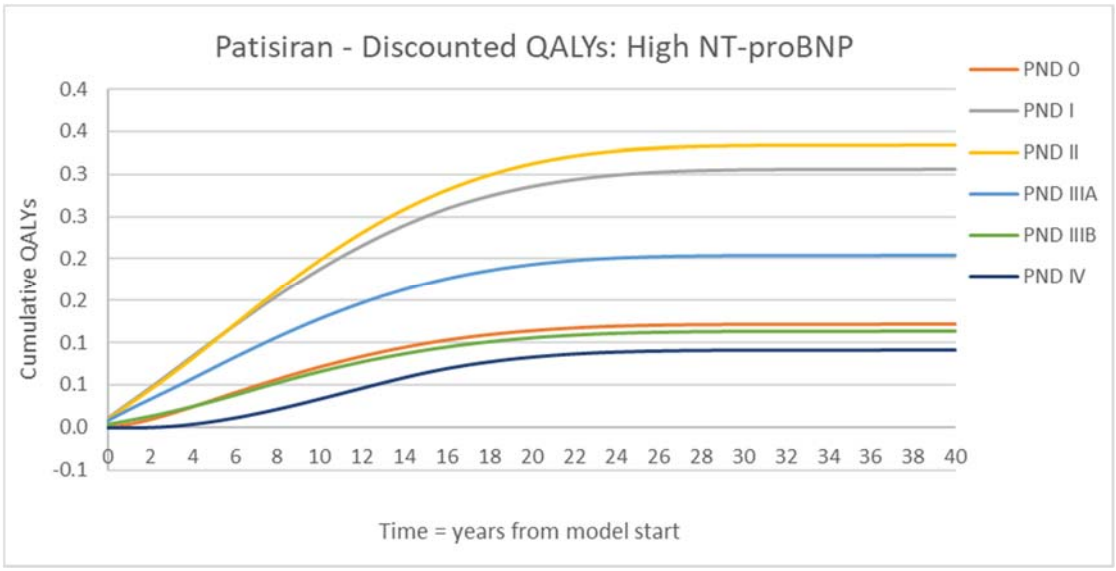


Figure 36. Discounted QALYs for high NT-proBNP over time in the patisiran arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

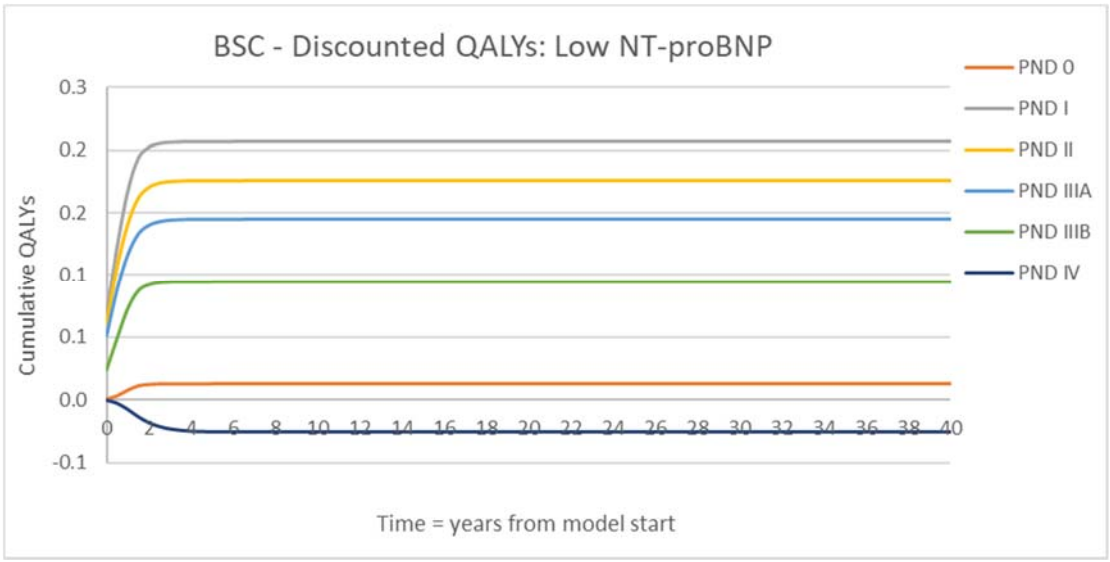


Figure 37. Discounted QALYs for low NT-proBNP over time in the BSC arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

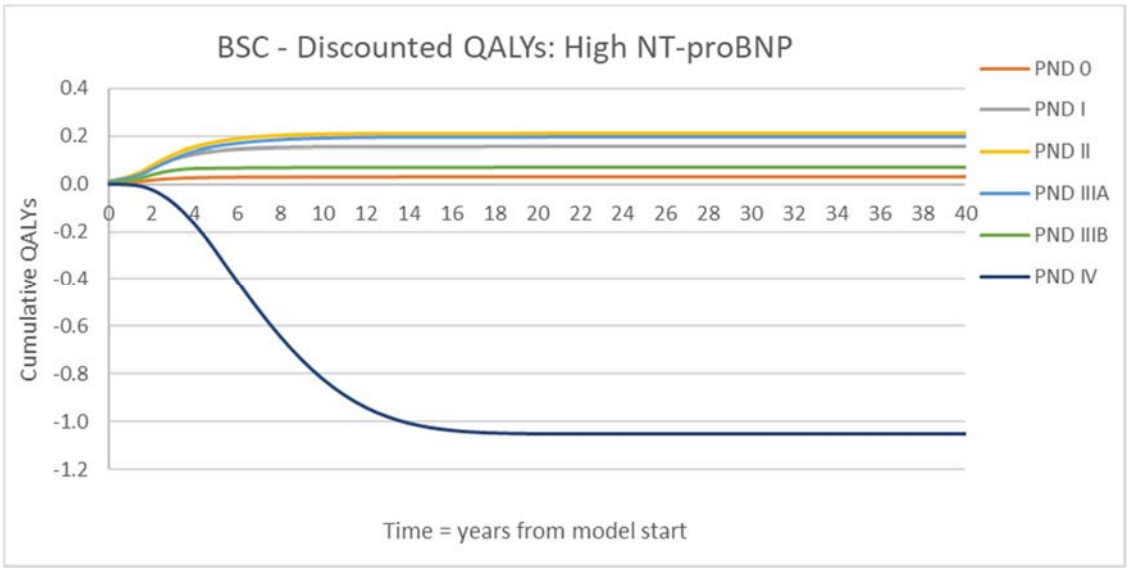


Figure 38. Discounted QALYs for high NT-proBNP over time in the BSC arm

NT-proBNP: N-terminal pro b-type natriuretic peptide; QALY: quality-adjusted life-year.

12.5.5 LYs and QALYs accrued for each clinical outcome listed for each comparator

The summary of undiscounted LYs gained by health state are shown in Table D24. The summary of discounted LYs gained by health state are shown in Table D25. QALYs accrued across health states are shown in Section 12.5.6.

Table D24. Summary of undiscounted LY gain by health state

	Low NT-proBNP						High NT-proBNP						Total
	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	
Patisiran	0.30412	3.81688	3.19307	2.92546	2.55628	0.67757	0.18254	0.46106	0.55135	0.38680	0.28026	0.44087	15.77626
Placebo	0.01736	0.32711	0.36179	0.34677	0.43945	0.20125	0.04975	0.29394	0.61938	0.86581	1.23830	3.60521	8.36612
Incremental	0.28676	3.48977	2.83128	2.57869	2.11683	0.47632	0.13279	0.16712	-0.06803	-0.47901	-0.95804	-3.16434	7.41014

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

Table D25. Summary of discounted LY gain by health state

	Low NT-proBNP						High NT-proBNP						Total
	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	
Patisiran	0.25994	3.28903	2.78951	2.56653	2.22671	0.58770	0.15685	0.40037	0.47992	0.33971	0.24446	0.38512	13.72585
Placebo	0.01707	0.32358	0.35772	0.34278	0.43332	0.19696	0.04787	0.28091	0.58587	0.80857	1.14843	3.23543	7.77851
Incremental	0.24287	2.96545	2.43179	2.22375	1.79339	0.39074	0.10898	0.11946	-0.10595	-0.46886	-0.90397	-2.85031	5.94734

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

12.5.6 Incremental QALYs by health state

The summary of undiscounted and discounted QALY gained by health state are shown in Table D26 and Table D27, respectively. Most of the QALYs gained with patisiran were accrued in the PND I, PND II and PND IIIA in the low NT-proBNP health states for both the discounted and undiscounted QALYs. This demonstrates the value of patisiran in terms of being able to keep patients from progressing to more severe health states with poorer HRQoL and higher risk of death.

Table D26. Summary of undiscounted QALY gain by health state

	Low NT-proBNP						High NT-proBNP						Total
	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	
Patisiran	0.23526	2.91284	2.21226	1.76567	1.20125	0.17571	0.14143	0.35247	0.38592	0.23434	0.13227	0.10996	9.85938
Placebo	0.01307	0.20902	0.17762	0.14617	0.09511	-0.02632	0.03385	0.16225	0.22141	0.20572	0.07389	-1.18057	0.13123
Incremental	0.22219	2.70382	2.03464	1.61949	1.10613	0.20202	0.10758	0.19022	0.16451	0.02862	0.05838	1.29054	9.72815

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

Table D27. Summary of discounted QALY gain by health state

	Low NT-proBNP						High NT-proBNP						Total
	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	
Patisiran	0.20150	2.51074	1.91879	1.53924	1.03136	0.14414	0.12174	0.30608	0.33390	0.20462	0.11379	0.09090	8.51679
Placebo	0.01285	0.20690	0.17580	0.14468	0.09401	-0.02560	0.03266	0.15536	0.21068	0.19478	0.07131	-1.05183	0.22159
Incremental	0.18864	2.30383	1.74299	1.39457	0.93735	0.16974	0.08909	0.15071	0.12322	0.00984	0.04249	1.14273	8.29520

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

12.5.7 Detailed cost per patient

Costs by category of cost per patient are shown in Table D28 and Table D29.

Table D28. Summary of undiscounted costs by category of cost per patient

Item	Patisiran costs (£)	BSC costs (£)	Increment
Technology cost	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]
Premedication	[redacted]	[redacted]	[redacted]
HCRU	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

HCRU: healthcare resource use; PN: polyneuropathy; CM: cardiomyopathy.

Table D29. Summary of discounted costs by category of cost per patient

Item	Patisiran costs (£)	BSC costs (£)	Increment
Technology cost	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]
Premedication	[redacted]	[redacted]	[redacted]
HCRU	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

HCRU: healthcare resource use; PN: polyneuropathy; CM: cardiomyopathy.

12.5.8 Costs by health state

The detailed costs by health state for patisiran and BSC are outlined in Table D30.

Table D30. Summary of costs by health state per patient

Health state	Patisiran costs (£)	BSC costs (£)	Increment
Low NT-proBNP			
PND 0	[redacted]	[redacted]	[redacted]
PND I	[redacted]	[redacted]	[redacted]
PND II	[redacted]	[redacted]	[redacted]
PND IIIA	[redacted]	[redacted]	[redacted]
PND IIIB	[redacted]	[redacted]	[redacted]
PND IV	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
High NT-proBNP			
PND 0	[redacted]	[redacted]	[redacted]
PND I	[redacted]	[redacted]	[redacted]
PND II	[redacted]	[redacted]	[redacted]
PND IIIA	[redacted]	[redacted]	[redacted]
PND IIIB	[redacted]	[redacted]	[redacted]
PND IV	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

PND: polyneuropathy disability score; NT-proBNP: N-terminal pro b-type natriuretic peptide.

12.5.9 Costs by AE

The summary of costs by AE is not applicable.

12.5.10 Sensitivity and scenario analysis results

The results of the deterministic one-way sensitivity analysis are summarised in Figure 39 which shows a tornado diagram highlighting the top 15 variables influencing cost-effectiveness in the comparison of patisiran to BSC. Figure 40 and Figure 41 show the PSA and cost-effectiveness acceptability curve, respectively. The results of the scenario analyses are summarised in Table D31 to Table D35.

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Figure 39. Results of the deterministic sensitivity analysis

CM: cardiomyopathy; HCRU: health-care resource use; HR: hazard ratio; NT-proBNP: N-terminal pro b-type natriuretic peptide; PN: polyneuropathy; PND: polyneuropathy disability.

Figure 40. Results of the 1000 simulations in the PSA for the ICER of patisiran vs BSC

ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

Figure 41. CE acceptability curve

CE: cost-effectiveness; WTP: willingness-to-pay; QALY: quality-adjusted life-year.

Table D31. Results of the analysis with conservative imputation of the missing data from the transition shift tables (Scenario 1A)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]				
Discounted (1.5% for benefits, 3.5% for costs)							
Patisiran	[redacted]	13.05	7.87	[redacted]	4.97	7.36	[redacted]
BSC	[redacted]	8.08	0.51				

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year.

Scenario 1A: Patients from APOLLO with missing data for PND score and/or NT-proBNP level at baseline or 18 months in the patisiran group were considered to have progressed to the next (worse) health state and those with similar missing data from the placebo group were considered to have improved to the previous (better) health state per

Table D19.

Table D32. Results of the analysis with optimistic imputation of the missing data from the transition shift tables (Scenario 1B)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Patisiran	[redacted]	16.47	10.55	[redacted]	8.27	10.51	[redacted]
BSC	[redacted]	8.20	0.04				
Discounted (1.5% for benefits, 3.5% for costs)							
Patisiran	[redacted]	14.26	9.07	[redacted]	6.63	8.94	[redacted]
BSC	[redacted]	7.63	0.14				

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year.

Scenario 1B: Patients from APOLLO with missing data for PND score and/or NT-proBNP level at baseline or 18 months in the patisiran group were considered to have improved to the previous (better) health state and those with similar missing data from the placebo group were considered to have progressed to the next (worse) health state per

Table D19.

Table D33. Results from analysis with no constraint on utilities (Scenario 2)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Patisiran	[redacted]	15.78	11.95	[redacted]	7.41	12.58	[redacted]
BSC	[redacted]	8.37	-0.63				
Discounted (1.5% for benefits, 3.5% for costs)							
Patisiran	[redacted]	13.73	10.18	[redacted]	5.95	10.61	[redacted]
BSC	[redacted]	7.78	-0.43				

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year.

Scenario 2: No limit to the calculation of utilities by regression formula was considered per

Table D19.

Table D34. Results from analysis using the exponential function for the ToT with patisiran (Scenario 3)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Patisiran	[redacted]	15.78	9.86	[redacted]	7.41	9.73	[redacted]
BSC	[redacted]	8.37	0.13				
Discounted (1.5% for benefits, 3.5% for costs)							
Patisiran	[redacted]	13.73	8.52	[redacted]	5.95	8.30	[redacted]
BSC	[redacted]	7.78	0.22				

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year; ToT: time on treatment.

Scenario 3: The exponential function was selected as the parametric function for ToT with patisiran per

Table D19.

Table D35. Results from analysis attributing no mortality by PND score (Scenario 4)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Patisiran	[redacted]	18.14	11.30	[redacted]	3.61	13.35	[redacted]
BSC	[redacted]	14.53	-2.05				
Discounted (1.5% for benefits, 3.5% for costs)							
Patisiran	[redacted]	15.54	9.62	[redacted]	2.75	11.17	[redacted]
BSC	[redacted]	12.79	-1.55				

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; PND: polyneuropathy disability; QALY: quality-adjusted life-year.

Scenario 4: 100% of mortality in the model was linked to cardiomyopathy symptoms per

Table D19.

12.5.11 What were the main findings of each of the sensitivity analyses?

Deterministic one-way sensitivity analysis

The model results were most sensitive to the discount rate for outcomes and discount rate for costs, followed by ToT with patisiran.

Probabilistic sensitivity analysis

Most simulations were generally consistent with the base-case ICER.

Scenario analyses

The results of Scenario 1A and 1B show that even considering the extreme cases for APOLLO participants with missing PND scores and/or NT-proBNP levels at baseline or at 18 months, the imputation of missing data did not greatly affect the results of the CEA compared with the base-case analysis (discounted ICER of [redacted]/QALY). Predictably, the ICER was lower for the optimistic scenario analysis [redacted]/QALY) and higher for the conservative scenario analysis ([redacted]/QALY).

In Scenario 2, the removal of the constraint on utilities used in the base case led to lower ICER results ([redacted]/QALY). The cap on utilities was retained in the base case as a conservative approach.

In Scenario 3, the choice of the exponential function for the ToT with patisiran reduced the ICER to [redacted]/QALY. The selection of the log-normal function in the base-case analysis was retained, since not only was it the best-fit function but it also had a conservative effect on the ICER as compared to the scenario analysis using the exponential function.

In Scenario 4, attributing all mortality in the model to cardiomyopathy as measured by NT-proBNP levels (i.e., assuming no mortality was attributable to polyneuropathy as measured by PND score) was shown to reduce the ICER in comparison to the base case ([redacted]/QALY vs [redacted]/QALY). The base-case analysis considering both mortality as measured by PND score and NT-proBNP levels was retained as a conservative approach compared to this scenario analysis.

12.5.12 What are the key drivers of the cost results?

The healthcare components that accrue most of the incremental costs for patisiran vs BSC were technology and administration costs. The health states that accrue most of the incremental costs for patisiran vs BSC were PND I and PND II in the low NT-proBNP state.

12.5.13 Miscellaneous results

All relevant results have been presented in the previous sections as part of the template.

12.6 **Subgroup analysis**

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Subgroup analysis

In line with the scope, no subgroup analyses were undertaken.

12.7 **Validation**

12.7.1 Validation and quality-assurance process

<u>Design of the model</u>

All stages of model design, including the main assumptions and data sources were reviewed and discussed by a group of expert UK health economic consultants (BresMed Health Solutions Ltd., Sheffield, UK).

hATTR amyloidosis is an ultra-rare disease and published UK-specific HCRU data were not available. The structured Delphi methodology was used to elicit HCRU estimates from clinical experts and to test assumptions relating to direct costs. The Delphi panel methodology and results were described in Section 10.1.10.

Model QC

The accuracy of the calculation performed in the CE model was checked in a number of ways. First, the interim and final results produced by the model were compared with the input data for clinical and economic plausibility. Second, random checks were made on specific elements of the calculation. Finally, the entire model was reviewed during model development and after completion by senior health economic consultants who were not previously involved in the project and whose comments and suggestions were incorporated into the model. The model was reviewed following an internal checklist and then cell by cell to validate the model both internally and externally.

The validation of the model included a comparison of its mortality predictions with the mortality observed in the pivotal RCT APOLLO. This analysis showed that the CE model underestimates mortality, in both treatment arms compared to 18-month observed data (Figure 42). In the longer term, there is a sharp increase in mortality that may compensate for the initial underestimate. Notably, the underestimation of mortality at 18 months is greater for BSC/placebo than for patisiran, which implies that the model is conservative towards patisiran—i.e., that it may underestimate the survival benefit of patisiran vs BSC.

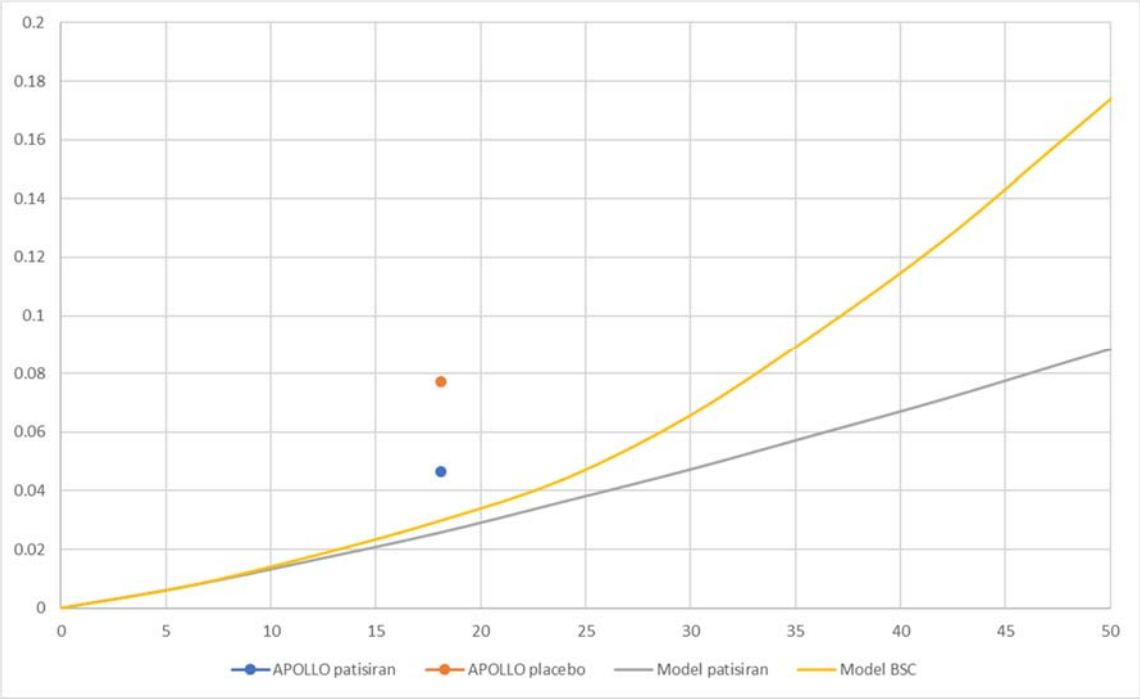

Figure 42. Mortality predicted by the CEA and observed in the APOLLO trial at 18 months

BSC: best supportive care; CEA: cost-effectiveness analysis.

12.8 **Interpretation of economic evidence**

12.8.1 Consistency with published economic literature

There is a scarcity of published data on the cost-effectiveness of treatments for hATTR amyloidosis worldwide. The SLR described in Section 11 did not identify any economic literature for comparison.

The lack of economic literature is likely due to the fact that hATTR amyloidosis is an ultra-rare disease. In the UK, no treatment options other than BSC are available. As BSC treats symptoms and not the disease, it cannot be considered a comparator to a disease-modifying treatment like patisiran.

12.8.2 Relevance to all groups of patients and specialised services in England identified in the scope

The CEA results were based on inputs from the pivotal RCT APOLLO which are highly representative of the UK patient population as identified in the scope. APOLLO is the largest study in hATTR amyloidosis patients to date and included patients with a broad range of genetic mutations including those most relevant to the UK population. Based on the fact that the applied settings and input data were extensively validated by the NAC, which treats all hATTR amyloidosis patients in the UK, the performed CEA is relevant to the patient population in England.

12.8.3 Strengths and weaknesses of the analysis

<u>Strengths</u>

- Data from the pivotal RCT APOLLO or published natural history data highly relevant to the UK were used to inform the model.
- The model inputs and assumptions were validated by the NAC who are the main diagnostic, treatment, and management centre for hATTR amyloidosis patients in the UK.
- The model was validated and quality-assured by a group of independent health-economist consultants

Weaknesses

- A single natural history reference that categorised survival by both PND score and NT-proBNP was not available.

12.8.4 Further analyses to enhance the robustness/completeness of the results

External validity of the model can be enhanced in future by incorporation of real-world data on the effectiveness and safety of patisiran in patients in routine clinical practice in the UK. No such data were available at the time this analysis was conducted.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

- The budget impact analysis did not consider potential cost savings due to decreased resource use and therefore represents a conservative estimate of the budget impact to the NHS
- The analysis did not incorporate VAT savings to the NHS due to the use of homecare infusion services that would be part of the service delivery model for this specialised technology.
- The projected budget impact and patient population for each of the 5 years following introduction of patisiran were [redacted] in Year 1, [redacted] in Year 2, [redacted] in Year 3, [redacted] in Year 4, and [redacted] in Year 5
- The addition of patisiran is likely to decrease resource use in the treatment of hATTR amyloidosis in the UK, including in areas not captured by NHS or PSS costs

13.1 Number of patients eligible for treatment in England over the next 5 years

Based on the number of patients registered at the NAC, there are 150 people in the UK with hATTR amyloidosis.[4,146] As the NAC is the reference centre for this disease in the UK, it is assumed that all patients with hATTR amyloidosis in England are diagnosed there.

The proportion of patients with stage 1 or stage 2 polyneuropathy is assumed to be equal to the proportion of patients who enter the cost-effectiveness model for patisiran

with a PND score of I to IIIB (99.56%). There are therefore 149 patients in the UK with stage 1 or 2 hATTR amyloidosis, of which 75% (112) are from England.[146]

Rowczenio et al. (2017) reported the number of new hATTR amyloidosis diagnoses at the NAC between 2000 and 2016.[21] The incidence of stage 1 or stage 2 hATTR amyloidosis in England in each of the first 5 years after the introduction of patisiran was assumed to be equal to the average UK incidence at the NAC (estimated by adjusting the number of new diagnoses by the proportion of patients who are stage 1 or stage 2 as discussed above) between 2012 and 2016 and multiplied by the proportion of NAC patients from England (75%).[4] This gives an incidence rate of 0.0001% or 0.1/100,000 people.[4,9,21]

According to the patisiran indication, the population eligible for treatment comprises adults with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy, with or without cardiomyopathy; thus, patients with cardiomyopathy in whom polyneuropathy symptoms have not yet manifested would be ineligible. Of the 149 patients in the UK with hATTR registered at the NAC, 39% (58) are Val122Ile mutation-positive, which results in patients presenting with primary cardiomyopathy.[21,58] According to an expert at the NAC, approximately 10% (6/58) of Val122Ile mutation-positive patients would also have polyneuropathy and thus be candidates for patisiran.[4] Considering the 91 UK patients with non-Val122Ile mutations associated with polyneuropathy plus the 6 Val122Ile patients with both cardiomyopathy and polyneuropathy, 65% (97/150) of all existing hATTR amyloidosis patients at the NAC would be eligible for treatment. This percentage was multiplied by the number of patients residing in England to estimate the number of prevalent hATTR amyloidosis patients in England eligible for treatment with patisiran. The number of patients eligible for treatment in year 1 of the budget impact analysis (BIA) is equal to the sum of the 2018 prevalent and eligible population (73) and the 2019 incident population (27), totalling 100 patients in Year 1. Figure 43 shows the hATTR amyloidosis patient population eligible to receive treatment with patisiran in Year 1.

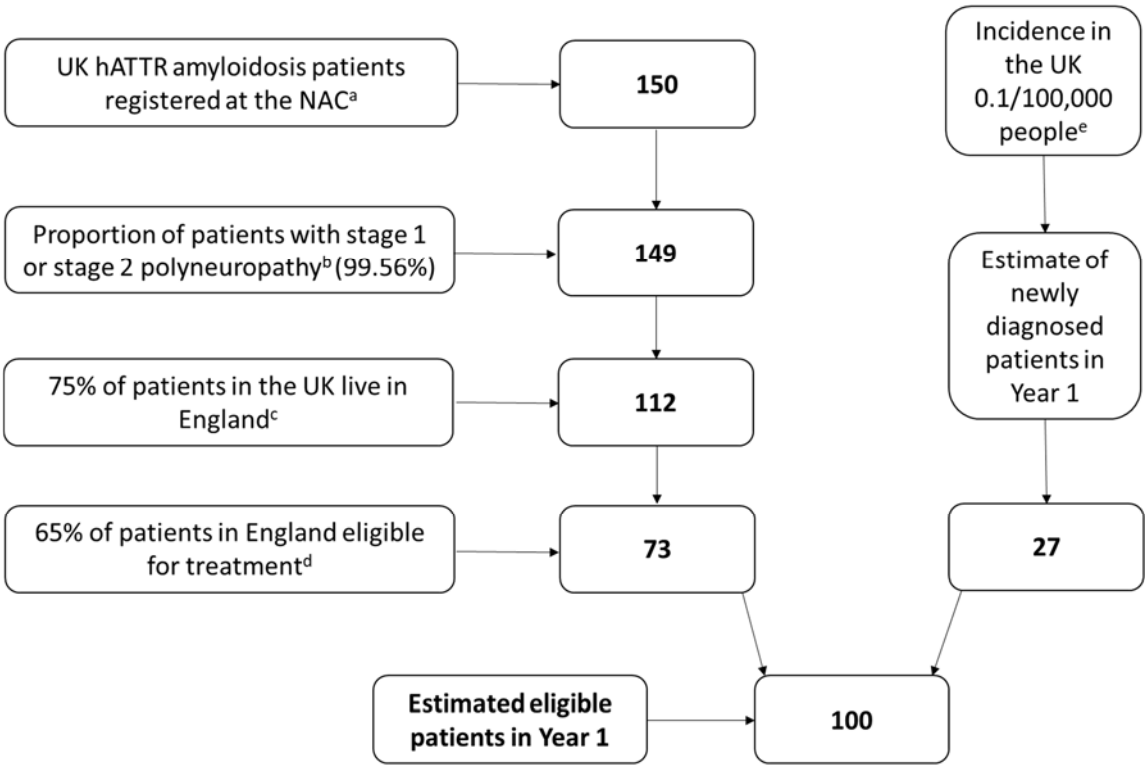

Figure 43. Eligible population of hATTR amyloidosis patients in England

[a]Prevalent patients registered at the NAC[4]

[b]Assumed to be equal to the proportion of patients who enter the CE model for patisiran with a PND score of I to IIIB (99.56%)

[c]75% of the patient population registered at the NAC are from England.[146]

[d]Based on the proportion of all 150 UK hATTR amyloidosis patients who present with polyneuropathy (non-Val122Ile: 91) or primary cardiomyopathy with polyneuropathy (estimated 10% of Val122Ile: 10%×59=6); i.e., [91+6]/150 = 65%.[4]

[e]The incidence of hATTR amyloidosis in England in each of the first 5 years after the introduction of patisiran was assumed to be equal to the proportion of NAC patients with stage 1 or stage 2 polyneuropathy (equal to the proportion of patients who enter the CE model with a PND score of I to IIIB [99.56%]) from England (75%) multiplied by the average UK incidence of diagnoses at the NAC between 2012 and 2016 as reported in Rowczenio et al. 2017[21]

Additional sources: ONS Table A1-4, Principal projection-England summary, 2017;[9] ONS United Kingdom population mid-year estimate 2017.[74]

Survival estimates for patisiran with and without established clinical management are incorporated into calculations of eligible patient numbers in accordance with the base-case CEA presented in Section 12.2.6. Five-year survival is predicted to be 92% for patients treated with patisiran and 84% for patients not treated with patisiran.

The total number of patients eligible for treatment with patisiran over 5 years is presented in Table D36.

Table D36. Eligible patients per year in England

	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients	100	125	148	169	187

13.2 Expected uptake of the technology over the next five years

Table D37 summarises the estimated uptake and market share of patisiran over the first 5 years after introduction based on the latest company market research.

Table D37. Estimated market share for patisiran over 5 years

Technology	Current practice	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population		100	125	148	169	187
Established clinical management with patisiran	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Established clinical management without patisiran	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.3 Other significant costs associated with treatment

The BIA considers the pre-medication, treatment acquisition, and administration costs associated with the introduction of patisiran within its licensed terms. These costs are consistent with those used in the base-case CEA reported in Section 12.3. The 5-year projections for these cost components are shown in Table D38.

Table D38. Treatment, administration, and pre-medication costs

Category	Year				
Patisiran	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-medication costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Established clinical management	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-medication costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.4 Estimates of resource savings

Patisiran is expected to yield savings with respect to the management of AEs and HCRU. Patisiran delays disease progression, which results in a larger number of patients with lower PND scores and lower NT-pro-BNP levels. As such, the NHS will

benefit from a disinvestment in resources and symptomatic treatments associated with polyneuropathy and cardiomyopathy in hATTR amyloidosis patients. Estimates of the costs associated with these resources over the 5-year time horizon are shown in Table D39.

Table D39. Resource costs

Category	Year				
Patisiran	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
HCRU costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Established clinical management	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
HCRU costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE: adverse effects; EOL: end-of-life; HCRU: healthcare resource utilisation.

13.5 Additional opportunities for resource savings

As noted above, opportunities for VAT savings to the NHS due to the provision of homecare infusion services were not considered and could offer opportunities for resource savings. Additionally, several costs outside of those captured by NHS the PSS were not considered.

13.6 Additional costs or savings incurred outside of the NHS and PSS.

No additional costs outside of the NHS and PSS are expected with patisiran. Cost savings for patients and carers are expected with patisiran. The service model proposed (Section 8.4) includes the option for homecare infusions of patisiran for patients who are eligible. This may result in considerable cost savings for patients who live outside London, some of who may even need to travel overnight to receive treatment at the NAC. This is described in previous sections.

13.7 Estimated budget impact for the NHS and PSS over the first year of uptake of the technology

Table D40 and Figure 44 summarise the net annual budget impact for patisiran projected over the next 5 years. The budget impact model is found in Appendix 6.

Table D40. Net budget impact for patisiran by year

	Year 1	Year 2	Year 3	Year 4	Year 5

Eligible population for treatment with patisiran	100	125	148	169	187
Population expected to receive patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway with patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 44. Annual budget impact of introducing patisiran in England

BI: budget impact.

Introducing patisiran for the treatment of hATTR amyloidosis in England is not anticipated to result in a net budget impact that exceeds £15 million in any of the first 3 financial years after introduction, nor exceed £20 million in any of the first 5 years after introduction.

13.8 Main limitations of the BIA

The budget impact model is consistent with the cost-effectiveness model for patisiran in patients with stage 1 or stage 2 hATTR amyloidosis. As such, the budget impact

analysis is subject to the same limitations, and many of the same underlying assumptions that are made in the cost-effectiveness analysis.

As with any market-share forecast, there is uncertainty surrounding the uptake of patisiran in each year following introduction

It is assumed in the BIA that the NHS faces the additional cost of 20% value-added tax (VAT) on drug, administration, AE management and HCRU. The company are not certain that VAT is applicable to all patients across all cost categories. If some of the costs of administration are not subject to VAT, *ceteris paribus* the approach will overestimate the net BI of patisiran.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

- On a per patient basis, patisiran is anticipated to enable significant economic benefit outside the NHS in both patient and caregiver productivity and ability to lead productive lives
- It is expected that the introduction of patisiran would reduce the expenditure currently incurred local government and non-government programs outside of the NHS

14.1 Cost savings or benefits outside of the NHS or PSS

Patisiran is anticipated to bring significant economic benefits outside the NHS in terms of patient and caregiver productivity and ability to participate in activities. Although these wider economic benefits have not been quantified, the magnitude of the current burden in the absence of patisiran therapy is revealed by the finding that, at baseline in APOLLO, 69% of hATTR amyloidosis patients reported being unable to work, and those who were able to work reported a mean of 39 days of lost work over a year.[24] Furthermore, 16% of patients reported that their symptoms prevented their caregiver from holding a paying job, and an additional 12% reported their symptoms limited their

caregivers to part-time work. With the significant symptom improvement demonstrated in APOLLO, patisiran may substantially reduce this burden.[24]

As hATTR amyloidosis progresses, patients become less mobile and require additional aids to walk and perform normal acitivities.[5,24] Respondents in the UK survey of burden of disease described incurring costs for mobility equipment, home equipment or adaptations, and travelling costs. For example, one patient reported expenses relating to travelling to London for treatment, and a caregiver reported having to buy a new car and pay to convert the hand controls and install a crane, as well as needing to install a stair lift in the house. Patients and caregivers also reported indirect costs such as paying for home repairs and maintenance which they were previously able to do themselves.[17] Patisiran has been shown to halt or reduce disease progression[11,33] meaning that patients will remain longer in the early stages of the disease and will likely require less help from others, and fewer mobility aids and/or home and car modifications. As well, the patient pathway service model proposed in Section 8.4 includes the option for eligible patients to receive home infusions, which will likely reduce travel and associated costs for patients and carers.

14.2 Costs and savings outside the NHS

Several participants in the UK patient and caregiver burden of disease survey indicated that they receive financial support from external sources such as continuing healthcare, disability allowance, and attendance allowance.[17]

It is expected that the introduction of patisiran would reduce the expenditure currently incurred by Local Government and County Council programmes that may currently provide support for some hATTR amyloidosis patients in the UK. As these cost savings are not possible to estimate at this time, they have not been considered in the CEA or BIA, resulting in conservative estimates of the cost-effectiveness and budget impact for patisiran.

14.3 Costs not reimbursed by the NHS

Patients and caregivers with hATTR amyloidosis face many additional costs not reimbursed by the NHS. As it is a hereditary disease, it is also possible that children who are caregivers may be suffering from earlier stages of the disease as well as having to care for their debilitated parent. Some of the financial costs typically borne by patients and caregivers and families that are not reimbursed by the NHS include:

- *The cost of transportation to and from hospitals to access specialised services and care, parking charges, and overnight accommodation/meals*

hATTR amyloidosis is an ultra-rare disease and few healthcare professionals in the UK have the specialised expertise needed to treat it—the only hATTR amyloidosis treatment centre, the NAC, is located in London.[142] For patients who live at a considerable distance, every visit may involve substantial travel time and transportation costs including overnight stays. The Delphi panel estimates of HCRU indicated that patients can expect to visit a specialist every 4–6 months in PNDI–PND IIIB and every 2.5 months in PND IV.[99] The costs of the cumulative visits may be considerable, and will be especially burdensome when both patient and carer are unable to work full-time due to the disease.

- *The cost of adaptations to the home and appliances, adaptations to the car, and other care equipment*

  Respondents in the UK survey of patient and caregiver disease burden described incurring costs for mobility equipment, home equipment or adaptations, and car modifications. As mentioned in Section 14.1, patients also report incurring costs for home repairs or maintenance that they were previously able to do themselves.[17]

- *Loss of income for both the patient and the caregiver*

  Both patients and caregivers reported a reduction in work productivity. Patients worried about their future financial situation due to the inability to work.[17] Due to the nature of the caregiver/patient relationship, families are often disproportionately affected as both adults working hours are reduced.

A common feature of these financial burdens borne by patients and carers is that they increase as hATTR amyloidosis progresses, providing an additional rationale for enabling patient access to patisiran as the only available treatment that can halt or reverse the disease course.

14.4 Estimate of caregiving time spent by family members

There is scant evidence in the literature on the time family members and caregivers spend taking care of patients with hATTR amyloidosis, and no overall estimates for the UK. There is one estimate in the literature, derived from an online survey in the US in which the Work Productivity & Activity Impairment questionnaire, EQ-5D, and HCRU questions were given to 33 hATTR amyloidosis patients and 18 caregivers. This study was published only as the abstract to a conference presentation by Stewart et al. 2013,[82] but additional details were summarised in a review article (Gertz et al. 2017).[6] While the conference abstract does not include the estimate, the

review article reported that the median amount of time a caregiver spent per week caring for an hATTR amyloidosis patient was 144 hours.[6,82]

14.5 Impact of the technology on the evidence base for clinical effectiveness of treatment

As is true for other rare diseases, hATTR amyloidosis has a limited evidence base to inform clinicians on its management. The APOLLO trial represents a major advance on research into management of hATTR amyloidosis, as it is the largest trial conducted in this patient population to date. It was a global, randomised, blinded trial that demonstrated the safety and efficacy of patisiran in hATTR patients with 39 different genotypes, over a wide range of neuropathy severity, and in patients with moderately severe cardiac involvement with clinical manifestations of heart failure at baseline.[10] Patients in the ongoing Global OLE are providing unique data on the long-term efficacy and safety of patisiran.[41]

14.6 Anticipated impact of the technology on innovation in the UK

By demonstrating the potential of an RNAi therapy to alter the hATTR amyloidosis disease course and bring tangible clinical and HRQoL benefit to patients with this life-threatening condition, the introduction of patisiran in the UK may stimulate innovative research on RNAi drugs for other diseases.

14.7 Patient registry or collection of clinical effectiveness data over the next 5 years

The MHRA has granted patisiran a PIM designation and released its Scientific Opinion for entry into EAMS on August 3, 2018. A data collection scheme for patient enrolled into EAMS as approved by the MHRA and is detailed in the EAMS protocol. Background data on the patients, such as age, gender, hATTR genotype, phenotype, time since diagnosis, underlying comorbidities and concomitant medication will be captured at the time the treating physician requests access to patisiran from the company. Table D41 outlines further data collection proposed during EAMS.

Table D41. Proposed data collection in EAMS

Data point	Measured by	Compiled by
Physician details		Alnylam
Eligibility criteria	NAC	Alnylam
Additional baseline clinical data		
CMT Neuropathy score, Norfolk QOL score, standing and lying BP, mBMI, 10MWT	NHNN	NAC
NT-proBNP, troponin I, NYHA class, cardiac MRI, echocardiography, DPD scintigraphy. 6MWT where possible	NAC	NAC
At 6 months		

NIS score, PND score, CMT Neuropathy score, Norfolk QoL score, standing and lying BP, mBMI, 10MWT	NHNN	NAC
NT-proBNP, troponin I, NYHA class, cardiac MRI, echocardiography, 6MWT where possible	NAC	NAC
At 12 months		
DPD scintigraphy	NAC	NAC
Nerve conduction tests where possible	NHNN	NAC
Shared Care data (baseline and 6-monthly)		
Treatment setting (NAC vs home)	NAC	Alnylam
Cost per infusion	NAC/ homecare provider	Alnylam
Patient and carer survey on impact of home infusion	Homecare provider	Alnylam
Patient survey on impact of treatment on daily living	Homecare provider	Alnylam
Safety data (ongoing)		
Safety data will be collected as described in the EAMS Treatment Protocol - Information on Pharmacovigilance System, and the Adverse Event Reporting Guideline	Healthcare professional (NAC, NHNN and/or homecare provider)	Medpace (Alnylam)

10MWT: 10-metre walk test; 6MWT: 6-minute walk test; imaging BP: blood pressure; mBMI: modified body mass index; CMT: Charcot-Marie-Tooth; DPD: 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid; EAMS: Early Access to Medicines Scheme; MRI: magnetic resonance imaging; NAC: National Amyloidosis Centre; NHNN: The National Hospital for Neurology and Neurosurgery; NIS: Neurological Impairment Score; NT-proBNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; PND: polyneuropathy disability; QoL: quality of life.

An Expanded Access Protocol study is currently enrolling adult patients who have not previously participated in an interventional hATTR amyloidosis clinical trial involving RNAi therapeutics within the last 12 months.[43] Patients who are eligible will receive patisiran at one of 21 study locations in the USA.[43]

14.8 Review of clinical effectiveness of the technology

No review of the clinical effectiveness of patisiran in the UK is planned outside of this submission.

14.9 Required level of expertise for the safe and effective use of the technology

As directed in the product label, patisiran therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis.[12] A detailed patient care pathway and model that will ensure that only experienced specialists administer patisiran in England are outlined in Sections 8.4 and 8.6.

14.10 Additional infrastructure related to the safe and effective use of the technology

No additional infrastructure will be required to ensure the safe and effective use of the technology and equitable access for all eligible patients.

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 Level of engagement with clinical and patient groups to develop the MAA

As would be expected of any innovative therapy before launch, there is currently limited information available on long-term treatment outcomes with patisiran. Longer-term data are accruing in the ongoing Global OLE (up to 5 years of therapy),[41] with additional real-world evidence forthcoming from the US Expanded Access Program for compassionate use of patisiran, and the anticipated EAMS programme for patisiran (see Section 4.1). At the time of the present HST submission, however, the main evidence base for patisiran is the APOLLO study.[11] The 18-month duration of APOLLO poses a challenge for quantifying the impact of patisiran on the HCRU and associated costs over the lifetime of a patient with hATTR amyloidosis, which is the relevant timescale for analysis in this incurable, life-long disease. As detailed in Section 12.2.5, Alnylam has endeavoured to mitigate this uncertainty by consulting with clinical experts at the NAC on extrapolations past 18 months. Nevertheless, the lack of long-term data represents an important gap in the evidence base for patisiran, especially as technology appraisal methods used by NICE require long-term modelling of costs and effects (lifetime horizon) even in the absence of long-term data. This type of uncertainty is a common issue in health technology assessment, particularly for rare diseases.[147]

15.2 Details of the MAA proposal

[redacted]

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144. BMJ Group, RCPCH Publications Ltd., Royal Phamaceutical Society of Great Britain. British National Formulary. 2018; https://www.bnf.org/products/bnf-online/. Accessed 16 July 2018.
145. National Institute for Health and Care Excellence. Technology appraisal guidance: Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [TA451].1–93.
146. National Institute for Health and Care Excellence. Patisiran for treating hereditary transthyretin-related amyloidosis, Draft scope (pre-invite) May 2018.
147. Nestler-Parr S, Korchagina D, Toumi M, et al. Challenges in research and health technology assessment of rare disease technologies: report of the ISPOR Rare Disease Special Interest Group. *Value Health.* 2018;21(5):493-500.

16 Appendices

Related procedures for evidence submission

16.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted

- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

16.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance.

Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

16.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technologies

Patisiran for treating hereditary transthyretin-related amyloidosis

Dear Anant,

The Evidence Review Group, School of Health Related Research – ScHARR, and the technical team at NICE have looked at the submission received on 14th August from Alnylam. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on 20 September. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

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

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Aminata Thiam, Technical Lead (Aminata.thiam@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Ongoing and future data collection

A1. Please provide any relevant results relating to the safety and/or efficacy of patisiran available from:

   a. Compassionate Use Programme (Company Submission [CS], Section 4.1, page 28)

   b. Latest data cut-off for the global OLE study (CS, Section 4.1, page 28)

A2. The text of Section 8.4 page 52 refers to "…*consistent standards with appropriate monitoring, data collection and reporting in line with the commissioning policy."* Please clarify the data that will be collected as part of the commissioning policy.

Decision problem

A3. Decision problem (Table A1 page 23):

   a. The text in column "variation from scope to submission" does not explain how the population addressed in the submission varies from the final scope. Please clarify.

   b. Please clarify why the third column states 'none' for "subpopulation" when a cardiac subpopulation was examined.

A4. Please clarify why 65% of people with hereditary transthyretin-related amyloidosis (hATTR amyloidosis) in England are eligible for treatment with patisiran (CS, page 20).

A5. Please clarify what evidence supports the following assumption: *"a very small minority of patients eligible for patisiran treatment might prefer to receive infusions in a setting other than the NAC or homecare"* (CS, Section 8.4, page 53). Please also clarify whether travel to London for the initiation of treatment might generate inequalities in access to treatment for those who live at increasing distance from the South East of England.

Literature searching

A6. Given the rarity of hATTR amyloidosis, please clarify why the searches produced more than 8,000 records across the polyneuropathy and cardiomyopathy searches? (CS, Figures 3, 4, 21, 22, 24 and 25)

A7. PRISMA diagrams (CS, Section 9.2.2): the numbers of records identified from database searches for the SLR (OS) and rescreen (R) are identical. Are these repeat searches? If not, why were records rescreened? Do the numbers for the original SLR (OS) represent numbers for both May 2017 and January 2018?

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A8. In Section 9.1.1. of the CS, the text states that *"two comprehensive SLRs were conducted to identify RCTs and observational studies reporting the safety and efficacy of current treatments for adult patients being treated for hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy."* Please clarify:

   a. when the two comprehensive SLRs searches were carried out

   b. whether date limits were applied and reasons for not searching all years

A9. Search strategy for clinical evidence (Appendix 1.1). Please confirm whether the full search strategies used for SLR report are the same as the strategies described in the draft study SLR protocol in September 2017 (Appendix 1.2). If not, please provide full search strategies as reported in the SLR and clarify any differences.

A10. Please update Table S1 of Appendix 1 to include a fourth column for the sources searched in the literature scan in July 2018.

A11. In Appendix 1.3 and Appendix 1.4, the literature searches carried out in July 2018 for hATTR amyloidosis with polyneuropathy SLR and ATTR amyloidosis with cardiomyopathy SLR differ from the original SLR search strategies in May 2017 and January 2018 (Appendix 1.2). Please state the reasons for not searching literature for all years for hATTR amyloidosis with cardiomyopathy (pre-2014, Embase) and the implications for finding relevant literature.

A12. Please comment on the implications of limiting publications to English-language only at the searching stage?

Systematic Review Methods

A13. **Priority question**. Please clarify why a systematic review of best supportive care (BSC) has not been undertaken. Please provide details of any relevant studies describing outcomes in patients receiving BSC which were excluded from the clinical effectiveness review.

A14. Please clarify why separate systematic literature reviews were undertaken according to whether patients had polyneuropathy or cardiomyopathy rather than undertaking reviews within hATTR as a single disease.

A15. In Figure 3 page 62, and Figure 4 page 63 of CS, please clarify the following:

   a. Where the manually added studies came from

   b. Why 2 different reviews (the "SLR" and the "submission" in the lower boxes of the PRISMA diagrams) were undertaken for each of hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy.

   c. Why studies were excluded according to the following when these were not mentioned in the exclusion criteria: observational study of <50 patients, being an NH study outside of the US or Europe, language, and being reported in an abstract <2015 (in Figure 3 only, page 62)

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A16. Please clarify why items 6(b), 9, 10, 11 and 12 from the CASP checklist for cohort studies (see https://casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Study-Checklist-Download.pdf) were omitted from Tables S7, S8 and S9 pages 17-19 of Appendix 1. Please provide answers to these items.

Population

A17. **Priority Question**. In the studies included in the SLR (CS, Section 9.3.1, page 64 and Table C2, page 65), please clarify whether patients were enrolled into more than one study, and if so how many, in which studies and which arms (if APOLLO)?

A.18. **Priority Question** Please clarify whether all patients in the OLE studies have the same on-treatment duration at the data cut-point reported. If not, please clarify how many patients are at each time point, and how many are missing (excluding those who did not receive the treatment for long enough).

Study Design

A19. **Priority question.** For the Phase 2 trials, the dose described (on page 70; doses ranging from 0.01 mg/kg to 0.3 mg/kg Q3W) appears to be different to that described in the licence and in APOLLO (0.3 mg/kg Q3W). Please clarify why the dosing regimens differ, and what effect this may have had on results.

A20. Please clarify how the randomisation was performed in the APOLLO study (e.g. simple randomisation or permuted blocks) in Section 9.1 of the CS?

A21. Table C5 page 81 states that *"Demographics and clinical characteristics were generally balanced between the patisiran and placebo treatment groups."* However, Table C4 page 78 suggests a noticeable difference in the proportion of patients with cardiac involvement between the groups. Please comment on how this may have impacted on the overall results of the study.

A22. Please provide details of prior therapies received by patients in the APOLLO study by treatment group (Section 9.9.4, page 115).

A23. Please clarify how many UK patients were recruited into each of the patisiran studies included in the SLR (section 9.4, page 72)?

A24. Please clarify how missing data were dealt with, particularly with respect to the primary outcome.

A25. In APOLLO (Section 9.3.2, page 67), *"Patients had the option of discontinuing the study drug if they experienced a protocol-defined rapid disease progression at 9 months (defined as ≥24-point increase in mNIS+7) and FAP stage progression relative to baseline and confirmed by an external adjudication committee."* Please clarify:

a. Whether patients or clinicians made the decision to discontinue.

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b. How many patients met the criteria, and how does this relate to the "progressive disease" discontinuation reason given in Table C3?

c. How many patients met the criteria and stopped treatment?

d. How the analyses handled missing data points for the patients who stopped treatment because of rapid disease progression at 9 months?

e. Whether this stopping rule will be applied in clinical practice, and therefore necessitate the use of mNIS+7 by clinicians.

A26. Please clarify the time period over which the Suhr *et al* (2015) study was conducted (Section 9.4.4, page 80). In the paper, results are only reported at 115 days.

A27. CS, Section 9.4.6, page 80. Please clarify whether "03 mg/kg" should be 0.3 mg/kg.

A28. Please clarify the criteria for moving to home care. Please clarify how many patients met the criteria in APOLLO and the OLE.

Outcomes

A29. **Priority Question**: Please clarify what the clinically important difference is for each outcome measure.

A30. Please clarify how the mNIS+7 was modified from the NIS+7 and provide details regarding the scoring system for this instrument (Section 4.2, page 46).

A31. Please provide results for the following outcomes (as stated in Section 9.4.1, page 69):

- Quantitative sensory testing
- Number of patients with rapid disease progression (at 9 months)
- Pathological evaluation of dermal amyloid burden
- Magnetic resonance neurography
- Pharmacodynamic biomarkers.

A32. Figure 9 (page 86) states, *"Change in mNIS+7 from baseline in patients with early or advanced neuropathy"*. Please clarify how the change in mNIS+7 relates to stage 1 and 2.

A33. Please clarify if there was any monitoring for treatment resistance (e.g. antibodies to treatment) and, if so, what the results of such monitoring were.

A34. Please clarify if there is any comparative evidence available on the impact of treatment with patisiran on mortality for patients who have been on treatment long-term, e.g. compared with historical data.

A35. Please provide details of the outcomes for all cardiac assessments listed in Section 9.4.4, page 79.

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Adverse events (AEs)

A36. **Priority Question**. Please comment on why cardiac adverse events do not seem greatly improved despite improvements in NT-proBNP levels, cardiac LV wall thickness and other cardiac measures. What implications does this have for the overall efficacy of the treatment for patients in the UK, in whom there is a predominance of cardiac disease? If possible, provide an analysis for cardiac adverse events as seen in Table C8 page 106 for other outcomes.

A37. Please explain why there is a high number of treatment-related AEs in the placebo group. Are these a consequence of infusion-related reactions?

A38. Please explain why diarrhoea is worse in the patisiran group, given that diarrhoea is a symptom of the disease and could be expected to be reduced by treatment.

Results

A39. **Priority Question**: Randomisation in APOLLO was *"stratified by NIS (5-49 vs 50-130), early-onset Val30Met (<50 years of age at onset) vs all other mutations (including late-onset Val30Met), and previous tetramer stabiliser use (tafamidis or diflunisal) vs no previous tetramer stabiliser use."* Please provide results of an analysis of the primary endpoint (change from baseline at 18 months in mNIS+7) adjusted for the stratification factors AND baseline mNIS+7.

A40. **Priority Question**: Please describe any other known or potential prognostic factors, and any covariates that were pre-specified in the APOLLO study protocol. Please provide results of an analysis of the primary endpoint (change from baseline at 18 months in mNIS+7) adjusted for the stratification factors, baseline mNIS+7 AND any pre-specified covariates, as appropriate; include any non-stratification continuous variables as continuous covariates.

A41. The text of Section 9.6.1 page 82 states *"Additional, pre-specified sensitivity analyses on the primary endpoint resulted in a consistent estimate of the treatment effect of patisiran compared to placebo".* Please comment on the potential treatment effect modifications according to region, NIS, age, genotype, genotype class, previous tetramer stabilizer use and cardiac involvement.

A42. Figure 17 page 96 suggests a rebound effect (i.e. loss of efficacy) for the mNIS+7 whereas text in Section 9.9.2 page 113 reports that *"the clinical benefit observed in the APOLLO trial was maintained in the OLE."* Please justify this statement in light of the mNIS+7 results.

A43. Please comment on whether the Norfolk QoL-DN responses to treatment with patisiran at 9 and 18 months are likely to reflect a plateau response or loss of response (Figure 11, Page 88).

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A44. Please clarify why fewer patients receiving placebo in APOLLO completed the study, compared to patients receiving patisiran (Figure 5 page 79), commenting on potential unblinding because of a lack of response and/or progressive disease. Please comment on the potential impact of the reasons for treatment discontinuation on the results.

A45. Please provide details of the results reported for the non-randomised studies, specifically, for the Phase 2 OLE:

- What were the serum TTR levels at baseline and after the first and second dose of patisiran;
- What was the sustained mean serum TTR knockdown over 18 months;
- What was the sustained decrease in mNIS+7 at 24 months for patients with cardiac involvement.

A46. The text in Section 9.9.1 page 111 states, *"The placebo group reported more patients who worsened on the PND score (58.2%) than the patisiran group (21.7%)."* Please comment on factors associated with worsening response to treatment with patisiran, and whether these patients should continue on treatment.

Section B: Clarification on cost-effectiveness data

Systematic reviews of economic evaluations, HRQol & resource/costs

B1. **Priority Question.** It appears that studies were only considered eligible for inclusion in the systematic reviews of economic evaluations, HRQoL and resource use/costs studies if they included patisiran (Sections 10.1.5 page 121 and 11.1.3 page 131).

a. Please provide the full inclusion and exclusion criteria for the systematic reviews which were used to select studies for these reviews.
b. Please explain why previous models/economic evaluations of inotersen, tafamidis and any other treatments for hATTR amyloidosis were not included in the review of existing economic studies. Were any of these considered for inclusion in the review (e.g. to inform the model structure, data sources and/or assumptions)?
c. Please clarify which HRQoL studies met the review inclusion criteria but were subsequently excluded because they did not include patisiran.

B2. The text of Section 12.1.3 page 136 states that: *"No economic models for patisiran or for other technologies used in UK clinical practice in the indicated population were published at the time of the model development."* Elsewhere in the CS, the text refers to a previous tafamidis AGNSS analysis. Why is this model not included either in the review of economic studies or in Appendix 3?

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Discounting

B3. **Priority Question.** The text in Section 12.1.7, page 143-146 states that: *"The discount rate for cost is set at 3.5% annually, according to UK NICE reference case. The discount rate for outcomes is set to 1.5% per year, based on the evidence that the treatment effects of patisiran are both substantial in restoring health and sustained over a very long period."*

a. Please explain why it is appropriate in this particular case to deviate from the discount rates specified in the NICE Reference Case.
b. Please comment specifically on why this argument for differential discounting should not apply to every NICE appraisal.
c. Please clarify which evidence demonstrates substantial health gains for patisiran over a very long period.

Model structure and assumptions

B4. **Priority Question.** Given that hATTR amyloidosis affects multiple body systems, please clarify why the model health states have been defined in terms of PND score rather than by stage, given that only the latter specifically includes autonomic function (e.g. the classification system devised by Ando *et al,* discussed in CS Section 6.1.2, page 46).

B5. The text in Section 12.1.4, page 139. states that: *"patients in the patisiran arm of APOLLO consistently scored better than patients in the placebo arm across all primary and secondary endpoints by PND score change category and even within PND score category for the small percentage (20%) of patients who worsened in PND score in the patisiran arm."* Please comment on whether this indicates that PND score is a poor indicator of treatment benefit according to other relevant disease-specific endpoints and HRQoL?

B6. **Priority Question.** The CS states that "*Patisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy*."

a. Which staging classification does this anticipated marketing authorisation relate to?
b. Given that the proposed indication is for stage 1 and 2, please clarify how eligibility for starting treatment relates to PND score (as used in the model).
c. Why does the model assume that patients in PND 0 (asymptomatic) and PND IIIB-IV (presumably more advanced than stage 2) are eligible to start treatment with patisiran?

B7. **Priority Question.** Please provide evidence justifying that:

a. patients will require treatment with patisiran indefinitely? Has the company explored the potential for patisiran stopping rules based on loss of efficacy?

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b. patients with severely progressed disease will continue to benefit from patisiran?

B8. **Priority Question.** In Section 12.1.6, page 143, the CS states that: *"the PND score has been shown to be significantly associated with the NIS score by Adams et al. 2015, and with mortality by Suhr et al. 1994".* Please comment on the appropriateness of the method of analysis used by Suhr *et al* for time-to-event data with censored event times. Please comment on what claims the method of analysis allows for the impact of PND score and PND score plus mBMI on mortality. Did your searches identify any other studies which indicate a relationship between PND score (or other baseline factors) with mortality?

B9. Please clarify why only serious adverse events have been included in the model.

B10. Please clarify what assumption was used for the efficacy of patisiran in patients who have discontinued patisiran treatment.

Model data and inputs - clinical inputs

B11. **Priority Question**. Please provide the equivalent patient count data by treatment group shown in Tables D5 and D6 (page 148) for the time periods 0-6 months, 6-12 months and 12-18 months.

B12. **Priority Question.** In Table C10 page 119, please present EQ-5D utility estimates at each observed time point in APOLLO for: (a) each treatment group, and (b) each treatment group by PND score. Please include the point estimate, the confidence interval and the number of patients contributing data.

B13. **Priority Question.** Model, Worksheet "TransMX" cells C164:N175: The model converts the observed 18-month probabilities to rates and then to 6-month probabilities based on formulae which are not appropriate for multinomial data. Please provide an analysis in which appropriate methods for converting the cycle length are applied (for example: Craig and Sendi, Estimation of the transition matrix of a discrete-time Markov chain, *Health Economics*, 2002, 11:1; or Chhatwal et al, Changing Cycle Lengths in State-Transition Models: Challenges and Solutions, *Medical Decision Making* 2016; 36(8):952-964).

B14. **Priority Question**. Please clarify why the observed BSC patient transition data are not used to inform the extrapolated portion of the time horizon.

B15. **Priority Question**. Table C10 page 119 states that 18-month EQ-5D data are not yet available from APOLLO. However, the text on page 129 states that, "*the utility score for PND IV in the placebo arm at 18 months is negative following conversion of the EQ-5D-5L scores with the UK tariff*" – this suggests that the 18 month EQ-5D data were available. And on page 129, it is stated that "*The change in HRQoL with disease progression is captured in the CEA by using the utilities at baseline in APOLLO for the first model cycle and subsequently changing them according to the average change by*

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PND score and treatment arm." Whilst ambiguous, this seems to indicate that only the baseline EQ-5D data have been used in the model.

a. Please clarify whether the 18-month EQ-5D data have been used in the utility regression model.
b. If the 18-month EQ-5D data from APOLLO have not been used in the utility regression model, please clarify how AEs are captured in the predicted utilities.
c. Please provide details of the statistical model fitted to the observed EQ-5D data, including the regression equation and error terms allowing for repeated measures.
d. Please fit a statistical model to the EQ-5D data including terms for all stratification factors and any main effects when interaction terms are included. Please provide details of the statistical model fitted and comment on the comparison with the model described in Table C12 page 126. [NOTE: It is not necessary that stratification factors are statistically significant for them to be included in the model.]
e. Given that cardiac involvement is described as an important determinant of HRQoL in the background section of the CS, please clarify why this has been excluded from the regression model. Please also comment on the validity of assuming the same utility scores for NT-ProBNP>3000 and NT-ProBNP<3000 and provide results of regression analyses with NT-ProBNP added to the models generated in parts c) and d).
f. Please explain how the "*patisiran maximum utility*" (ceiling) and the "*BSC minimum utility*" (floor) have been derived.
g. Please explain why patients with PND 0 (asymptomatic) receiving BSC are assumed to experience HRQoL which is considerably lower than that of the general population.

B16. Model, worksheet "QoL Data" cells A41:D48. Please clarify why the Kind *et al* utilities have been used rather than a newer source such as Ara and Brazier (*Value in Health*, 2010;13:5).

B17. Model. Worksheet "Markov Patisiran" cells P6:Z6. Please explain why a fixed probability of NT-proBNP<3000 pg/mL is applied to the initial PND distribution. Why was the observed baseline distribution by PND and NT-proBNP not used?

B18. Please clarify the data cut-off for the APOLLO study data used in the model.

B19. The CS Section 14.1 page 206 states that patisiran *"is anticipated to bring significant economic benefits outside the NHS in terms of patient and caregiver productivity and ability to participate in activities."* Is there any evidence of the impact of patisiran on improving absenteeism and productivity and/or caregiver impacts?

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Model data and inputs - resource use and costs

B20. **Priority Question**. The patisiran cost calculations seem to be double-counting reductions in costs relating to treatment discontinuations (due to being a function of both relative dose intensity and time on treatment)

a. Please clarify whether this is the case.
b. Please clarify if the RDI calculation was based only on those patients who were alive and still on treatment, or if it included those who discontinued and/or died.

B21. Please clarify whether the time-on-treatment data include both death and discontinuation as events.

B22. The CS page 148 states that "*The log-logistic function was selected to inform the fraction of patients still on treatment at each time point in the simulation based on the goodness of fit*." However, the model appears to use the log normal distribution. Please explain which curve the company intended to use in the model and whether the extrapolation is consistent with clinical plausibility.

B23. Please investigate whether there has been an error in the fitting of the exponential distribution to the time on treatment data. This does not appear to have worked correctly (Section 12.2.1, page 149).

B24. Do the cost calculations shown in Appendix 3 account for double-counting associated with previous one-off costs already incurred for less severe PND states? E.g. if a patient requires a wheelchair in PND III, does the analysis account for the fact that they will not need a new one on progression to PND IV? Please also explain why the one-off costs are not applied to the high NT-proBNP group.

B25. Model, Worksheets "Markov Patisiran" and "Markov BSC", one-off costs. It appears that the model is double-counting one-off costs for patients who progress to a worse health state, regress to a better state and subsequently progress to a worse state. Please provide an analysis in which these costs are not double-counted.

B26. CS, Section 13, page 199. Who will administer the homecare infusions? Why have the costs of homecare infusions not been included in the model?

B27. Please provide details of the proposed homecare service (Section 13 page 199).

Model implementation

B28. **Priority Question**. Model, Worksheet "mortality data" cells G29:G76. Please clarify what these calculations are intending to do.

B29. **Priority Question**. Model, Worksheet "mortality data" cells G86:K92. Please clarify the logic underlying all of these calculations. Please clarify why NT-proBNP score data from APOLLO are used in these calculations.

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B30. **Priority Question**. Worksheet “Mortality Data” cells J89:92. The brackets appear to be misplaced within these formulae. Please confirm whether these calculations contain an error.

B31. **Priority Question**.. Please explain how to generate the results that are presented in Tables D31, D32, D33, D34 and D35 pages 192-94 using the model.

B32. Model, Worksheet “TransMX” cells C63:N74. The CS states that a prior of 1% was used in the model. However, the model actually uses a value of 1/12 for all transitions. Please clarify the value of the intended prior. Please also clarify why priors are applied to the BSC matrix during the observed period but not during the extrapolated period.

B33. Model, Worksheet “HRQoL.” Some of the regression parameters for the lower PND states allow for utilities which are greater than 1. Please comment.

B34. The minimum and maximum utility values shown in the Table C12 page 126 do not match those used in the model. Please clarify which values are correct.

B35. The tornado diagram presented in Figure 39, page 188 does not match that generated from the model. Please explain this discrepancy.

Budget Impact

B36. The budget impact results on page 201 states that “*Five-year survival is predicted to be 92% for patients treated with patisiran and 84% for patients not treated with patisiran*”. These estimates do not match the predictions from the economic model - please clarify how these estimates have been derived.

B37. Please clarify the source of the [redacted] uptake rate for patisiran.

20 September 2018

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Re: Highly Specialised Technologies

Patisiran for treating hereditary transthyretin-related amyloidosis

Response to ERG and NICE Technical Team Questions

Dear Sheela,

Thank you for sending through the ERG clarification questions regarding our submission for patisiran.

Following the two teleconferences we had with the ERG and the NICE technical team, we believe that we have a sufficient understanding of the ERG's requests and have done our best to address each of the questions. Of course, should any additional information be required, please let me know.

Finally, the ERG and the NICE technical team were kind enough to grant us additional time for some questions. However, we were able to address them by the deadline thanks in part to input we received from the ERG during the second teleconference organized by NICE.

We would like to note that our responses contain confidential information that has been marked accordingly. A confidential information checklist has been submitted alongside this response.

I look forward to subsequent steps for this appraisal.

Yours sincerely,

Anant Murthy, PhD
Vice President
Market Access
Alnylam Pharmaceuticals

Section A: Clarification on effectiveness data

Ongoing and future data collection

A1. Please provide any relevant results relating to the safety and/or efficacy of patisiran available from:

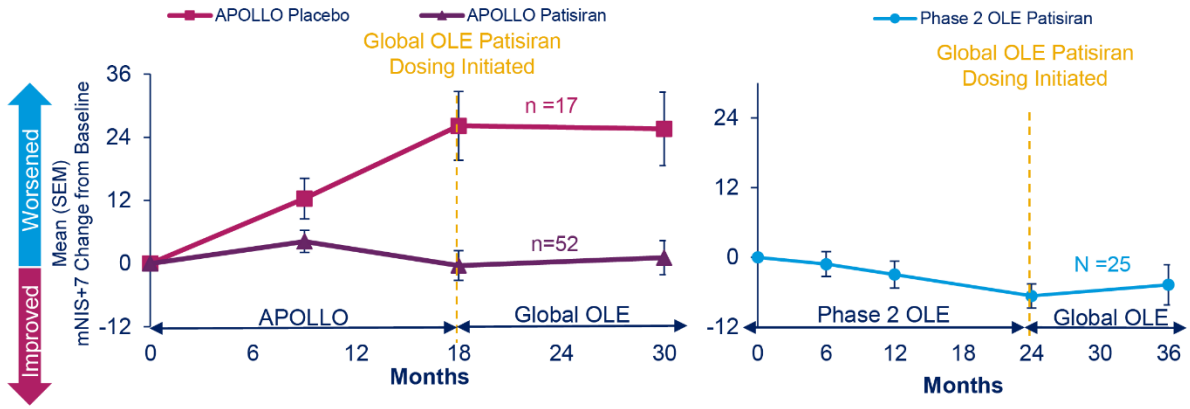
a. Compassionate Use Programme (Company Submission [CS], Section 4.1, page 28)

Response: The National Amyloidosis Centre (NAC) is compiling data from patients with hereditary transthyretin-mediated (hATTR) amyloidosis in the Compassionate Use Programme. However, as this prospective data collection was not conducted by us, we are not in a position to report the safety or efficacy findings.

b. Latest data cut-off for the global OLE study (CS, Section 4.1, page 28)

Response: The most recent data cut-off for the global open-label extension (OLE) was 1 December 2017, and interim results at this date were presented at the International Symposium on Amyloidosis in March 2018.[1] At this cut-off, 94 (44.5%) of the 211 patients enrolled in the global OLE had completed their 52-week assessment. Of these, 17 patients had entered the global OLE from the APOLLO placebo group, 52 from the APOLLO patisiran group, and 25 from the phase 2 OLE. Neuropathy improvement or stabilisation was observed in all three groups (Figure 1). Notably, patients from the APOLLO placebo group had previously shown disease progression during the randomised trial, but experienced disease stabilisation while receiving patisiran in the global OLE, with a mean (standard error) change of -0.58 (2.98) on the modified Neuropathy Impairment Score+7 (mNIS+7).

Figure 1. mNIS+7 results for patients in the global OLE, stratified by parent study.



mNIS+7: modified Neuropathy Impairment Score+7.
Source: Suhr et al. 2018[1]

Safety results were available at this data cut-off for patients treated with patisiran for up to 48 months, representing 211 patient-years and 3506 patisiran doses (Table 1).[1] Most common study-drug–related adverse events (AEs) were mild or moderate infusion-related reactions (IRRs) (10.4%). Two patients had serious AEs (SAEs) related to study drug: one patient with an event of phlebitis secondary to drug extravasation, cellulitis and hypotension; and one patient with abdominal discomfort who withdrew from the study. All deaths were due to causes consistent with the natural history of hATTR amyloidosis, and none were considered related to study drug.

Table 1. Safety results for patients in the global OLE, stratified by parent study.

	Parent study			
	APOLLO placebo (n=49)	**APOLLO patisiran (n=137)**	**Phase 2 OLE patisiran (n=25)**	**Total (N=211)**
AE	45 (91.8)	119 (86.9)	25 (100.0)	189 (89.6)
AE related to study drug	22 (44.9)	30 (21.9)	7 (28.0)	59 (28.0)
Severe AE	16 (32.7)	19 (13.9)	3 (12.0)	38 (18.0)
Severe AE related to study drug	1 (2.0)	1 (0.7)	0	2 (0.9)
SAE	19 (38.8)	30 (21.9)	6 (24.0)	55 (26.1)
SAE related to study drug	2 (4.1)	0	0	2 (0.9)
AE leading to study withdrawal	9 (18.4)	7 (5.1)	0	16 (7.6)
Study-drug–related AE leading to study withdrawal	1 (2.0)	0	0	1 (0.5)
Death	7 (14.3)	4 (2.9)	0	11 (5.2)

AE: adverse event; OLE: open-label extension; SAE: serious adverse event.
Source: Suhr et al. 2018[1]

A2. The text of Section 8.4 page 52 refers to "…*consistent standards with appropriate monitoring, data collection and reporting in line with the commissioning policy."* Please clarify the data that will be collected as part of the commissioning policy.

Response: Section 2.2 Service description/care pathway in NHS England's "2013/14 NHS Standard Contract for Diagnostic Service for Amyloidosis (All Ages)" available at https://www.england.nhs.uk/wp-content/uploads/2013/06/e13-diag-serv-amyloidosis.pdf states that:

"The centre uniquely provides a one-stop comprehensive clinical and laboratory evaluation of amyloidosis and related disorders for about 500 new patients per year, and follow-up at 6-12 months for about 1,750 patients each year. The clinical service includes:

- *Clinical consultation with expertise gained from experience of over 4000 patients with amyloidosis and related disorders, the largest experience anywhere in the world*
- *Whole body SAP scintigraphy, a nuclear medicine scan, to diagnose, quantify and serially monitor amyloid deposits throughout the body. Radiolabelled SAP scintigraphy is not available anywhere else and is the only means of quantitatively monitoring amyloid*
- *Definitive amyloid fibril protein immunohistochemistry; independent clinical chemistry immunoassays for amyloid fibril precursor proteins to assist diagnosis and monitoring treatment; samples posted in during treatment and follow-up*
- *Specialised echocardiography and evaluation of cardiac amyloidosis*
- *Extraction of amyloid fibril proteins from tissues, and biochemical / proteomic characterisation*
- *DNA analysis and genetic counselling for all types of hereditary amyloidosis (10% of cases) and inherited periodic fever syndromes*
- *Open telephone access, counselling and provision of information to patients and their local medical teams*
- *Liaison and work with the patient organization Myeloma UK, to improve information and access to state of the art treatments*
- *Leadership and organisational support for UK Amyloidosis Network*
- *Affiliation with UCL Medical School's Centre for amyloidosis and acute phase proteins.*

The service is predominantly but not exclusively a tertiary referral service opens to all NHS patients in England and Scotland (and elsewhere in the EU via the overseas visitor regulations) with suspected or proven amyloidosis and/or inherited periodic fever syndromes."

In addition, the NAC have previously informed us that they typically collect the following data in hATTR amyloidosis patients:

- 6 monthly:
  - Cardiac status by biomarkers, electrocardiogram, and echocardiography
  - General health including weight, Eastern Cooperative Oncology Group (ECOG) performance status, New York Heart Association (NYHA) class, and bioimpedance measurements
  - Functional status by 6-minute walk test
  - Routine biochemical and haematological tests of organ function
- 12 monthly:
  - Assessment of neuropathy in selected patients with neuropathy: polyneuropathy disability (PND) score, Familial Amyloid Polyneuropathy (FAP) Stage, Charcot Marie Tooth (CMT) score, Neuropathy Impairment Score+7 (NIS+7), and assessment of autonomic neuropathy
  - Cardiac magnetic resonance imaging scan
  - 99Tc DPD SPECT-CT scan
  - Quality of life assessment using Kansas City Cardiomyopathy Questionnaire (KCCQ), Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN), and Composite Autonomic Symptom Score-31 (COMPASS-31) questionnaires

Decision problem

A3. Decision problem (Table A1 page 23):

a. The text in column "variation from scope to submission" does not explain how the population addressed in the submission varies from the final scope. Please clarify.

Response: In the final scope, the population was defined as, "People with hereditary transthyretin-related amyloidosis." The submission addresses the population subsequently refined in the approved patisiran indication, namely treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adults with polyneuropathy. This population aligns with that studied in the APOLLO trial. The potential for a change in the indication over the course of the regulatory procedure was flagged to NICE and the ERG during the Decision Problem Meeting. Finally, following CHMP opinion and finalisation of the indication, we notified NICE immediately.

b. Please clarify why the third column states 'none' for "subpopulation" when a cardiac subpopulation was examined.

Response: The APOLLO trial did include a prespecified cardiac subpopulation of patients. Although data for the cardiac subgroup were presented in CS Section 9.6 to confirm that the clinical benefit of patisiran extends to this group, the cardiac subpopulation was not examined separately in any of the economic sections of the submission.

A4. Please clarify why 65% of people with hereditary transthyretin-related amyloidosis (hATTR amyloidosis) in England are eligible for treatment with patisiran (CS, page 20).

Response: The full details of how this 65% estimate was derived are presented in CS Section 13.1 and are based on information provided to us by clinical experts at the NAC. Briefly, since eligibility per the patisiran indication requires polyneuropathy, this was calculated based on the proportion of all 150 UK hATTR amyloidosis patients who present with polyneuropathy (non-Val122Ile: 91) or primary cardiomyopathy with polyneuropathy (estimated by the NAC at 10% of Val122Ile: 10%×59=6); i.e., [91+6]/150 = 65%.
The result is mathematically equivalent if we perform the calculations solely within the 112 patients resident in England as estimated from NAC data as of February 2018, with the following genotypes:

- 45 V122I (assume that 90% of these patients present with cardiomyopathy only and so are ineligible for patisiran treatment)
- 22 T60A
- 45 mix of other genotypes

Thus, 5 V122I + 23 T60A + 45 other genotypes = 73 patients, and 73/112 = 65%.

A5. Please clarify what evidence supports the following assumption: *"a very small minority of patients eligible for patisiran treatment might prefer to receive infusions in a setting other than the NAC or homecare"* (CS, Section 8.4, page 53). Please also clarify whether travel to London for the initiation of treatment might generate inequalities in access to treatment for those who live at increasing distance from the South East of England.

Response: This assumption is based on 3 sources:

1. A multistakeholder meeting that Alnylam arranged through NICE's Office for Market Access on 13 July 2018, attended by representatives from Alnylam, the NAC, the National Hospital for Neurology and Neurosurgery, the Amyloidosis Research Consortium, NHS England, and NICE. The consensus view of those at the meeting, based on prior experience and knowing their patient population, was that the vast majority of patients eligible for patisiran treatment would be satisfied with the choice of either receiving infusions at the NAC or through homecare.
2. Alnylam and the NAC's experience with patients accessing patisiran through a compassionate use scheme and the Early Access to Medicines scheme. The NAC believes that all English patients enrolled into the scheme would be happy to either travel to the NAC for therapy or receive infusions through homecare.
3. The Alnylam team's previous experience working with therapies for lysosomal storage disorders, a heterogeneous range of rare diseases requiring lifelong fortnightly infusions with enzyme replacement therapy. The Alnylam team's experience from this therapy area is that the vast majority of patients (>90%), have a strong preference for home administration after initial administration at a national centre.

We do not believe that requiring travel to London to initiate treatment will generate inequalities in access to treatment. The NAC is already commissioned to "provide a comprehensive range of diagnostic, staging and disease monitoring investigations" for "all English and Scottish patients with suspected and histologically demonstrated amyloidosis"

(quotations taken from the contract referenced in response A2). This means that the vast majority of UK hATTR patients are already required to visit the NAC, for diagnosis and disease monitoring.

Literature searching

A6. Given the rarity of hATTR amyloidosis, please clarify why the searches produced more than 8,000 records across the polyneuropathy and cardiomyopathy searches? (CS, Figures 3, 4, 21, 22, 24 and 25)

Response: There are two reasons for the large number of records reported for the systematic literature review (SLR) searches. The first reason is that the search strategies for both SLRs were structured broadly. The search strategies were intended to capture clinical, economic, and health-related quality of life (HRQoL) studies, and so no restrictions were made with respect to study design or outcomes in the search strategies. Also, there were no search restrictions made with respect to interventions or comparators as per the PICOS Criteria.

The second reason for the large number of records is that the original search for the polyneuropathy SLR (labelled OS in Figures 3, 21, and 24 of the CS) was re-screened for the purpose of identifying single-armed and observational studies of clinical effectiveness and safety. The original search produced 3126 records, and so this number of records is counted twice in the figures – once for the original search and once for the rescreen (R). The actual number of unique records for both SLRs combined is 5407.

A7. PRISMA diagrams (CS, Section 9.2.2): the numbers of records identified from database searches for the SLR (OS) and rescreen (R) are identical. Are these repeat searches? If not, why were records rescreened? Do the numbers for the original SLR (OS) represent numbers for both May 2017 and January 2018?

Response: The records identified from the polyneuropathy original search were re-screened, hence the same number of records for both OS and the re-screen (R). The reason for the re-screen was to identify single-arm and observational studies of clinical effectiveness and safety that had not been identified in the original search's screening. The numbers relating to the original search were from the search executed in May 2017 (n=3126), the rescreen of the original search took place in December 2017 (again, n=3126), and the update search ("U") was executed in January 2018 (n=1237).

A8. In Section 9.1.1. of the CS, the text states that *"two comprehensive SLRs were conducted to identify RCTs and observational studies reporting the safety and efficacy of current treatments for adult patients being treated for hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy."* Please clarify:

a. when the two comprehensive SLRs searches were carried out

Response: The original polyneuropathy SLR search was executed on 30 May 2017 and its update was executed on 10 January 2018. The cardiomyopathy SLR search was executed on 18 January 2018.

b. whether date limits were applied and reasons for not searching all years

Response: The original polyneuropathy SLR search applied date limits to the published abstracts, with abstracts published prior to 2015 being excluded. There were no other date

limits placed on the searches. The update of the polyneuropathy SLR included studies published between 31 May 2017 and 10 Jan 2018. The cardiomyopathy SLR search also applied date limits to published abstracts, with abstracts published prior to 2015 being excluded. There were no other restrictions based on date.

A9. Search strategy for clinical evidence (Appendix 1.1). Please confirm whether the full search strategies used for SLR report are the same as the strategies described in the draft study SLR protocol in September 2017 (Appendix 1.2). If not, please provide full search strategies as reported in the SLR and clarify any differences.

Response: The search strategies used in the SLR report are the same as the core searches described in the draft SLR study protocol (September 2017) with the following additions:

1) At the update executed on 10 January 2018, in addition to all the core searches of the September 2017 protocol, the strategies used in Medline and EMBASE were repeated, this time identifying only non-English reports and reports without abstracts. There were no date limits placed on these supplemental searches, and so the results were current to 10 January 2018. This was done to identify any possible relevant publications with these characteristics that were excluded by the original search. The details of the Medline and EMBASE searches are presented in Table 2.

Table 2. Search strategies for the Medline and EMBASE searches, polyneuropathy SLR update.

Search Number	Search Terms	Yield
PubMed Medline Search: 10 Jan 2018 - All Articles Without an Abstract OR all non-English Articles with an Abstract (i.e., all Articles Without an Abstract & all non-English Articles)		
#1	"amyloid neuropathies, familial"[MeSH Terms] OR “familial amyloid polyneuropathy”[tiab]	1311
#2	hattr[tiab] OR (“familial”[tiab] OR “inherited”[tiab] OR “hereditary”[tiab] OR val30met[tiab] OR v30m[tiab] AND (attr[tiab] OR ttr[tiab] OR transthyretin[tiab] OR amyloid*[tiab]))	7265
#3	polyneuropath*[tiab] OR neuropath*[tiab]	123131
#4	#1 OR (#2 AND #3)	2609
#5	#4 AND hasabstract[text] NOT (("animals"[MeSH Terms:noexp] NOT “humans”[MeSH]) OR editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR “in vitro techniques”[MeSH])	2168
#6	#5 NOT Review[ptyp] NOT ((systematic[tiab] AND review[tiab]) OR MEDLINE[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Ovid[tiab] OR Meta-Analysis[ptyp] OR meta-analy*[tiab] OR (indirect[tiab] OR mixed[tiab] AND “treatment comparison”[tiab]))	1767
#7	#6 NOT English[lang]	117 (non-English articles with an abstract)
#8	#4 NOT (("animals"[MeSH Terms:noexp] NOT “humans”[MeSH]) OR editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR “in vitro techniques”[MeSH]))	2404

Search Number	Search Terms	Yield
#9	#8 NOT Review[ptyp] NOT ((systematic[tiab] AND review[tiab]) OR MEDLINE[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Ovid[tiab] OR Meta-Analysis[ptyp] OR meta-analy*[tiab] OR (indirect[tiab] OR mixed[tiab] AND "treatment comparison"[tiab]))	1980
#10	Search (#9 NOT hasabstract[text])	213 (all articles w/out an abstract)
#11	Search (#7 or #10)	330
OVID Embase: 1974 to 10 January 2018 -- All Articles Without an Abstract OR all non-English Articles with an Abstract (i.e., all Articles Without an Abstract & All non-English Articles)		
#1	exp *familial amyloid polyneuropathy/ or 'familial amyloid polyneuropathy'.ti,ab.	1662
#2	(hattr or (('familial' or 'inherited' or 'hereditary' or val30met or V30m) and (attr or ttr or transthyretin or amyloid*))).ti,ab.	9819
#3	(polyneuropath* or neuropath*).ti,ab.	171499
#4	1 or (2 and 3)	3482
#5	limit 4 to abstracts	3149
#6	limit 5 to English language	2901
#7	5 not 6	248
#8	7 not ((exp animal/ or nonhuman/) not exp human/)	248
#9	8 not (exp case study/ or case report/ or exp letter/ or exp editorial/ or animal model/ or in vitro study/)	187
#10	limit 9 to (editorial or letter or note)	0
#11	9 not 10	187
#12	limit 11 to (yr="1960 - 2014" and conference abstract)	0
#13	11 not 12	187
#14	"review"/	2257914
#15	((systematic and review) or MEDLINE or Embase or Cochrane or Ovid or meta-analy* or ((indirect or mixed) and 'treatment comparison')).ti,ab.	315072
#16	exp meta analysis/	137007
#17	15 or 16	344802
#18	14 not 17	2132571
#19	13 not 18	138 (non-English articles with an abstract)
#20	4 not 5	333
#21	20 not ((exp animal/ or nonhuman/) not exp human/)	328
#22	21 not (exp case study/ or case report/ or exp letter/ or exp editorial/ or animal model/ or in vitro study/)	178
#23	limit 22 to (editorial or letter or note)	14
#24	22 not 23	164

Search Number	Search Terms	Yield
#25	limit 24 to (yr="1960 - 2014" and conference abstract)	0
#26	24 not 25	164
#27	26 not 18	142 (all articles w/out an abstract)
#28	19 or 27	280
#29	limit 19 to (conference abstract or conference paper or "conference review")	22 (conference abstracts)
#30	28 not 29	258 (journal articles)

2) Additional searches in PsychInfo, WHO ICTRP, NICE, SMC, CADTH, and AWMSG were conducted. A search of these sites was not part of the September 2017 study protocol. The searches conducted on these websites were as shown in Table 3.

Table 3. Additional search strategies for the polyneuropathy SLR update.

Search Number	Search Terms	Yield
PsycINFO via APA PsychNet: January 10, 2017		
#1	((Any Field: (polyneuropath*) OR Any Field: (neuropath*))) AND ((((Any Field: (familial)) OR (Any Field: (inherited)) OR (Any Field: (hereditary)) OR (Any Field: (val30met)) OR(Any Field: (v30m))) AND ((Any Field: (attr)) OR (Any Field: (ttr)) OR (Any Field: (transthyretin)) OR (Any Field: (amyloid*)))) OR (((Any Field: (hattr)))) OR (((Any Field: (familial amyloid polyneuropathy)))))	376
WHO ICTRP: January 11, 2018		
#1	(amyloidosis OR amyloid OR transthyretin) AND (neuropathy OR polyneuropathy) in title	24
#2	(amyloidosis OR amyloid OR transthyretin) AND (neuropathy OR polyneuropathy) in condition	34
NICE: January 11 2018		
#1	Using Google advanced: allintitle: amyloidosis OR amyloid OR transthyretin OR Diflunisal OR Tafamidis OR "liver transplant" OR "IONIS TTR" site: https://www.nice.org.uk/	2
SMC: January 11 2018		
#1	Using Google advanced: amyloidosis OR amyloid OR transthyretin OR Diflunisal OR Tafamidis OR "liver transplant" OR "IONIS TTR" site: https://www.scottishmedicines.org.uk/	1
CADTH: January 11, 2018		
#1	Using Google advanced: amyloidosis OR amyloid OR transthyretin OR Diflunisal OR Tafamidis OR "liver transplant" OR "IONIS TTR" site: https://www.cadth.ca/	0

Search Number	Search Terms	Yield
AWMSG: January 11, 2018		
#1	Using Google advanced: amyloidosis OR amyloid OR transthyretin OR Diflunisal OR Tafamidis OR "liver transplant" OR "IONIS TTR" site: http://www.awmsg.org/	2

AWMSG: All Wales Medicines Strategy Group; CADTH: Canadian Agency for Drugs and Technologies in Health; EMA: European Medicines Agency; FDA: Food and Drug Administration; ICTRP: International Clinical Trials Registry Platform; NICE: National Institute for Health and Care Excellence; SLR: systematic literature review; SMC: Scottish Medicines Consortium; WHO: World Health Organization

A10. Please update Table S1 of Appendix 1 to include a fourth column for the sources searched in the literature scan in July 2018.

Response: The sources for the literature scan are the same as those for the January update. Following is a revised version of the Appendix table with the requested fourth column.

Table 4. Revised version of CS Appendix 1, Table S1.

Database	Original SLR (to 30 May 2017)	SLR Update (31 May 2017 to 10 Jan 2018)	Study Scan (11 Jan 2018 to 08 July 2018)
Medline (PubMed)	✓	✓*‡	✓
Embase	✓	✓*‡	✓
Embase (Conference abstracts)	✓	✓*‡	✓
Cochrane Library	✓	✓*	✓
Econlit	✓	✓*	✓
PsychInfo		✓	✓
ClinicalTrials.gov	✓	✓†	✓
WHO ICTRP		✓	✓
FDA	✓	✓†	✓
EMA	✓	✓†	✓
NICE		✓	✓
SMC		✓	✓
CADTH		✓	✓
AWMSG		✓	✓

*Also searched retroactively for observational and single-arm interventional studies
‡Also searched retroactively for non-English-language citations, and citations with no abstract
†Also searched retroactively for single-intervention trials
AWMSG: All Wales Medicines Strategy Group; CADTH: Canadian Agency for Drugs and Technologies in Health; EMA: European Medicines Agency; FDA: Food and Drug Administration; ICTRP: International Clinical Trials Registry Platform; NICE: National Institute for Health and Care Excellence; SLR: systematic literature review; SMC: Scottish Medicines Consortium; WHO: World Health Organization

A11. In Appendix 1.3 and Appendix 1.4, the literature searches carried out in July 2018 for hATTR amyloidosis with polyneuropathy SLR and ATTR amyloidosis with cardiomyopathy SLR differ from the original SLR search strategies in May 2017 and January 2018 (Appendix 1.2). Please state the reasons for not searching literature for all years for hATTR amyloidosis with cardiomyopathy (pre-2014, Embase) and the implications for finding relevant literature.

Response: The search strategies of May 2017 were supplemented in January 2018 with searches for non-English studies and studies without an abstract (please see response to Question A9 above). In July of 2018, these conditions for including non-English studies and studies without an abstract were integrated into the Medline and EMBASE searches, thus resulting in some modification to the original search. All other aspects of the searches

remained the same. There was also a supplemental search of PsychInfo as well as key HTA websites in January 2018 and July 2018, which has also been described in the response to Question A9.

The only date restriction made in EMBASE (pre-2014) was in relation to conference abstracts. It is common practice to exclude abstracts published >2 years prior to the search date in SLRs. Full papers published on any date would have been identified through EMBASE and included in the SLRs. The exclusion of conference abstracts published prior to 2015 is unlikely to have had an important impact on this review as abstracts published over a 3½-year period (January 2015 to July 2018) were eligible for inclusion, and evidence for interventions in hATTR amyloidosis is fairly recent.

A12. Please comment on the implications of limiting publications to English-language only at the searching stage?

Response: At the time of preparing the update to the polyneuropathy SLR, it was decided that the English-language–only restriction should be removed (please see detailed response to Question A9 for the search that was used to identify non-English studies). Non-English language studies, with no date restrictions, were searched for systematically in the polyneuropathy SLR update, and no language restrictions were placed on the cardiomyopathy SLR searches.

Systematic Review Methods

A13. **Priority question**. Please clarify why a systematic review of best supportive care (BSC) has not been undertaken. Please provide details of any relevant studies describing outcomes in patients receiving BSC which were excluded from the clinical effectiveness review.

Response: Best supportive care was not excluded as an intervention or as a comparator, as per the PICOS Criteria. Nevertheless, the SLRs did not identify any studies that explicitly compared a treatment to BSC. Although not explicitly described as such by the studies we reviewed, it is likely that some studies provided BSC in conjunction with a pharmacological intervention or with a placebo; however, we were not able to determine if this was the case from the information provided in the published reports that were reviewed.

A14. Please clarify why separate systematic literature reviews were undertaken according to whether patients had polyneuropathy or cardiomyopathy rather than undertaking reviews within hATTR as a single disease.

Response: Due to the historical concept of two separate diseases, two SLRs were conducted, one for hATTR amyloidosis with polyneuropathy and the other for hATTR amyloidosis with cardiomyopathy. The two SLRs were conducted separately as there was some concern that running them together may have complicated the searches. We did find a great deal of overlap and so we are confident that we captured all the relevant studies.

A15. In Figure 3 page 62, and Figure 4 page 63 of CS, please clarify the following:

a. Where the manually added studies came from

Response: One study was manually added to the polyneuropathy SLR (as reported in CS Figure 3). This was an abstract for a single-arm open-label trial of diflunisal that was discovered while reviewing the selected studies.

Six studies were manually added to the cardiomyopathy SLR (see CS Figure 4). One of the studies was the diflunisal study described above from the polyneuropathy SLR, which also contained a cardiac subpopulation. Three studies were from a recent 2017 conference that was hand-searched (one study each for patisiran, inotersen, and tafamidis), one was a paper that did not contain cardiomyopathy-related keywords in the title or abstract but had a cardiac subpopulation and was known to us from the polyneuropathy SLR and so was included (tafamidis), and one was an abstract that was not detected by the literature search but that was known to the manufacturer (patisiran).

b. Why 2 different reviews (the "SLR" and the "submission" in the lower boxes of the PRISMA diagrams) were undertaken for each of hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy.

Response: The number of studies in the submission excludes the natural history studies and the grey literature reports that were identified in the original SLR search. These types of studies were not screened for or included in the polyneuropathy SLR update or in the submission. This has been noted in CS Figure 3.

c. Why studies were excluded according to the following when these were not mentioned in the exclusion criteria: observational study of <50 patients, being an NH study outside of the US or Europe, language, and being reported in an abstract <2015 (in Figure 3 only, page 62)

Response: The observational studies of <50 patients were natural history (NH) studies and were not searched for in the polyneuropathy SLR update nor were they part of the submission. The exclusion of NH studies outside the US or Europe (in the PICOS table of the September 2017 protocol) was part of the original search; again, natural history studies were not included in the update and were not part of the submission. The September 2017 protocol for the polyneuropathy SLR indicated that studies would be limited to the English language (page 3); however, this restriction was reversed with the SLR update conducted in January 2018 and non-English language studies were searched for systematically with no date limits (please see detailed response to question A9 in this document). The exclusion of abstracts published prior to 2015 was not explicitly stated in the text of the protocol of September 2017; however, this exclusion is made in line 5 of the search algorithm for EMBASE on page 4 of that protocol.

A16. Please clarify why items 6(b), 9, 10, 11 and 12 from the CASP checklist for cohort studies (see https://casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Study-Checklist-Download.pdf) were omitted from Tables S7, S8 and S9 pages 17-19 of Appendix 1. Please provide answers to these items.

Response: The quality appraisal was conducted in accordance with the suggested format for the critical appraisal of observational studies, provided in Table C8 (page 28) of the NICE HST Interim specification for company submission of evidence (May 2017). The HST template specifies a modified version of the CASP checklist, which does not include the items that you noted we have omitted.

Population

A17. **Priority Question**. In the studies included in the SLR (CS, Section 9.3.1, page 64 and Table C2, page 65), please clarify whether patients were enrolled into more than one study, and if so how many, in which studies and which arms (if APOLLO)?

Response: There was no overlap between patients in the phase 2 study (NCT01617967) and the APOLLO trial (NCT01960348), and no overlap between patients in the phase 2 OLE study (NCT01961921) and APOLLO. All 27 patients enrolled in the phase 2 OLE had previously participated in the phase 2 study.[2] All 211 patients enrolled in the global OLE (NCT02510261) had previously participated in either the phase 2 OLE (n=25) or APOLLO (patisiran arm n=137, placebo arm n=49).[1]

A.18. **Priority Question** Please clarify whether all patients in the OLE studies have the same on-treatment duration at the data cut-point reported. If not, please clarify how many patients are at each time point, and how many are missing (excluding those who did not receive the treatment for long enough).

Response: The latest available data on the OLE studies were published by Suhr et al. 2018.[1] Patients enrolled in the global OLE study have not all had the same on-treatment duration at the data cut-point reported. As of December 2017, 25 patients had completed 36 months of total patisiran treatment, all of whom were patients rolling over from the Phase 2 OLE into the global OLE study. As of this date, 52 patients had completed 30 months of patisiran treatment, namely those patients rolling over from the APOLLO study into the global OLE study.

In total, 44% of 211 patients enrolled in the OLE study had completed their 52-week assessment (i.e., received at least 30 months of patisiran treatment experience). The remainder had not.

Study Design

A19. **Priority question.** For the Phase 2 trials, the dose described (on page 70; doses ranging from 0.01 mg/kg to 0.3 mg/kg Q3W) appears to be different to that described in the licence and in APOLLO (0.3 mg/kg Q3W). Please clarify why the dosing regimens differ, and what effect this may have had on results.

Response: The different dosing regimens reflect the different objectives of the phase 2 study and the phase 3 APOLLO trial. Phase 2 studies are often dose-ranging studies concerned with determining the optimal dosage for a drug, and accordingly the phase 2 patisiran study objectives were to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple ascending doses of patisiran. The results of the phase 2 study informed the dosage selected for the APOLLO trial. The difference in dosages between the phase 2 study and the APOLLO study has no effect on the results of the cost-effectiveness analysis in the CS because the efficacy, safety and drug utilisation parameters in the model were all derived from APOLLO data.

A20. Please clarify how the randomisation was performed in the APOLLO study (e.g. simple randomisation or permuted blocks) in Section 9.1 of the CS?

Response: Randomisation to treatment arms in APOLLO was stratified at entry for Neuropathy Impairment Score (NIS; 5-49 vs 50-130), early-onset V30M (<50 years of age at onset) vs all other mutations (including late-onset V30M), and previous tetramer stabiliser use (tafamidis or diflunisal) vs no previous tetramer stabiliser use.[3] Patients were centrally randomised via an interactive response system using permuted blocks.[4] Randomisation numbers were assigned sequentially within the eight combinations of the stratification factors:

1. NIS 10-49, early onset V30M, previous tetramer stabiliser use
2. NIS 10-49, early onset V30M, no previous tetramer stabiliser use
3. NIS 10-49, later onset V30M and all other mutations, previous tetramer stabiliser use
4. NIS 10-49, later onset V30M and all other mutations, no previous tetramer stabiliser use
5. NIS 50-100, early onset V30M, previous tetramer stabiliser use
6. NIS 50-100, early onset V30M, no previous tetramer stabiliser use
7. NIS 50-100, later onset V30M and all other mutations, previous tetramer stabiliser use
8. NIS 50-100, later onset V30M and all other mutations, no previous tetramer stabiliser use

The 2:1 treatment allocation (patisiran to placebo) was maintained within each of the eight combinations of stratification factors.[4] However, there was no restriction on the numbers of subjects randomised within any given combination of factors, because the randomisation scheme produced sufficient randomisation numbers to allow for an arbitrary number of subjects to be enrolled within a given combination of factors. In particular, within a given stratum (i.e., combination of stratification factors), 36 blocks of size six were generated for a total of 216 randomisation numbers per stratum, and a grand total of 1728 randomisation numbers across all eight strata.

Treatment codes were generated using a permuted block design utilising SAS© PROC PLAN.[4] Eligible subjects were randomised to the next available treatment assignment within the block open for the relevant stratum.

A21. Table C5 page 81 states that *"Demographics and clinical characteristics were generally balanced between the patisiran and placebo treatment groups."* However, Table C4 page 78 suggests a noticeable difference in the proportion of patients with cardiac involvement between the groups. Please comment on how this may have impacted on the overall results of the study.

Response: The proportion of patients who were in the cardiac subpopulation of APOLLO was higher in the patisiran arm (n=90/148, 60.8%) than in the placebo arm (n=36/77, 46.8%).[3] In a randomised study, particularly one with relatively small sample size, it is not unusual to observe baseline imbalances by chance, which was the reason for this imbalance.

The academic literature suggests that hATTR amyloidosis patients with cardiac involvement have a worse prognosis than those without.[5,6] Therefore, one may speculate that the higher rate of cardiomyopathy in the patisiran arm could have biased the results on several secondary and exploratory endpoints against patisiran, potentially including all measures of HRQoL, gait speed, and cardiac assessments. This imbalance is not expected to have had a substantial effect on the primary endpoint of APOLLO, change from baseline to 18 months in the mNIS+7, because this is a measure of neuropathy, not cardiomyopathy or its associated symptoms.

Despite this unfavourable imbalance, patisiran showed highly significant efficacy results, with an acceptable safety profile.

A22. Please provide details of prior therapies received by patients in the APOLLO study by treatment group (Section 9.9.4, page 115).

Response: The details of which prior therapies APOLLO patients had received are presented in Table 5. Notably, both treatment arms had a similar distribution of previous tetramer stabiliser use (achieved by balancing patients at randomisation by this variable), and patients in each arm were diverse in their prior therapy experience.

Table 5. Previous tetramer stabiliser use in APOLLO.

	Placebo (N=77)	Patisiran (N=148)	Total (N=225)
Previous tetramer stabiliser use, n (%)	41 (53.2)	78 (52.7)	119 (52.9)
Tafamidis	27 (35.1)	47 (31.8)	74 (32.9)
Diflunisal	14 (18.2)	31 (20.9)	45 (20.0)
Days from discontinuation of tetramer stabiliser to start of study drug, mean±SD	31.4±29.32	54.2±124.94	46.4±102.94

Source: Alnylam, data on file (APOLLO CSR)[7]

A23. Please clarify how many UK patients were recruited into each of the patisiran studies included in the SLR (section 9.4, page 72)?

Response: The number of UK patients in each of the patisiran studies is presented in Table 6.

Table 6. Number of UK patients in patisiran studies.

Study	Number of UK patients
Phase 2 trial, NCT01617967	0
Phase 2 open-label extension, NCT01961921	0
APOLLO phase 3 trial, NCT01960348	2
Global open-label extension, NCT02510261	1

A24. Please clarify how missing data were dealt with, particularly with respect to the primary outcome.

Response: As reported in the final protocol accompanying the APOLLO primary publication (in its Supplementary Appendix), patients who prematurely discontinued from the study had their 78-week mNIS+7 change from baseline value (i.e., primary outcome) imputed using a stepwise regression approach for identification of explanatory variables (e.g., demographics, stratifying variables, and baseline/9-month mNIS+7 data when available); treatment assignment was not included in the imputation.[3] A minimum of 100 imputed datasets were analysed as complete cases via the ANCOVA model specified for the primary analysis, and then combined to produce inferential results.

The following additional details are excerpted from the APOLLO Statistical Analysis Plan (SAP) that outlines how missing data was dealt with (the appendices and other sections referred to can be found in the full SAP, which is attached):[8]

"All efficacy data collected during study, regardless of whether before or after treatment discontinuation, will be included for analyses, with the exception of mNIS+7, Norfolk QOL, and NIS-W assessments collected post alternative FAP treatment (discussed in Section 3.7).

3.8.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints

For each patient, missing subcomponents within the primary mNIS+7 endpoint and secondary efficacy endpoints will be imputed whenever possible according to the algorithm specified in Appendix 7.2.1 through Appendix 7.2.5. When this "partial imputation" is successful (i.e., complete mNIS+7 values are produced), these values will be used in all statistical analyses.

When partial imputation is unsuccessful, the efficacy endpoint will be treated as completely missing.

3.8.2. Summary of Missing Data

For each of the primary and secondary efficacy endpoints, the number and percentage of missing data (completely missing) at each visit (baseline, 9-month, and 18-month) will be summarised by study arm.

Time to treatment discontinuation will be estimated descriptively using Kaplan-Meier method by treatment arm. Patients completing study treatment will be censored at the last dose of study drug.

Spaghetti plots will be presented to display the trajectories over time for individual patient's change from baseline in mNIS+7 and Norfolk QOL-DN for patients who have missing 18-month assessments.

3.8.3. Handling of Missing Data

For the primary and secondary efficacy endpoints, the primary analysis will be based on the mixed-effects model repeated measures (MMRM) method, which makes use of fully and partially observed data sequences from individual patients by estimating the covariance between data from different time points. The MMRM will be implemented using an unstructured approach to modelling both the treatment-by-time means and the (co)variances, leading to what is essentially a multivariate normal model wherein treatment arm means at the primary time point are adjusted to reflect both the actually observed data and the projected outcomes from the patients with missing data [11]. In this primary analysis, missing data will not be imputed and are assumed to be missing-at-random (MAR). For the primary endpoint mNIS+7 and the first secondary endpoint Norfolk QOL, sensitivity analyses will be conducted to assess the impact of missing data as discussed in Section 4.3."

A25. In APOLLO (Section 9.3.2, page 67), *"Patients had the option of discontinuing the study drug if they experienced a protocol-defined rapid disease progression at 9 months (defined as ≥24-point increase in mNIS+7) and FAP stage progression relative to baseline and confirmed by an external adjudication committee."* Please clarify:

a. Whether patients or clinicians made the decision to discontinue.

Response: The patient's treating physician provided the patient with the option of discontinuing study drug.

b. How many patients met the criteria, and how does this relate to the "progressive disease" discontinuation reason given in Table C3?

Response: A total of seven patients met these pre-defined criteria for rapid disease progression: six in the placebo group and one in the patisiran group. Details for these patients are presented in Table 7. The "progressive disease" category given in CS Table C3 corresponds to the same rapid disease progression criteria.

Table 7. Patients with rapid disease progression in APOLLO.

Treatment arm	Last dose study day	Patient's decision*	Completed treatment/ completed study	mNIS+7			FAP stage		
				Baseline	Change from baseline at Month 9	Change from baseline at Month 18	Baseline	Month 9	Month 18
Placebo	547	1	Y/Y	58.0	29.3	27.3	I	II	II
	275	2	N/Y	99.0	34.3	-3.8	I	II	II
	295	2	N/Y	81.1	32.1	54.9	I	II	II
	315	2	N/Y	136.5	31.0	27.2	II	III	III
	253	2	N/Y	87.5	36.0	50.8	II	III	III
	253	3	N/N	70.0	45.4	-	II	III	-
Patisiran	337	2	N/Y	79.8	35.5	28.3	I	II	II

Note: each row presents details for one patient.
FAP: familial amyloidotic polyneuropathy; mNIS+7: modified Neuropathy Impairment Score+7.
*1=Remain on study drug and continue with the current visit schedule; 2=Discontinue study drug and will now follow the Modified Schedule of Assessments; 3=Discontinue study drug and participation in the study.
Source: Alnylam, data on file (APOLLO CSR)[7]

c. How many patients met the criteria and stopped treatment?

Response: As shown in Table 7 above, a total of six patients met the pre-defined criteria for rapid disease progression and stopped treatment: five in the placebo group (including four who remained in the study and one who withdrew from the study) and one in the patisiran group who remained in the study. The 5.2% of placebo patients and 0.7% of patisiran patients with treatment discontinuation due to progressive disease mentioned in CS Table C3 correspond to these patients with rapid disease progression who stopped treatment but remained in the study.

d. How the analyses handled missing data points for the patients who stopped treatment because of rapid disease progression at 9 months?

Response: Please see the answer to A24.

e. Whether this stopping rule will be applied in clinical practice, and therefore necessitate the use of mNIS+7 by clinicians.

Response: Alnylam is not proposing that this stopping rule be used in clinical practice, and to the best of our knowledge, UK clinicians do not intend to use this stopping rule in clinical practice. We therefore do not believe that this rule will necessitate the use of mNIS+7 by clinicians.

A26. Please clarify the time period over which the Suhr *et al* (2015) study was conducted (Section 9.4.4, page 80). In the paper, results are only reported at 115 days.

Response: Assessments in this phase 2 study were performed over a 56-day study period.[9] However, patients returned to the site for outpatient visits for safety, pharmacokinetic and pharmacodynamic monitoring for up to 208 days post dose. The duration of patient participation in this study was approximately 36 weeks.

A27. CS, Section 9.4.6, page 80. Please clarify whether "03 mg/kg" should be 0.3 mg/kg.

Response: Apologies for this typo, which should indeed read "0.3 mg/kg".

A28. Please clarify the criteria for moving to home care. Please clarify how many patients met the criteria in APOLLO and the OLE.

Response: As specified in the patisiran SmPC, "infusion … at home may be considered for patients who have tolerated at least 3 infusions well in the clinic. The decision for a patient to

receive home infusions should be made after evaluation and recommendation by the treating physician."

Home infusion was not offered to patients in the APOLLO study.

It is not possible to say how many OLE patients met the above criteria because:

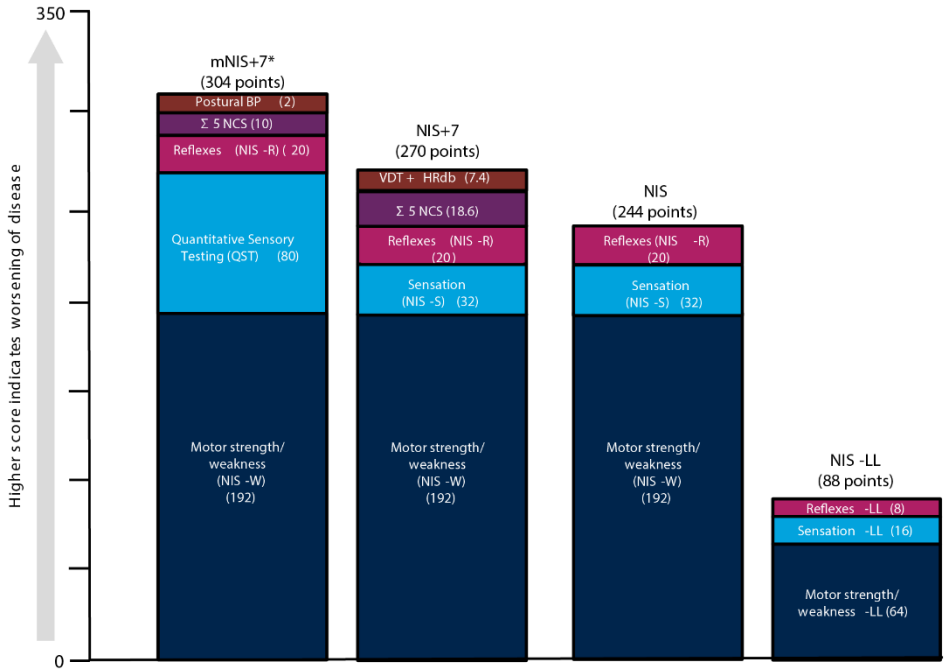
- Home infusion was only offered to patients in selected regions where local and country regulations allowed; not all OLE participants were therefore considered for homecare and because, as per the SmPC, the decision to move a patient onto homecare is a clinical decision involving clinical judgment it is not possible to infer this from APOLLO data.
- The criteria for home infusion in the OLE were different (more stringent) than that in the SmPC. In the OLE, home infusions were allowed following three completed doses at a clinical site with no evidence of IRRs or other AEs.

Outcomes

A29. **Priority Question**: Please clarify what the clinically important difference is for each outcome measure.

Response: Clinically important differences for the APOLLO outcome measures are reported in Table 8.

Table 8. Clinically important difference for measures in APOLLO.

Outcome measure	Clinically important difference
mNIS+7	A consensus report of the international Peripheral Nerve Society defined a 2-point change as the MCID for the original NIS score (the predecessor to the NIS+7 and the mNIS+7).[10] The rationale for this threshold is that it represents the degree of change that is twice (for the two sides of the body) the least degree of neurological impairment change that can be recognised on physical exam by an examining physician. Although this MCID was estimated for the original NIS scale, this 2-point threshold was used to define "responders" in a phase 3 trial of tafamidis that used the NIS-Lower Limbs (NIS-LL) as a co-primary endpoint,[11] and was also identified to represent a minimally clinically detectable change in polyneuropathy progression as measured by NIS+7 in a phase 3 trial of diflunisal.[12] This same 2-point MCID was also applied to the mNIS+7 in a phase 3 study of inotersen.[13] The following graph shows a side-by-side alignment of the NIS, NIS-LL, NIS+7 and mNIS+7. The NIS, NIS+7, and mNIS+7 use the same NIS-W component, which is the largest component of all the scales. The NIS-LL assesses motor weakness in the lower limbs, but not in upper limbs or body, and thus has a lower total NIS-W score; however, in the tafamidis phase 3 trial it was used in early-stage patients in whom polyneuropathy was limited to the lower limbs.  At present, no minimal clinically significant difference has been defined for mNIS+7; however, given the rationale in the consensus report and precedents in trials using NIS-LL and NIS+7 as endpoints, a similar threshold of 2 points could be applied to mNIS+7.
Norfolk QoL-DN	The MCID of the Norfolk QoL-DN has not yet been reported in the literature. However, this measure has been demonstrated to clearly distinguish between FAP stages.[14]
TTR knockdown	Disease modelling indicates that on a population basis, TTR reduction of ≥80% is predicted to lead to halting or reversal of neuropathy progression, as indicated by stabilisation or improvement in mNIS+7 from baseline.[15]
PND score	Because functional impairment worsens with each higher level of PND score, any change of PND score should be considered clinically important.
NT-proBNP	Data with regard to changes in NT-proBNP as a response to treatment are available from the cardiac amyloidosis literature, in which changes in NT-proBNP of 30% and 300 ng/L, in response to therapy, are predictive of outcomes in large, independent studies.[16,17] Furthermore, as reviewed in CS Section 6.1.4, NT-proBNP levels above ~3000 pg/mL are associated with poor short-term survival in patients with hATTR amyloidosis.[5,18] This supports the stratification of patients by NT-proBNP <3000 pg/mL vs ≥3000 pg/mL in the CS.

Outcome measure	Clinically important difference
10MWT	Among older adults, including those with mobility disabilities and subacute stroke survivors, a mean increase of 0.05 m/s represents a small meaningful change in gait speed and of 0.10 m/s represents a substantial clinically meaningful change, based on distribution- and anchor-based approaches.[19]
Grip strength	A change in grip strength of 4.7–6.2 kg has been reported to be clinically meaningful.[20]
COMPASS-31	The MCID of the COMPASS-31 has not yet been reported in the literature. However, this measure has been demonstrated to correlate with other measurements of pain and HRQoL.[21]
R-ODS	The MCID of the R-ODS has not yet been reported in the literature. However, an analysis of data from APOLLO and the phase 2 OLE using Rasch measurement methods indicated that the R-ODS is a reliable and valid measure of activity and social participation limitations in patients with hATTR amyloidosis.[22]

Σ5 NCS: sum of five nerve conduction study parameters; 10MWT: 10-metre walk test; AL: immunoglobulin light chain; BP: blood pressure; COMPASS-31: Composite Autonomic Symptom Score-31; hATTR: hereditary transthyretin-mediated amyloidosis; HRdb: heart rate variation with deep breathing; LL: lower limbs; MCID: minimal clinically important difference; mNIS+7: modified NIS+7; NIS: Neurologic Impairment Score; NIS+7: Neurologic Impairment score +7; NIS-LL: NIS-lower limbs; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PND: Polyneuropathy Disability; NT-proBNP: N-terminal pro B-type natriuretic peptide; R-ODS: Rasch-built Overall Disability Scale; TTR: transthyretin; VDT: vibration detection threshold.

A30. Please clarify how the mNIS+7 was modified from the NIS+7 and provide details regarding the scoring system for this instrument (Section 4.2, page 46).

Response: The mNIS+7 scale is a multi-dimensional composite score designed specifically to assess both small and large nerve fibre impairment in hATTR amyloidosis clinical trials. It encompasses the totality of the sensory, motor and autonomic polyneuropathy in hATTR amyloidosis and is therefore a robust and clinically meaningful measure of neuropathy progression in this disease. The mNIS+7 was developed by the Mayo Clinic Peripheral Nerve Research Laboratory for use specifically in patients with hATTR amyloidosis with polyneuropathy.[23]

Table 9 describes the scoring of the different components of the mNIS+7. These components make the mNIS+7 well suited for use in hATTR amyloidosis, allowing it to track motor, sensory and autonomic signs combined with objective diagnostic assessments of motor (motor nerve NCS) and sensory function (sensory nerve NCS and S-ST QST).[24] Additionally, S-ST QST measurements not only capture the degree of abnormality but also the location where the abnormality occurred. These features allow mNIS+7 to capture the varied symptomatology of hATTR amyloidosis, which ranges from a length-dependent, small-fibre sensory-motor polyneuropathy in early-onset disease, to a more severe, multisystemic disease that can affect all fibres in late-onset disease.[25,26] Furthermore, interrogation of the separate elements of the mNIS+7 scale allows investigators to pinpoint how individual symptoms are affected.

Table 9. mNIS+7 components, scoring and methodology.

Component	Body regions/nerves evaluated	Methodology including scoring
Motor strength/weakness Neurological impairment score-weakness (NIS-W) (192 points)	48 muscle groups in lower limb, upper limb and body and cranial nerve components Assessments are performed separately for the right and left side of the body	Physical exam evaluating motor strength is performed. A score of 0 (normal), 1 (25% weak), 2 (50% weak), 3 (75% weak) to 4 (paralysis) is applied to muscle groups. The scores for individual muscle groups are summated to get the total NIS-W score.

Component	Body regions/nerves evaluated	Methodology including scoring
Quantitative sensory testing (QST) (80 points)	Up to 10 anatomical sites Assessments are performed on one side of the body	Touch pressure by body surface area (QST-BSATP) and heat pain by body surface area (QST-BSAHP) are assessed at up to 10 anatomical sites using CASE (Computer Aided Sensory Evaluator) IV. A score of 0 (< 95th percentile), 1 (≥95th and <99th percentile) or 2 (≥99th percentile) is applied at each anatomical site, summated across all anatomical sites and then multiplied by 2 (for 2 sides of body).
Reflexes (NIS-reflexes or NIS-R) (20 points)	5 reflexes in lower limb, upper limb and body Assessments are performed separately for the right and left-hand side of the body	A physical exam evaluating 10 reflexes is performed. A score of 0 (normal), 1 (decreased) or 2 (absent) is applied to each reflex and summated to get the total NIS-R score.
Σ5 Nerve Conduction Studies (Σ5 NCS) (10 points)	Ulnar CMAP Ulnar SNAP Sural SNAP Tibial CMAP Peroneal CMAP	Nerve conduction studies are performed on one side of the body. Values are transformed to percentile value correcting for applicable variables of age, gender, height, or weight based on earlier studies of a large healthy-subject reference cohort and expressed as points: >5th percentile = 0 points; ≤5th percentile to >1st percentile = 1 point; ≤1st percentile = 2 points.
Postural blood pressure (2 points)	Autonomic nerves	Postural blood pressure test is performed, and points assigned based on the change in blood pressure with standing: blood pressure decrease of <20 mmHg = 0 points, 20 to <30 mmHg = 1 point, ≥30 mmHg = 2 points.

CMAP: compound muscle action potential; mNIS+7: Modified Neurological Impairment Score+7; SNAP: sensory nerve action potential; VDT: vibration detection threshold

The differences between the mNIS+7 and the NIS+7 can be compared in Table 10, which also provides their points for their scoring.

Table 10. Comparison of the components of the NIS+7 and the mNIS+7.

	Total points	Components (points)
NIS+7	270	• Neurologic exam of lower limbs, upper limbs and cranial nerves (NIS) ◦ Weakness (192) ◦ Sensation (32) ◦ Reflexes (20) • Nerve conduction studies ∑5 (18.6) ◦ Sural SNAP, tibial motor n. distal latency, peroneal SNAP/motor n. conduction velocity/motor n. distal latency • Vibration detection threshold (3.7) • Heart rate response to deep breathing (3.7)
mNIS+7	304	• Neurologic exam of lower limbs, upper limbs and cranial nerves (mNISa) ◦ Weakness (192) ◦ Reflexes (20) • Nerve conduction studies ∑5 (10) ◦ Ulnar CMAP and SNAP, sural SNAP, tibial CMAP, peroneal CMAP • Quantitative sensory testing: QST-BSA$_{TP+HP5}$ (80) • Postural blood pressure (2)

CMAP: compound muscle action potential; mNIS+7: modified Neuropathy Impairment Score+7; NIS+7: Neuropathy Impairment Score+7; QST-BSA$_{TP+HP5}$: QST touch pressure by body surface area; SNAP: sensory nerve action potential.

A31. Please provide results for the following outcomes (as stated in Section 9.4.1, page 69):

- Quantitative sensory testing
- Number of patients with rapid disease progression (at 9 months)
- Pathological evaluation of dermal amyloid burden
- Magnetic resonance neurography
- Pharmacodynamic biomarkers.

Response: The requested results are reported in Table 11.

Table 11. Exploratory endpoint results in APOLLO.

	Placebo	Patisiran
Quantitative sensory testing (80 points max. possible score)		
LS mean (95% CI) change from baseline	7.0 (4.1, 9.9)	-6.0 (-8.0, -4.1)
LS mean (95% CI) difference (patisiran - placebo)	-	-13.05 (-16.3, -9.8)
Rapid disease progression at 9 months, n patients	6	1
Dermal amyloid burden, %		
Distal thigh		
LS mean (95% CI) change from baseline	0.996% (-2.640, 4.633)	0.044% (-2.358, 2.446)
LS mean (95% CI) difference (patisiran - placebo)		-0.953% (-5.104, 3.198)
Distal leg		
LS mean (95% CI) change from baseline	2.152% (-2.451, 6.755)	0.011% (-3.029, 3.051)
LS mean (95% CI) difference (patisiran - placebo)		-2.141% (-7.492, 3.211)
Magnetic resonance neurography	Performed only on 2 patients in placebo group and 10 patients in the patisiran group who volunteered for serial scans; given the small number of patients, no conclusions can be drawn	
TTR		
Mean±SE percent reduction from baseline	4.8±3.38	84.3±1.48
	See additional TTR results reported in CS pages 93–94, including Figure 16	
Retinol binding protein		
Mean±SE percent reduction from baseline	0.48%±1.637	45.31%±1.854
Vitamin A		
Mean±SE percent reduction from baseline	0.1%±1.79	62.4%±1.19

Note: unless specified otherwise, results are at 18 months.
CI: confidence interval; LS: least square; TTR: transthyretin.
Source: Alnylam, data on file (APOLLO CSR)[7]

A32. Figure 9 (page 86) states, *"Change in mNIS+7 from baseline in patients with early or advanced neuropathy"*. Please clarify how the change in mNIS+7 relates to stage 1 and 2.

Response: CS Figure 9 defines benefits as improvement on mNIS+7. Early and progressively advanced neuropathy in this figure were not measured by PND score or FAP stage, but rather by quartiles of baseline NIS score, which do not map directly to FAP or PND scoring systems. What the figure shows is that if one stratifies the cohort by disease severity based on the NIS score at baseline (the higher the NIS score, the higher is the neuropathy severity), one can see that irrespective of the severity level at baseline, patients on patisiran improve while those receiving placebo worsen.

A33. Please clarify if there was any monitoring for treatment resistance (e.g. antibodies to treatment) and, if so, what the results of such monitoring were.

Response: Blood samples were collected in APOLLO to test for the presence of antidrug antibodies (ADA).[7] The presence of ADA was defined as serum immunoglobulin (Ig) G

(IgG)/IgM antibodies specific to PEG2000-C-DMG. A validated ELISA method was used for the screening and confirmatory ADA assays. Serum samples were first analysed with a screening assay. Samples testing ADA-positive in the screening assay were further evaluated in a confirmatory assay. For the ADA samples that tested positive for ADA in the confirmatory assay, titre (expression of level of ADA) was then determined as the reciprocal of the highest dilution of the sample that yielded a positive result. Results of the assessment are reported in Table 12. In the patisiran group, primary endpoint results were similar for ADA-positive and ADA-negative patients (mean ± SD mNIS+7 change from baseline at Month 18: -2.9 ± 18.1 vs -4.3 ± 18.24, respectively). ADA-positive patients on patisiran had a similar pattern of adverse events as observed in the overall population, and there was no evidence of an association of ADA and anaphylactic reactions, severe hypersensitivity, or infusion-related reactions.

Table 12. Summary of antidrug antibody results in APOLLO.

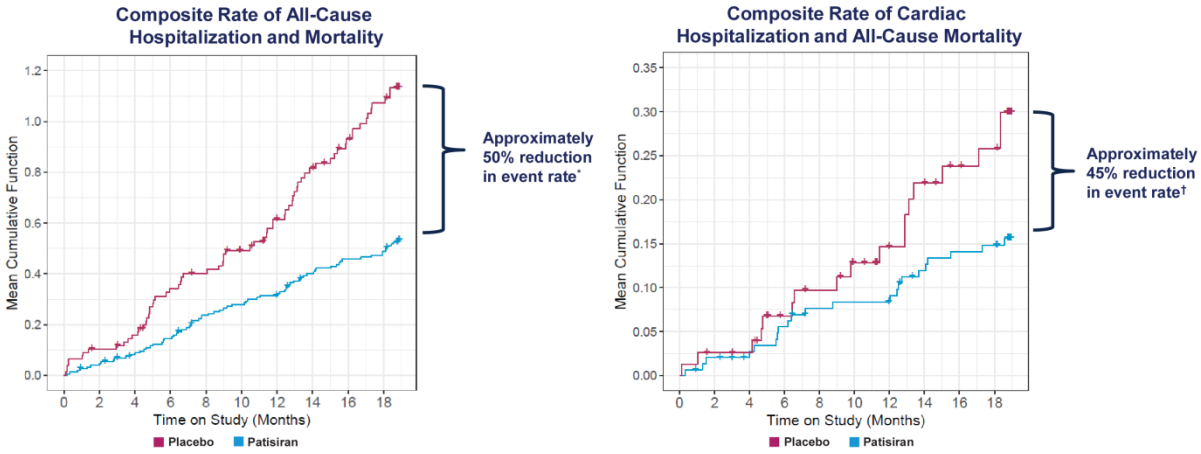
	Placebo (n=77)	**Patisiran (n=148)**
Patients with ADA measurement at baseline, n	77	147*
Patients that were ADA positive at baseline, n (%)	1 (1.3)†	1 (0.7)†
Patients with ≥1 postdose ADA measurement, n	77	146‡
Patients that were ADA positive postdose, n (%)	1 (1.3)§	6 (4.1)§
Patients with a baseline and ≥1 postdose ADA measurement, n	77	145¶
Patients with treatment-emergent ADA, n (%)	1 (1.3)	5 (3.4)

ADA: antidrug antibodies.
Baseline is defined as Day 0 predose.
Treatment-emergent ADA is defined as number of patients that were ADA positive postdose over number of patients with a baseline and at least 1 postdose ADA measurement.
*One patient 081-0002 in the patisiran group had a missing ADA measurement at baseline (Day 0 predose).
†Two patients tested ADA positive at baseline as follows: In the patisiran group one patient tested positive for ADA at baseline (titre=40) and on Day 126 (titre = 40); ADA status was not treatment-induced or boosted. In the placebo group, one patient tested positive for ADA at baseline (titre=40) and was ADA negative post-treatment for all visits.
‡Two patients in the patisiran group had missing postdose ADA measurements, but had baseline measurements available.
§In the patisiran group six patients tested positive for ADA postdose. In the placebo group, one patient tested positive for ADA postdose.
¶In the patisiran group, two patients had missing postdose ADA measurements, but had baseline measurement available; one patient had missing baseline ADA measurement, but had postdose ADA measurements available.
Source: Alnylam, data on file (APOLLO CSR)[7]

A34. Please clarify if there is any comparative evidence available on the impact of treatment with patisiran on mortality for patients who have been on treatment long-term, e.g. compared with historical data.

Response: Post-hoc analysis of data from APOLLO showed that patients on patisiran had an approximately 50% reduction in the event rate of all-cause hospitalisation and mortality vs placebo after 18 months (Figure 2).[27]

Figure 2. Composite rate of hospitalisation and mortality in APOLLO.



*For any hospitalisation/death analysis: negative binomial regression rate ratio 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio 0.48 [0.34, 0.69]
†For cardiac hospitalisation/death analysis: negative binomial regression rate ratio 0.54 [0.25, 1.16]; Anderson-Gill hazard ratio 0.54 [0.28, 1.01]
Source: Adams et al. (2018)[27]

A35. Please provide details of the outcomes for all cardiac assessments listed in Section 9.4.4, page 79.

Response: Results of the cardiac assessments are reported on CS pages 92–93 and summarised here in Table 13.

Table 13. Results of cardiac assessments in the APOLLO cardiac subpopulation.

	Placebo	Patisiran
Mean LV wall thickness, cm		
LS mean (95% CI) change from baseline	-0.007 (-0.073, 0.059)	-0.100 (-0.138, -0.061)
LS mean (95% CI) difference (patisiran - placebo)	-	-0.093 (-0.169 -0.017)
LV mass, g		
LS mean (95% CI) change from baseline	0.63 (-18.05, 19.31)	-15.12 (-25.81, -4.42)
LS mean (95% CI) difference (patisiran - placebo)	-	-15.75 (-37.27, 5.78)
Longitudinal strain, %		
LS mean (95% CI) change from baseline	1.46 (0.50, 2.41)	0.08 (-0.47, 0.64)
LS mean (95% CI) difference (patisiran - placebo)	-	-1.37 (-2.48, -0.27)
Ejection fraction, %		
LS mean (95% CI) change from baseline	0.57 (-2.15, 3.29)	1.00 (-0.53, 2.52)
LS mean (95% CI) difference (patisiran - placebo)	-	0.43 (-2.69, 3.55)
Troponin I, µg/L		
LS mean (95% CI) change from baseline	-0.000 (-0.045, 0.045)	0.004 (-0.021, 0.029)
LS mean (95% CI) difference (patisiran - placebo)	-	0.004 (-0.047, 0.056)
NT-proBNP, pmol/L		
LS mean (95% CI) change from baseline	227.196 (107.893, 346.499)	12.537 (-54.264, 79.338)
LS mean (95% CI) difference (patisiran - placebo)	-	-214.659 (-351.383, -77.934)

LS: least square; LV: left ventricular; NT-proBNP: N-terminal pro B-type natriuretic peptide.
Source: Alnylam, data on file (APOLLO CSR)[7]

Adverse events (AEs)

A36. **Priority Question**. Please comment on why cardiac adverse events do not seem greatly improved despite improvements in NT-proBNP levels, cardiac LV wall thickness and other cardiac measures. What implications does this have for the overall efficacy of the treatment for patients in the UK, in whom there is a predominance of

cardiac disease? If possible, provide an analysis for cardiac adverse events as seen in Table C8 page 106 for other outcomes.

Response: In the APOLLO modified intent-to-treat (mITT) population, 28.4% of patients on patisiran were recorded as having a cardiac AE vs 36.4% of those on placebo.[7] A cardiac arrhythmia AE was recorded for 18.9% of patients on patisiran vs 28.6% on placebo. These data, and others, are summarised in **Error! Reference source not found.**.

We do not believe that it is appropriate to draw conclusions about treatment efficacy from AE reports. Instead, we would highlight the significance of the "improvements in NT-proBNP levels" that you refer to. NT-proBNP has been widely cited in studies as predictive of outcomes in study populations that include hATTR as well as in patients with wild-type ATTR and immunoglobulin light chain (AL) amyloidosis with predominant cardiomyopathy.[5,16-18,28,29]

In addition, we would highlight the results of the post-hoc analysis referred to in the response to question A34, which concluded that patisiran treatment was associated with a ~45% relative reduction in the event rate for cardiac hospitalisation and all-cause mortality.[27] All-cause death instead of cardiac death was chosen for this analysis because:

- In this advanced disease setting, cardiac and non-cardiac deaths are competing risks; patients who died with non-cardiac causes were no longer at risk for cardiac death
- The adjudication for cause of death can be subjective while all-cause death is entirely objective with no risk of bias
- The composite endpoint of all-cause death and cardiac hospitalisation is consistent with the endpoint used in the ATTR-ACT study in ATTR amyloidosis patients with cardiomyopathy[30]

A37. Please explain why there is a high number of treatment-related AEs in the placebo group. Are these a consequence of infusion-related reactions?

Response: We believe that the high number of treatment-related AEs in the placebo group was a consequence of:

- The investigators (who were responsible for determining the relationship of an AE to study drug) being blinded as to whether a patient was on placebo or patisiran
- The fact that hATTR is a multisystemic disease with a very wide range of manifestations and so patients in the trial may have been manifesting a broad range of disease symptoms that were recorded as AEs

A38. Please explain why diarrhoea is worse in the patisiran group, given that diarrhoea is a symptom of the disease and could be expected to be reduced by treatment.

Response: In fact, in APOLLO, the proportion of patients with diarrhoea was comparable between the patisiran (37.2%) and placebo (37.7%) groups.[7] Over the course of the study, patients treated with patisiran had lower rates of diarrhoea compared to patients who received placebo, which may correlate with an improvement in the gastrointestinal manifestations of hATTR (Table).

Table 14. Diarrhoea in APOLLO (safety population).

	Placebo (n=77)	**Patisiran (n=148)**
Diarrhoea, patients (%)	29 (37.7%)	55 (37.2%)
Events of diarrhoea	95	165
Cumulative exposure, person-years	96.1	218.9
Events per 100 person-years	98.9	75.4

Source: Alnylam, data on file (APOLLO CSR)[7]

Overall, the results from APOLLO indicated that patisiran had a favourable impact on the frequency and severity of diarrhoea, consistent with its impact on other disease manifestations. This impact can be seen in the results of the COMPASS-31 and Norfolk QoL-DN patient questionnaires.

COMPASS-31

The COMPASS-31 is a patient-reported measure of autonomic neuropathy symptoms and is composed of six domains. Diarrhoea is represented by the Gastrointestinal domain which assesses early satiety, vomiting, colicky abdominal pain, diarrhoea, and constipation.

There are four questions pertaining to diarrhoea symptoms within the Gastrointestinal domain.

Diarrhoea question 1: In the past year, have you had any bouts of diarrhoea (yes/no)

Almost 70% of patients reported bouts of diarrhoea at baseline, emphasizing diarrhoea as a common symptom in these patients. A similar proportion of patisiran and placebo patients reported diarrhoea, and this stayed relatively stable at Month 18.

Diarrhoea question 2: How frequently does this occur? (rarely/ occasionally/ frequently/ constantly)

At baseline, a similar percentage of patisiran and placebo patients had constant or frequent diarrhoea (53.1% and 52.1%, respectively).

At 18 months, more patients in the placebo group (57.9%) had frequent or constant diarrhoea than at baseline, whereas in the patisiran group, fewer (43.0%) patients had frequent or constant diarrhoea than at baseline.

Thus, these data suggest that patisiran reduced the frequency of constant or frequent diarrhoea.

Diarrhoea question 3: How severe are these bouts of diarrhoea (mild/moderate/severe)

At baseline, a similar proportion of patients in the placebo and patisiran group had severe diarrhoea (26.5% vs 27.6%, respectively).

At 18 months, more placebo patients developed severe diarrhoea (42.1%) than at baseline, whereas the number of patient with severe diarrhoea in the patisiran group decreased (22.6%), indicating that patisiran can reduce the occurrence of severe diarrhoea.

Diarrhoea question 4: Are your bouts of diarrhoea getting (much worse/somewhat worse/about the same/somewhat better/much better/completely gone)

At 18 months, more patients reported that their bouts of diarrhoea were getting better and fewer patients reported that their bouts of diarrhoea were getting worse in both the patisiran and placebo groups. No between-group differences were observed.

Norfolk QOL-DN

The Norfolk QoL-DN Autonomic Symptom domain evaluates diarrhoea with the question: "Have you had a problem with diarrhoea and/or loss of bowel control? (not a problem=0, very mild problem=1, mild problem=2, moderate problem=3, severe problem=4)." Compared to baseline, more patients in the placebo group progressed to having moderate or severe problems with diarrhoea at 18 months (Table). In contrast, fewer patients in the patisiran group reported moderate or severe diarrhoea symptoms at 18 months compared to baseline, suggesting improvement of diarrhoea in some patients.

Table 15. Responses in APOLLO on the Norfolk QoL-DN Autonomic Symptom domain Diarrhoea question*.

Treatment Group	Problem with diarrhoea and/or loss of bowel control	Baseline	Month 18
Placebo	N	76	49
	Moderate or Severe	25 (32.9)	21 (42.9)
	Moderate	10 (13.2)	12 (24.5)
	Severe	15 (19.7)	9 (18.4)
Patisiran	N	147	136
	Moderate or Severe	50 (34.0)	37 (27.2)
	Moderate	26 (17.7)	21 (15.4)
	Severe	24 (16.3)	16 (11.8)

Data are n (%).

*"Have you had a problem with diarrhoea and/or loss of bowel control? [not a problem=0, very mild problem=1, mild problem=2, moderate problem=3, severe problem=4]."

Results

A39. **Priority Question**: Randomisation in APOLLO was *"stratified by NIS (5-49 vs 50-130), early-onset Val30Met (<50 years of age at onset) vs all other mutations (including late-onset Val30Met), and previous tetramer stabiliser use (tafamidis or diflunisal) vs no*

previous tetramer stabiliser use." Please provide results of an analysis of the primary endpoint (change from baseline at 18 months in mNIS+7) adjusted for the stratification factors AND baseline mNIS+7.

Response: As specified in our statistical analysis plan,[8] the primary analysis of the primary endpoint was performed by controlling for these factors stated above in the question, including baseline mNIS+7. Specifically:

"The primary analysis will be performed using a restricted maximum likelihood (REML) based MMRM approach. The outcome variable is change from baseline in mNIS+7. The model includes baseline mNIS+7 score as a continuous covariate and fixed effect terms including treatment arm, visit (Month 9 or Month 18), treatment-by-visit interaction, genotype (V30M vs. non-V30M), age at hATTR Symptom onset (< 50; ≥ 50), region (North America, Western Europe, and Rest of World), and previous tetramer stabilizer use (yes vs. no)."

A40. **Priority Question**: Please describe any other known or potential prognostic factors, and any covariates that were pre-specified in the APOLLO study protocol. Please provide results of an analysis of the primary endpoint (change from baseline at 18 months in mNIS+7) adjusted for the stratification factors, baseline mNIS+7 AND any pre-specified covariates, as appropriate; include any non-stratification continuous variables as continuous covariates.

Response: No other known or potential prognostic factors have been identified. As discussed above, other relevant covariates had already been included in the primary analysis of the primary endpoint.

A41. The text of Section 9.6.1 page 82 states *"Additional, pre-specified sensitivity analyses on the primary endpoint resulted in a consistent estimate of the treatment effect of patisiran compared to placebo".* Please comment on the potential treatment effect modifications according to region, NIS, age, genotype, genotype class, previous tetramer stabiliser use and cardiac involvement.

Response: Subgroup analyses were pre-specified in the statistical analysis plan and conducted to assess the consistency of treatment effect within various subgroups, as described above. All subgroup analyses (e.g., age, region, genotype) performed for the primary endpoint, mNIS+7, and the key secondary endpoint, Norfolk QoL-DN, showed consistent treatment effect of patisiran compared to placebo. These forest plots are included in Figures S3 and S4 in the Supplementary Appendix of the primary APOLLO trial publication in the New England Journal of Medicine.[3]

A42. Figure 17 page 96 suggests a rebound effect (i.e. loss of efficacy) for the mNIS+7 whereas text in Section 9.9.2 page 113 reports that *"the clinical benefit observed in the APOLLO trial was maintained in the OLE."* Please justify this statement in light of the mNIS+7 results.

Response: We continue to believe that CS Figure 17 demonstrates that the clinical benefit observed in the APOLLO trial was maintained in the OLE. Figure 17 demonstrates that at both 24 months and 36 months, the mNIS+7 scores of patients treated with patisiran are below their baseline scores (i.e., there is an improvement). The confidence intervals of the improvement in mNIS+7 at both 24 months and 36 months overlap to a very large degree meaning that there is no evidence to support any conclusion other than the benefit is maintained.

A43. Please comment on whether the Norfolk QoL-DN responses to treatment with patisiran at 9 and 18 months are likely to reflect a plateau response or loss of response (Figure 11, Page 88).

Response: CS Figure 11 shows that HRQoL scores for patients treated with patisiran at both 9 months and 18 months are significantly improved vs baseline, and there is a highly significant beneficial difference vs patients treated with placebo.

The improvement in HRQoL score at 9 months and at 18 months in the patisiran arm vs baseline is very similar (7.5-point improvement and 6.7-point improvement) and the confidence intervals overlap to a very large degree. We believe that this demonstrates maintenance of the effect seen at 9 months.

A44. Please clarify why fewer patients receiving placebo in APOLLO completed the study, compared to patients receiving patisiran (Figure 5 page 79), commenting on potential unblinding because of a lack of response and/or progressive disease. Please comment on the potential impact of the reasons for treatment discontinuation on the results.

Response: The reasons for study treatment discontinuation are outlined below:

- **Withdrawal of consent by patient**: A total of 13 (5.8%) patients discontinued study treatment due to withdrawal of consent by the patient (1 [0.7%] patisiran, 12 [15.6%] placebo). The reason for withdrawal of consent was captured in a free-text field on the case report form (CRF). The reason provided for withdrawal of consent by the one patient (160--0012) in the patisiran group was because they “felt traveling fatigue.” Reasons provided for withdrawal of consent in the placebo group were: nine patients withdrew consent because they “felt worsening of disease” or “felt disease progression”, one patient withdrew consent to have a liver transplant, one was unable to travel to the study center, and one patient had advanced disease
- **Adverse Events:** Ten (4.4%) patients did not complete treatment due to AEs; three (2.0%) patients in the patisiran group and seven (9.1%) patients in the placebo group.
- **Death**: A total of 13 deaths were reported in the study. For nine (4.0%) of these patients, death was cited as the reason for not completing treatment (5 [3.4%] patisiran, 4 [5.2%] placebo). None of the reported deaths in this study were considered related to study treatment by the Investigators.
- **Progressive disease**: Patients with rapid disease progression had a choice to discontinue or continue study treatment, and those who chose to discontinue treatment were classified as having discontinued treatment due to progressive disease. A total of five patients (1 patisiran, 4 placebo) cited progressive disease at 9 months as the reason for treatment discontinuation.
- **Physician decision**: Two (2.6%) patients in the placebo group discontinued study treatment due to physician decision. There were no discontinuations from treatment due to physician decision in the patisiran group.
- **Protocol deviations**: One patient in the patisiran group discontinued treatment due to a protocol deviation (elevated bilirubin levels at baseline); there were no protocol deviations leading to study discontinuation in the placebo group.

Reasons for study withdrawal were generally similar to the reasons for study treatment discontinuation. These data are summarised in Table 16.

Table 16. Patient disposition in APOLLO

Disposition	Placebo (n=77)	Patisiran (n=148)	Overall (N=225)
Total number of patients	n (%)		
Randomised	77	148	225
Treated	77 (100.0)	148 (100.0)	225 (100.0)
Completed treatment*	48 (62.3)	137 (92.6)	185 (82.2)
Completed study†	55 (71.4)	138 (93.2)	193 (85.8)
Discontinuation of treatment	29 (37.7)	11 (7.4)	40 (17.8)
Primary reason for treatment discontinuation			
Adverse event	7 (9.1)	3 (2.0)	10 (4.4)
Death	4 (5.2)	5 (3.4)	9 (4.0)
Progressive disease‡	4 (5.2)	1 (0.7)	5 (2.2)
Physician decision	2 (2.6)	0	2 (0.9)
Protocol deviation	0	1 (0.7)	1 (0.4)
Withdrawal by subject	12 (15.6)	1 (0.7)	13 (5.8)
Withdrawal from study	22 (28.6)	10 (6.8)	32 (14.2)
Primary reason for study withdrawal			
Adverse event	6 (7.8)	2 (1.4)	8 (3.6)
Death	4 (5.2)	6 (4.1)	10 (4.4)
Physician decision	1 (1.3)	0	1 (0.4)
Protocol deviation	0	1 (0.7)	1 (0.4)
Withdrawal by subject	11 (14.3)	1 (0.7)	12 (5.3)
Patients with rapid disease progression§	6 (7.8)	1 (0.7)	7 (3.1)
Patients who discontinued treatment but completed study	8 (10.4)	1 (0.7)	9 (4.0)
Patients who completed treatment but withdrew from study	1 (1.3)	0	1 (0.4)

CRF: case report form; FAP: familial amyloidotic polyneuropathy.

*A patient was considered to have completed study treatment if they had completed the drug regimen without permanently stopping treatment prior to the last dose at the Week 78 visit. Patient completion is indicated by the Investigator on the End of Treatment CRF.

†A patient was considered to have completed the study if they completed protocol-specified procedures through the Month 18 efficacy assessment visit (Week 79-80). Patient completion is indicated by the Investigator on the End of Study CRF.

‡Patients with rapid disease progression who decided to stop treatment due to this progressive disease.

§Rapid disease progression is defined as patients with a ≥24-point increase from baseline in mNIS+7 and a ≥ 1 level increase from baseline in FAP stage at Month 9 as determined by the Clinical Adjudication Committee.

Source: Alnylam, data on file (APOLLO CSR)[7]

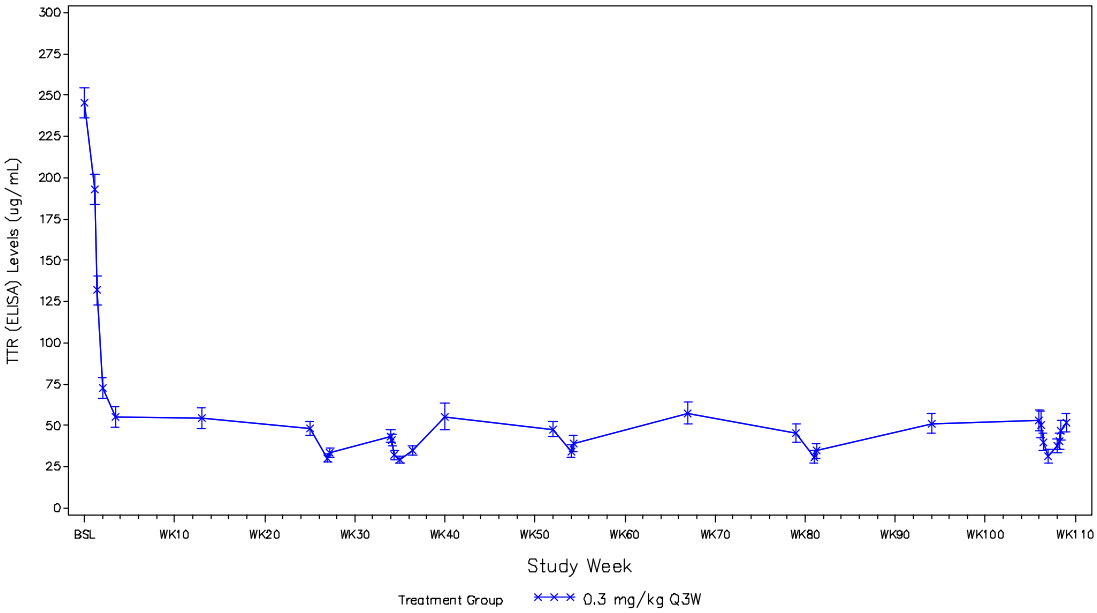
A45. Please provide details of the results reported for the non-randomised studies, specifically, for the Phase 2 OLE:

- What were the serum TTR levels at baseline and after the first and second dose of patisiran;
- What was the sustained mean serum TTR knockdown over 18 months;
- What was the sustained decrease in mNIS+7 at 24 months for patients with cardiac involvement.

Response: The following graphs summarise the requested data on TTR knockdown in the full analysis set of the phase 2 OLE. Figure 3 shows the absolute mean TTR levels over time through Week 109 (21-day follow-up visit) and excludes the TTR assessment at Week 114 because this was performed for only two patients. Substantial reduction in TTR levels

occurred over the first 2 weeks after the first patisiran dose, and mean TTR levels at Day 18 were similar to the values maintained over 24 months.[31]

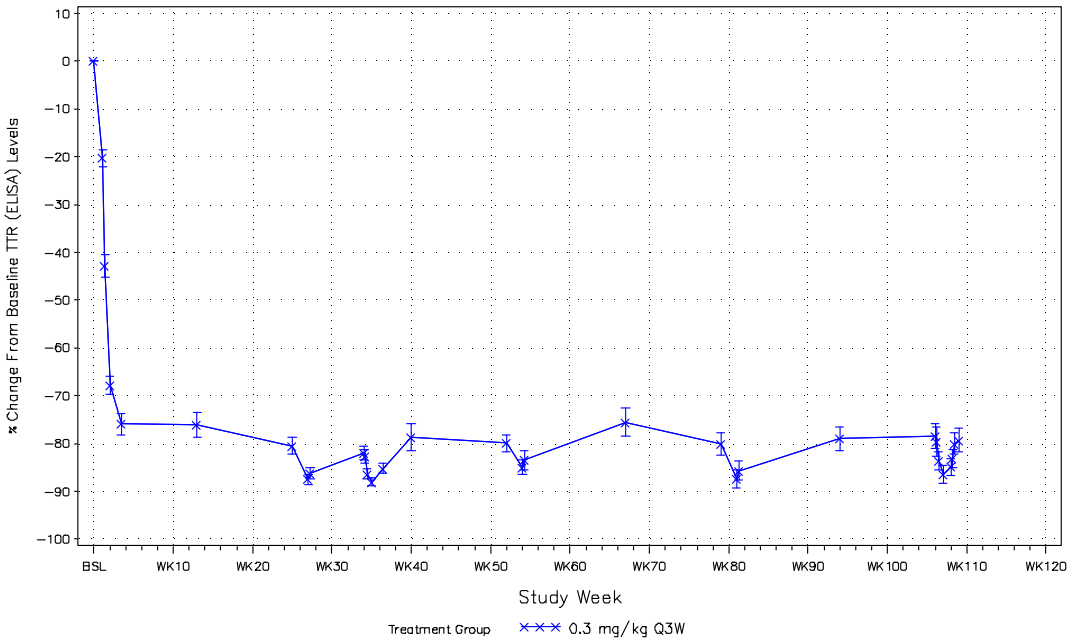
Figure 3. Absolute mean (± SE) TTR levels over time in the phase 2 OLE.



OLE: open-label extension; TTR: transthyretin.
Source: Alnylam, data on file (phase 2 OLE CSR)[31]

Figure 4 shows the mean percent TTR change from baseline over the same time period. Over 24 months of patisiran treatment, the mean percent reduction in TTR was 82.06%, which was similar to the percent reduction from baseline values observed at Day 18.[31]

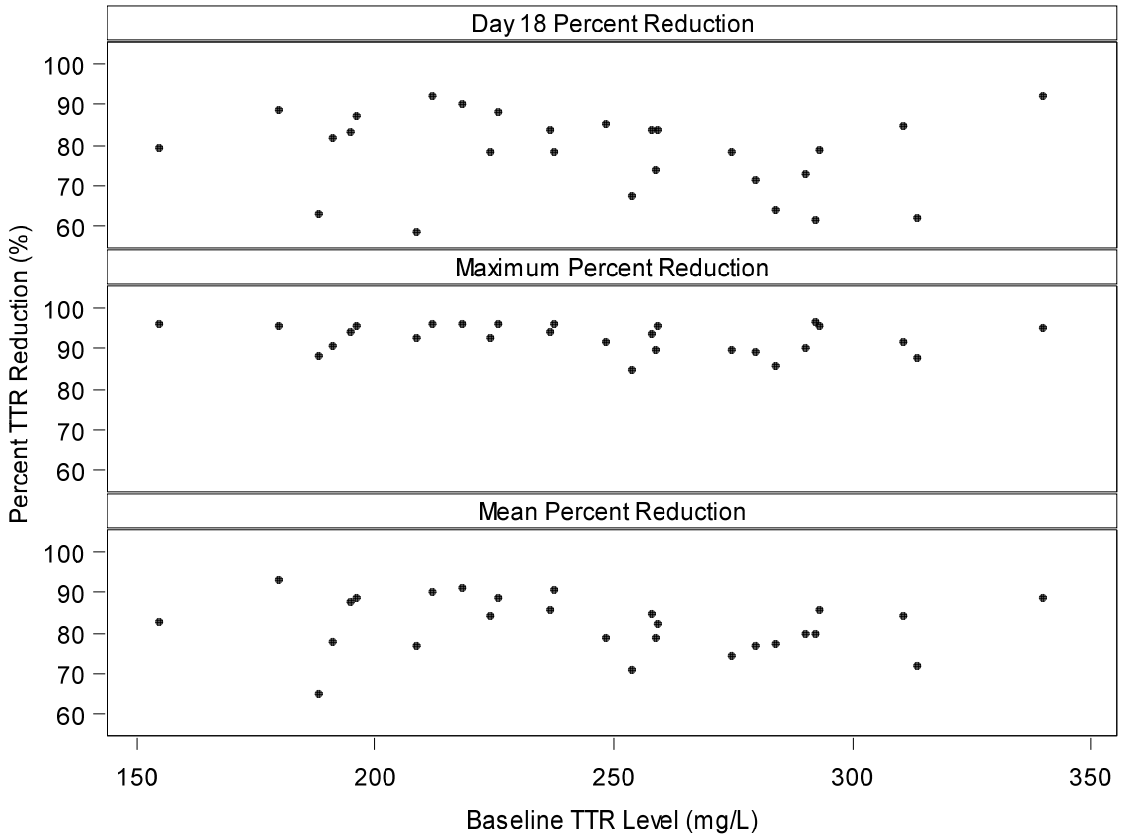
Figure 4. Mean (± SE) percent change from baseline in TTR levels over time in the phase 2 OLE.



OLE: open-label extension; TTR: transthyretin.
Source: Alnylam, data on file (phase 2 OLE CSR)[31]

As shown in Figure 5, which presents TTR levels in individual patients, the percent reduction in TTR levels achieved at Day 18 and over 24 months of patisiran treatment was consistent irrespective of baseline TTR levels.[31]

Figure 5. Percent TTR reduction by baseline TTR levels over time in the phase 2 OLE.



OLE: open-label extension; TTR: transthyretin.
Source: Alnylam, data on file (phase 2 OLE CSR)[31]

The mean ± SE change from baseline to 24 months in mNIS+7 for patients in the cardiac subgroup of the phase 2 OLE was -9.98 ± 3.29, compared with -4.73 ± 2.50 in the non-cardiac subgroup.[31] These results confirm that the benefit of patisiran for improving symptoms of polyneuropathy is achieved even in patients with cardiomyopathy.

A46. The text in Section 9.9.1 page 111 states, *"The placebo group reported more patients who worsened on the PND score (58.2%) than the patisiran group (21.7%)."* Please comment on factors associated with worsening response to treatment with patisiran, and whether these patients should continue on treatment.

Response: Using an increase of mNIS+7 of 10 points or more as a proxy for "worsening response to treatment with patisiran", we performed an analysis to identify any baseline demographics or patient characteristics that would lead to an absence of treatment effect with patisiran.

We were unable to identify any demographics or characteristics or anti-drug antibodies that would lead to an absence of treatment effect. Furthermore, patients with an increase in mNIS+7 of ≥10 points on patisiran had improvement in neuropathy (mNIS+7) and experienced clinical benefit across multiple health measures compared to placebo patients. A cumulative distribution curve of change in mNIS+7 showed a continuous benefit of

patisiran compared to placebo at all response thresholds. Additionally, cumulative distribution curves for all secondary endpoints (Norfolk QoL-DN, NIS-W, R-ODS, 10-MWT, mBMI, COMPASS-31 endpoints) and the exploratory endpoint, the cardiac biomarker NT-proBNP, showed separation between patisiran- and placebo-treated patients, favouring patisiran, across all response thresholds.

These data show that patisiran shows benefit across all response thresholds for multiple clinical manifestations of this multisystemic disease. For this reason, we believe that even patients who show a 'worsening response to treatment with patisiran' should continue on treatment.

Section B: Clarification on cost-effectiveness data

Systematic reviews of economic evaluations, HRQol & resource/costs

B1. **Priority Question.** It appears that studies were only considered eligible for inclusion in the systematic reviews of economic evaluations, HRQoL and resource use/costs studies if they included patisiran (Sections 10.1.5 page 121 and 11.1.3 page 131).

Response: This assumption is not correct. There were no exclusions made in the systematic reviews of economic evaluations, HRQoL, and resource use/costs studies if they did not include patisiran. What was meant in the sections mentioned above was that studies that were not of patisiran were excluded from the submission because they were outside the NICE scope; however, all non-patisiran studies were included in the SLRs.

a. Please provide the full inclusion and exclusion criteria for the systematic reviews which were used to select studies for these reviews.

Response: The full inclusion and exclusion criteria are provided in Table C1 (page 59) of the submission and are as follows:

Table 17. Selection criteria used for published studies (per CS Table C1).

	hATTR amyloidosis with polyneuropathy SLR	hATTR amyloidosis with cardiomyopathy SLR
Inclusion criteria		
Population	Populations or subgroups enrolling at least 80% patients per treatment arm with hATTR amyloidosis with polyneuropathy	Patients with hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis*
Interventions	Any treatments	Any treatments
Comparators	Any	Any
Outcomes	From RCTs: safety and efficacy outcomes, patient-reported outcomes From single-arm studies: safety and effectiveness outcomes From observational studies: clinical effectiveness, safety, patient-reported outcomes From economic studies: costs, cost-effectiveness, and resource use	From RCTs: safety and efficacy outcomes, patient-reported outcomes From single-arm studies: safety and effectiveness outcomes From observational studies: clinical effectiveness, safety, patient-reported outcomes From economic studies: costs, cost-effectiveness, and resource use
Study design	RCTs and non-randomised controlled trials Open-label extensions Observational studies (prospective, cross-sectional, and retrospective [ie, chart	RCTs and non-randomised controlled trials Open-label extensions Observational studies (prospective, cross-sectional, and retrospective [i.e. chart

	hATTR amyloidosis with polyneuropathy SLR	hATTR amyloidosis with cardiomyopathy SLR
	reviews, registries, surveys, etc.]) of clinical effectiveness and safety Single-arm trials Cost-effectiveness, cost-utility, or cost-minimisation studies Healthcare resource use studies Utility assessments or patient-reported outcome studies	reviews, registries, surveys, etc.]) of clinical effectiveness and safety Single-arm trials Cost-effectiveness, cost-utility, or cost-minimisation studies Healthcare resource use studies Utility assessments or patient-reported outcome studies
Language restrictions	None	None
Search dates	Original SLR: 30 May 2017 SLR Update: 10 January 2018	28 January 2018
Exclusion criteria		
Population	Not hATTR amyloidosis (such as wtATTR amyloidosis) hATTR amyloidosis not presenting with predominant polyneuropathy or hATTR amyloidosis in which polyneuropathy is attributable to another cause Mixed populations or subgroups with <80% adult hATTR amyloidosis with polyneuropathy hATTR amyloidosis patients who have undergone OLT	hATTR amyloidosis patients who have undergone OLT
Interventions	N/A	N/A
Comparators	Dose-finding clinical trials (ie, studies in which all treatment arms are different doses of the same agent)	Dose-finding clinical trials (ie, studies in which all treatment arms are different doses of the same agent)
Outcomes	Pharmacodynamic/pharmacokinetic studies or non-clinical studies (such as gene expression or protein expression studies)	Pharmacodynamic/pharmacokinetic studies or non-clinical studies (such as gene expression or protein expression studies)
Study design	Letters, literature reviews, expert opinion articles, etc.	Letters, literature reviews, expert opinion articles, etc.
Language restrictions	None	None
Search dates	Original SLR and rescreen: 30 May 2017 SLR Update: 10 January 2018	January 18, 2018

hATTR: hereditary transthyretin-mediated amyloidosis; NA: not applicable; OLT: orthotopic liver transplantation; RCT: randomised, controlled trial; SLR: systematic literature review; wtATTR: wild-type transthyretin-mediated amyloidosis. *May include patients with ATTR with primary cardiomyopathy (hereditary or wild type), hATTR with primary polyneuropathy who also have cardiomyopathy, or ATTR with cardiomyopathy alone (hereditary or wild type).

b. Please explain why previous models/economic evaluations of inotersen, tafamidis and any other treatments for hATTR amyloidosis were not included in the review of existing economic studies. Were any of these considered for inclusion in the review (e.g. to inform the model structure, data sources and/or assumptions)?

Response: Previous models or economic evaluations of inotersen, tafamidis, or any other treatments of hATTR amyloidosis were not excluded in the systematic reviews of existing economic studies. There were in fact no economic models of any treatment identified by the SLRs. The polyneuropathy SLR identified only three studies containing economic data: a healthcare resource utilisation (HCRU) study, and two studies of HCRU and associated

costs. None of these studies were treatment-specific. The cardiomyopathy SLR identified only one study that reported hospitalisation rates, and this study was not treatment-specific.

c. Please clarify which HRQoL studies met the review inclusion criteria but were subsequently excluded because they did not include patisiran.

Response: No HRQoL studies were excluded from the SLRs because they did not include patisiran. Studies were only excluded from the submission if they were outside the NICE scope (i.e., patisiran or BSC). The studies listed in Table 18 were included in the SLRs but excluded from the submission review of HRQoL studies because they did not meet the NICE scope criteria:

Table 18. HRQoL studies excluded for not meeting the NICE scope criteria.

- Adams D, Théaudin M, Lozeron P, et al. Management of stage 1 TTR FAP: French experience. Orphanet J Rare Dis. 2015;10(Suppl 1):P65.
- Barroso FA, Judge DP, Ebede B, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. Amyloid. 2017;24(3):194-204.
- Benson M, Waddington-Cruz M, Wang A, et al. Safety and efficacy of inotersen in patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN). [Presented at the 1st European Meeting for ATTR Amyloidosis for Doctors and Patients, Paris, France, 2–3 November 2017]. Orphanet J Rare Dis. 2017;12(Supplement 1).
- Berk J, Suhr O, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. 2013;310(24):2658-2667.
- Coelho T, Conceicao IM, Barroso F, et al. Long term effects of tafamidis treatment on transthyretin familial amyloid polyneuropathy (TTR-FAP): Interim results from the Fx1A-303 study. Eur J Neurosci. 2014;21:81.
- Coelho T, Conceicao IM, Barroso F, et al. Long term effects of tafamidis treatment on transthyretin familial amyloid polyneuropathy (TTR-FAP): Interim results from the Fx1A-303 study. J Neurol. 2014;261:S59-s60.
- Coelho T, Da Silva AM, Alves C, et al. Familial amyloid polyneuropathy treatment with Tafamidis - Evaluation of one- and two-year treatment in Porto, Portugal. Orphanet J Rare Dis. 2015;10.
- Coelho T, Maia L, Martins da Silva A, et al. Long-term effects of tafamidis - a new therapeutic option for patients with transthyretin familial amyloid polyneuropathy (TTR-FAP). J Hepat. 2012;56(Suppl 2):S543.
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- Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79(8):785-792.
- Inês M, Coelho T, Conceicão I, et al. Health-related quality of life in patients with transthyretin familial amyloid polyneuropathy. Value Health. 2015;18(7):A675-A676.
- Inês M, Coelho T, Conceicão I, et al. Transthyretin familial amyloid polyneuropathy impact on health-related quality of life. Value Health. 2015;18(7):A672.
- Inês M, Coelho T, Conceicão I, et al. Transthyretin familial amyloid polyneuropathy impact on health-related quality of life. Orphanet J Rare Dis. 2015;10.
- Keohane D, Schwartz J, Gundapaneni B, et al. Tafamidis delays disease progression in patients with early stage transthyretin familial amyloid polyneuropathy: additional supportive analyses from the pivotal trial. Amyloid. 2017;24(1):30-36.
- Lane T, Bangova A, Fontana M, et al. Quality of life in ATTR amyloidosis. Orphanet J Rare Dis. 2015;10(1):O26.
- Lopes A, Sousa A, Fonseca I, et al. Life paths of patients with transthyretin-related familial amyloid polyneuropathy Val30Met: a descriptive study. J Community Genet. 2017;9(1):93-99.
- Lopes A, Sousa A, Fonseca I, et al. Psychopathological dimensions in familial amyloid polyneuropathy patients. Orphanet J Rare Dis. 2015;10.
- Merlini G, Plante-Bordeneuve V, Judge DP, et al. Effects of Tafamidis on Transthyretin Stabilization and Clinical Outcomes in Patients with Non-Val30Met Transthyretin Amyloidosis. J Cardiovasc Transl Res. 2013;6(6):1011-1020.
- Oliveira-e-Silva T, Campos Pinheiro L, Rocha Mendes J, et al. Peripheral Polyneuropathy and Female Sexual Dysfunction-Familial Amyloidotic Polyneuropathy as an Example Besides Diabetes Mellitus. J Sex Med. 2013;10(2):430-438.
- Stewart M, Keohane D, Short S, et al. Positive real-world effectiveness of tafamidis for delaying disease progression in transthyretin familial amyloid polyneuropathy. Orphanet J Rare Dis. 2015;10(Suppl 1):P4.

- Stewart M, Mundayat R, Alvir J, et al. Clinical characteristics and health state utilities in patients with transthyretin familial amyloid polyneuropathy in Brazil. Value Health. 2017;20 (5):A223.
- Yukio A, Yoshiki S, Konen O, et al. Effects of tafamidis treatment on transthyretin (TTR) stabilization, efficacy, and safety in Japanese patients with familial amyloid polyneuropathy (TTR-FAP) with Val30Met and non-Varl30Met: A phase III, open-label study. J Neurol Sci. 2016;362:266-271.

B2. The text of Section 12.1.3 page 136 states that: *"No economic models for patisiran or for other technologies used in UK clinical practice in the indicated population were published at the time of the model development."* Elsewhere in the CS, the text refers to a previous tafamidis AGNSS analysis. Why is this model not included either in the review of economic studies or in Appendix 3?

Response: The AGNSS analysis of tafamidis was not identified by the searches conducted for the SLRs. This was likely due to the fact that AGNSS no longer exists and has no website, and thus the model is no longer publicly available. The AGNSS report was identified independently by our team and was used to inform the economic model for patisiran.

Discounting

B3. **Priority Question.** The text in Section 12.1.7, page 143-146 states that: *"The discount rate for cost is set at 3.5% annually, according to UK NICE reference case. The discount rate for outcomes is set to 1.5% per year, based on the evidence that the treatment effects of patisiran are both substantial in restoring health and sustained over a very long period."*

a. Please explain why it is appropriate in this particular case to deviate from the discount rates specified in the NICE Reference Case.

Response: The decision was taken to deviate from the discount rates specified in the NICE Reference Case because we considered that these resulted in an underestimation of the true value of patisiran relative to its costs. We would like to reiterate the argument we presented in the CS that although differential discounting remains controversial, prominent health economists have made a compelling argument that differential discounting of health benefits is the appropriate method for correctly adjusting for the growth in the value of health benefits over time.[32-34]

There is considerable support in the literature for the argument that the value of health is expected to grow over time; put another way, health is considered by society as more valuable over time, and the monetary value of a QALY will increase in future.[33-37] Gravelle and Smith (2001) analysed cost-effectiveness from both a behavioural and social welfare point of view and found that in both cases, the value of health grows with time and that if the focus of decision makers is to maximise social welfare, a discounting scheme must account for this growth.[35]

A CEA with similar discount rates for cost and health benefits may not properly reflect how the value in health effects changes over time.[33,34] When health effects are not valued in monetary terms (as is the case when health effects are measured in QALYs) an equal discount for costs and benefits risks undervaluing future health benefits.[34] When health effects are measured in QALYs, the growth in the value of health effects is appropriately accounted for by lowering the discount rate for health effects relative to costs. In this case,

differential discounting gives more weight to future health effects, reflecting that the value of health effect is expected to grow over time.[32,34,35]

The NICE Guide to the methods of technology appraisal (2013) states that a discount of 1.5% on costs and health effects may be considered for technologies that provide a long-term health benefit, over a very long period of at least 30 years, and which restore people who would otherwise die or have a very severely impaired life to full or near full health.[38]

The high morbidity and mortality of hATTR amyloidosis and the severe impairment of the disease on patients' HRQoL have been established in Section 6 and Section 7, respectively. Patisiran has shown a high level of safety and effectiveness over the long term and has demonstrated the ability to halt or reverse disease progression and improve HRQoL in hATTR amyloidosis patients.[3,39] Thus, patisiran for hATTR amyloidosis treatment meets most of the criteria established by NICE for the consideration of a 1.5% discount rate on health effects.

One criterion that should not be applied to patients with hATTR amyloidosis is the 30-year threshold for maintenance of health benefit. O'Mahony and Paulden (2014) have established that the requirement that health benefits must be sustained for at least 30 years can result in discrimination on the basis of age, as a patient with a remaining healthy life expectancy of less than 30 years would be subject to equal discounting, yielding a less favourable ICER.[37] According to the latest statistics, the life expectancy for women and men in England and Wales is 83.08 and 79.46 years, respectively.[40] As such, the requirement that health benefits be sustained over at least 30 years would unfairly penalise patients with hATTR amyloidosis, who are often older at diagnosis (median age at baseline in APOLLO was 62 years)[3], and thus would have had an additional life expectancy less than 30 years even in the absence of this disease.

Additional support for the selection of a 1.5% discount rate for health effects in our model is provided by consideration of research by Gravelle and Smith (2001), who proposed that in cases where health only affects income (i.e., the inability to work) the discount rate on health effects should be 3.5% and in cases where health has no effect on income (i.e., in cases where a patient relies entirely on social services or on private insurance) the appropriate discount would be 1%.[35] Given that many patients with hATTR amyloidosis may be close to or already past retirement at diagnosis, this patient population would fall along the continuum between these two values and therefore a discount of 1.5% on health effects should be considered appropriate.

Given the supporting literature, the age of the hATTR amyloidosis patient population in the UK, and the demonstrated clinical safety and efficacy of patisiran to halt or reverse disease progression and improve patient's HRQoL over the long-term, a discount rate of 1.5% for health benefits is appropriate for the present CEA.

b. Please comment specifically on why this argument for differential discounting should not apply to every NICE appraisal.

Response: The argument for differential discounting is less relevant for NICE appraisals in which the time horizon is very short. However, we do not specifically rule out application of differential discounting as the general rule for NICE appraisals. Notably, some other countries mandate a differential discount rate in reference-case analyses (e.g., Belgium, The Netherlands, among others), and indeed NICE itself used to request discounting at 6% for costs and 1.5% for effects.[36]

c. Please clarify which evidence demonstrates substantial health gains for patisiran over a very long period.

Response: The most recent presentation of global OLE data reports results for patients treated with patisiran for up to 48 months.[1] Although this clearly does not qualify as a very long period in the context in which discount rates are generally considered, it is nevertheless a relatively long timeframe for this exceedingly rare disease with reduced life expectancy. As shown in Figure 1 above, the most recent efficacy results from the global OLE indicate that patients receiving patisiran can expect to maintain clinical benefit over a 3-year period, with no apparent trend for loss of efficacy near the end of observed data.

Indeed, the fact that these patients actually persist on therapy for a >36-month period is remarkable in the context of the expected poor survival for patients with hATTR amyloidosis in the UK. For example, based on calculations using data for UK hATTR amyloidosis patients reported by Gillmore et al. 2017,[41] the median overall survival is only 4.02 years from diagnosis. Furthermore, all patients in APOLLO already had extant disease when they entered the study, with a median time since diagnosis of 1.4 years,[3] so they were already well along a trajectory toward death. Thus, the fact that patients in the global OLE are still alive on patisiran (as opposed to all dead) should be taken as compelling evidence of substantial health gains over a prolonged period.

Model structure and assumptions

B4. **Priority Question.** Given that hATTR amyloidosis affects multiple body systems, please clarify why the model health states have been defined in terms of PND score rather than by stage, given that only the latter specifically includes autonomic function (e.g. the classification system devised by Ando *et al,* discussed in CS Section 6.1.2, page 46).

Response: While the FAP stages and the PND functional scores have a different description, there is a general understanding in clinical practice that the two scales coincide and a mapping can be established between the two; see Table 2 in the review by Adams 2013.[42] The FAP classification system described by Ando et al. 2013 was actually originally devised by Coutinho et al. 1980.[43] Although the FAP staging adaptation presented by Ando et al. 2013 does mention autonomic involvement,[44] that classification system does not separate autonomic function from the other criteria in each stage, and thus should not be considered to provide additional discrimination. In order to capture the changes in the health states with the maximum possible precision, we selected the PND classification as the basis for the definition of health states in the model because with its five scores for symptomatic patients (I, II, IIIA, IIIB, IV) it provides a more granular assessment of the disease than is possible using only the three FAP stages applicable to symptomatic patients (I, II, III).

B5. The text in Section 12.1.4, page 139. states that: *"patients in the patisiran arm of APOLLO consistently scored better than patients in the placebo arm across all primary and secondary endpoints by PND score change category and even within PND score category for the small percentage (20%) of patients who worsened in PND score in the patisiran arm."* Please comment on whether this indicates that PND score is a poor indicator of treatment benefit according to other relevant disease-specific endpoints and HRQoL?

Response: It is well recognised that no single test captures all of the symptoms and the multisystemic nature of hATTR amyloidosis.[24] While it is true that PND score cannot fully capture all aspects of the treatment benefit of patisiran, it was the only feasible choice of clinical staging scale to characterise health states within our pharmacoeconomic model. As explained in our response to the previous question, PND score was chosen over FAP stage because of its greater granularity. The APOLLO trial used a modified version of the NIS score as its primary endpoint[3,24] (as have other RCTs in this therapeutic area, albeit with different versions of the NIS[11-13]), but as discussed in paragraph 12.1.4 of the CS, the mNIS+7 score was not directly usable to define health states in the model. The selection of the PND score to define health states in the model was therefore necessary. Importantly, this was an approach taken after input and validation by clinical experts at the NAC.

Rather than considering the PND score to be a poor indicator of treatment benefit, it would be more accurate to describe it (or any other single assessment) as an incomplete indicator, thus highlighting the importance of taking into account the other disease-specific endpoints and HRQoL measures included in the APOLLO trial. As noted in CS Section 10.1.11 (see especially CS Figure 23), within any given PND score change category (i.e., improved/stable or worsening) patisiran patients consistently scored better than those treated with placebo across all primary and secondary endpoints including the Norfolk QoL-DN, R-ODS, 10MWT, and COMPASS-31. Given these considerations, it is probable that the design of the model itself underestimates the overall treatment benefits of patisiran, and thus the cost-effectiveness analysis results should be viewed as conservative.

B6. **Priority Question.** The CS states that "*Patisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy*."

a. Which staging classification does this anticipated marketing authorisation relate to?

Response: The staging classification in the indication refers to FAP staging, as defined in CS Table B2 and used in the APOLLO study.[3]

b. Given that the proposed indication is for stage 1 and 2, please clarify how eligibility for starting treatment relates to PND score (as used in the model).

Response: According to Adams 2013, Stage I corresponds to PND I, and Stage II corresponds to PND II, IIIA and IIIB.[42] Thus the only patients not eligible for starting patisiran treatment would be those in Stage 0/PND 0 or Stage III/PND IV. Please see the following response for further clarification.

c. Why does the model assume that patients in PND 0 (asymptomatic) and PND IIIB-IV (presumably more advanced than stage 2) are eligible to start treatment with patisiran?

Response: No patients enter the model (i.e., initiate treatment) in PND 0. The only way for patients in PND 0 to receive patisiran in the model is if they improve from a higher PND score to PND 0, in which case they may remain on patisiran. Only a very small number of patients—just 0.4% of the cohort—enter the model in PND IV. The reason that this percentage was not set to zero was in order to correspond to the patient distribution in APOLLO, so that the model would be coherent with the data from the trial.

B7. **Priority Question.** Please provide evidence justifying that:

a. patients will require treatment with patisiran indefinitely? Has the company explored the potential for patisiran stopping rules based on loss of efficacy?

Response: Because hATTR amyloidosis is a life-long disease and patisiran is not a one-time cure, patisiran treatment will need to continue indefinitely. Given that patisiran has demonstrated clinical benefit on multiple different endpoints, it is unclear that it would be appropriate to impose stopping rules based on apparent loss of efficacy on any one measure, since benefit may still be achieved on other measures. This conclusion is also based on clinical opinion received from experts at the NAC. At a multi-stakeholder meeting organised by NICE, various suggestions regarding stopping rules or similar mechanisms for improving value to the NHS were discussed. In fact, we did explore the potential for these approaches and our original submission did contain some suggestions for consideration in this regard based on feedback we received from clinical experts and others. However, we were requested by NICE to remove all references to these exploratory analyses and subsequently did so. We would be happy to discuss these with NICE or the ERG at your convenience.

b. patients with severely progressed disease will continue to benefit from patisiran?

Response: There is a significant gap in the evidence base for patisiran in patients with PND score IV, which is a terminal state of hATTR amyloidosis. Patients in PND IV are wheelchair bound and were excluded from the APOLLO study because they were unlikely to be able to perform the 10MWT, which was an important secondary endpoint in the study. Clinical data in PND IV come from patients who progressed to PND IV in APOLLO and supports a favourable risk-benefit of patisiran treatment in these patients. By 18 months, the number of APOLLO patients in PND IV had increased to 17 (7.5%),[7] and additional experience in patients with advanced disease will be gathered over time in the ongoing global OLE.

Data from six APOLLO patients in PND IV for 9 months or more (one patient who was in PND IV at baseline and five patients who progressed to PND IV by Month 9) who received placebo demonstrated worsening of polyneuropathy (mNIS+7) and rapid disease progression as assessed by several complementary, clinically relevant measures important to these patients (e.g., Norfolk QoL-DN, R-ODS, mBMI, COMPASS 31, grip strength).[45] The rate of progression was consistent with the rate of progression seen in patients with less advanced neuropathy (PND score I through IIIB).[45]

Efficacy data reported from six patients who were in PND IV at baseline in the ongoing OLE, and who received patisiran for 12 months, showed a stabilisation of mNIS+7 and of overall disease progression as assessed by the aforementioned clinically relevant measures of importance to these patients.[45] The stabilisation of disease was consistent with that seen in patients with less advanced neuropathy (PND score I through IIIB).[45]

In our correspondence with clinical experts from the NAC, they also noted that patients in PND IV who receive patisiran are expected to continue receiving these treatment benefits. Specifically, the experts agreed with the hypothesis that patients who transition to PND IV may still benefit from treatment with patisiran because hATTR amyloidosis is a multi-systemic disease that affects multiple organs, leading to polyneuropathy, autonomic, and cardiac symptoms. As demonstrated in the APOLLO trial, which measured a wide range of clinical parameters affecting multiple organs, patisiran has beneficial effects on all those

variables. Consequently, patients may derive benefit across any number of parameters and may do so unevenly. Specifically, patients who initiate treatment in earlier PND stages and progress to a later stage may still see improvement in other clinical parameters.

As noted in our response to the prior question, we did explore scenarios to improve the value to the NHS in these patients but were instructed by NICE to remove these from our submission at this time.

B8. **Priority Question.** In Section 12.1.6, page 143, the CS states that: *"the PND score has been shown to be significantly associated with the NIS score by Adams et al. 2015, and with mortality by Suhr et al. 1994".* Please comment on the appropriateness of the method of analysis used by Suhr *et al* for time-to-event data with censored event times. Please comment on what claims the method of analysis allows for the impact of PND score and PND score plus mBMI on mortality. Did your searches identify any other studies which indicate a relationship between PND score (or other baseline factors) with mortality?

Response: We acknowledge the limitations of the paper by Suhr et al. 1994[46] in providing evidence of mortality by PND score, including:

- The study is dated (1982–1993).
- The number of patients included is modest (N=27) and from a single country (Sweden).
- It is unclear how time to event and censoring were managed in the calculation of the mean survival by PND score, as presented in Fig. 3 of the paper. Furthermore, Fig. 3 reports a time to death for each of the 27 patients investigated in the study, whereas the text reports that only 13 patients died during the observation period.
- PND III was considered as a single score, whereas today it is split into PND IIIA and IIIB.

Despite these limitations, it should be emphasised that this is the only study available in the literature that provides data on the relationship between PND score and mortality. Moreover, the parameters for the model derived from this study are not based on the absolute estimates of survival, but rather on the relative mortality hazard for PND IIIA–IIIB vs PND I–II and of PND IV vs PND I–II.

There are some studies in the literature with information on the relationship between other factors and death (Table). Several variables present at the time of diagnosis are associated with shorter survival, including:

- Higher age
- The presence of Val122Ile or Thr60Ala mutations (the most prevalent variants in the UK)
- Malnutrition leading to weight loss
- Peripheral neuropathy
- Cardiac biomarker levels (NT-proBNP levels ≈ ≥3000 pg/mL)

However, we have identified no study other than Suhr et al. 1994 that correlated PND and survival in patients with hATTR amyloidosis. The possibility of considering other indexes, such as for instance the mBMI, for the definition of health states in the model was explored, but ultimately discarded due to the paucity of the data available in the literature. It should be noted that we did perform a scenario analysis (Scenario 4; see CS Section 12.4.2 and Table D35) in which mortality associated with polyneuropathy was excluded, considering only mortality due to cardiomyopathy. Attributing all mortality in the model to cardiomyopathy as

measured by NT-proBNP levels (i.e., assuming no mortality was attributable to polyneuropathy as measured by PND score) was shown to reduce the ICER in comparison to the base case. Therefore, the base-case analysis incorporating the data from Suhr et al. yields less favourable results for patisiran, and are therefore a more conservative approach.

Table 19. Literature on risk factors for mortality in amyloidosis.

Reference	Population	Characteristics	Organ involvement	Risk factors (statistically significant only; p<0.05)
Connors et al. 2016[47]	WT TTR amyloidosis	Country=US N=121	98% cardiac amyloidosis	Multivariate predictors: • BNP • Serum uric acid • LVEF • Increased relative wall thickness
Damy et al. 2016[5]	Cardiac amyloidosis	Country=France n=118 AL n=57 hATTR n=23 WT-TTR	100% cardiac symptoms	Univariate predictors (TTR) • IVST • NT-proBNP • LVEF • Systolic blood pressure Multivariate predictors: • NT-proBNP quartiles • NYHA class • Cardiac output • Pericardial effusion
Gertz et al. 1992[48]	hATTR amyloidosis	Country=US N=52	83% peripheral neuropathy 33% autonomic neuropathy 27% cardiomyopathy	Univariate predictors • Age (HR=1.67 for 10 y) • Cardiomyopathy (HR=3.22) Multivariate predictors • Cardiomyopathy (HR=5.29)
Grogan et al. 2016[18]	Cardiac WT TTR amyloidosis	Country=US N=320	100% cardiac amyloidosis	Predictors (significance NR) • Troponin T (cutpoint 0.05 ng/mL; HR=2.34 • NT-proBNP (cutpoint 3,000 pg/mL; HR=2.22 • Combination of the above factors: one above (HR=1.42); two above (HR=3.60) (none above overlapping to age and sex mortality)
Kristen et al. 2017[29]	TTR amyloidosis	Country=mixed (THAOS registry) N=165 WT N=1210 V30M N=242 non-V30M	31.4% cardiac symptoms 64.2% neurological symptoms	Univariate predictors • Age • Sex • Duration of disease • eGFR Multivariate predictors • Age • Val30Met • NT-proBNP
Martinez-Naharro et al. 2017[49]	Cardiac TTR amyloidosis	Country=UK N=263	100% cardiac amyloidosis	Multivariate analysis • NT-proBNP, each 100 pmol/L increase
Rapezzi et al. 2009[50]	Cardiac amyloidosis	Country=Italy N=157 AL N=61 hATTR N=15 WT-TTR	100% cardiac symptoms 11% peripheral neuropathy (in hATTR)	Multivariate predictors • Age • hATTR vs AL • WT-TTR vs AL • Mean LV wall thickness
Ruberg et al. 2012[51]	Cardiac TTR amyloidosis	Country=US N=18 WT N=11 V122I	100% cardiac symptoms	Univariate predictors • Duration of disease from diagnosis • Heart rate >70 beats/min • LVEF <50% • Mutation

Reference	Population	Characteristics	Organ involvement	Risk factors (statistically significant only; p<0.05)
Sattianayagam et al. 2012[52]	hATTR amyloidosis	Country=UK and Canada N=60 Cardiac amyloidosis = 97%	75% Autonomic neuropathy 54% Peripheral neuropathy 97% Cardiac symptoms	Univariate predictors • Age HR 2.49 • IVST HR 0.31 • NT-proBNP HR 0.39 (cut-off 400 pmol/L) • Diastolic dysfunction HR 0.33 • LVPW thickness HR 0.42 • Weight loss at diagnosis HR: 2.85 Multivariate predictors • NT–proBNP HR 0.17 (cut-off 400 pmol/L) • LVPW thickness HR: 0.17
Sperry et al. 2016[53]	Cardiac amyloidosis	Country=US N=191 AL N=169 ATTR (40.5% hereditary)	100% Cardiac symptoms	Univariate predictors (ATTR) • Age • NYHA Class ≥3 • Body surface area • Ejection fraction • LVEDD • LV mass index • TR grade ≥3 • Global LS • Log Troponin T • Log NT-proBNP Multivariate predictors (ATTR) • Ejection fraction • NYHA class ≥3
Swiecicki et al. 2015[54]	hATTR amyloidosis	Country=US N=266	70% peripheral neuropathy 53% autonomic neuropathy 61% cardiomyopathy 34% weight loss	Univariate predictors • Age (RR=11.95) • Thr60Ala (RR=1.46) • Val122Ile (RR=1.76) • Autonomic neuropathy (RR=1.38) • Weight loss (RR=1.73) • Cardiomyopathy (RR=1.51) Multivariate predictors • Age (RR=15.65) • Thr60Ala (RR=1.52) • Val122Ile (RR=2.83) • Peripheral neuropathy (RR=1.69) • Weight loss (RR=1.81)
Tsay et al. 2013[55]	Cardiac TTR amyloidosis	Country=US N=91	NR	Univariate predictors • BNP >600 pg/mL, HR 2.77 • Troponin >0.1 ng/mL, HR 2.76 • eGFR <30 mL/min/m^2, HR 3.99 • mBMI (BMI x albumin) <100 (kg×g)/(m^2×dL), HR 2.4 Multivariate predictors: • mBMI HR 5.3 • eGFR HR 9.5

AL: immunoglobulin light chain; BNP: B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; hATTR: hereditary transthyretin-mediated amyloidosis; HR: hazard ratio; IVST: intraventricular septal thickness; LS: longitudinal strain; LV: left ventricular; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVPW: left ventricular posterior wall; mBMI: modified body mass index; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; NR: not reported; RR: relative risk; TR: tricuspid regurgitation; TTR: transthyretin; WT: wild-type.

B9. Please clarify why only serious adverse events have been included in the model.

Response: As defined in the APOLLO study, a Serious Adverse Event (SAE) was defined as any medical occurrence that at any dose: resulted in death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; or was an important medical event that may not have been immediately life-threatening or resulted in death or hospitalisation but may have jeopardised the patient or may have required intervention to prevent one of the other outcomes listed in the definition above.

On this basis we considered that SAEs would be the relevant level of adverse event to include in the model since they would have required hospitalisation or other interventions to manage them, thereby generating associated healthcare costs, and would have led to decreases in patients' HRQoL.

B10. Please clarify what assumption was used for the efficacy of patisiran in patients who have discontinued patisiran treatment.

Response: We assumed that after discontinuation of the treatment patients maintained the progression rate characteristic of patisiran. While there are no clinical data to support this assumption, some degree of sustained benefit after discontinuation seems reasonable in the light of the mechanism of action of the drug, because the active strand of a small interfering RNA remains stable within the endogenous cytoplasmic RNA-induced silencing complex for weeks, continuing to knock down target gene expression.[56]

To assess the uncertainty around this assumption, we explored a scenario in which the effectiveness of patisiran instantaneously vanishes at the moment of treatment discontinuation, even though this scenario seems to be improbable from the clinical point of view as outlined above. The results of this scenario and the comparison with the submitted base case are reported in Table . Compared with the base-case scenario, assuming no patisiran benefit after discontinuation reduces the discounted QALY gain by 5.4%, has minimal impact on the total incremental cost, and increases the ICER by [redacted]. Therefore, the assumption of maintained efficacy does not have a substantial impact on the model results.

Table 20. Comparison of the submitted model base-case analysis with a scenario analysis in which patisiran benefit ceases upon discontinuation.

	LY		QALY		Costs (£)	
	Undiscounted	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
Base-case analysis: efficacy maintained after discontinuation						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran - BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]
Scenario analysis: no benefit beyond discontinuation						
Patisiran	15.38	13.41	9.32	8.07	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran - BSC	7.01	5.63	9.19	7.84	[redacted]	[redacted]

ICER	**Undiscounted**		**Discounted**	
	Cost (£)/LY	**Cost (£)/QALY**	**Cost (£)/LY**	**Cost (£)/QALY**
Base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year.

Model data and inputs - clinical inputs

B11. **Priority Question**. Please provide the equivalent patient count data by treatment group shown in Tables D5 and D6 (page 148) for the time periods 0-6 months, 6-12 months and 12-18 months.

Response: These patient count data cannot be generated at the 6- and 12-month time points requested because, per the study protocol, efficacy assessments for the measures in question were collected at baseline, 9, and 18 months. Patient count data were presented for the baseline and 18-month time points for a number of reasons. The study was designed

so that all objectives (i.e., primary, secondary, and exploratory) examine differences between baseline and 18 months in the patisiran and placebo groups. We also believe using the patient count data from the 18-month time point—the latest time point in the study—is most appropriate, because it gives us a clearer idea of treatment separation over time, thus allowing us to more accurately extrapolate the treatment benefits of patisiran relative to best supportive care over a longer duration than if we had used data from other efficacy assessments in the study period.

Transition data from Tables D5 and D6 were converted to 6-month time periods to match routine clinical practice in the UK, in which patients visit a physician one to two times a year for a clinical examination. During the course of routine clinical practice during these 6-month intervals, the physician could be expected to examine patients to determine if they have experienced substantial disease progression.

B12. **Priority Question.** In Table C10 page 119, please present EQ-5D utility estimates at each observed time point in APOLLO for: (a) each treatment group, and (b) each treatment group by PND score. Please include the point estimate, the confidence interval and the number of patients contributing data.

Response: The data requested are reported below in Table 21 (utility estimates) and Table 22 (number of patients). Please note that the interquartile range around the utility estimates is presented in lieu of the 95% confidence interval. A 95% confidence interval could not be generated for certain health states due to small patient numbers. We did not make use of these data directly in the cost-effectiveness model because of the instability of the utility means in some subgroups due to the small number of patients contributing to them. Also, while the means suggest a clear trend toward improvement for patisiran and toward worsening for placebo, they are inadequate to quantitatively estimate the values for the model. These major limitations pointed to the clear need to develop a statistical model (i.e., the regression analysis on utilities) that can allow more systematic and stable estimates (during the initial 18 months) and projections (in the extrapolation period) to be included in the model.

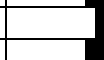
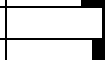
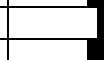
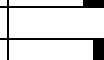
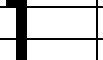
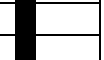
Table 21. Mean (IQR) UK EQ-5D statistics by APOLLO treatment group, study visit, and PND score.

	Baseline		Month 9		Month 18	
	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PND 0				[redacted]		[redacted]
PND I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PND II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PND IIIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PND IIIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Baseline		Month 9		Month 18	
	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
PND IV						

EQ-5D: EuroQol five dimension questionnaire; IQR: interquartile range; PND: Polyneuropathy Disability.
Source: ad hoc APOLLO data analysis performed for this response, Alnylam data on file.

Table 22. Number of APOLLO patients contributing EQ-5D data, by treatment group, study visit, and PND score.

	Baseline		Month 9		Month 18	
	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
Overall						
PND 0						
PND I						
PND II						
PND IIIA						
PND IIIB						
PND IV						

EQ-5D: EuroQol five dimension questionnaire; PND: Polyneuropathy Disability.
Source: ad hoc APOLLO data analysis performed for this response, Alnylam data on file.

B13. **Priority Question.** Model, Worksheet “TransMX” cells C164:N175: The model converts the observed 18-month probabilities to rates and then to 6-month probabilities based on formulae which are not appropriate for multinomial data. Please provide an analysis in which appropriate methods for converting the cycle length are applied (for example: Craig and Sendi, Estimation of the transition matrix of a discrete-time Markov chain, *Health Economics*, 2002, 11:1; or Chhatwal et al, Changing Cycle Lengths in State-Transition Models: Challenges and Solutions, *Medical Decision Making* 2016; 36(8):952-964).

Response: We recognise that the traditional method used to convert 18-month transition matrices to 6-month transition matrices is imperfect, and that a more accurate method could have been used in place of it, as reported in the two publications you mentioned. Both publications refer to the same method, namely the spectral decomposition of the transition matrix in order to obtain its n-root (in our case n=3). The method of spectral decomposition is based on the estimation of the eigenvalues and the eigenvectors. The implementation of this method would require some level of sophistication to be added in the calculation engine of the model, including the addition of specific VBA libraries to support advanced matrix calculations in Excel. However, the real problem is that we have to plan for a general solution that allows for the estimation of the cubic root of any possible 12x12 matrix. The two 18-month transition matrices (one for patisiran and one for BSC) obtained from the APOLLO study, are in fact subject to the probabilistic sensitivity analysis, according to the Bayesian method described in CS Section 12.2.1. Consequently, the algorithm to be implemented should a general one, capable of estimating the cubic root of a general 12x12 matrix. As clarified in both Craig and Sendi and Chhatwal et al., the method of spectral decomposition has limitations and cannot be applied on all possible matrices. In our base case, for both patisiran and placebo matrices, it turns out that not all the eigenvalues are real numbers (i.e., some of the roots of the characteristic polynomial are complex numbers). Consequently, we regret that we are not in the position of fulfilling the request from the ERG and amending the model as suggested.

Based on this finding we tried to assess the bias generated by the traditional conversion method that we used in the submitted model. To do so we compared the distribution of patients in health states produced by the submitted model after 18 months (3 cycles of simulation) with the distribution at the same time point produced by a model that employs directly the 18-month transition matrices (and consequently has a 18-month cycle length). The implicit assumption in this process is that the distribution of patients in health states at month 18 produced with just one cycle of simulation should be the correct one and that we would have obtained exactly this distribution after 3 cycles of simulation if we had been able to estimate 6-month transition matrices with an exact conversion method. In this exercise we turned off the probability of death, to avoid the bias of competing risks being estimated on a different number of cycles.

Table 23 illustrates the health-state distribution of the simulated patients at 18 months obtained with the submitted model in comparison with a model that has an 18-month cycle length.

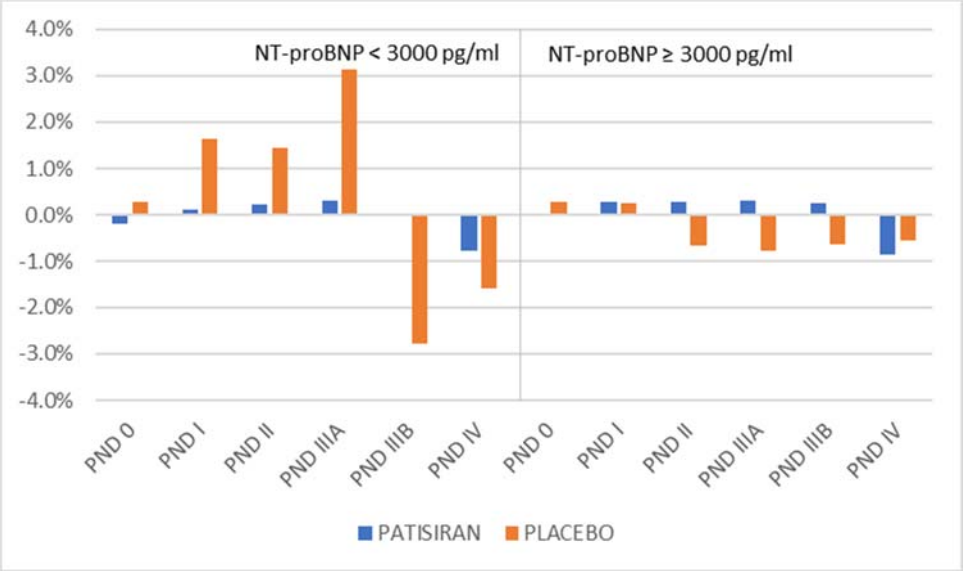
Table 23. Comparison of distribution of patients at 18 months obtained with the submitted model (A) and with an 18-month–cycle model (B).

	Low NT-proBNP						High NT-proBNP					
	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
Patisiran												
Model A	[redacted]											
Model B	[redacted]											
Diff. (A-B)	[redacted]											
BSC												
Model A	[redacted]											
Model B	[redacted]											
Diff. (A-B)	[redacted]											

BSC: best supportive care; Diff. difference; NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.

As shown in Figure 6, which graphs the differences reported above in Table 23, the bias introduced by the traditional method employed for converting transition matrices does not apply uniformly to all health states and comparators.

Figure 6. Difference in patient distribution at 18 months between the submitted model and an 18-month–cycle model.



Note: graph shows the difference for Model A - Model B from Table .
NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.

In the health sates with NT-proBNP <3000 pg/mL the submitted model seems to overestimate the population with low PND and to underestimate the population with high PND. This behaviour is more marked in the BSC arm. In the health states with NT-proBNP ≥3000 pg/mL the model overestimates PND I to IIIB in the patisiran arm, while it more severely under predicts PND II to IV in the placebo arm. The total fraction with high NT-proBNP is overestimated (+0.3%) in the patisiran arm and underestimated (-2.4%) in the placebo arm. Overall, the bias introduced may be considered neutral in the patisiran arm as the two main trends (underestimating the shift to PND IV and overestimating the shift to high NT-proBNP) act in favour and against the value of the treatment, respectively. Conversely, both of the trends identified in placebo arm (underestimating the shift to PND IV and the shift to high NT-proBNP) work against patisiran. Additionally, the magnitude of the effect is much higher in the placebo arm.

In conclusion, we acknowledge the limitations of the simple conversion method applied, but we believe that the error introduced can be considered relatively small as compared to the overall uncertainty surrounding the analysis. Additionally, the error introduced is likely to bias the results of the cost-effectiveness analysis against patisiran, so the approach in the submitted model should be considered to be conservative.

B14. **Priority Question**. Please clarify why the observed BSC patient transition data are not used to inform the extrapolated portion of the time horizon.

Response: The approach used was driven by availability of data. In the case of patisiran we have evidence from the phase 2 OLE study that in the longer-term transitions between PND states and between high and low NT-proBNP are similar to those observed during the 18 months of the APOLLO trial (see Table D8 in the CS). Consequently, it seems reasonable to extend the use of the observed transition matrix for patisiran in the extrapolation period.

The same sort of confirmation of APOLLO transitions is missing for the placebo arm, since patients randomized to placebo in APOLLO received patisiran in the OLE. There is no

available longitudinal data on PND score in the natural history, so we believe it is reasonable to use the observed BSC patient transition data on PND Score in the extrapolation period.

Regarding cardiac parameters, we observe that patients had relatively low cardiac severity at the time of enrolment in the APOLLO study (e.g., NYHA I and II). However, the available literature suggests that the rate of cardiac progression accelerates substantially over time, especially for parameters like NT-ProBNP. As documented in the Transthyretin Amyloidosis Cardiac Study (TRACS), patients quickly transitioned to more severe cardiac failure: 73% of patients were in NYHA I or II at baseline but 100% were in NYHA III or IV by 18 months.[57] In parallel, NT-ProBNP also increased sharply over this observation period. As a result, we do not believe it is appropriate to consider that the observed BSC patient transition data for cardiac parameters will continue to be observed into the extrapolation period. Instead, we believe they will more closely parallel the evolution of cardiac severity seen in TRACS, which is the largest prospective, longitudinal study specifically designed to assess the natural history and disease progression among these patients. Finally, this approach was chosen after consultation with clinical experts at the NAC who felt the TRACS cardiac data would appropriately represent clinical practice in the UK.

Therefore, we applied a transition matrix in the extrapolated time for BSC consistent with the evidence available on the natural history of the disease.

B15. **Priority Question**. Table C10 page 119 states that 18-month EQ-5D data are not yet available from APOLLO. However, the text on page 129 states that, "*the utility score for PND IV in the placebo arm at 18 months is negative following conversion of the EQ-5D-5L scores with the UK tariff*" – this suggests that the 18-month EQ-5D data were available. And on page 129, it is stated that "*The change in HRQoL with disease progression is captured in the CEA by using the utilities at baseline in APOLLO for the first model cycle and subsequently changing them according to the average change by PND score and treatment arm*." Whilst ambiguous, this seems to indicate that only the baseline EQ-5D data have been used in the model.

a. Please clarify whether the 18-month EQ-5D data have been used in the utility regression model.

Response: We apologize for any confusion caused. The text in question in table C10 merely means that the EQ-5D utility data were not yet available to the APOLLO study authors in time to be included in their abstract and presentation at the 1st European Congress on Hereditary ATTR Amyloidosis in November 2017.[58] Thus, the comment relates to the lack of publication of the EQ-5D results at the time of writing the CS, rather than their availability for use in the model. Accordingly, we confirm that the regression model, described in section 10.1.9, was conducted on the pooled EQ-5D measurements at baseline, 9 and 18 months in both treatment arms.

b. If the 18-month EQ-5D data from APOLLO have not been used in the utility regression model, please clarify how AEs are captured in the predicted utilities.

Response: As explained in the previous point, we confirm that 18-month EQ-5D data from APOLLO have been included in the regression model for utilities.

c. Please provide details of the statistical model fitted to the observed EQ-5D data, including the regression equation and error terms allowing for repeated measures.

Response: The regression equation for this statistical model is reported in Equation A:

```
eq5d = trt01pn*time pndcat                                    (A)
```

where trt01pn codes treatment group (1=placebo, 2=patisiran); pndcat is a categorical version of PND scores (0, I, II, IIIA, IIIB, IV); and time is a continuous variable that denotes the time in months elapsed from baseline (time=0).

The data used for model development were EQ-5D scores indexed for the UK in the mITT population of the APOLLO study. All observations by treatment arm (patisiran and placebo) and time point (baseline, month 9, and month 18) were pooled (data=one in SAS code).

We started with a “full model”:

```
eq5d = trt01pn time trt01pn*time pndcat bnpcat2       (B)
```

where bnpcat2 is a binary version of NT-proBNP: bnpcat2 =1 if NT-proBNP <3000 ng/L and bnpcat2 =2 if NT-proBNP ≥3000 ng/L. All other variables are as described previously.

We applied a forward selection process using the smallest Akaike Information Criterion (AIC) to build the model. The SAS code is reported below:

```
proc glmselect data=one ;
  class trt01pn(ref="1")  pndcat bnpcat2 ;
  model eq5d = trt01pn time trt01pn*time pndcat bnpcat2/noint
selection=forward(select=AIC) details=all SHOWPVALUES;
run;
```

This eventually led to model A. We did not consider potential correlations pertaining to the same subject over repeated measures of EQ-5D index. Table 24 presents the estimates of model parameters.

Table 24. Utility parameter estimates for the final statistical model A.

Parameter	Estimate	Standard error	Pr > |t|
PND 0	[redacted]	[redacted]	<0.0001
PND I	[redacted]	[redacted]	<0.0001
PND II	[redacted]	[redacted]	<0.0001
PND IIIA	[redacted]	[redacted]	<0.0001
PND IIIB	[redacted]	[redacted]	<0.0001
PND IV	[redacted]	[redacted]	0.4951
VISITNUM*TRTPN Patisiran	[redacted]	[redacted]	0.0326
VISITNUM*TRTPN Placebo	[redacted]	[redacted]	0.0080

PND: Polyneuropathy Disability.

The final model fitting gives AIC = -1199.01760. The full model based on equation B had AIC = -1196.48816.

d. Please fit a statistical model to the EQ-5D data including terms for all stratification factors and any main effects when interaction terms are included.

Please provide details of the statistical model fitted and comment on the comparison with the model described in Table C12 page 126. [NOTE: It is not necessary that stratification factors are statistically significant for them to be included in the model.]

Response: The "full" model, described as in equation B in the previous point, was fitted to the APOLLO dataset. The estimated parameters are report in Table 25 below. We can see that treatment and NT-proBNP are not statistically significant. Time is quite significant at the 0.05 alpha level but is left out in the forward selection process. Statistically, we should keep all components if we have interaction in the model so that the results are more interpretable.

Table 25. Utility parameter estimates for the full statistical model B.

Parameter	Estimate	Standard error	Pr > |t|
TRTPN Patisiran	[redacted]	[redacted]	0.3082
TRTPN Placebo	[redacted]	[redacted]	0.6946
Time	[redacted]	[redacted]	0.0053
VISITNUM*TRTPN Patisiran	[redacted]	[redacted]	0.0002
VISITNUM*TRTPN Placebo	[redacted]		
PND 0	[redacted]	[redacted]	<0.0001
PND I	[redacted]	[redacted]	<0.0001
PND II	[redacted]	[redacted]	<0.0001
PND IIIA	[redacted]	[redacted]	<0.0001
PND IIIB	[redacted]	[redacted]	<0.0001
PND IV	[redacted]		
NT-ProBNP (<3000 pg/mL)	[redacted]	[redacted]	0.6754
NT-ProBNP (≥3000 pg/mL)	[redacted]		

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.

As discussed in the previous point the AIC statistics show a better fit for model A than for model B.

e. Given that cardiac involvement is described as an important determinant of HRQoL in the background section of the CS, please clarify why this has been excluded from the regression model. Please also comment on the validity of assuming the same utility scores for NT-ProBNP>3000 and NT-ProBNP<3000 and provide results of regression analyses with NT-ProBNP added to the models generated in parts c) and d).

Response: To assess the effect of NT-proBNP on the utility we considered another model by adding bnpcat2 back to Model A—please note that NT-proBNP parameter is already included in model (B):

```
eq5d = trt01pn*time pndcat bnpcat2                    (C)
```

The parameter estimates for model (C) are show in Table 26.

Table 26. Utility parameter estimates for statistical model (C) incorporating bnpcat2.

Parameter	Estimate	Standard error	Pr > |t|
VISITNUM*TRTPN Patisiran	[redacted]	[redacted]	0.0347
VISITNUM*TRTPN Placebo	[redacted]	[redacted]	0.0086
PND 0	[redacted]	[redacted]	<0.0001
PND I	[redacted]	[redacted]	<0.0001
PND II	[redacted]	[redacted]	<0.0001
PND IIIA	[redacted]	[redacted]	<0.0001
PND IIIB	[redacted]	[redacted]	<0.0001
PND IV	[redacted]	[redacted]	0.4321
NT-ProBNP (<3000 pg/mL)	[redacted]	[redacted]	0.6779
NT-ProBNP (≥3000 pg/mL)	[redacted]	[redacted]	

To compare models (A), (B) and (C) we used the SAS mixed-model procedure. Model fitting parameters will be different from using the GLM procedure. The reason we used the mixed model here is that SAS PROC GLM does not produce model AIC and Bayesian Information Criterion (BIC) statistics.

Example SAS statements are as below:

```
proc mixed data=one ;
  class subjid trt01pn(ref="1") pndcat bnpcat2 ;
  model eq5d = trt01pn time trt01pn*time pndcat bnpcat2/noint solution;
run;
```

The table below compares models A, B, and C in terms of AIC and BIC from PROC MIXED.

Table 27. Comparison of AIC and BIC for models A, B, and C.

	AIC	BIC
Model A (final submitted model)	-34.8	-30.3
Model B (full model)	-25.7	-21.3
Model C (final model with bnpcat2 added back)	-29.6	-25.2

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Table 27 shows that, in terms of AIC and BIC, Model A provides the best fit. In other words, adding a non-significant NT-proBNP term as in model C makes the model worse.

f. Please explain how the "*patisiran maximum utility*" (ceiling) and the "*BSC minimum utility*" (floor) have been derived.

Response: We apologise for the lack of clarity in the data reported in Table C12. The set of data that are described as "Patisiran, maximum utility" and as "BSC, minimum utility" in fact operate as upper and lower boundaries for the utilities in *both* the patisiran and BSC arms. Additionally, the constraint was imposed such that utilities at any time cannot exceed the utility of the general UK population with corresponding age and sex (as per Kind et al.1999[59]).

Minimum and maximum utilities were calculated as the minimum and maximum in the range of 25th–75th percentiles by PND score measured at any time in the APOLLO study. The application of this interquartile range was done to remove the influence of possible outliers. Alternatives explored in scenario analyses suggested that our approach was conservative (e.g. to the disadvantage of patisiran) as compared, for example, to using unconstrained utility values in the modelled time period.

g. Please explain why patients with PND 0 (asymptomatic) receiving BSC are assumed to experience HRQoL which is considerably lower than that of the general population.

Response: In the APOLLO data we observed that utilities are not fixed within the same PND health state. There is a clear pattern of improving HRQoL among patients treated with patisiran and toward decreasing HRQoL among patients receiving placebo, even within the same PND score. This effect may be explained by the broad functional definition of the PND score, which is mainly linked to the ability to walk. As a consequence, it seems reasonable that patients who are temporarily classified as PND 0 (and thus with no impairment in the ability to walk) may experiment a decrease in their HRQoL due to other manifestations of the disease that are not directly captured by the PND score.

B16. Model, worksheet "QoL Data" cells A41:D48. Please clarify why the Kind *et al* utilities have been used rather than a newer source such as Ara and Brazier (*Value in Health*, 2010;13:5).

Response: We thank the ERG for highlighting to us the availability of a newer source for the reference utility of the general UK population. When comparing the model proposed by Ara and Brazier with the reference table from Kind et al. in the range of ages of interest for the current analysis, it appears that reference utilities in the newer source are on average higher than in the older reference. For instance the utility for a 60-year-old male is 0.837 using Model 1 from Ara and Brazier[60] and 0.78 from the tables in Kind et al.[59] The same utility values for a 60-year-old female are 0.82 and 0.81, respectively.

To test the impact of using these difference sources, we developed a sensitivity analysis in which the utility of the general population is calculated from the formula of Ara and Brazier, instead of the tables in Kind et al. The comparison with the results of the submitted base case is presented in Table 28. The ICER in the sensitivity analysis differs by only [redacted] from the ICER in the submitted base case. Thus, for practical purposes the two sources of utility norms appear to yield very similar results.

Table 14. Comparison of the submitted model base-case analysis (UK population norm utilities based on Kind et al. 1999[59]) with a sensitivity analysis using UK population norm utilities based on Ara and Brazier 2010.[60]

	LY		QALY		Costs (£)	
	Undiscounted	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
Base-case analysis: population norm utilities based on Kind et al. 1999[59]						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran - BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]
Sensitivity analysis: population norm utilities based on Ara and Brazier 2010[60]						
Patisiran	15.78	13.73	9.88	8.54	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran - BSC	7.41	5.95	9.75	8.32	[redacted]	[redacted]

ICER	**Undiscounted**		**Discounted**	
	Cost (£)/LY	**Cost (£)/QALY**	**Cost (£)/LY**	**Cost (£)/QALY**
Base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year.

B17. Model. Worksheet "Markov Patisiran" cells P6:Z6. Please explain why a fixed probability of NT-proBNP<3000 pg/mL is applied to the initial PND distribution. Why was the observed baseline distribution by PND and NT-proBNP not used?

Response: This solution was adopted to simplify the model calculations and to standardise the definition of the initial characteristics of the simulation, in order to allow subgroup analysis. We verified, however, that the distribution of patients by high and low NT-proBNP was almost uniform across PND scores in the baseline APOLLO data, as can be seen in Table 29.

Table 2915. Patient distribution at baseline in APOLLO by PND score and NT-proBNP level.

	NT-proBNP			
	<3000 pg/mL		≥3000 pg/mL	
	N	%	N	%
PND 0	[redacted]		[redacted]	
PND I	[redacted]	[redacted]	[redacted]	[redacted]
PND II	[redacted]	[redacted]	[redacted]	[redacted]
PND IIIA	[redacted]	[redacted]	[redacted]	[redacted]
PND IIIB	[redacted]	[redacted]	[redacted]	[redacted]
PND IV	[redacted]	[redacted]	[redacted]	[redacted]

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.
Source: APOLLO, Alnylam data on file.

B18. Please clarify the data cut-off for the APOLLO study data used in the model.

Response: The data used in the model are based on finalised data after the completion of the APOLLO study. In other words, the cost-effectiveness analysis was not conducted on the basis of interim data from the APOLLO study.

B19. The CS Section 14.1 page 206 states that patisiran *"is anticipated to bring significant economic benefits outside the NHS in terms of patient and caregiver productivity and ability to participate in activities."* Is there any evidence of the impact of patisiran on improving absenteeism and productivity and/or caregiver impacts?

Response: While no direct evidence is currently available on the benefit of patisiran in these societal areas (i.e., change in absenteeism, productivity, and/or caregiver impacts in response to patisiran therapy), the expectation of such benefits is logical given the demonstrated difference in disability experienced by patients receiving patisiran vs placebo, described in CS Section 7.2.

Model data and inputs - resource use and costs

B20. **Priority Question**. The patisiran cost calculations seem to be double-counting reductions in costs relating to treatment discontinuations (due to being a function of both relative dose intensity and time on treatment)

a. Please clarify whether this is the case.
b. Please clarify if the RDI calculation was based only on those patients who were alive and still on treatment, or if it included those who discontinued and/or died.

Response: The RDI was aimed at taking into account all temporary reductions or missed doses while patients are in treatment, whereas the extrapolation of the time-on-treatment (ToT) curve was meant to account for permanent interruptions of the treatment (i.e., discontinuations).

The RDI was calculated as the total number of doses received during the APOLLO study (3740 doses, according the CSR) divided by the theoretical number of doses. We recognise,

however, that in this way the number of missed doses due to permanent discontinuations is included in the estimate of the RDI, leading to a possible double counting. To understand the magnitude of the error, we tried to estimate the number of missed doses due to permanent discontinuations. This can be done by assessing the area above the ToT curve in the time period from baseline to 18 months. We did this considering the parametric function that was chosen to extrapolate the ToT (i.e., the log-normal function). We then re-calculated the RDI removing the effect of doses missed after permanent discontinuation. The re-calculated RDI was 0.99 (vs 0.97 in the model originally submitted). Table 30 presents the results of the model when including this updated RDI. The ICER is increased by about [redacted] with respect to the submitted base-case analysis.

Table 30. Comparison of the submitted model base-case analysis (RDI 0.97) with a sensitivity analysis removing the effect of doses missed after permanent discontinuation (RDI 0.99).

	LY		QALY		Costs (£)	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Base-case analysis: potential double-counting of missing dose						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran – BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]
Sensitivity analysis: corrected RDI						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran – BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]

ICER	Undiscounted		Discounted	
	Cost (£)/LY	Cost (£)/QALY	Cost (£)/LY	Cost (£)/QALY
Base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year; RDI: relative dose intensity.

B21. Please clarify whether the time-on-treatment data include both death and discontinuation as events.

Response: The parametric survival on treatment analysis was conducted on the set of patient-level data from the APOLLO study where only discontinuations for any reason except death was considered as "failure" events. Deaths were considered as "censoring" events.

B22. The CS page 148 states that "*The log-logistic function was selected to inform the fraction of patients still on treatment at each time point in the simulation based on the goodness of fit*." However, the model appears to use the log normal distribution. Please explain which curve the company intended to use in the model and whether the extrapolation is consistent with clinical plausibility.

Response: The text at page 148 is incorrect, and we apologise for this mistake. We confirm that the function that is used in the base-case analysis is the log normal. The choice of this function was mainly driven by the goodness of fit statistics (AIC and BIC). However, it can be observed from Figure 27 in the CS that all parametric models (except the exponential) provided a very similar extrapolation function in the long term, and CS Table D7 shows that the difference in the AIC and BIC statistics was very small. From a clinical point of view the trend of all parametric models, except the exponential, suggests that the fraction of patients interrupting the treatment is constant after some time. This means that in the long term no patient discontinues unless he/she dies. We discussed this concept with clinical experts and

they suggested that this assumption may be not realistic. However, the only function that provides a different trend in the long term is the exponential. The clinicians suggested that this may be closer to clinical reality. We explored the application of the exponential model to ToT in a scenario analysis, and presented the results as Scenario 3 in Sections 12.5.10–11 of the CS. Nevertheless, we preferred to retain the log normal function in the base-case analysis since not only was it the best-fit function but it also had a conservative effect on the ICER compared with the scenario analysis using the exponential function.

B23. Please investigate whether there has been an error in the fitting of the exponential distribution to the time on treatment data. This does not appear to have worked correctly (Section 12.2.1, page 149).

Response: Upon inspection, the fitting of the exponential function seems to be correct. We also kindly remind the ERG that the use of the exponential function was only in a sensitivity analyses to explore uncertainties surrounding our base case. It was not used in the base case itself. Please advise what aspect of the curve appears to be problematic to the ERG/technical team.

B24. Do the cost calculations shown in Appendix 3 account for double-counting associated with previous one-off costs already incurred for less severe PND states? E.g. if a patient requires a wheelchair in PND III, does the analysis account for the fact that they will not need a new one on progression to PND IV? Please also explain why the one-off costs are not applied to the high NT-proBNP group.

Response: There was a mistake in the calculation of the costs associated with one-off HCRU. We implemented a correction in order to ensure that the sum of the resources (for instance a wheelchair) adopted when progressing to PND I, PND II, PND IIIa, PND IIIb and PND IV could not exceed 100%, meaning that each resource could have been adopted in just one state and maintained in the following. When implementing this correction, the results of the base-case analysis change by a minimal amount, as can be seen from Table 31.

Table 31. Comparison of the submitted model base-case analysis (potential double-counting of HCRU) with a sensitivity analysis in which all HCRU was calculated as one-off costs.

	LY		QALY		Costs (£)	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Base-case analysis:						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran – BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]
Sensitivity analysis: one-off HCRU						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran – BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]

ICER	Undiscounted		Discounted	
	Cost (£)/LY	Cost (£)/QALY	Cost (£)/LY	Cost (£)/QALY
Base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; HCRU: healthcare resource utilisation; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year.

For NT-proBNP, we impute the average costs incurred per patient with NT-proBNP <3000 pg/mL or ≥3000 pg/mL, rather than attempt to see how many patients have specific HCRU.

B25. Model, Worksheets “Markov Patisiran” and “Markov BSC”, one-off costs. It appears that the model is double-counting one-off costs for patients who progress to a worse health state, regress to a better state and subsequently progress to a worse state. Please provide an analysis in which these costs are not double-counted.

Response: Due to the nature of the Markov model, which has no memory, the implementation of this feature would require the design of a large number of additional states (e.g., to mark patients who already progressed once to PND I, patients who already progressed once to PND II, patients who progressed to PND I and PND II, etc.) making the management of them all practically unfeasible.

To assess the magnitude of the error introduced by this potential double counting we estimated a sensitivity analysis in which one-off costs are removed. The comparison of the submitted base case and the described scenario is presented in Table 32, which demonstrates that only minimal changes in the ICER are introduced by excluding one-off costs.

Table 32. Comparison of the submitted model base-case analysis (potential double-counting of HCRU) with a sensitivity analysis in which all one-off costs have been excluded.

	LY		QALY		Costs (£)	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Base-case analysis: potential double-counting of HCRU						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran - BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]
Sensitivity analysis: one-off costs excluded						
Patisiran	15.78	13.73	9.86	8.52	[redacted]	[redacted]
BSC	8.37	7.78	0.13	0.22	[redacted]	[redacted]
Patisiran - BSC	7.41	5.95	9.73	8.30	[redacted]	[redacted]

ICER	Undiscounted		Discounted	
	Cost (£)/LY	Cost (£)/QALY	Cost (£)/LY	Cost (£)/QALY
Base-case analysis	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; HCRU: healthcare resource utilisation; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year.

B26. CS, Section 13, page 199. Who will administer the homecare infusions? Why have the costs of homecare infusions not been included in the model?

Response: The homecare service model is still under discussion between Alnylam and the NHS. It has not yet been determined if the option of home infusion will be available, and if so, which party will pay for home infusion. Given this uncertainty, it was decided to adopt the assumption that all patients will need to come to the NAC for their infusions, both in the cost-effectiveness model and in the budget impact model.

B27. Please provide details of the proposed homecare service (Section 13 page 199).

Response: To date the homecare service model has not yet been agreed with the NHS, so details are not yet available.

Model implementation

B28. **Priority Question**. Model, Worksheet “mortality data” cells G29:G76. Please clarify what these calculations are intending to do.

Response: The aim of all calculations in the "Mortality data" worksheet is to estimate the hazard ratios (HRs) of mortality used in the cost-effectiveness model. The schema used for the estimation of mortality in the model is described in CS section 12.2.1 and is summarised in CS Table D4, repeated here for convenience.

Table 33. CS Table D4: Schema of the mortality risks applied in the simulation.

	NT-proBNP <3000 pg/mL	NT-proBNP ≥3000 pg/mL
PND 0-II	Low-risk group HR=2.01 over the mortality of the general UK population	HR=2.04 vs patients with NT-proBNP<3000 pg/mL and same PND score
PND III	HR=1.30 over the low-risk group	
PND IV	HR=4.73 over the low-risk group	

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.

In the "Mortality data" worksheet we calculate the HRs vs PND 0–II of 1.30 and 4.73 for PND III and IV, respectively (explained in response to question B29), the HR of 2.04 for high NT-proBNP (derived from Gillmore et al. 2018[61]), and the HR=2.01 for the low-risk group (explained in this response).

In this response we provide more details on the estimation of the HR of death of the low-risk group, defined as those patients with PND score 0–II and NT-proBNP <3000 pg/mL, with respect to the mortality of the general UK population with corresponding age and sex.

The starting point of this calculation is the estimated mean survival in the hATTR-amyloidosis cohort in Gillmore et al. 2018 that had NT-proBNP <3000 pg/mL at baseline. From the publication of this study it can be estimated that the mean survival was 7.7 years. It should be noted that this cohort is not equivalent to the defined low-risk group—in fact, we do not have information on PND score from the Gillmore et al. 2018 study. However, we believe that PND score has an impact on mortality. For this reason, we assumed that PND score in Gillmore paper was distributed at baseline as in the APOLLO study, and more specifically that 54.2% of the cohort was in PND 0–II and 45.8% was in PND III–IV.

The block of cells A29:I76 represents the implementation of a small survival model aimed at replicating the survival of the cohort in Gillmore et al. 2018 that had NT-proBNP <3000 pg/mL at baseline based on the assumption that:

- The effect of the disease on mortality when there are no specific risk factors (i.e., NT-proBNP <3000 pg/mL and PND I–II), can be expressed as a constant HR to be applied to the mortality of the general population;
- The group with NT-proBNP <3000 pg/mL in Gillmore et al. 2018 had baseline PND distribution as in the APOLLO study.

We calculated the HR of the low-risk group with the Excel's Solver tool, by imposing the condition that the survival estimated in this survival model is 7.7 years.

In cells B29:D76 we have the death probability of a sample of the general UK population with the same age and sex as the cohort in Gillmore et al. 2018 that had NT-proBNP <3000 pg/mL at baseline. Please note that Gillmore et al. propose their own staging system—not to be confused with FAP stages—based on NT-proBNP and eGFR. As discussed in section 12.2.1 of the CS, we assume that Stage I corresponds to NT-proBNP <3000 pg/mL without considering eGFR.

The formulae in cells G29:G76 are calculating, year after year, the death probability of this group of hATTR patients with NT-proBNP <3000 pg/mL from the Gillmore et al. study. For the fraction of the cohort that was in PND 0–II (assumed as 54.2%) this is given by the mortality of the general UK population to which is added the HR of the low-risk group. For the fraction of the cohort that was in PND III–IV the probability is given by the mortality of the general UK population, to which is added the HR of the low-risk group, and further increased by the HR for death of PND III–IV vs PND I–II (derived from Suhr et al. 1994[46] and contained in cell K92 in worksheet "Mortality Data").

In cells H29:H72 we have the survival cycle after cycle, and in cells I29:I72 the survival adjusted by half-cycle correction. The results of this analysis (i.e., HR=2.01 for the low-risk group) is estimated with the Solver tool, imposing the constraint that the result of cell I27 is equal to 7.7 years.

B29. **Priority Question**. Model, Worksheet "mortality data" cells G86:K92. Please clarify the logic underlying all of these calculations. Please clarify why NT-proBNP score data from APOLLO are used in these calculations.

Response: The objective of the group of cells G86:K92 in worksheet "Mortality Data" is to estimate the HRs for death of hATTR amyloidosis patients who are in PND III (A and B) vs those who are in PND I–II, and the mortality HRR of PND IV vs PND I–II. To do so we considered the mean survival in each PND score, derived from Suhr et al. 1994[46] (cells H87:H90). The mean survival for the pooled PND I–II scores was calculated as the average of the mean survivals in PND I and II, weighted by the relative number of patients (cell H91). In cells J89:J91 we estimated the hazard rates of exponential survival functions that have the mean survival as in corresponding cells H89:H91. In doing so we took into consideration the potential effect of NT-proBNP distribution. Since we don't know the NT-proBNP distribution in the study by Suhr et al. we assumed that this variable was distributed as in the APOLLO study, uniformly across PND scores (87.7% below 3000 pg/mL and 12.3% above 3000 pg/mL, cells I97 and I98). Consequently, the equation to derive the hazard rate of the exponential survival function that takes into account only the effect of PND is

$$HR_{PND} * (87.7\% + 12.3\% * 2.04) = \frac{1}{mean}$$

Where HR_{PND} is the hazard rate that takes into account only the effect of PND; 2.04 is the HR for death of NT-proBNP ≥3000 pg/mL vs NT-proBNP <3000 pg/mL (from Gillmore et al. 2018[61]).

We finally calculated the HR=1.30 (cell K89) as the ratio of the hazard rate in PND III over PND I–II and the HR=4.73 (cell K90) as the ratio of the hazard rate in PND IV over the hazard rate in PND I–II.

B30. **Priority Question**. Worksheet "Mortality Data" cells J89:92. The brackets appear to be misplaced within these formulae. Please confirm whether these calculations contain an error.

Response: We have checked, and it does not seem that cells J89:J92 in worksheet "Mortality Data" contain an error.

B31. **Priority Question**. Please explain how to generate the results that are presented in Tables D31, D32, D33, D34 and D35 pages 192-94 using the model.

Response: CS Table D31: imputation of missing data with a conservative hypothesis (all missing patients in the patisiran arm are imputed as progressors to the next health state; all missing patients in the BSC arm are imputed as improvers to the next health state). The results of this scenario analysis can be generated by substituting the transition matrices in worksheet “TransMx” cells A43:C58 and R43:AG58 with the following tables.

Table 34. Scenario analysis 1A: transition matrix for patisiran.

From\To		NT-proBNP <3000 pg/mL						NT-proBNP ≥3000 pg/mL						Missing	Total
PND score		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV		
NT-proBNP <3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
NT-proBNP ≥3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
Missing															
Total															

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.
Source: APOLLO, Alnylam data on file.

Table 35. Scenario analysis 1A: transition matrix for BSC.

From\To		NT-proBNP <3000 pg/mL						NT-proBNP ≥3000 pg/mL						Missing	Total
PND score		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV		
NT-proBNP <3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
NT-proBNP ≥3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
Missing															
Total															

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.
Source: APOLLO, Alnylam data on file.

CS Table D32: imputation of missing data with an optimistic hypothesis (all missing patients in the patisiran arm are imputed as improvers to the next health state; all missing patients in the BSC arm are imputed as progressors to the next health state). The results of the scenario can be generated by substituting the transition matrices in worksheet “TransMx” cells A43:C58 and R43:AG58 with the following tables.

Table 36. Scenario analysis 1B: transition matrix for patisiran.

From\To		NT-proBNP <3000 pg/mL						NT-proBNP ≥3000 pg/mL						Missing	Total
PND score		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV		
NT-proBNP <3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
NT-proBNP ≥3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
Missing															
Total															

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.
Source: APOLLO, Alnylam data on file.

Table 37. Scenario analysis 1B: transition matrix for BSC.

From\To		NT-proBNP <3000 pg/mL						NT-proBNP ≥3000 pg/mL						Missing	Total
PND score		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV		
NT-proBNP <3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
NT-proBNP ≥3000 pg/mL	0														
	I														
	II														
	IIIA														
	IIIB														
	IV														
Missing															
Total															

NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.
Source: APOLLO, Alnylam data on file.

CS Table D33: scenario analysis with no constraint on utilities. Input the value 1 in worksheet “HRQoL” cells E22:E27, the value -1 in worksheet “HRQoL” cells E31:E36, the value 1 in worksheet “Markov Patisiran” cells DJ6:DJ86, and the value 1 in worksheet “Markov BSC” cells DJ6:DJ86.

CS Table D34: scenario analysis using the exponential function for the ToT with patisiran. Change the selection in the drop-down list in worksheet “Costs” cell E28 to “Exponential”.

CS Table D35: scenario analysis attributing no mortality by PND score. Input the value 1 in worksheet “Clinical” cells E47 and E48.

B32. Model, Worksheet “TransMX” cells C63:N74. The CS states that a prior of 1% was used in the model. However, the model actually uses a value of 1/12 for all transitions.

Please clarify the value of the intended prior. Please also clarify why priors are applied to the BSC matrix during the observed period but not during the extrapolated period.

Response: The actual prior value used in the model is 1/12=0.08. In CS section 12.1.10 this was mistakenly reported as 1%. Please accept our apologies for the typo.

Regarding the transition matrix in the BSC arm for the extrapolation period, we clarified that the transition matrix is not applied (see response to question B14). In this case we apply a transition matrix estimated based on the natural history of the disease. As a consequence the Bayesian method is not applicable.

B33. Model, Worksheet "HRQoL." Some of the regression parameters for the lower PND states allow for utilities which are greater than 1. Please comment.

Response: In principle this is true, but in practice this does not generate errors since the utilities actually applied in the model are constrained such that (a) utilities are never higher than the maximum threshold by PND score, and (b) in no case can a utility value exceed the utility of the general UK population with corresponding age and sex.

B34. The minimum and maximum utility values shown in the Table C12 page 126 do not match those used in the model. Please clarify which values are correct.

Response: There appears to have been a transcription error in CS Table C12. The correct values are those considered in the model. The following is a corrected version of the table.

Table 3816. Corrected version of CS Table C12.

State	Utility value	SE(*)	Lower value, Upper value	Reference in submission
Parameters of the regression				
PND 0	[redacted]	[redacted]	[redacted]	APOLLO trial
PND I	[redacted]	[redacted]	[redacted]	APOLLO trial
PND II	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IIIA	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IIIB	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IV	[redacted]	[redacted]	[redacted]	APOLLO trial
Per-month change with patisiran treatment	[redacted]	[redacted]	[redacted]	APOLLO trial
Per-month change with BSC treatment	[redacted]	[redacted]	[redacted]	APOLLO trial
Patisiran, maximum utility				
PND 0	[redacted]	[redacted]	[redacted]	APOLLO trial
PND I	[redacted]	[redacted]	[redacted]	APOLLO trial
PND II	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IIIA	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IIIB	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IV	[redacted]	[redacted]	[redacted]	APOLLO trial
BSC, minimum utility				
PND 0	[redacted]	[redacted]	[redacted]	APOLLO trial
PND I	[redacted]	[redacted]	[redacted]	APOLLO trial
PND II	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IIIA	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IIIB	[redacted]	[redacted]	[redacted]	APOLLO trial
PND IV	[redacted]	[redacted]	[redacted]	APOLLO trial
HRQoL other settings				
Caregiver disutility (PND IV)	[redacted]	[redacted]	[redacted]	Tafamidis submission

BSC: best supportive care; HRQoL: health-related quality of life; NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability; SE: standard error. *When not available in the original sources a standard value of 10% of the mean was considered for the SE.

B35. The tornado diagram presented in Figure 39, page 188 does not match that generated from the model. Please explain this discrepancy.

Response: The graph in CS Figure 39 of the original submission was mistakenly generated with an earlier version of the model. Please accept our apologies for this error. The following is the correct figure.

Figure 7. Corrected version of CS Figure 39.

HCRU: healthcare resource utilisation; HR: hazard ratio; NT-proBNP: N-terminal pro B-type natriuretic peptide; PND: Polyneuropathy Disability.

Budget Impact

B36. The budget impact results on page 201 states that "*Five-year survival is predicted to be 92% for patients treated with patisiran and 84% for patients not treated with patisiran*". These estimates do not match the predictions from the economic model - please clarify how these estimates have been derived.

Response: Column AA of worksheets "Markov Patisiran" and "Markov BSC" of the economic model tracks cumulative death membership. These estimates were calculated as one minus the proportion of the cohort in cell AA:14 of the respective worksheets, rounded to the nearest percentage. Please accept our apologies for confusion caused as the use of row 14 from the economic model was erroneous. Five-year death should have been calculated based on row 16 of these columns. However, the estimates cited were not used directly in budget impact calculations, so this mistake does not impact the results.

B37. Please clarify the source of the [redacted] uptake rate for patisiran.

Response: Our patient number estimate, as outlined in the answer to question A4 anticipates 73 patients out of 112 may be eligible for treatment. At any point in time we must allow for patients participating in clinical trials, choosing an alternative treatment or being

unwilling to undertake a chronic treatment. In collaboration with the clinical team at the NAC we estimate that at any given time point [redacted] patients may be participating in studies and another [redacted] may wish to defer going on treatment or choose another treatment.

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Patisiran – Follow-up Questions for the Company

(1) The ERG has noticed that some of the data in the CS does not match the data in the CSR? Please can the company clarify why this is the case? For example:

   a. According to Table 12 of the CSR, mean age at screening in the mITT APOLLO population was 60.5 years, whereas the model uses a value of 58.8 years and cites APOLLO as the source

   b. Similarly, Table 12 of the CSR states that 74.2% of the mITT APOLLO population were male, whereas the model uses a value of 70.5% and cites APOLLO as the source

(2) In response to question B11, the company has clarified that the assessment intervals relate to 0, 9 and 18 months but have not provided the requested matrices. Please can the company provide the requested matrices for months 0-9 and 9-18?

(3) The ERG is unclear how the analyses in response to question B10 have been done. What has been changed in the model?

(4) The ERG is unclear how the analyses in response question B24 have been done. What has been changed in the model?

John Stevens
25 September 2018

Patisiran – Follow-up Questions for the Company

PLEASE NOTE THAT THE COMPANY RESPONSES BELOW CONTAIN CONFIDENTIAL INFORMATION MARKED AS 'CIC'

(1) The ERG has noticed that some of the data in the CS does not match the data in the CSR? Please can the company clarify why this is the case? For example:

   a. According to Table 12 of the CSR, mean age at screening in the mITT APOLLO population was 60.5 years, whereas the model uses a value of 58.8 years and cites APOLLO as the source

   b. Similarly, Table 12 of the CSR states that 74.2% of the mITT APOLLO population were male, whereas the model uses a value of 70.5% and cites APOLLO as the source

RESPONSE: We apologise for neglecting to explain in Section 12 of the CS that the economic model used demographic data from the subgroup of the mITT APOLLO population with non-Val30Met (non-V30M) mutations of the transthyretin gene (i.e., *post hoc* subgroup analyses of APOLLO data on file). We used demographic datafor the Non-V30M cohort to reflect the demographic characteristics of hATTR amyloidosis patients in the UK, who mostly have non-V30M mutations.[1] Information on the mutations present in the UK was also validated with clinical experts at the NAC. Importantly, only the demographic data from patients with Non-V30M mutations was used in the model. Effectiveness data and all other relevant parameters used the full mITT APOLLO population. As noted in the forest plots and subgroup analyses included in our first set of responses to the ERG's questions, patisiran demonstrated consistent benefit across all pre-specified subgroups – including those with V30M or Non-V30M mutations.

(2) In response to question B11, the company has clarified that the assessment intervals relate to 0, 9 and 18 months but have not provided the requested matrices. Please can the company provide the requested matrices for months 0-9 and 9-18?

RESPONSE: Please find below the matrices for baseline to 9 months and for 9 to 18 months transitions.

Table 1: Transitions from baseline to 9 months: Patisiran

Baseline		Month 9													
Planned Treatment for Period 01 (N)=Patisiran 0.3 mg/kg		NT proBNP<3000 pg/mL						NT proBNP≥3000 pg/mL						Missing	Total
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV		
NT proBNP< 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
NT proBNP≥ 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
Missing															
Total															

Table 2: Transitions from baseline to 9 months: Placebo

Baseline		Month 9													
Planned Treatment for Period 01 (N)=Placebo		NT proBNP<3000 pg/mL						NT proBNP≥3000 pg/mL						Missing	Total
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV		
NT proBNP< 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
NT proBNP≥ 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
Missing															
Total															

Table 3: Transitions from 9 to 18 months: Patisiran

Month 9		Month 18													
Planned Treatment for Period 01 (N)=Placebo		NT proBNP<3000 pg/mL						NT proBNP≥3000 pg/mL						Missing	Total
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV		
NT proBNP< 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
NT proBNP≥ 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
Missing															
Total															

Table 4: Transitions from 9 to 18 months: Placebo

Month 9		Month 18													
Planned Treatment for Period 01 (N)=Placebo		NT proBNP<3000 pg/mL						NT proBNP≥3000 pg/mL						Missing	Total
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV		
NT proBNP< 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
NT proBNP≥ 3000 pg/mL	PND 0														
	PND I														
	PND II														
	PND IIIA														
	PND IIIB														
	PND IV														
Missing															
Total															

(3) The ERG is unclear how the analyses in response to question B10 have been done. What has been changed in the model?

RESPONSE: the original model was modified in order to allow the analysis presented in the answer to question B10. The modifications that were introduced in the model are the following:

- The entire calculation structure in the worksheet “Markov Patisiran” is duplicated in order to have one Markov model to simulate patients while on treatment and one Markov model to simulate patients off treatments. More specifically the content of cells A5:GN86 (being the model “on-treatment”) is copied in cells A95:GN176 (being the model “off-treatment”)
- In the worksheet “Functions” one column is added to calculate the probability of discontinuation at each cycle. The formulas are added in column K. For instance the probability of discontinuing at the first cycle is calculated in cell K3 with the formula “=(I3-I4)/I3”
- In the “Markov Patisiran” worksheet patients discontinuing are removed from the “on-treatment” model and are added to the “off-treatment” model. This is done by adding “*(1-Functions!K3)” to each of the formulas in the cells AE6:AP6 and copying down the formulas to the entire “on-treatment” model. The same quantities are then added in the “off-treatment” model. For instance in cell AE96 the quantity given by “+O6*(1-H6)*Functions!$K3” is added to the existing formula. In the same way the quantity “+P6*(1-H6)*Functions!$K3” is added to the existing, etc. As a check the total population in the “on-treatment” model and in the “off-treatment” model is summing up to 1 at every cycle.
- The “off-treatment” model is modified to reflect the efficacy of BSC. This change is introduced in the calculation of Transitions (cells O95:AB176), Pts progressing to PND stages (cells AR95:AV176), Adverse Events (cells BS95:CF176), and Utilities (cells DK95:DV176). Additionally, cells estimating Drug, Administration and premedication costs (cells EZ95:FB176) are set to zero.
- As a final step, the links related to Patisiran arm in the worksheet “Results” are modified in order to take into account both the contributions of the “on-treatment”

and the “off-treatment” models. For instance the formula in cell E18 is “='Markov Patisiran'!CT3+'Markov Patisiran'!CT93”

(4) The ERG is unclear how the analyses in response question B24 have been done. What has been changed in the model?

RESPONSE: Mean one-off resources in worksheet “HCRU data” were modified as follows

One-off costs	PND II (cells M75:M88)	PND IIIA (cells R75:R88)	PND IIIB (cells W75:W88)	PND IV (cells AB75:AB88)
Electric wheelchair	0.00%	6.25%	16.25%	77.50%
Manual wheelchair	0.00%	23.76%	33.74%	42.50%
Stick	42.00%	58.00%	0.00%	0.00%
Crutch	16.67%	9.58%	7.08%	0.00%
Walking chair	0.00%	12.50%	37.50%	50.00%
Walking frame	1.25%	9.75%	72.75%	16.25%
Permobil	0.00%	12.50%	22.50%	65.00%
Shower chair	28.75%	31.25%	30.00%	10.00%
Adjustment, kitchen	25.00%	21.67%	3.33%	0.00%
Adjustment, bathroom	31.67%	61.67%	6.67%	0.00%
Door opener	5.00%	32.50%	75.00%	0.00%
Rails	16.67%	60.00%	6.67%	0.00%
Ramps	7.50%	26.25%	36.25%	30.00%
Homecare bed including lift	0.00%	11.25%	23.75%	60.75%

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

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.

Information on completing this submission

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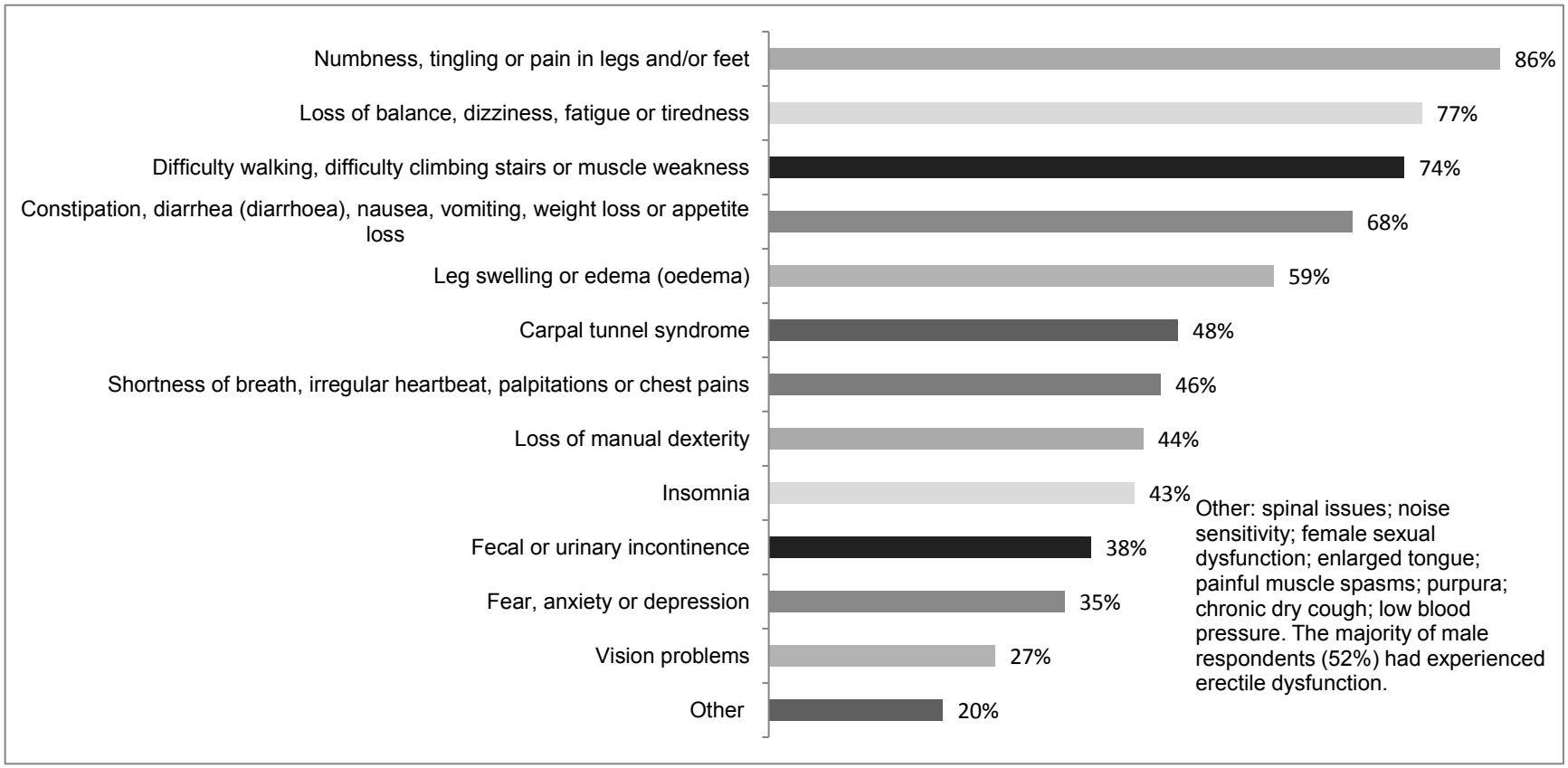
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Amyloidosis Research Consortium UK (ARC UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	ARC UK aims to tackle the most pressing unmet needs in systemic amyloidosis and improving the lives of amyloidosis patients and their families. In building links between patients, academia, the pharmaceutical industry, regulators and other stakeholders we hope to advance the best research and accelerate new treatments to patients. We aim to address the challenges in diagnosis and research to ensure that patients benefit from the most important advances, while at the same time driving forward priority areas of research and innovation in amyloidosis. We have four strategic objectives that inform everything we do: early and accurate diagnosis; better research for better outcomes; access to effective treatments; and access to quality care, information and support. We are a patient representative organisation which, as part of our day to day work, sets out to support and represent amyloidosis patients and families from across the UK. However, we are not a membership organisation. We currently receive funding from various sources including from a range of pharmaceutical companies, patients and their families as well as grant-giving bodies.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and their families drive everything we do. This submission draws on conversations with patients and carers with whom we are in everyday contact. In addition, we have included information from survey-based research we conducted with hATTR patients and carers in Spring 2018. 101 patients and 51 carers provided information about their experiences, the impact of the disease on their lives and their goals and concerns about treatment. In parallel, we held two online focus groups, involving nine patients and carers to explore aspects of this topic in more depth. We also interviewed five patients and carers by telephone. The research was not limited to UK patients, due to practical reasons, although 25 (16%) of the survey participants and five (56%) of the focus group participants reside in the UK and Republic of Ireland. Evaluation of the responses by country of residence showed no geographic associations. All but five patients (95%) in our research had experienced symptoms associated with polyneuropathy in the last 12 months. A copy of the summary report is attached. *Burden of disease and perspectives on treatment: summary report from research with hereditary transthyretin amyloidosis (hATTR) patients and carers.* ARC UK. July 2018 (unpublished). In addition to our own research,

	we have included information from other published sources, including research by Stewart et al. *Characterizing the high disease burden of transthyretin amyloidosis for patients and caregivers.* Neurol Ther. August 2018. While based on a US and Spanish survey, the findings provide some additional insight into the burden of disease and closely correlate with ARC UK's research.
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?	The patient population covered by patisiran's indication is hATTR patients with symptoms of polyneuropathy. We are limiting our comments, where relevant, to polyneuropathy. However, hATTR is a multi-system disease and while some patients have predominantly polyneuropathy or cardiomyopathy phenotypes, many patients have mixed symptomology. **hATTR has a very high burden on patients: the multi-systemic nature of the disease affects all aspects of life** Patients usually experience multiple symptoms, including sensory, motor and autonomic deficits and, for some patients, cardiac involvement. These translate into numerous effects on daily living, including mobility issues, insomnia, pain, intermittent diarrhoea, sexual dysfunction, vision and motility problems, imbalance and instability and an effect on patients' abilities to undertake daily activities. *Figure 1* below shows the range of symptoms reported by patients to our survey.

Figure 1. Symptom burden over the last 12 months (ARC UK survey 2018)



Each of these symptoms can be individually highly problematic for patients as well as contributing to an overall cumulative burden, as shown in the examples from *Table 1* below.

Table 1. Examples reported by patients of how symptoms affect their daily lives (ARC UK survey 2018)

Mobility problems	"I was an avid runner, having completed 22 marathons. Now I walk slowly with the help of a cane." "Because not too long ago I led an active, athletic lifestyle that now I can only dream of."
Chronic pain	"Keeps me awake and/or awakens me. It also affects my driving, household chores, and is a constant reminder that I have this disease." "It hurts all the way up to my belt."
Loss of manual dexterity	"Difficult to do things (buttons, zips, earrings). Dropping things, turning pages in a book. So many things that require tactile sense."
Diarrhoea	"I am never sure when I will get diarrhoea, so I cannot go out in case. Or I won't eat in case it happens." "It has brought my life to a complete standstill." "I'm afraid to eat out of home away from bathroom. Diarrhoea comes on suddenly."
Insomnia	"If I cannot sleep, I steadily decline in all aspects."
Neuropathy in hands	"I can't cook anymore as I'll burn myself and not even notice". "I can no longer make quilts because I can't pick up the fabric and pins."
Confusion / mental functioning	"Other things I can live with, even the constipation and diarrhoea."
Combination of symptoms	"Anything I like to do is gone."

In Stewart's study, almost half of all patients (48%) reported they were unable to complete typical household chores and many patients reported impairments in mobility, self-care and usual activities. An earlier study by Stewart et al found that SF-12 physical health summary scores were substantially lower in hATTR patients compared with age-matched controls (Stewart et al 2013). Patients also reported missing more than a working day on average a week due to their disease, as well as high levels of productivity impairment while working (Stewart et al 2018).

Our survey findings largely reflect this. As well the effects on their physical health, patients reported a considerable impact from the disease on their work or professional lives. When asked to rate the impact of the disease on different domains of their lives over the previous 12 months (on a scale where 0 is no impact and 10 is a very significant impact):

- 50% patients gave a ≥8 impact on their work/professional life
- 40% patients gave a ≥8 impact on their physical health
- 32% patients gave a ≥8 impact on their social/family relationships
- 29% patients gave a ≥8 impact on their emotional wellbeing

- 25% patients gave a ≥8 impact on their financial wellbeing

Patients tell us that one of the most challenging aspects of having the disease is losing independence and becoming dependent on other family members. As symptoms deteriorate, patients may lose the ability to walk, drive and work, leading to additional financial, emotional and carer burden. Another common theme is losing the ability to undertake 'normal' day to day activities that others take for granted, such as participating in family life, socialising with friends or enjoying hobbies.

The hereditary nature of the disease contributes to the emotional burden of the disease. Many patients have been carers for loved ones before succumbing to the disease themselves and they know 'what is to come'. They also live with the knowledge that they may pass, or have already passed, the disease onto their children, and experience feelings of guilt and anxiety for future generations of their family.

hATTR considerably impacts on carers and other family members

The disease has a substantial lifelong impact on entire families. It places a significant burden on family members as they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own in dealing with the realities of the disease. Family members often become full or part-time unpaid carers with consequences on their work, social and financial situation.

Carers of hATTR patients tell us that dealing with gastrointestinal problems (especially diarrhoea), patients' mental functioning and the combination of multiple symptoms are particularly problematic for them in their caring capacity. As carers they experience the burden of the disease on their own lives and similarly to patients, multiple domains of their lives are affected by hATTR.

When asked to rate the impact of the disease on different domains of their lives over the previous 12 months (on a scale where 0 is no impact and 10 is a very significant impact):

- 55% carers gave a ≥8 impact on their social/family relationships (compared to 32% patients)
- 54% carers gave a ≥8 impact on their emotional wellbeing (compared to 29% patients)
- 37% carers gave a ≥8 impact on their physical health
- 31% carers gave a ≥8 impact on their work/professional life
- 22% carers gave a ≥8 impact on their financial wellbeing

These are similar to Stewart et al's findings that the greatest impacts on carers related to their mental health, although they too observed impacts on physical health.

	Key themes that emerged from our survey related to fatigue and anxiety. Carers told us they feel exhausted from worry and from taking on an additional burden of household chores, juggling work and informal caring. Some carers told us they could no longer have a social life because of exhaustion and feeling unable to leave the patient alone. Many carers said that their career or work productivity had suffered because of their caring responsibilities and fatigue. In Stewart's study, carers reported spending an average of 46 hours a week providing care, which is more than the equivalent of a full-time job. There is also a considerable emotional burden experienced by carers. Some feel anger or sadness that their life is no longer their own; carers also commonly reported they were anxious about seeing the patient deteriorate further and were further worried about their children and future generations of the family who could have the disease.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are no other licensed disease-modifying treatments available on the NHS, although patients may be offered off-label treatments, including diflunisal and doxycycline. A very small number of patients have liver transplants. Beyond this, treatment is primarily aimed at managing the symptoms of the disease. Several participants in our survey had tried an off-label treatment. These patients generally indicated that they did not feel certain that their disease had improved. Patients report varying levels of efficacy in relation to symptom management approaches. In responses to our survey, there was considerable dissatisfaction with the effectiveness of treatment to manage neuropathic pain and fatigue. Seven in 10 patients who had tried treatment to deal with fatigue were dissatisfied or very dissatisfied with treatment; and six in 10 were similarly dissatisfied or very dissatisfied with approaches to manage neuropathic pain. Around four in 10 patients were also dissatisfied or very dissatisfied with treatments to manage gastrointestinal symptoms, cardiac symptoms or blood pressure. The symptoms mentioned here are often highly problematic for patients and can have a very negative impact on their ability to live 'a normal life.'
8. Is there an unmet need for patients with this condition?	Yes. While existing treatments can offer a degree of symptomatic relief, there is very high unmet need for new effective and safe disease-modifying treatments that could have a lasting and/or deeper positive impact on patients' disease and symptoms. Even marginal improvements in symptomology can be transformational for patients. Patients told us, for example, that slowing further deterioration in their neuropathy would enable them to maintain hobbies for longer, take on more of a share of household chores and maintain a healthy family dynamic. Others explained that achieving a small improvement in the symptoms they found to be most problematic could dramatically transform their lives:

	"Success is being able to participate in my life rather than be a bystander… To do up to three errands a day instead of one. I can walk my kids to school multiple days in a row instead of paying for it the next day with pain." "If we could go out for a whole day without worrying where the nearest toilet is – it will change our lives completely to go back to some normality which we haven't had for many years, and take the pressure off our families who are supporting us."
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Many factors are important to hATTR patients and their carers when it comes to thinking about treatment. The prospect of new treatments designed for slowing/stabilising hATTR offers significant hope to patients and their families. This is especially so given the context of the disease being hereditary, the negative impact it has on patients and carers' quality of life, and there being no other licensed alternatives available with which to treat the disease. Current treatment preferences and values are influenced by a lack of effective alternatives and high unmet need/symptom burden; whereas choice is likely to become an increasingly important consideration in the future. Our recent research explored in some depth the question of what value new treatments have for hATTR patients and their families. Unsurprisingly, the most important factors for treatment relate to the impact a treatment can have on slowing the underlying disease and improving symptoms. Alongside this, many patients expressed a preference for either a local or home-based treatment option. Patients and carers expressed concern about fatigue and taking time off work should frequent travel be required. However, they also said that a current lack of alternatives means they would be willing to put up with some inconvenience and that efficacy is the most important consideration overall. Similarly, while they would desire significant outcomes, they still highly value what might be perceived as 'modest' improvements in their health condition. Twenty patients in our research had had direct experience of patisiran. We asked these patients additional questions about how well it managed their disease, any experiences they had of side-effects and their views on its (in)convenience. All these patients indicated that they considered patisiran to have had a positive effect on managing their disease and minimising their symptoms. Many of these patients, did, however report that they found the travelling for treatment to be inconvenient, although they felt it 'was worth it' due to the positive effects they were experiencing. When discussing this issue patients told us they would like to have the option for the treatment to be available locally.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Until now patisiran has only been delivered at the National Amyloidosis Centre (NAC) under the trial and compassionate use protocols. We know that some patients and carers are concerned about the long-term impact of travelling regularly to the NAC for patisiran treatment, e.g. on their work, finances and physical capability to travel long distances. Should patisiran only be available at the NAC this would be perceived as a significant disadvantage, and involving a burden on patients and cares We are aware that the company is in discussions with NICE and NHS England about making the treatment available as a home infusion service, as well as having the option for treatment at a designated specialist service that may be closer to home and allowing patients who choose to continue to receive treatment at the NAC to do so (beyond the initial cycles). We would strongly support all these options to be available; and the desire to have this range of options to meet individual preferences and other personal and disease considerations is evidenced in our research with patients and carers. We would expect the company to carry out patient/ carer experience/satisfaction surveys throughout the duration of treatment and for this data to be provided (where permissible) to the patient's clinical team to inform ongoing needs assessment.
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.	From the available evidence, it is our view that the technology would benefit patients with either stage 1 or stage 2 polyneuropathy in terms of achieving the potential for delaying disease progression and improving the symptoms caused by the disease.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues. However, we believe it is important for this patient community to have accessible, convenient treatment options available to them and not have choices limited to them according to where they live, their financial means (e.g. to travel) or their mobility. As such, we believe it is of paramount importance that patients can receive patisiran is available in a number of ways, including an option at home.
Other issues	
13. Are there any other issues that you would like the committee to consider?	There are several contextual issues we wish to emphasise. **A treatment that involves minimal inconvenience for this patient population ought to carry a value premium** Although in the current context patients are willing to endure some inconvenience in order to slow or stabilise their disease, the issue of convenience should also reflect on a treatment's value. Due to the symptom burden patients often give up work or reduce their hours. Those who do work often say it is a struggle to manage and are concerned about their ability to continue working. Carers, providing informal care, also experience an impact on their ability to work. Patient and carers are concerned about losing more working time should they need to travel frequently for treatment. Furthermore, the common symptoms experienced by this population such as gastrointestinal symptoms, peripheral neuropathy and fatigue can make it hard to travel or prevent travel altogether. Finally, hATTR patients often lose their independence, increasingly relying on family members to care for them. Having a treatment that can be administered in a way that does not bear an additional burden on family members and, by its nature, supports patients to be independent is incredibly important. **Patients' suitability and preferences for treatment options need formal assessment and evaluation** Having a treatment that can be taken at home is extremely positive and welcome. However, there are risks. Patients told us they want to have a clear point of contact within the specialist clinical team to whom they can ask questions. The criteria patients apply to choosing between treatments or whether to have treatment are very individual and can change over time in response to disease-related, family, social and personal factors. Holistic needs assessment to support patients in making decisions about treatment and care should be carried out prior to and routinely throughout treatment, ideally as a condition of prescribing and reflected in NICE

	guidance. This will have the benefit of ensuring that only patients who are both clinically eligible and otherwise suitable for treatment receive it and that they receive it in the most appropriate way for them. **Accounting for benefits not fully captured by the clinical trial data** There are numerous health benefits that are not fully captured by the clinical data. hATTR is a heterogenous disease and patients are affected by symptoms in different ways. Fatigue, peripheral neuropathy, gastrointestinal events, incontinence, sexual dysfunction, muscle weakness, pain, insomnia and vision problems are particularly cited by patients and family members in our research as having a significant impact on their quality of life. Not all of these are captured by the clinical data or quality of life tools, yet it is important to recognise that control of the disease could improve the specific symptoms that matter most to patients. **The need for a flexible approach to deal with uncertainty** ARC UK recognises that patisiran has some limitations including, at this point, a lack of long term data. We also anticipate that as a treatment for an ultra-rare disease demonstrating value for money may be a challenge. We would urge NICE, NHS England and Alnylam to find a solution that achieves both access and affordability and that is a fair reflection of patisiran's value. It is critical that NICE can be flexible in considering both the available evidence and the additional benefits / pertinent contextual issues. Alongside this, it is vital that patisiran is appropriately priced according to its value.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • hATTR is a devastating disease. The heavy symptom burden *affecting all areas of life* and hereditary nature of the disease are two crucial factors contributing to the quality of life deficit experienced by patients and carers. • There is significant unmet need – no other available licensed treatments are approved and symptom management approaches have variable / limited effectiveness. • Patisiran offers a significant step change in the management of this disease: it has strong safety and efficacy data and the fact that we anticipate it to be offered as a home-based treatment is especially positive. • This is a situation where there are clearly additional benefits (e.g. on carers, productivity, convenience, independence etc) that may not be captured in either the clinical evidence or modelling; and these need to be factored in.	

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Burden of disease and perspectives on treatment

Summary report from research with hereditary transthyretin amyloidosis (hATTR) patients and carers

Amyloidosis Research Consortium UK

www.arci.org

July 2018

Contents

Amyloidosis Research Consortium UK

Background

Rationale

- An absence of burden of disease research for hereditary transthyretin amyloidosis (hATTR)
- Few available treatment options; no routinely available, licensed disease-modifying treatments in the UK and US
- Two new treatments exiting phase III studies and due for regulatory and health technology assessment reviews
- Need for patient and carer-level data to better understand preferences and values in relation to potential new treatments for this disease

The study sought to obtain perspectives of hATTR patients and caregivers on key issues

- Disease symptom burden
- Impact of the disease on day to day life
- Views on existing treatments
- Goals and concerns for future treatment: through exploratory and stated preference elicitation methods

Methods

Design

- ARC UK designed two online surveys with input from patients, carers, NICE and ICER
- The surveys were tested extensively with patients and carers

Survey recruitment

- ARC UK sent the surveys to hATTR patients and carers from ARC / ARC UK's database
- The surveys were promoted through social media and the web
- The National Amyloidosis Centre (UK) and Amyloidosis Support Groups (USA) publicised them on online forums
- The surveys were open from April – June 2018
- **101 patients and 51 carers provided valid data**

Focus groups / interviews

- Survey participants who opted in were invited to take part in an online focus group or telephone interview to explore perspectives on the benefits and risks of treatment in more depth
- **Nine patients and carers participated in one of two online focus groups** (5 UK; 4 US participants)
- **Five individual telephone interviews** were conducted with patients and carers who preferred an interview format

Analysis

- The focus groups and telephone interviews were audio-recorded and thematically analysed
- The surveys were analysed for summary statistics and the free text thematically analysed

Summary findings

1. hATTR has a very high burden on patients and families. A multi-systemic disease, it affects *all* aspects of life
2. hATTR significantly impacts on patients' independence and sense of normality: their ability to work, participate in family and social life, be mobile and undertake daily activities and hobbies
3. hATTTR considerably impacts on carers: the emotional burden of 'knowing what's to come', practical caring burden and the effect on their own ability to work
4. Patients have mixed experiences of symptom and disease management approaches: there is unmet need with regard to efficacy, side-effect burden and convenience/choice
5. New treatments specifically for hATTR offer significant hope to patients and their families, especially in the context of the disease being hereditary, high impact on quality of life, and no/few alternatives
6. Patients and carers value multiple factors as important for treatment, including efficacy, convenience, risk of side-effects and knowledge of benefits-risks
7. The most important factors for treatment are related to impact on the disease. Patients are likely to accept risks of side-effects for 'modest' gains
8. Treatment preferences and values are influenced by a lack of effective alternatives and high unmet need/symptom burden; as choice increases, convenience and side-effects are likely to become increasingly important considerations

Patient survey demographics

115 survey responses were received. Of these 14 were excluded as duplicates or because no useable data was provided.

Of the 101 valid responses, 91 patients completed all sections of the survey and 10 partially completed the survey.

Time since diagnosis (n=101)			
Less than 12 months ago	1-2 years ago	2-5 years ago	More than 5 years ago
11	17	44	29

Age (n=101)					
39 and under	40-49	50-59	60-69	70-79	80 and over
6	11	18	36	27	3

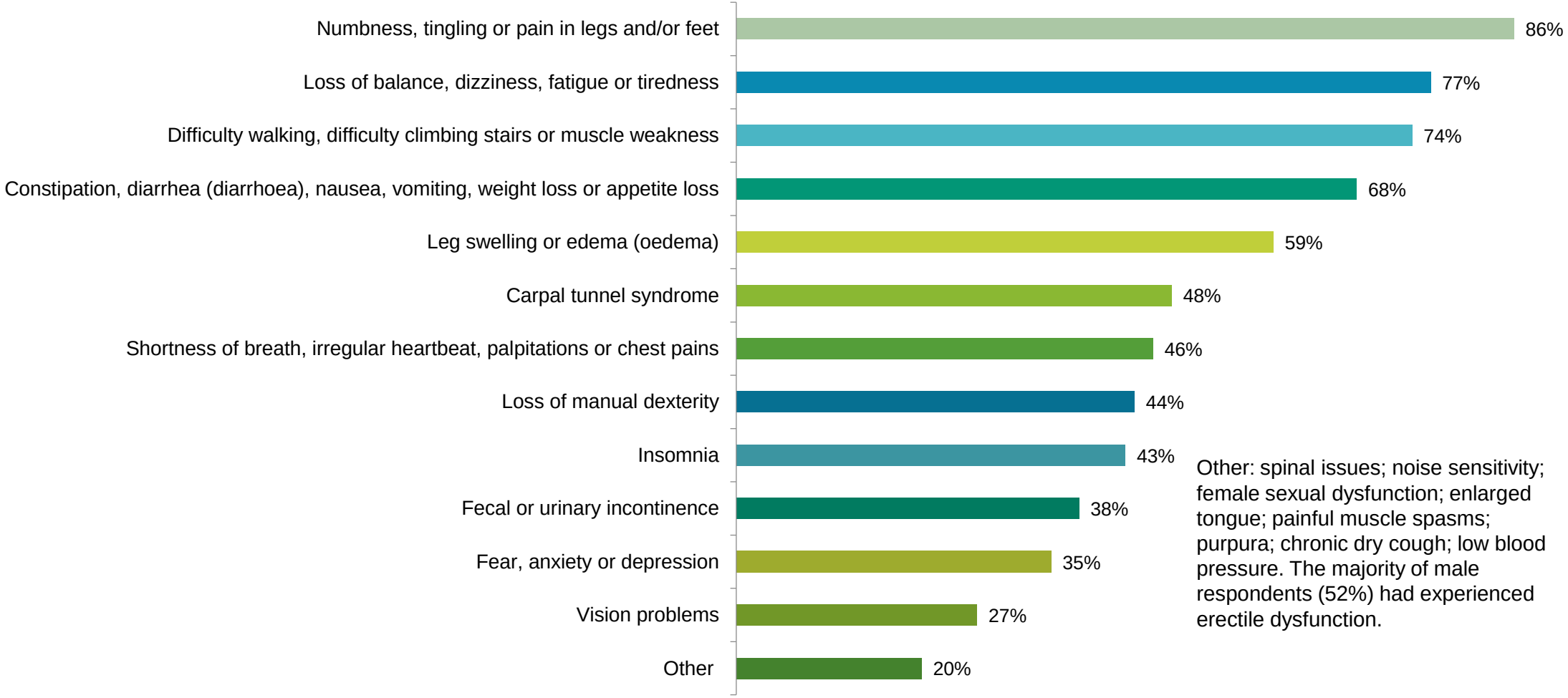
Employment status (n=100)				
Employed full-time	Employed part-time	Not employed, looking for work	Not employed, currently unable to work	Retired
20	18	1	13	48

Live with dependents (n=100)			
Yes, child dependents	Yes, adult dependents	Yes, both adult and child dependents	No
17	19	7	57

Place of residence (n=101)		
USA	UK and Republic of Ireland	Other
65	14	Netherlands (3), Canada (3), Mexico (3), Australia (2), New Zealand (2), Malaysia (2), Colombia (1), Spain (1), Italy (1), Portugal (1), Brail (1), France (1) and Denmark (1)

Genetic mutation (if known) (n=101)	
Val30Met	15
Val122 Ile	11
Glu89Gln	2
Gly53Glu	0
Glu54Gly	3
Ile68Leu	0
Thr60Al	18
Leu111Met	1
not typed	2
Not sure	21
Other	28

Patients experience a high, multi-systemic symptom burden



Other: spinal issues; noise sensitivity; female sexual dysfunction; enlarged tongue; painful muscle spasms; purpura; chronic dry cough; low blood pressure. The majority of male respondents (52%) had experienced erectile dysfunction.

Q. In the last 12 months which symptoms have you experienced? (n=98)

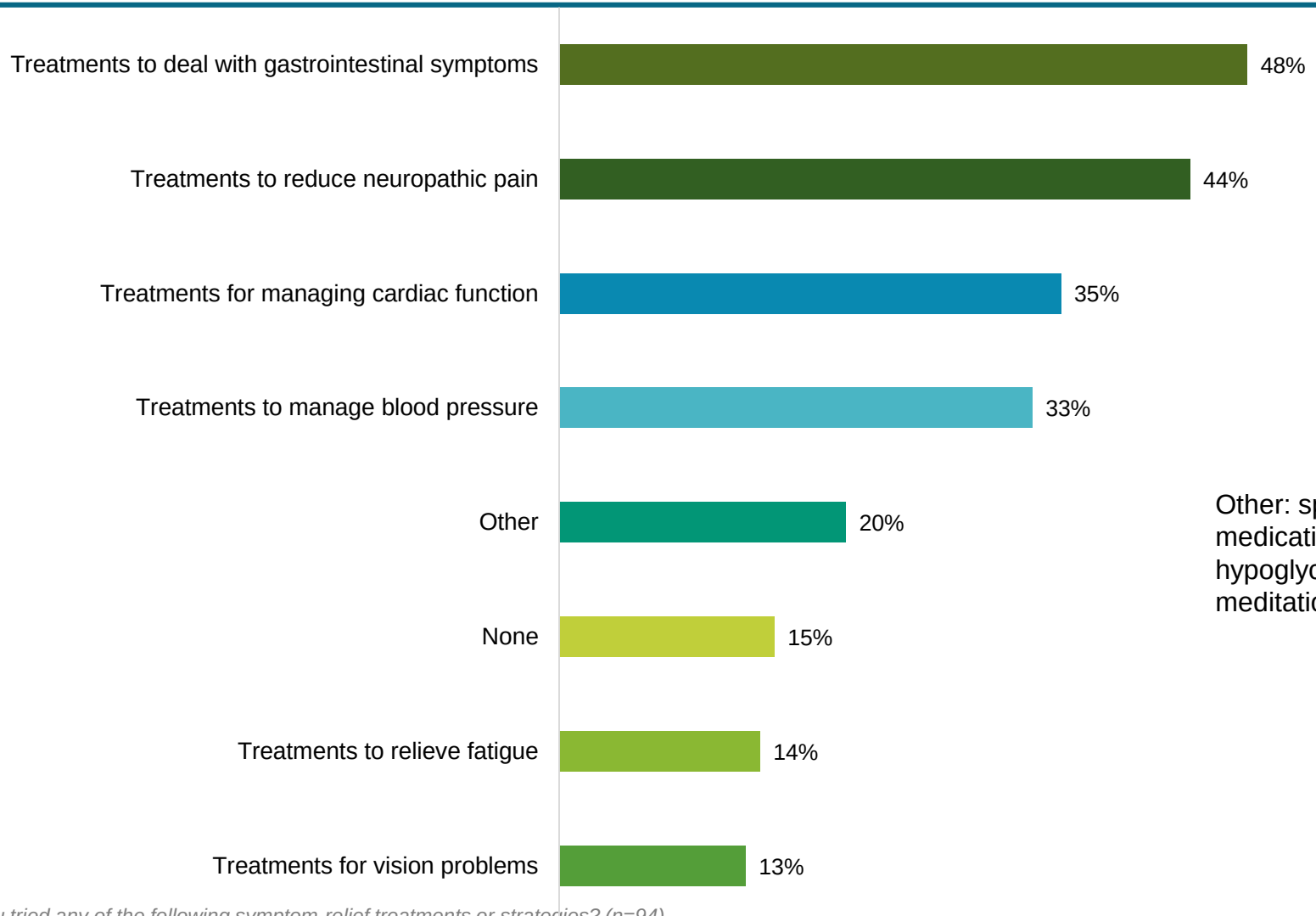
Symptoms have a pervasive impact on patients' ability to lead 'a normal life'

Amyloidosis Research Consortium UK

Which symptom is the most problematic for you?	Why?
Shortness of breath	"Makes me very anxious that my heart is going to stop working." "She feels like she is passing out, she can't go for a walk or enjoy some of the very simple things in life."
Mobility problems	"I was an avid runner, having completed 22 marathons. Now I walk slowly with the help of a cane." "Because not too long ago I led an active, athletic lifestyle that now I can only dream of."
Chronic pain	"Keeps me awake and/or awakens me. It also affects my driving, household chores, and is a constant reminder that I have this disease." "It hurts all the way up to my belt."
Loss of manual dexterity	"Difficult to do things (buttons, zippers, earrings). Dropping things, turning pages in a book. So many things that require tactile sense."
Diarrhoea	"I am never sure when I will get diarrhoea so I can not go out in case. Or I won't eat in case it happens." "It has brought my life to a complete standstill." "I'm afraid to eat out of home away from bathroom. Diarrhoea comes on suddenly."
Insomnia	"If I cannot sleep, I steadily decline in all aspects."
Neuropathy in hands	"I can't cook anymore as I'll burn myself and not even notice". "I can no longer make quilts because I can't pick up the fabric and pins."
Confusion / mental functioning	"Other things I can live with, even the constipation and diarrhoea."
Combination of symptoms	"Anything I like to do is gone."

Q. Which of these symptoms is the most problematic for you? Why?

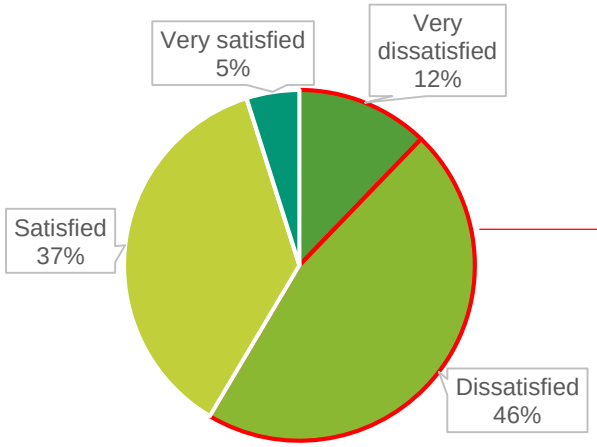
Most patients have tried a range of treatments or strategies to help manage their symptoms



Other: spine surgery; defibrillator; depression medication; edema treatment; dialysis; hypoglycaemia treatment; migraine meds; meditation; PT/OT

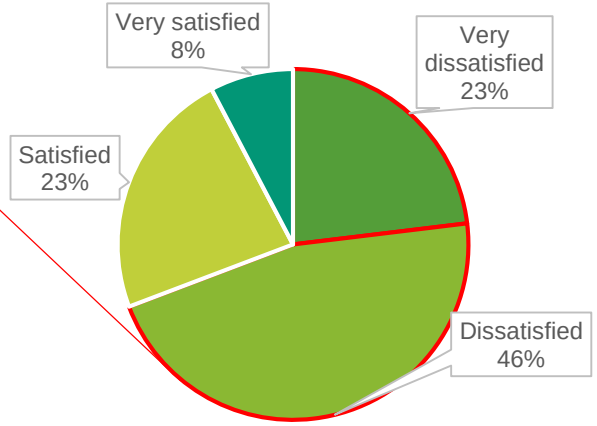
Q. Have you tried any of the following symptom-relief treatments or strategies? (n=94)

There is variable satisfaction with symptom-relief treatments and strategies

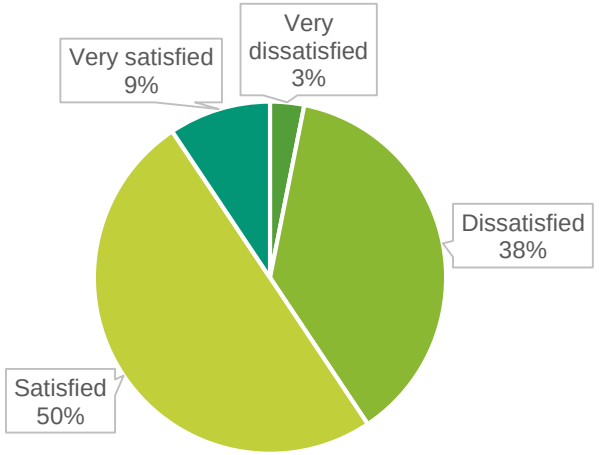


Treatments to reduce neuropathic pain (n=41)

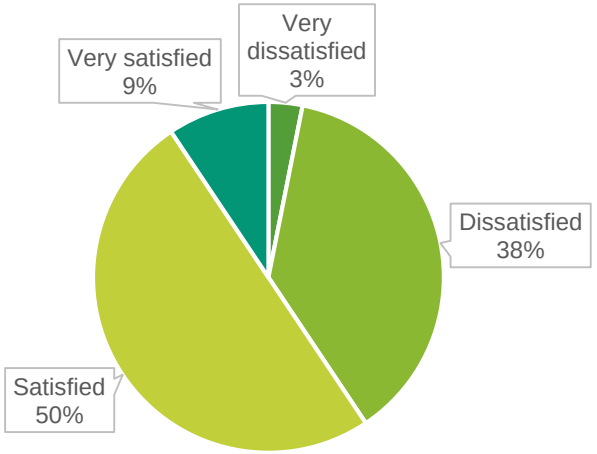
Considerable dissatisfaction with treatments to relieve neuropathic pain and fatigue



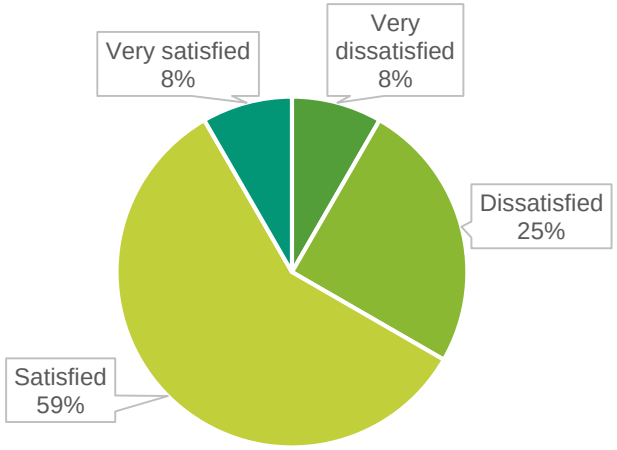
Treatments to relieve fatigue (n=13)



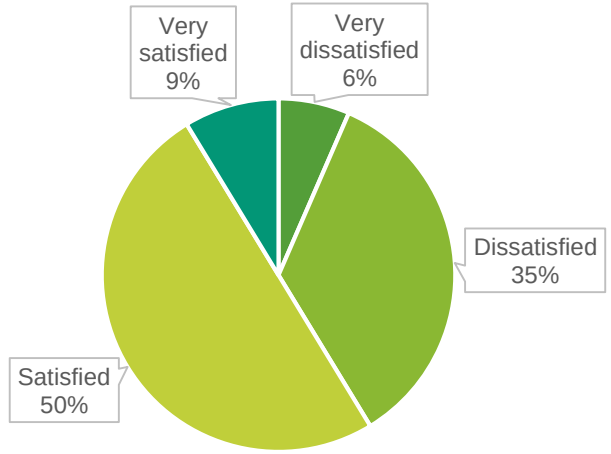
Treatments for managing cardiac function (n=32)



Treatments for managing blood pressure (n=31)



Treatments for vision problems (n=12)

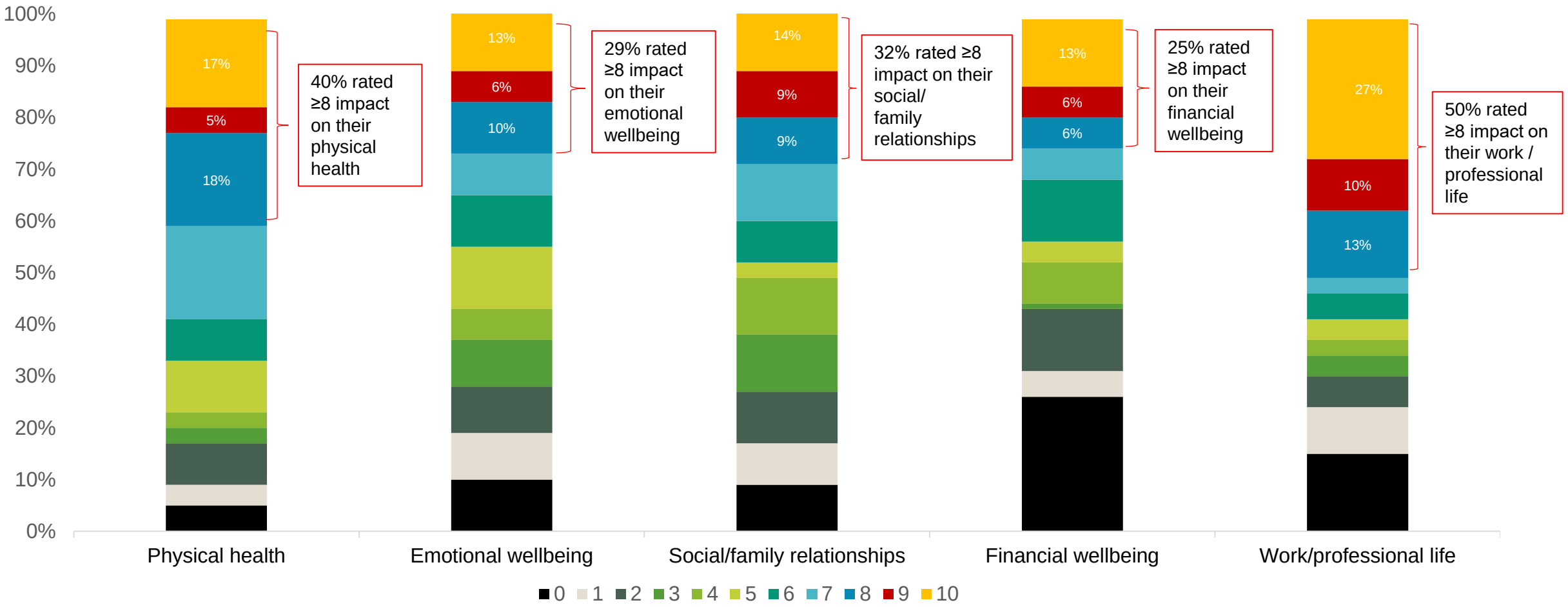


Treatments for gastro-intestinal symptoms (n=46)

Q. How satisfied have you been with symptom relief treatments?

Many different areas of patients' lives are affected by hATTR

Respondents rated the impact hATTR had on different aspects of their life over the last 12 months using a scale between 0 and 10 (0=no impact and 10=extreme impact)



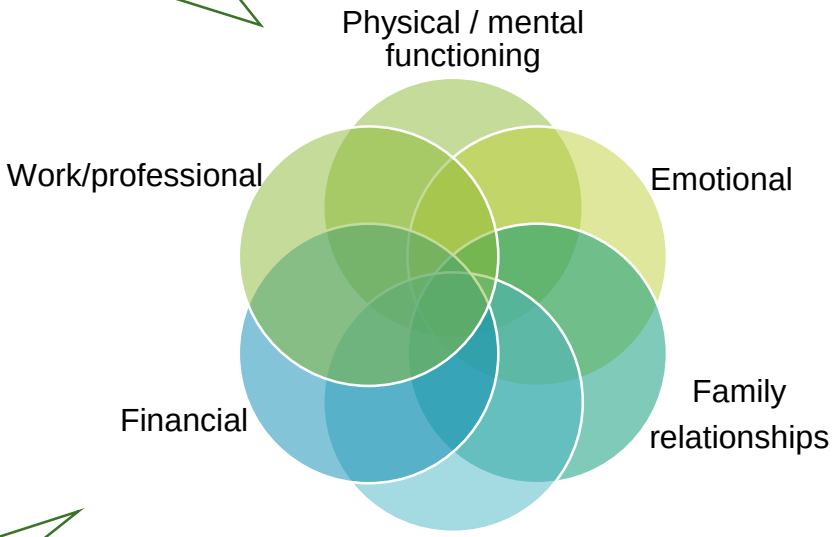
Q. Over the last 12 months how have the following aspects of your life been affected by hATTR? Please indicate between 0 and 10 where 0=no impact and 10=extreme impact (n=93)

Impacts on quality of life domains are inextricably linked

Amyloidosis Research Consortium UK

"Physically I'm not as strong, can't run or do anything in a hurry, I won't holiday abroad, financially I can't work as an investigator as I use to do."

"Overall, being diagnosed with hATTR has meant a huge change in my life. Sadly, my mother passed away from the disease two years ago and two days later I got my diagnosis. It has been a very traumatic time in my life and has massively affected all of my life and relationships."



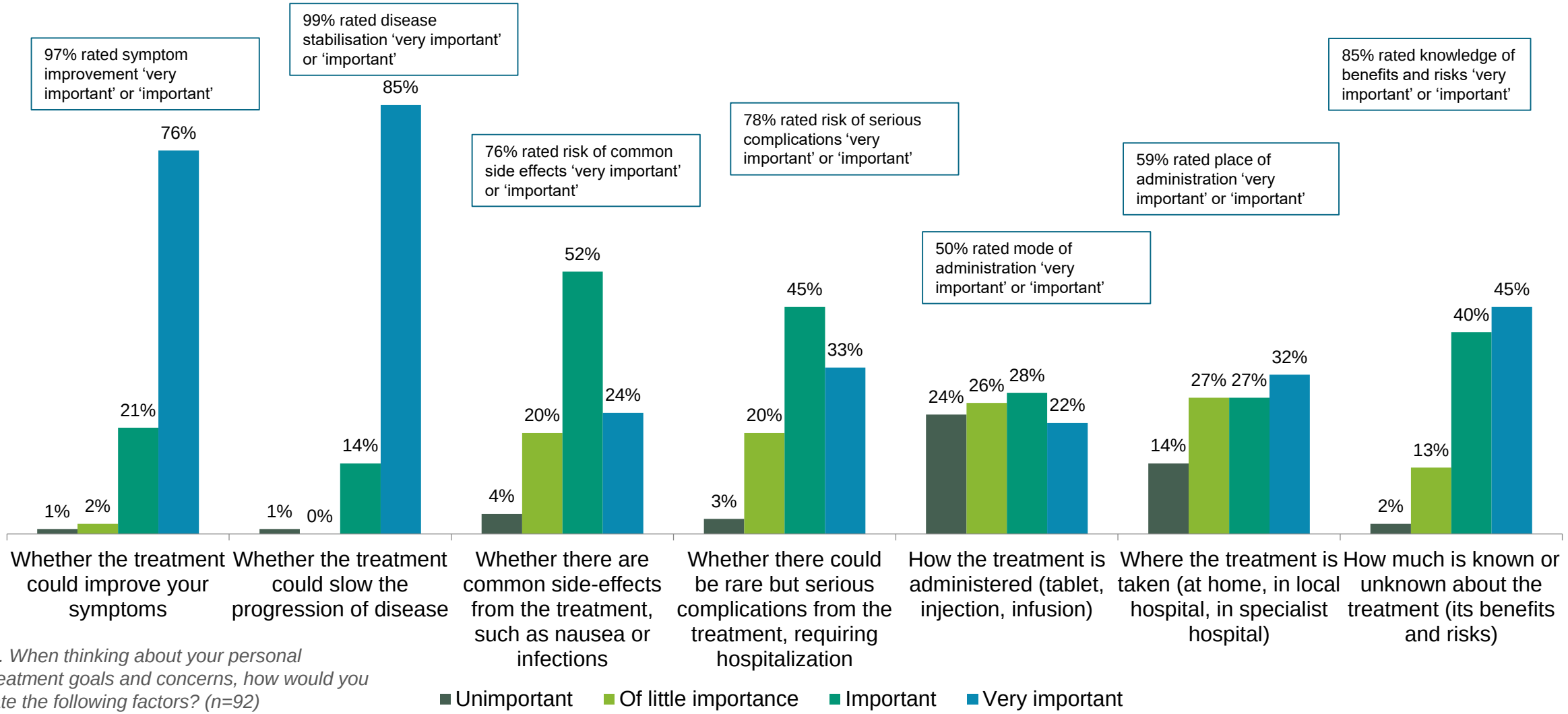
"I only have energy to work and then I come home and rest. I don't have much energy for family or a social life."

I am still able to work. My energy level is dropping as well as my productivity. I usually will avoid social engagements after work so I can rest instead. I try to keep a positive attitude and have solid relationships with my family and friends. Unfortunately I have not seen a lot of my loved ones because of fatigue."

"Had to give up work and with no bowel control we had quite a lot of expenses for hygiene products and personal stuff such as clothing, bed pans and bedding."

"Unable to work or lead a meaningful life . Family is affected by my illness for they are taking care of me. This has affected their social life as well as mine."

Patients' treatment attribute ratings favour efficacy; however, many different factors are important



Q. When thinking about your personal treatment goals and concerns, how would you rate the following factors? (n=92)

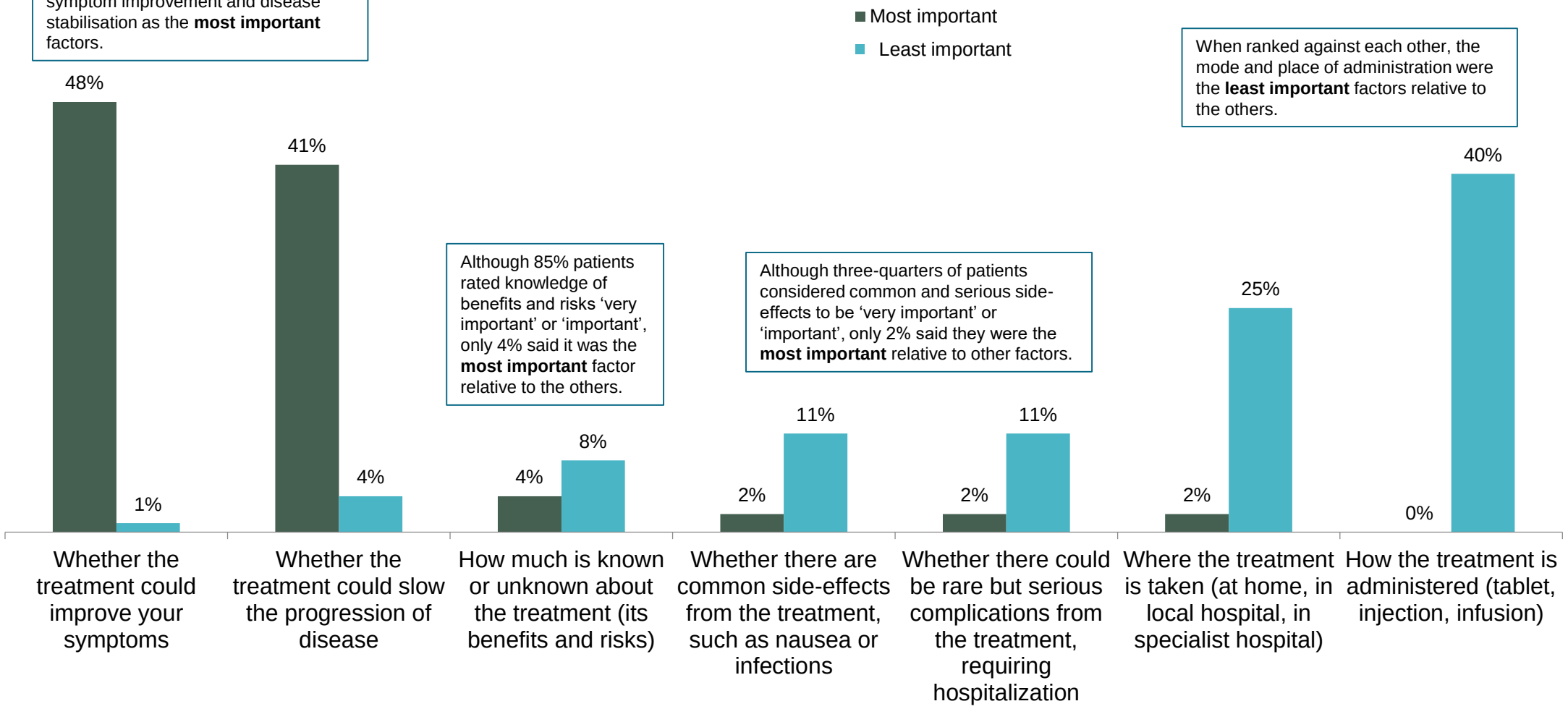
Forced ranking shows patients give greatest weight to efficacy and least to convenience

A clear preference emerged for symptom improvement and disease stabilisation as the **most important** factors.

Although 85% patients rated knowledge of benefits and risks 'very important' or 'important', only 4% said it was the **most important** factor relative to the others.

Although three-quarters of patients considered common and serious side-effects to be 'very important' or 'important', only 2% said they were the **most important** relative to other factors.

When ranked against each other, the mode and place of administration were the **least important** factors relative to the others.



Q. Which of these is the single most important and the single least important factor to you? (n=92)

Patients' preferences take into account complex trade-offs, individual goals and concerns for the future

Amyloidosis Research Consortium UK

"I don't care about minor side effects. I'm dying."

"If it helps at all, I want it. I do prefer not to travel."

"I understand about rare complications but I would not want more digestive problems."

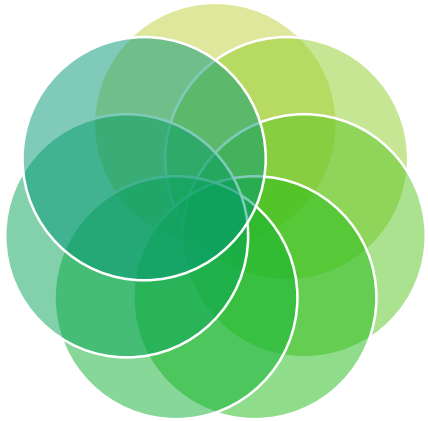
Trade-offs between efficacy, convenience and risks

"The most important thing is to stop this disease before quality of life becomes so deteriorated that you become a burden on your family."

Desire to see any improvement on current situation

Desire to improve functioning in daily life

"It is extremely important to find something that will stop the numbness and help me become mobile again."



Desire to remain / retain independence

Desire to improve overall symptom burden / particular symptoms

"Would like to reclaim some of my prior abilities to take care of my home and reduce the time it takes to do tasks I never thought about."

Desire to repair existing damage

Concern about disease progression

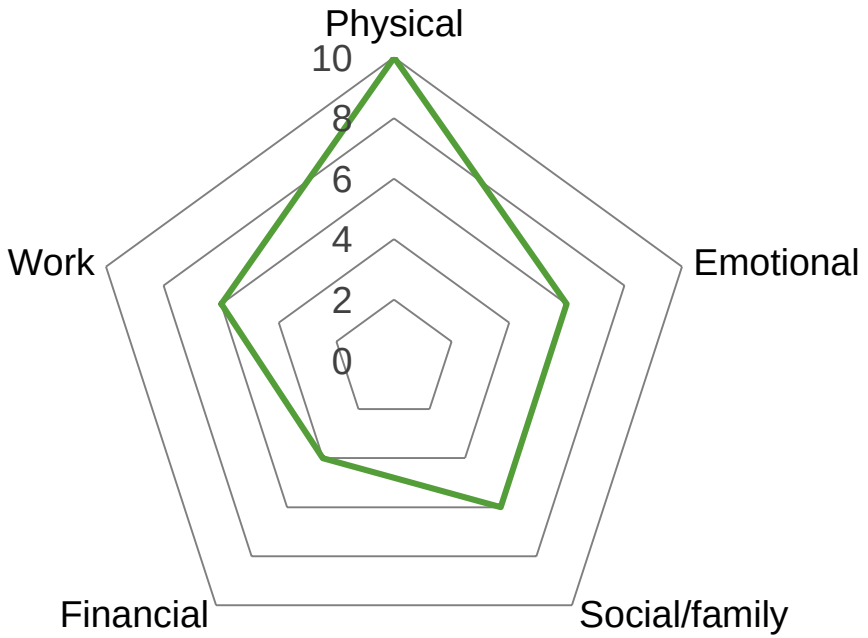
"My wife is experiencing loss of short-term memory. There is a history of Alzheimer's in her family. I must remain functional and able to provide care."

"Time commitment. I still have a part time job, and if I lose that, then its just the disease I have to think about."

Patient case study 1

- Male, diagnosed 2-5 years ago
- Late forties
- Full-time caregiver to his wife who has dementia
- First in family with hATTR diagnosis
- Symptoms in last 12 months: Difficulty walking, difficulty climbing stairs or muscle weakness; Numbness, tingling or pain in legs and/or feet; Constipation, diarrhoea, nausea, vomiting, weight loss or appetite loss; Loss of balance, dizziness, fatigue or tiredness
- Most problematic: **Dizziness** ‘every time I stand’
- Negative experiences on all amyloid-targeting treatments to date
- Can’t easily travel away from home due to caring responsibilities
- Most important factor: where treatment is taken
- Least important factor: risk of mild or common side-effects

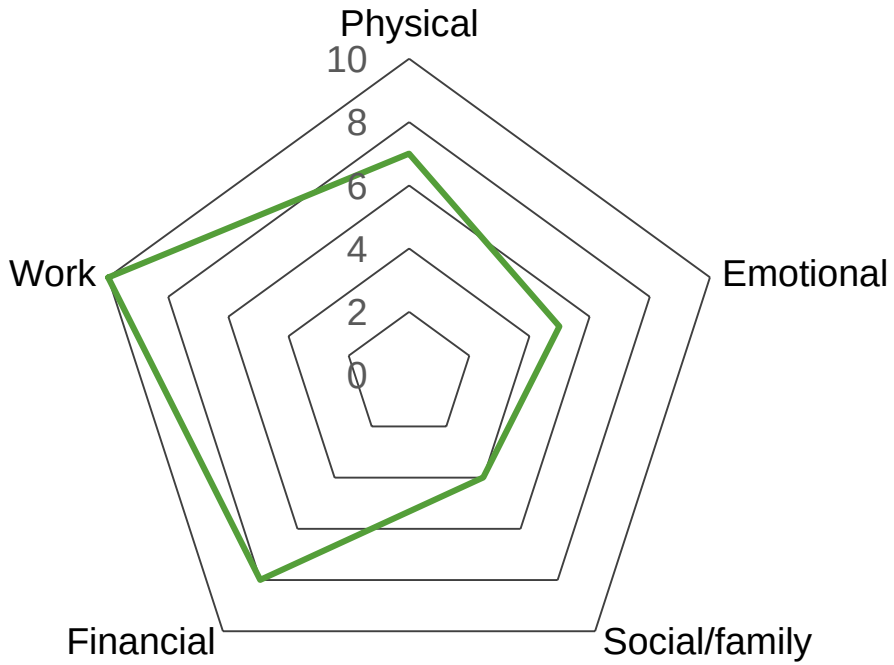
Impact of hATTR on your life over last 12 months



Patient case study 2

- Male, diagnosed more than 5 years ago
- Mid sixties
- Employed part-time
- Mother, uncle and brother with hATTR diagnosis
- Symptoms in last 12 months: Difficulty walking, difficulty climbing stairs or muscle weakness; Numbness, tingling or pain in legs and/or feet; Constipation, diarrhoea, nausea, vomiting, weight loss or appetite loss; Loss of balance, dizziness, fatigue or tiredness; Fecal or urinary incontinence; Erectile dysfunction; Loss of manual dexterity
- Most problematic: **Loss of balance/endurance** is the ‘biggest hindrance from doing normal things’
- No bad effects from prior treatment; seeing positive signs on disease on current treatment
- Most important factor: symptom improvement
- Least important factor: risk of severe side-effects requiring hospitalisation

Impact of hATTR on your life over the last 12 months



Carer survey demographics

52 survey responses were received. Of these 1 was excluded because no useable data was provided.

Of the 51 valid responses, 46 carers completed all sections of the survey and 5 partially completed the survey.

Time since diagnosis (n=51)			
Less than 12 months ago	1-2 years ago	2-5 years ago	More than 5 years ago
5	12	16	18

Age (n=51)					
39 and under	40-49	50-59	60-69	70-79	80 and over
3	15	8	16	8	1

Employment status (n=50)				
Employed full-time	Employed part-time	Not employed, looking for work	Not employed, currently unable to work	Retired
14	13	2	3	18

Relationship to the patient (n=50) *could select more than one				
Parent	Child	Spouse/partner	Sibling	Other
0	6	40	5	1

Place of residence (n=51)		
USA	UK and Republic of Ireland	Other
36	9	Canada (2), Australia (2), New Zealand (1), Spain (1)

Genetic mutation of patient (if known) (n=51)	
Val30Met	8
Val122 Ile	4
Glu89Gln	2
Gly53Glu	0
Glu54Gly	1
Ile68Leu	1
Thr60Al	13
Leu111Met	0
not typed	0
Not sure	15
Other	7

GI, mental function and the combination of multiple symptoms are particularly problematic for carers

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Which symptoms do you think are the most problematic?	Why?
Symptoms can have a different impact on caregivers	"For me, it's that he can't go on walks anymore. That's the time we spoke the most. For him, it's wearing a diaper." "For my husband, the numbness and difficulty in walking and dizziness....although the bowel issues are getting more regular. For me it's not knowing how long I have him for....and the coughing."
Combination of symptoms	"All symptoms because they affect everyday life." "Everything is devastating." "Cannot leave home, cannot do ordinary tasks. Must have help with everything as symptoms worsen. Hard on caregivers physically.." "Difficulty feeding himself, holding items, picking up things, loss of strength to do every day functions."
Mental / emotional functioning	"Unable to process information quickly enough to function effectively in daily life - can't work, perform any complex tasks or make difficult decisions." "It worries me. He's become more unstable mentally."
Insomnia	"He says its the diarrhoea, but for me its that he's depressed and cant sleep. It worries me."
Anxiety	"Shortness of breath and chest pains which feed into anxiety attacks. My dad is increasingly more frightened."
Pain, balance, weakness	"Constant nerve pain arms, hands, legs spine and loss of balance, weakness."
Gastro-intestinal	"The passing out and the inability to keep any nutrients down. My husband is slowly starving to death." "The GI issues seem to be the most that interfere with her lifestyle and well-being." "Intermittent diarrhoea – embarrassing in public." "Diarrhoea takes a lot of strength away."

Carers experience a significant practical and emotional everyday burden

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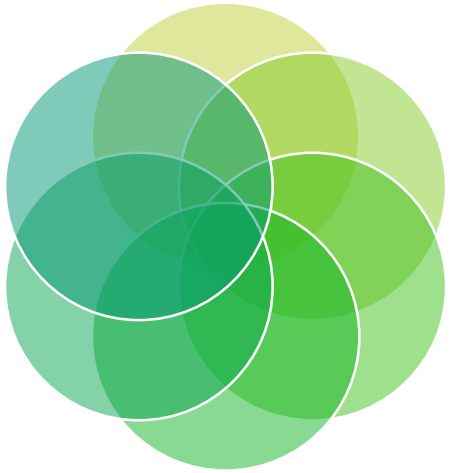
"Supporting him with his disappointment and frustration regarding the increased symptoms."

Providing emotional support to deal with patient's disappointment

"Accompanying my husband to London for each infusion, which takes a whole day including travel. It's a very long and tiring day."

I've gone part-time to fully support him during the various hospital appointments he attends."

Dealing with own worries, concerns and disappointment



Accompanying to appointments

"Had to give him the injection, which was so painful, it made me cry causing him so much pain."

Taking time off work

Administering treatment

"It's very hard to see when medicine does not work and you don't have any hope. Some days I feel very low."

Managing treatment regimen

"Ongoing changes in medications keep me on my toes, as I am the one who arranges meds daily."

Carers report a higher impact on their emotional wellbeing and social/family relationships than patients

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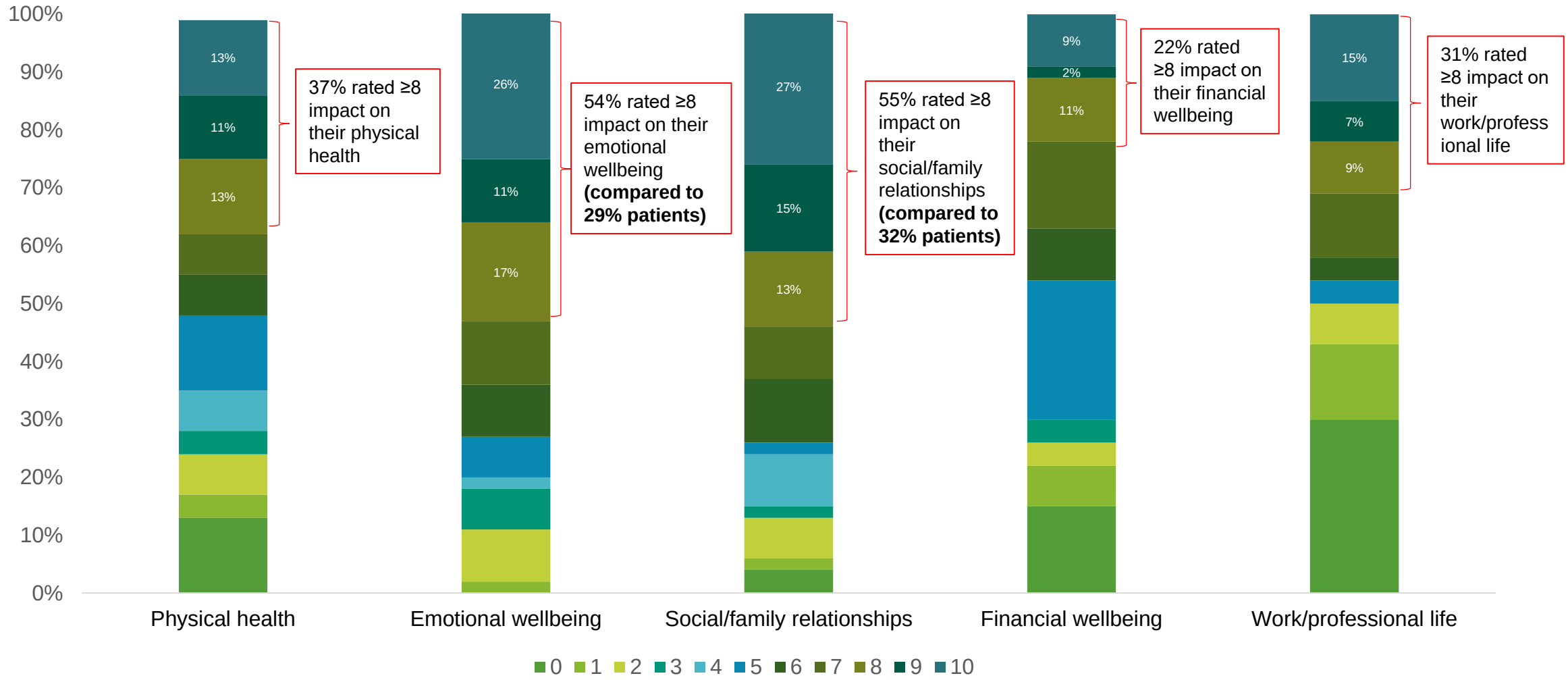
Respondents rated the impact hATTR had on different aspects of their life over the last 12 months using a scale between 0 and 10 (0=no impact and 10=extreme impact)



Q. Over the last 12 months how have the following aspects of your life been affected by hATTR? Please indicate between 0 and 10 where 0=no impact and 10=extreme impact (n=45)

Fatigue and anxiety affect many carers' quality of life

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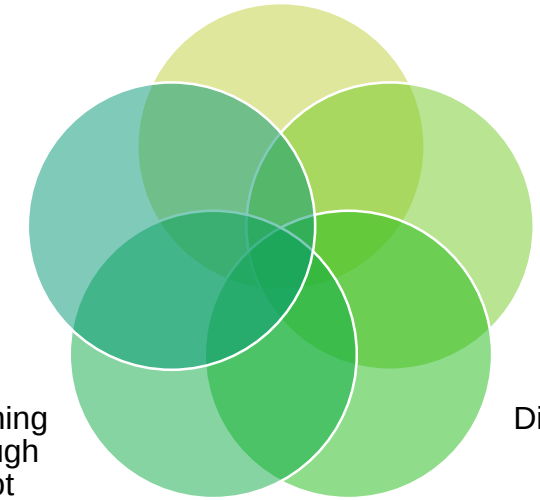
"It's just super sad watching the deterioration and depression then thinking that your nephew could be next, heart-breaking."

Worrying about children / grandchildren who have or may have the disease

"I no longer have any social life because I don't want to leave him alone at night when he's been alone all day. He is emotionally dependent on me so he gets sad when I am not around."

Feeling that their life is no longer their own / having to focus all energy on the patient



Exhaustion from worrying and taking on a greater burden of caring / chores

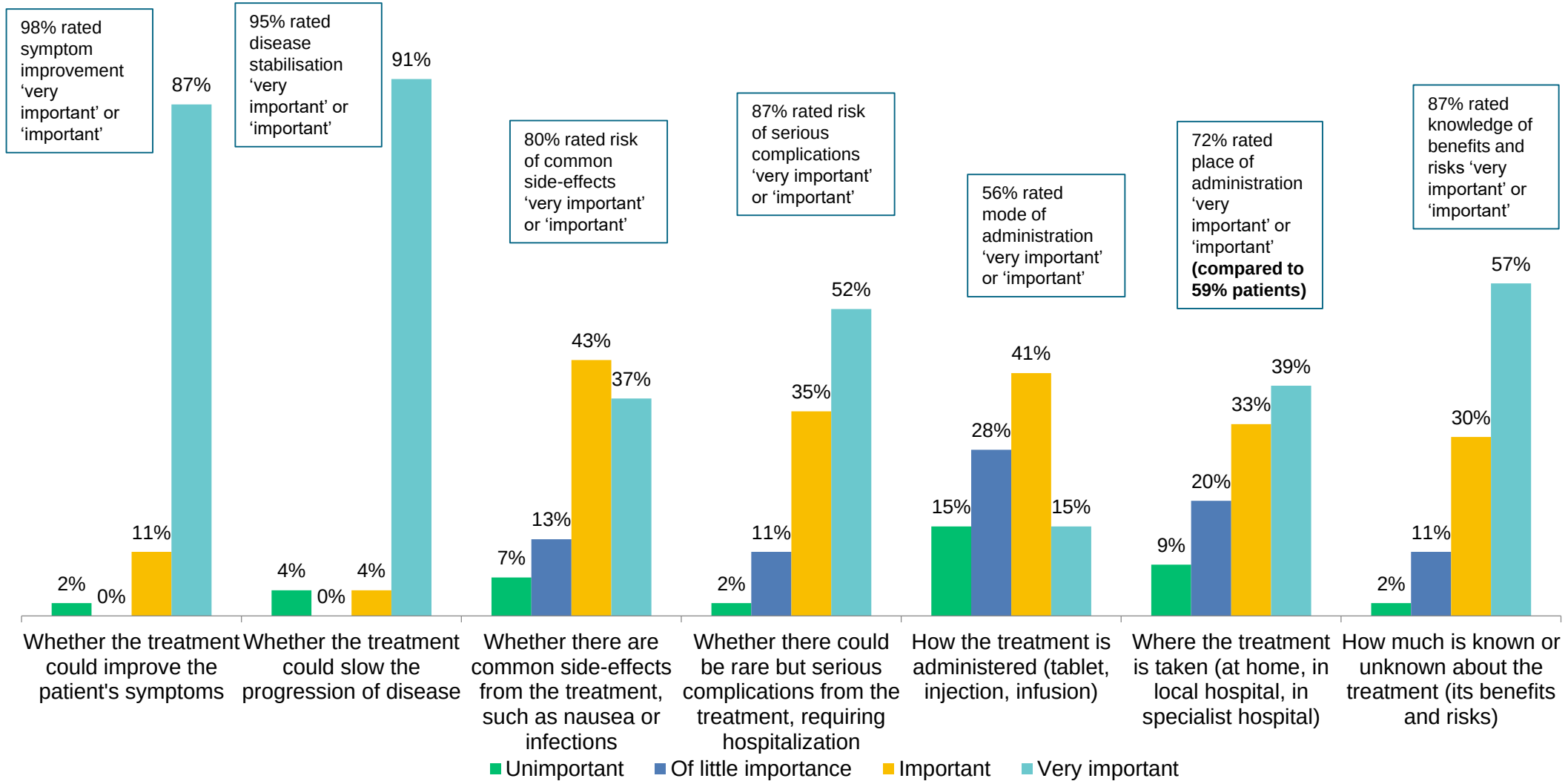
"There has been little support offered to my father and my mother, who cares for him full time. Their mental health has been mostly ignored. I too have had no support and I have had to bear the burden of working full time, caring for my dad and caring for my mum as her mental health has been significantly impacted by my dad's diagnosis."

Difficulty maintaining a social life through exhaustion / not feeling able to leave the patient

Difficulty maintaining a career through caring responsibilities / fatigue

"I recently got a promotion at work which was great because we needed the salary increase, but now the higher level of responsibility is causing me stress because I can't work late or be mentally "present" as much as I should be. He can't help out at home at all so I have to do everything. It's exhausting having to work full time, care for him all night and take care of the rest of the families needs."

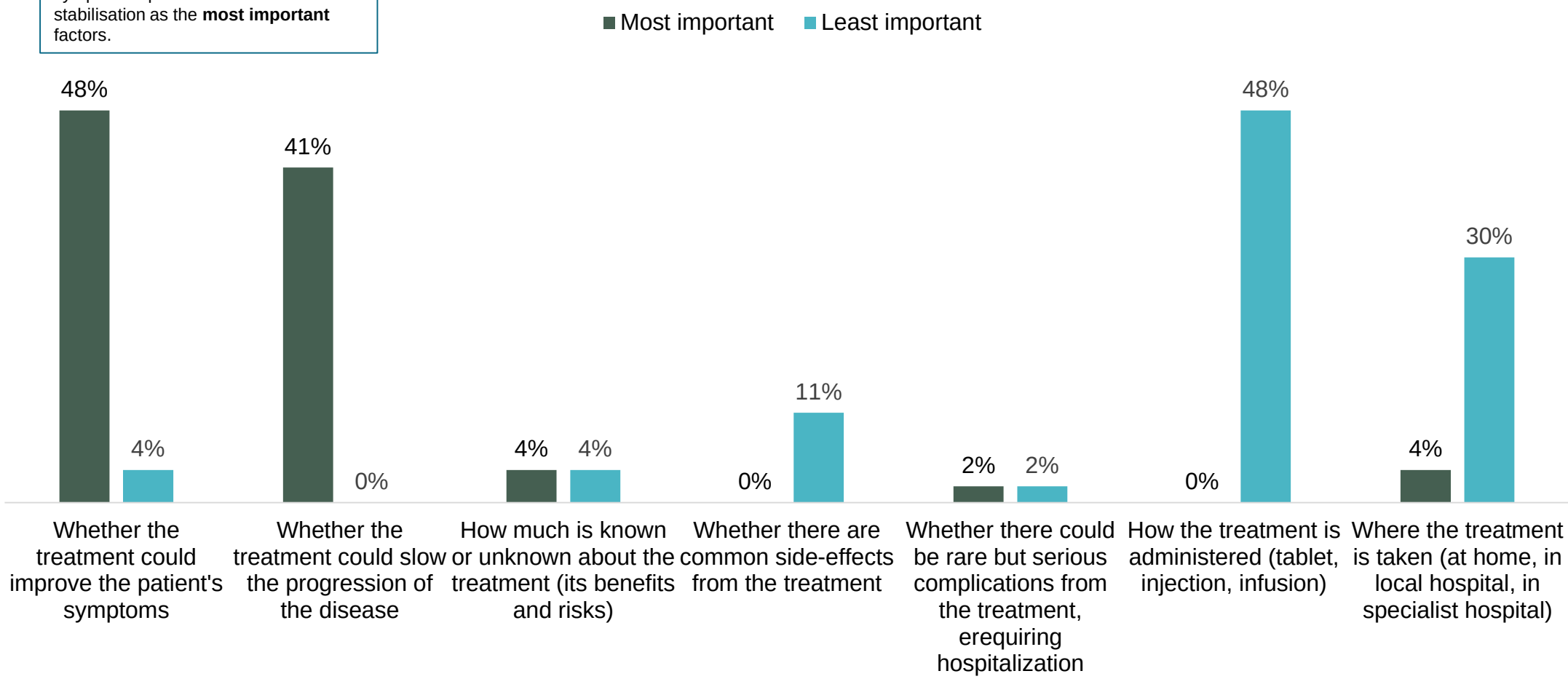
Carers rate the importance of most treatment factors similarly to patients



Q. When thinking about your personal treatment goals and concerns, how would you rate the following factors? (n=46)

Forced ranking shows that carers, like patients, prioritise efficacy over convenience

A clear preference emerged for symptom improvement and disease stabilisation as the **most important** factors.



Q. Which of these is the single most important and the single least important factor to you? (n=46)

Like patients, carers view modest improvements to be a significant outcome in the current context

Amyloidosis Research Consortium UK

"Things are so bad right now that he is willing to try anything to relieve his symptoms and slow it down even to the point that we don't care what possible complications or side effects there are. He has no other choice."

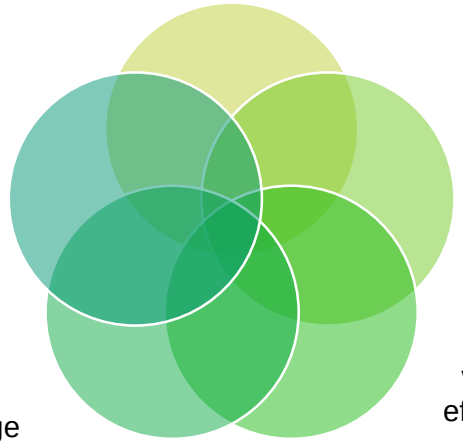
"We want a cure - but right now we are fighting for slowing down the disease progression."

"Would prefer not to have to travel to a special hospital for treatment. Also would prefer an injection to a five hour infusion."

"That this disease can be maintained until a cure is found or the disease is able to be maintained by the use of medication. With having children we worry that our sons and grandchildren will be at risk."

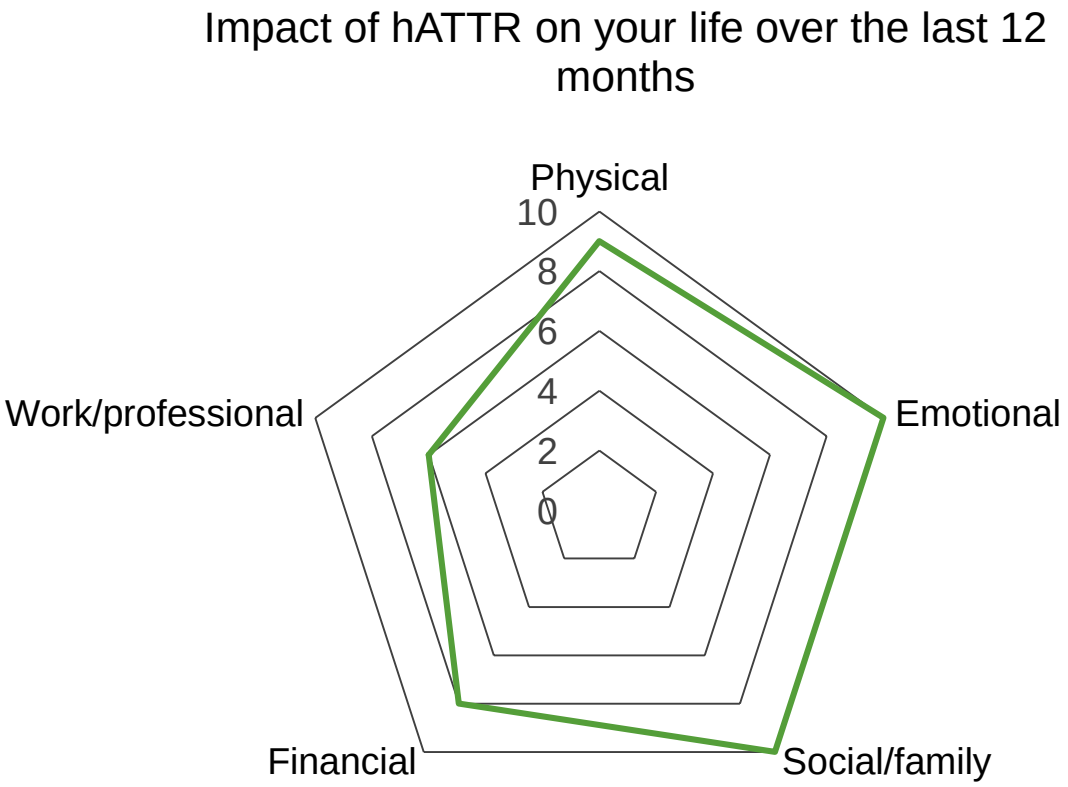
"My goal is for his life to not only be prolonged, but for him to have a good quality of life for as long as possible - for him to be able to live, not just be alive."

"Living longer and lifestyle are by far the top issues. Amyloidosis patients (and caregivers) will put up with a lot of other factors in order for the patient to live longer and with a better quality-of-life."



Carer case study

- Spouse, mid fifties.
- Full-time employment.
- “I no longer have any social life because I don't want to leave him alone at night when he's been alone all day. He is emotionally dependent on me so he gets sad when I am not around. He can't help out at home at all so I have to do EVERYTHING. It's exhausting having to work full time, care for him all night and take care of the rest of the families needs. I am in a constant state of stress and worry about everything from his declining health, to the thought of losing him, to our finances, to my work life. Just constantly worrying.”
- Most important factor: slowing disease progression
- Least important factor: how treatment is administered



Analysis of treatment preferences qualitative sub-study: focus groups and interviews

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Aim: to explore four key issues in depth around values and preferences for treatment, including trade-offs and relative importance of different factors

Themes:

A. The first disease-modifying treatments offer major hope for a disease that has destroyed families' lives
B. Treatment value relates to functional improvements, retaining/regaining 'normality' and independence
C. Side effect concerns are relative to patients' existing symptom burden
D. Convenience is likely to have a significant influence in a context of multiple treatment options

A. The first disease-modifying treatments offer major hope for a disease that has destroyed families' lives

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Key theme	Example
Patients and families talk of having hope and a brighter outlook for the future, in the context of there being no other effective alternatives at the moment	• "We didn't plan to have a family because of the disease. We might adopt in the future.. We didn't even think we had that option." • "It's exciting to know there are options. I've been grasping at straws. Nothing is helping me." • "I'm not feeling so dark about my future. There's a lot more light."
Patients express hope that they may not experience / or may delay experiencing the 'fate' of family members who have died from the disease	• "The prospect of what's facing us down the road isn't good. We've all seen family members go through it." • "I'm now looking at not absolutely going down the same path my dad did." • "Mum's final years were horrendous."
Patients and carers also expressed the significance of having new treatments for future generations, including their own children	• "The timing is hopefully right for us. And not just for us, it's huge for our families and children."

B. Treatment value relates to functional improvements, retaining/regaining ‘normality’ and independence

Amyloidosis Research Consortium UK

Key theme	Example
Value in stopping progression of the disease in order to regain functionality / normality	• “[Success is] being able to participate in my life rather than be a bystander… To do up to three errands a day instead of one. I can walk my kids to school multiple days in a row instead of paying for it the next day with pain.” • “To get back to doing normal things, back into the garden or out for a walk..” • “If we could go out for a whole day without worrying where the nearest toilet is – it will change our lives completely to go back to some normality which we haven’t had for many years, and take the pressure off our families who are supporting us.”
Value in slowing progression to prevent further loss of functionality or deterioration	• “Slowing or stopping disease progression is still progress.” • “If it stops me where I am at now in my disease, that’s success. That’s good enough for me. If it will let me carry on doing what I can do now.” • “One day I would love to see it improved; but at this point I’m just focused on slowing.”
Value in maintaining independence for as long as possible	• “I would hate my independence to be taken away and for my wife to be my 100% carer. I don’t want to burden anyone with that.”
Modest benefits are meaningful	• “Even a small effect would build upon your quality of life. The measurement scales don’t take account of pain, embarrassment or social impact. If there is any small benefit it would be worth it.”

C. Side effect concerns are relative to patients' existing symptom burden

Amyloidosis Research Consortium UK

Key theme	Example
Side effects are a consideration but it depends on their severity and how manageable they are	• "As long as it's not to the point where it's a detriment to your health i.e. you're not going to land up in hospital, it's a risk worth rolling the dice on." • "Sometimes your body recovers or gets used to it. Or you find mechanisms to cope with them." • "If it causes you not to live then 'no', but if seeing the results working then 'yes'." • "You have to ask yourself are they inhibiting quality of life?" • "It's important to be knowledgeable about the risks, vigilant and have a back up plan"
A risk of side effects is acceptable and 'worth it' for a potential improvement, however small	• "The side-effects would have to be pretty bad to be worse than the disease." • "I'll try to stop the disease first and then deal with the side-effects."
If side effects become unmanageable or begin to outweigh the benefits / disease effect then it wouldn't be 'worth it'	• "You don't want side-effects that are going to make you worse than you already are." • "I'd probably try it as some people don't get the side-effects. But if it got really bad and I couldn't see any improvement in my condition I'd come off it." • "If it becomes too oppressive I'm out."

D. Convenience is likely to have a significant influence in a context of multiple treatment options

Amyloidosis Research Consortium UK

Key theme	Example
A clear preference for oral medication, followed by self-injection, followed by infusion (when all other things are equal)	• "If all other factors were equal I'd go for a pill, then injection, then travel to hospital.. But side-effects would come into it and so would the benefits."
Place of administration / reducing the need to travel for treatment is more important than method of administration	• "Administration isn't the issue, it's the time taken to get there and come back. We're all ill and have weariness and lots of other issues." • I'd prefer patisiran at home if the effects were just as good."
Convenience is not as important as other issues e.g. efficacy; however, over a period of time travelling for treatment could be problematic for some	• "I'm working full-time. I have to take time off work or arrange for someone to take him." • "If you have GI, then logistics are everything… You have to factor in the bathroom or not feeling well. It's something you have to logistically plan with everything else you have going on." • "I appreciate what the drug is doing but the three-weekly travel… I'm anxious the day before, the day you're there you're wiped out and the day after I don't sleep well."
Patients want choice and they want treatments to be convenient; however, at the moment – with no alternatives – convenience is less important than it might be in the future	• "If you've seen what this disease can do you take whatever you can get." • "As choice increases, convenience will become a bigger factor." • "It would be a nice dream for a treatment to be convenient. But we're not at that point. We're still at life-saving and halting disease progression."

Conclusions

Amyloidosis Research Consortium UK

1. hATTR has a very high burden on patients and families. A multi-systemic disease, it affects *all* aspects of life
2. hATTR significantly impacts on patients' independence and sense of normality: their ability to work, participate in family and social life, be mobile and undertake daily activities and hobbies
3. hATTTR considerably impacts on carers: the emotional burden of 'knowing what's to come', practical caring burden and the effect on their own ability to work
4. Patients have mixed experiences of symptom and disease management approaches: there is unmet need with regard to efficacy, side-effect burden and convenience/choice
5. New treatments specifically for hATTR offer significant hope to patients and their families, especially in the context of the disease being hereditary, high impact on quality of life, and no/few alternatives
6. Patients and carers value multiple factors as important for treatment, including efficacy, convenience, risk of side-effects and knowledge of benefits-risks
7. The most important factors for treatment are related to impact on the disease. Patients are likely to accept risks of side-effects for 'modest' gains
8. Treatment preferences and values are influenced by a lack of effective alternatives and high unmet need/symptom burden; as choice increases, convenience and side-effects are likely to become increasingly important considerations

Referencing the report and ARC UK contacts

The findings here are pre-publication and should not be published or shared without prior permission from the Amyloidosis Research Consortium UK.

Any use of the findings in the report should be referenced as follows:

Amyloidosis Research Consortium UK. *Burden of disease and perspectives on treatment: summary report from research with hereditary transthyretin amyloidosis (hATTR) patients and carers.* July 2018 (unpublished).

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Association of British Neurologists and the British Peripheral Nerve Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

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

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Based on the recent study by Schmidt et al. (PMID 29211930), the mid estimated prevalence of hATTR is 97 patients. I would expect the majority to receive treatment with the technology.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The condition is currently managed by the national amyloidosis centre, a NHS commissioned highly specialised service. The national amyloid centre receives patient referrals from throughout the UK. Patients with hATTR and significant neuropathy are also seen at the National Hospital for Neurology, UCLH.

The current treatment options for hATTR are limited. The TTR stabilising drug diflusinal is often used but has little impact on the natural history of the disease. Liver transplantation is currently used to treat hATTR, however, only a small subset of patients are eligible for this treatment, the costs are high and the treatment is also limited by the availability of donor organs.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There are significant differences in age of disease onset dependent on the type of mutation and ethnic background. As a general rule, patients presenting with cardiac involvement have a worse prognosis than those presenting with a peripheral neuropathy.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

It is possible that patients receiving new genetic therapies will require closer neurological surveillance than is currently undertaken.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The current available treatment for hATTR is liver transplantation. The proposed technology is likely to be safer, cheaper and with comparable or reduced clinical follow up costs.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Thank you for your time.

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: British Society of Heart Failure/ Royal College of Physicians

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
-
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
-
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? √
-
- On the board of the BSH and Fellow of RCP.
- Employee of National Amyloidosis Centre in London as Consultant Cardiologist.

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
none

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

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

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

How is the condition currently treated in the NHS?

Hereditary transthyretin (TTR) amyloidosis is a devastating, debilitating disease with a heavy burden of symptoms including peripheral neuropathy with progressive disabling sensory and motor neuropathy; autonomic neuropathy with postural hypotension, alternating diarrhoea and constipation, erectile dysfunction and in some patients, cardiomyopathy with progressive heart failure symptoms. In those with neuropathy, estimated survival is 8-10 years over which time, patients become progressively immobile and ultimately are wheelchair bound. Once there is cardiac involvement, the survival is around 4-5 years. As this is hereditary, often patients have witnessed a parent or other relative's demise and have been the main carer during that time. It is inherited in an autosomal dominant fashion with variable penetrance. There are over 100 TTR mutations which have been found to be amyloidogenic.
At the National Amyloidosis Centre, over the last 5 years around 200 patients have been diagnosed with either neuropathy or neuropathy and cardiomyopathy. We see around 30 new cases each year. The majority of these patients are based in England but around 5-10 patients are from Scotland, Northern Ireland or Ireland. We would anticipate that the majority of these patients would be eligible for treatment.

Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients are referred to the National Amyloidosis Centre (NAC) in London from all over the UK and also from Ireland. This is a highly specialised service or the diagnosis of this condition. Patients are reviewed on a 6 monthly basis at the NAC. More patients are referred to the NAC from the South of England than from the North as patients may find it too challenging to travel long distances. There is no difference in opinion as current practice is largely supportive in the management of symptoms. Currently there is no approved treatment available to patients in the UK. Some patients may receive diflunisal off licence, an old fashioned NSAID, which may stabilise the transthyretin protein in the liver. This drug has been increasingly difficult to source over the last 2-3 years (it is not manufactured in the UK). It can cause renal dysfunction, peripheral oedema and stomach ulceration. The trial data which demonstrated slowing down of neuropathy was seen in a population that is uncommon in the UK (ATTR V30M) and therefore may be less relevant for the English population. We have not experienced halting of progression with this drug. Tafamidis, another TTR stabiliser, which is available in the rest of Europe, is not available in the UK (or America).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The majority of patients seen at the NAC have both neuropathy and cardiomyopathy and therefore the median survival is reduced to 4-5 years from diagnosis. Patients are most likely to benefit if they are diagnosed early (stage 1). Patients with significant mobility problems may benefit from the home based care rather than travelling to a centre for an intravenous infusion. Alnylam plan to provide a home infusion service Patients may have side effects from long term steroid use. No side effects related to steroid use were detected in the trial setting. Patisiran was not shown to cause thrombocytopenia or renal dysfunction and therefore routine blood tests are not required.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

There will be an increase in referrals to the specialised service. Relatives may wish to be actively screened for the TTR mutation and monitored for the development of the disease. Home care provision will need to increase, as mentioned.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not applicable

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Since there are no treatments available at present in the UK, there are no relevant clinical guidelines for the treatment of this condition at present. With the possibility of 2 new treatments, guidelines for their use should be developed.

The advantages and disadvantages of the technology

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There is no current alternative used in the UK. However, Inotersen can be given at home by injection whereas patisiran is given by intravenous infusion in a centre.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Starting criteria will be led by how Patisiran is licensed. The company should collect robust outcome data for those patients receiving Inotersen in terms of neuropathy progression and quality of life.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The Apollo trial, which included the UK, met its primary endpoints halting neuropathy progression and improving quality of life. Patients received patisiran by intravenous infusion on a 3 weekly basis. Prior to the infusion they were given steroids to limit infusion reactions. In some patients there was an improvement in their neuropathy score demonstrating a reversal of the neuropathy. There were no significant adverse events. Deaths were similar in both arms and felt to be related to disease progression.
The most important outcomes are halting progression of the neuropathy and improving quality of life.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

No significant adverse events were reported or have come to light in routine clinical practice through the compassionate use programme.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

We would advocate that patients have the diagnosis confirmed at the NAC and if eligible for patisiran, would be prescribed patisiran from the NAC with follow up in the TTR clinic. They would also have local follow up with their neurologist and /or cardiologist. Their clinical condition would be monitored at the NAC. Alnylam should allow provision of home infusions of patisiran.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Since there is a plan for patisiran to be administered at home by infusion, people with disabilities would not be discriminated against.

Thank you for your time.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

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

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

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

Information on completing this submission

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

About you	
1. Your name	**Edmund Jessop**
2. Name of organisation	**NHS England**

3. Job title or position	**Public health adviser**
4. Are you (please tick all that apply):	Commissioning services for NHS England for the condition for which NICE is considering this technology?
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion per annum in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England has not published any guidelines for this condition.

7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The National Amyloid Centre (NAC) at the Royal Free hospital in London is the recognised centre for diagnostic evaluation of patients suspected of amyloid-forming conditions. The pathway for ongoing care and treatment of patients with an established diagnosis is less well defined and although most patients will be under the care of the NAC, some patients may be under the care of local neurologists or other specialists.
8. What impact would the technology have on the current pathway of care?	The availability of disease modifying treatment is likely to improve the definition and clarity of pathways for ongoing care and treatment of patients with the condition
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Not in use
10. Will the technology be used (or is it already used) in	

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The main extra resource use will be in monitoring the effects of treatments – increased outpatient attendance and costs of investigations or imaging.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment should be initiated and monitored by the NAC but with arrangements for local shared care where appropriate.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will a small requirement for staff training.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	To be decided

11. What is the outcome of any evaluations or audits of the use of the technology?	None to date
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Clinical expert statement – condition

Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Thank you for agreeing to give us your views for these highly specialised technologies evaluations.

You can provide a unique perspective on the condition 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.

Because of the nature of these two evaluations, we would be grateful if we could ask you to comment on the condition and current treatments only, and not on the individual technologies. Where the questionnaire refers to the new technologies, you are welcome to comment on new disease-modifying treatments for hATTR amyloidosis in general, but we ask you not to comment on the relative merits of patisiran and inotersen specifically.

Information on completing this expert statement

- 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.

About you	
1. Your name	**Prof Philip Hawkins**
2. Name of organisation	**UCL and Royal Free Hospital**
3. Job title or position	**Prof of Medicine, Head of National Amyloidosis Centre**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not	☐ yes

have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aims of treatment are to slow or ideally stop progression, enable gradual improvement and recovery, and thereby improve mobility and prevent disability. The disease is caused by a build-up of amyloid protein in peripheral and autonomic nerves, the gut and the heart, which causes progressive damage to these tissues and impairs their function. The new technologies inhibit production of transthyretin in the liver by up to ~85%, and hence very substantially reduces the supply of the plasma protein from which ATTR amyloid is derived. Such treatment is expected to massively inhibit the further formation and accumulation of amyloid protein, greatly altering the natural balance of amyloid deposition and its slow natural clearance in favour of the latter. In time, one would expect this type of treatment to at the very least greatly slow disease progression, and very likely lead to gradual recovery of damaged nerve, heart and gut function.
8. 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.)	Slowing of disease progression in terms of peripheral nerve, autonomic nerve and heart function. I strongly agree with the sophisticated nerve measurements performed in the phase III RCTs, i.e. modified Neuropathy Impairment Score +7 (mNIS+7) to assess motor strength, reflexes, sensation, nerve conduction and postural blood pressure. Clinical benefits of the treatment were reflected in quality of life assessments, and in very simple clinical metrics such as aids required to assist walking (i.e simple disease stage and polyneuropathy disability score). A very clinically significant outcome would be to maintain ability to walk, and without greater walking aids (or better still, an improvement of this).

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, a massive unmet need. It is a rare, progressive, devastating and dignity-removing disease that leads to death within 7-10 years. It causes reduced mobility, ultimately complete, and a range of extremely unpleasant autonomic nerve problems, including uncontrollable diarrhoea, urinary retention and incontinence, severe low blood pressure causing nausea and syncope, and wasting. There are currently no specific treatments available for UK patients.
What is the expected place of the technologies in current practice?	
10. How is the condition currently treated in the NHS?	Supportive care only to ease symptoms, eg with analgesics for nerve pain, walking aids, nutritional support, care of pressure sores, diuretics for heart failure, treatment of infections etc.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Various guidelines published, but none of any particular value in practice.
• 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 the UK, patients are assessed and followed-up 6 monthly at the NHS National Amyloidosis Centre, for definitive diagnosis and evaluation of overall clinical status, neuropathy progression and cardiac involvement. Management guidance is provided an MDT meeting attended by ~6 specialist amyloidosis consultants. Additional neurological measurements are made by colleagues at the National Hospital, Queen Square. There is no specific pathway of care given the variable way in which it can affect peripheral and autonomic nerves, the gut and the heart – each patient will have specific individual needs and recommendations, but it is important to understand that there is no particular treatment or treatment pathway available.

• What impact would new disease-modifying therapies have on the current pathway of care?	Patients would continue to be diagnosed, assessed and monitored 6 monthly at the NHS National Amyloidosis Centre (NAC). The real-world value of new disease modifying treatments would thus be assessed by the standard compressive clinical assessments performed at the NAC. The expectation is that patients would become less dependent on supportive healthcare.
11. Will the technologies be used (or are they already used) in the same way as current care in NHS clinical practice?	Current care in NHS clinical practice will continue as now.
• How does healthcare resource use differ between the technologies and current care?	Not at all, other than providing and delivering the new treatments, both by injection.
• In what clinical setting should the technologies be used? (For example, primary or secondary care, specialist clinics.)	The treatments should be prescribed by specialists, though hopefully mostly administered in patients' homes. Patients must be followed by experts in the disease.
• What investment is needed to introduce the technologies? (For example, for facilities, equipment, or training.)	Essentially just the resources to enable administration in patients' homes. The infrastructure and resources otherwise are already available at the NAC.

12. Are there any groups of people for whom the technologies would be more or less effective (or appropriate) than the general population?	Not known to be so. Unfortunately it was impracticable for the RCTs to be performed in patients with so-called Stage 3 disease (unable to walk), and yet I believe many such patients would likely benefit.
The use of the technologies	
13. Will the technologies be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for their use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	These would be the first specific treatments available, and therefore will be delivered in addition to current supportive care. Neither of the new technologies are inherently complicated to deliver, and both should be easily possible in patients' homes. There may be need for additional simple blood monitoring.

14. Will any rules (informal or formal) be used to start or stop treatment with the technologies? Do these include any additional testing?	A definitive diagnosis of hereditary transthyretin amyloidosis causing neuropathy will be required to start treatment. There may need to be rules regarding the appropriateness of treating patients with very advanced disease, which was not specifically studied in the relevant phase III RCTs. Consideration of stopping treatment should be made when there is evidence of intolerance or lack of efficacy, the latter for example over a period of 12 months or more. No additional testing should be needed.
15. Do you consider that the use of the technologies will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Difficult to be specific about this, given the fact that the disease affects many organs and many bodily functions in quite different degrees and permutations from patient to patient. However, I have great confidence, extrapolating from experience to date and treatments that knock-down production of amyloid precursor proteins in other types of amyloidosis, that substantial benefits in autonomic related impairment will occur. Autonomic nerve symptoms are extremely difficult to quantify and yet actually cause many of the most unpleasant, disabling and quality of life destroying symptoms in hATTR amyloidosis.

16. Do you consider the technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits and how might they improve the way that current need is met?	I believe that these technologies will completely revolutionise the outcome of this disease and have very substantial impact on health-related benefits. The mechanism of action is 100% plausible, i.e. massive reduction in the supply of the amyloid-forming protein is expected to massively inhibit new amyloid formation. Experience in all much more common forms of amyloidosis have definitively confirmed that substantial knock-down of the respective amyloid forming protein will greatly reduce or halt disease progression, and frequently results in net clearance of amyloid in affected organs associated with gradual recovery of organ function in many cases. These new technologies are profoundly innovative in achieving TTR protein knock-down, the first technologies able to do this at all, but are not innovative at all in the expectation that this will be an effective treatment for amyloidosis!
• Are the technologies a 'step-change' in the management of the condition?	Not a step-change, but to quote Neil Armstrong, a giant leap.
• Does the use of the technologies address any particular unmet need of the patient population?	It has potential to benefit all unmet needs, given sufficient time for existing amyloid deposits to gradually regress. I believe that gradual improvement in autonomic function will have huge impact on quality of life.
Sources of evidence	

17. Do clinical trials in this condition reflect current UK clinical practice?	Yes, very much so.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes for people with this condition?	Preservation or potential for improvement in mobility; autonomic bladder, bowel and hypotension symptoms; cardiac failure symptoms; and life expectancy.
• If surrogate outcome measures are used, do they adequately predict long-term clinical outcomes?	Yes.
18. Are you aware of any relevant evidence that might not be found by a systematic review of published evidence?	Growing experience by specialists who have patients on open label long-term extensions of the phase III RCTs, and their real-world experience with early access to medicine schemes .

19. How do data on real-world experience in this condition compare with clinical trial data?	The experience of my colleagues at the NAC treating patients through compassionate access (over one year) and early access to medicine schemes has been extremely favourable. Remarkable clinically significant improvements of well-being and function have occurred in a majority of cases, including regaining the ability to walk unaided.
Equality	
20a. Are there any potential equality issues that should be taken into account when considering this treatment?	A specific mutation in the TTR gene that can cause hereditary ATTR amyloidosis (TTR V122I) occurs almost exclusively in black individuals. This form of hereditary ATTR amyloidosis is predominantly associated with amyloid cardiomyopathy, but can also cause peripheral neuropathy in some cases. The latter is not widely appreciated and often overlooked by physicians attending to cardiac symptoms. It will be important to raise awareness of this issue, and promote access to new effective treatments.
20b. Consider whether these issues are different from issues with current care and why.	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Hereditary ATTR amyloidosis is an exceptionally rare progressive, massively unpleasant, disabling and ultimately fatal disease.
- There is enormous unmet need.
- There is currently no specific treatment for hATTR amyloidosis.
- The two new technologies are ground-breaking in the novel mechanism by which they inhibit production of the disease-causing amyloid protein, but are entirely rational and plausible given the well-established benefit of knock-down approaches in many other types of more common forms amyloidosis.
- It is likely that long-term use of the new technologies will result in gradual but progressive benefit and greatly reduce mortality.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Mr Vincent Nicholas**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Amyloidosis Research Consortium UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	As my mother died of Amyloidosis in 1991 I was automatically tested for the gene by the NAC. At that time there was very little known about the disease and treatment was limited. It had a major impact on my life and my family. My wife and I went away and wrote our bucket lists!

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Since getting symptoms of Amyloidosis in 2009 it has had a major impact on my life and the family's life. In 2010 I had a liver transplant which had a huge affect on me and the family with regards to stress and emotional anxiety. My wife and I spent a lot of time having counselling. I believe that by having the liver transplant it has slowed down the progression of the disease. It has affected my life and the family's life in many ways: - I can no longer do too many physical activities. Day to day general activities is harder and slower. - My wife has had to take on all the physical house chores and DIY. - Do to the neuropathy and muscle wastage very day to day activities are harder and slower to do. - The worst thing is the affect it has on my bowl movements. I have to be careful what I eat and have quick access to toilet facilities. This restricts where we travel and holiday types. - I have become emotional about things and get frustrated by the simplest problem. - My wife who is my carer has had to take on most of the running of the family. I'm still able to help with cooking and running the girls to school at the moment. - I get very tired and am unable to do more than 2/3 jobs a day. I had to retire 2 years ago due to ill health. - Luckily on the financial side I am ok due to having a good pension.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Currently there are no drug treatments available. Also the majority of the NHS apart from the NAC has knowledge or training about Amyloidosis.
11. Is there an unmet need for patients with this condition?	Lack of understanding by GP's and hospitals about Amyloidosis.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also	This new drug will have a major impact on our lives. It will ease the disabilities that come with this disease and holt its progression. Amyloidosis then is longer a terminal illness!

include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	The current treatment is easy but takes about 3 hours. The main problem is the time and cost needed to get to the NAC in London. This takes place every 3 weeks. Also someone has to travel with me just in case I need support after the treatment.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they	As the side effects with this drug is very minimal the only disadvantages is where the treatment is taken and the time and cost to get there.

long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Not qualified or have the knowledge to answer this.
Equality	
16. Are there any potential equality issues that should be taken into account when	**No**

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	No
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • This drug treatment is life changing. • It will hopefully stop and reverse some of the symptoms that we have. • Quality of life will be improved for the patient and their families. • No longer will liver transplants be needed. • The next generation will no longer have to suffer with this debilitating disease.	

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Carlos Heras-Palou**
2. Are you (please tick all that apply):	**X** a patient with the condition? ☐ a carer of a patient with the condition? X a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	I am the chair of UK TTR Amyloidosis Patient Association www.ttramyloidosis.uk Nominated by Alnylam
4. Did your nominating organisation submit a submission?	X yes, they did no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	X yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	The difficulty is that most doctors are not aware of the disease, and only very specialist centres have the knowledge and facilities to investigate and diagnose ttr amyloidosis. This can cause a lot of anxiety and a delay in treatment.

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Living with disease is painful, depressing and disabling. Main problems are: -Very difficult to control diarrhoeas. This results is weight loss, can cause incontinence that often leads 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 vey 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 vey intense pain that is short in duration, and aches that last a long time. The pains usually start affecting the feet, and then progress proximally as the neuropathy advances. Then it affects the hands. Sometimes the pain feels like burning, like being scalded, but there is nothing to show for it. 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, including feeling light headed and fainting, digestive (vomiting, problems swallowing and abdominal pain as well as the mentioned diarrhoea), sexual (including impotence), urinary (difficulty voiding can result in frequent urinary infections) -Cardiac involvement often start with tiredness and shortness of breath. This affects walking distance and later ability to self-care. Often palpitations and arrythmias require a pacemaker. -The numbness due to neuropathy starts in the feet. This causes problems with shoes with ulcers like in the diabetic foot situation. Also a sensory ataxia due to loss of proprioception. For example, it is difficult to just stand up and balance. This results in movements that make the patient look like he or she is drunk. -Weakness and muscle atrophy causes difficulty, first walking, then using the hands. 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 well aware of what is waiting for them. Psychologically this is devastating. -Thee 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 more than one patient is affected in one family, 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.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	The only treatment licenced and recommended in the UK has been liver transplant. Many patients are not suitable for this. The results (I have known more than 20 patients who underwent liver transplant) are not very good, in my view. It seems to slow the disease for a while, but then it comes back perhaps after 7 or 8 years. Having a liver transplant does not seem to protect the eyes or the brain. The incidence of cancer in this patients -anecdotally- seems to be high, and the complication rate is very significant. My mother and may godmother (aunty) had liver transplants and they survived for about 8 or 9 years with a poor quality of life. One of my cousins have had a liver transplant and now has breast cancer, which presents a very difficult problem.
11. Is there an unmet need for patients with this condition?	There is no available good treatment at present for the patients in the UK.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease,	The advantages of this new treatment is that it seems to stop progression of the disease, with a low complication rate. If started early, this treatment allows for a normal quality of life. I have had this treatment and know about 10 patients that are currently on this drug. The unanimous view is that this treatment is effective with no significant side-effects. This is often describe by patients as “revolutionary” or “magic”.

physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	To have a treatment that is effective with no side-effects is a dream come true. We expected that the treatment may stop progression of the disease. We are now seeing that patients are recovering some functions that they had already lost, particularly from the digestive system point of view and muscle strength. This recovery seems to continue in time, and patients that have been on the drug for several years (since trial phase II) show an amazing improvement. Fortunately, my sister is one of them. .
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	It means having an infusion every three weeks. The whole process takes about three hours, by the time the patient has been checked, pre-med administered and infusion prepared and given. Patients find having to attend a specialist centre for treatment and inconvenience, particularly if they have to travel a long distance.

Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	Patients perceive having an infusion every three weeks, as a minor inconvenience for a treatment that saves their lives and their quality of life. In general, patients feel no side effects, and the drug does not seem to make any aspects of the disease worse. Travelling to hospital for treatment can be a disadvantage for some patients.
Patient population	
15. Are there any groups of patients who might benefit more or less from the	Perhaps some genotypes will respond better to treatment than others.

treatment than others? If so, please describe them and explain why.	
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**Not that I can see**
Other issues	
17. Are there any other issues that you would like the committee to consider?	Patients with advanced disease were not included in the trial. However they could benefit significantly from this treatment.
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • This is a devastating and lethal disease • There is no treatment at present • This new drug has proven to be effective	

- The safety profile seems excellent from the point of view of the patient
-
-

Thank you for your time.

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About you	
1.Your name	**Eric Low**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Amyloidosis Research Consortium UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	n/a

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	n/a

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	There are no other licensed disease-modifying treatments available on the NHS, although patients may be offered off-label treatments, including diflunisal and doxycycline. A very small number of patients have liver transplants. Beyond this, treatment is primarily aimed at managing the symptoms of the disease.
11. Is there an unmet need for patients with this condition?	The unmet need is substantial. The hTTR amyloidosis is debilitating and progressive. Marginal improvements in slowing or stopping progression could have transformational improvements in the quality of life for patients and their families. Patients usually experience multiple symptoms, including sensory, motor and autonomic deficits and, for some patients, cardiac involvement. These translate into numerous effects on daily living, including mobility issues, insomnia, pain, intermittent diarrhoea, sexual dysfunction, vision and motility problems, imbalance and instability and an effect on patients' abilities to undertake daily activities.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to	Patisiran appears to work in the majority of patients and the side-effects and potential inconvenience of treatment administrations are outweighed by the benefits. Patisiran has the ability to improve the symptoms associated with hTTR amyloidosis, providing much needed hope for the future, improved physical and emotional performance, meaning patients can be more socially and economically active.

work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	n/a
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is	There are few disadvantages. It is important to have choice regarding where patients can receive treatment. For some, travelling to hospital regularly may be inconvenient and costly and therefore a home care option is a must. Conversely, some patients prefer not to receive treatment at home and therefore should be able to continue to receive treatment at a specialist centre. Doctors and nurses should conduct a patient/family holist needs assessment before treatment starts, and at appropriate time points during

taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	treatment so see if anything has changed in the situation of the patient or the family requiring a potential change in treatment arrangements. Further, we would expect the company to carry out patient/ carer experience/satisfaction surveys throughout the duration of treatment and for this data to be provided (where permissible) to the patient's clinical team to inform ongoing needs assessment.
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Patients should be treated within the licensed indication and following an appropriate discussion and holistic needs assessment with their doctor and nurse about the potential benefits and risks of the treatment including how and where it is administered. These are the patients most likely to benefit.

Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	No
Other issues	
17. Are there any other issues that you would like the committee to consider?	No

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

- This condition is debilitating and progressive and has a significant impact emotionally, socially, economically and physically on patients and their families
- There are currently no licensed or any other effective treatments and therefore the unmet need is significant
- Patisiran offers a significant step change in the management of this disease: the fact that it offers a convenient method of administration is especially positive
- This is a situation where there are clearly additional benefits (e.g. on carers, productivity, convenience, independence etc) that may not be captured in either the clinical evidence or modelling; and these need to be factored in

Thank you for your time.

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Patisiran for treating hereditary transthyretin-related amyloidosis: A Highly Specialised Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	John W Stevens, Reader in Decision Science, ScHARR, University of Sheffield, Sheffield, UK Paul Tappenden, Reader in Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Emma Hock, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Sue Harnan, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Alison Scope, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	John W Stevens, Reader in Decision Science, ScHARR, University of Sheffield, Sheffield, UK
Date completed	17th October 2018

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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We would like to thank Professor Philip Hawkins, Professor Julian Gillmore and Dr Helen Lachmann at the National Amyloidosis Centre (NAC), University College London Division of Medicine and Dr John Hunter, Consultant Rheumatologist, NHS Greater Glasgow and Clyde, for providing clinical advice to the ERG.

We also thank Becky Pennington, Research Fellow, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and for preparing and formatting 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 HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

John Stevens acted as the overall project lead. Ruth Wong critiqued the company's search strategy. Emma Hock, Sue Harnan and Alison Scope summarised and critiqued the clinical effectiveness evidence reported within the company's submission. John Stevens critiqued the statistical aspects of the clinical effectiveness data and health economic analysis. Paul Tappenden and Aline Navega Biz critiqued the company's health economic analysis. All authors were involved in drafting and commenting on the final report.

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Abbreviations

10MWT	10-metre walk test
ADL	Activity of daily living
ALT	Alanine transaminase
AST	Aspartate transaminase
AE	Adverse event
AGNSS	Advisory Group for National Specialised Services
AIC	Akaike Information Criterion
ALL	Acute lymphocytic leukaemia
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian Information Criterion
BL	Baseline
BMI	Body mass index
BP	Blood pressure
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CASP	Critical Appraisal Skills Programme
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMAP	Compound muscle action potential
CML	Chronic myeloid leukaemia
COMPASS-31	Composite Autonomic Symptom Score-31
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DSAs	Deterministic sensitivity analyses
EAMS	Early Access to Medicines Scheme
eGFR	Estimated glomerular filtration rate
eMIT	Electronic market information tool
EPARs	European Public Assessment Reports
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions, Three Level Questionnaire
EQ-5D-5L	EuroQol 5-Dimensions, Five Level Questionnaire
EQ-VAS	EuroQoL visual analogue scale
ERG	Evidence Review Group
FAD	Final appraisal determination
FAP	Familial amyloidotic polyneuropathy
FDA	Food and Drug Administration
GI	Gastrointestinal
hATTR	Hereditary transthyretin-related amyloidosis

HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly Specialised Technologies
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
INR	International normalised ratio
IQR	Interquartile range
IRR	Infusion-related reaction
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IU	International units
IV	Intravenous
LV	Left ventricular
LSM	Least squares mean
LYG	Life year gained
mBMI	Modified body mass index
MCID	Minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
mITT	Modified intention-to-treat
MMRM	Mixed model repeat measurement
mNIS+7	Modified Neuropathy Impairment Score +7
MRN	Magnetic resonance neurography
mRNA	Messenger ribonucleic acid
NAC	National Amyloidosis Centre
NCS	Nerve conduction studies
NH	Natural history
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Neuropathy Impairment Score
NIS+7	Neuropathy Impairment Score +7
NIS-W	Neuropathy Impairment Score-Weakness
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
OLS	Ordinary least squares
OLT	Orthotopic liver transplantation
OS	Overall survival
PAS	Patient Access Scheme

PD	Pharmacodynamics
pg/mL	nanogram/millilitre
PK	Pharmacokinetics
PND	Polyneuropathy disability
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
QST-BSA_{TP}	Quantitative sensory testing touch pressure by body surface area
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
R-ODS	Rasch-built Overall Disability Scale
RNAi	RNA interference
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
siRNA	Small interfering ribonucleic acid
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query Drug Related Hepatic Disorders
SNAP	Sensory nerve action potential
TTR	Transthyretin
TUDCA	Taurosodeoxycholic acid
ULN	Upper limit of normal
VDT	Vibration detection threshold
wtATTR	Wild-type transthyretin-mediated amyloidosis
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) assesses the clinical effectiveness and cost-effectiveness of patisiran (Onpattro®) within its licensed indication for the treatment of hereditary transthyretin-related amyloidosis (hATTR). The CS highlights that there are currently no effective disease-modifying therapies for hATTR amyloidosis, hence the anticipated place of patisiran is as a first-line treatment for adult patients with hATTR amyloidosis with Stage 1 or Stage 2 polyneuropathy (in combination with best supportive care [BSC]). The decision problem addressed by the CS reflects a deviation from the final scope issued by the National Institute for Health and Care Excellence (NICE). However, the population addressed in the decision problem is in line with both the APOLLO trial (the main source of clinical evidence within the CS) and the marketing authorisation for patisiran. The CS does not contain any evidence relating to the use of patisiran for the treatment of patients with predominantly cardiac forms of hATTR in the absence of polyneuropathy.

The final NICE scope defines the comparator for the appraisal as *"established clinical management without patisiran."* The comparator within the company's decision problem is defined as BSC. The Evidence Review Group (ERG) notes that other pharmacological treatments may be used for the treatment of hATTR, including tafamidis and diflusinal. However, tafamidis is not currently available in England due to a negative Advisory Group for National Specialised Services (AGNSS) recommendation. In addition, whilst diflunisal is sometimes used off-label, the CS highlights that this drug may not be an option for many hATTR patients, as it is contraindicated in patients with severe heart failure, gastrointestinal (GI) bleeding, or hepatic or renal failure. The ERG also notes that the APOLLO trial did not define a standardised BSC regimen, hence trial outcomes may be subject to variations in the care delivered between participating centres. The company's economic analysis assumes that BSC is comprised of interventions targeting a variety of symptoms of hATTR amyloidosis, based on published guidelines.

1.2 Summary of clinical effectiveness evidence submitted by the company

The ERG is content that the relevant population and intervention have been included in the CS, that is, patients with hATTR amyloidosis treated with patisiran. The company did not present a systematic review of the comparator, BSC. The CS includes evidence relating to all of the outcomes specified in the final NICE scope, except for effects of amyloid deposits in other organs and tissues (including the eye), and health-related quality of life (HRQoL) for carers.

In the APOLLO study, the primary outcome was the difference between the patisiran and placebo groups in change from baseline Modified Neuropathy Impairment Score +7 (mNIS+7) at 18 months.

There was a significant difference between the groups in change from baseline on mNIS+7 score at 18 months in favour of patisiran; patients in the placebo group worsened, and those in the patisiran group slightly improved (least squares mean (LSM) difference between groups: -34.0 points, $p<0.001$). Mean transthyretin (TTR) knockdown over 18 months in APOLLO was 87.8% in the patisiran group and 5.7% in the placebo group. Mean serum knockdown at 24 months in the Phase 2 open-label extension (OLE) study was 82%. Clinical advice received by the ERG suggests that this indicates a clinically meaningful impact of patisiran on hATTR amyloidosis. HRQoL assessed using the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) was a key secondary endpoint in APOLLO. There was a significant difference between the groups in change from baseline on Norfolk QoL-DN score at 18 months in favour of patisiran; patients in the placebo group worsened, and those in the patisiran group slightly improved (LSM difference between groups: -21.1, 95% CI -27.2 to -15.0, $p<0.001$). Cardiac outcomes were shown to be improved on most outcomes in the patisiran group compared with placebo (relative to baseline) at 18 months in APOLLO, among the cardiac subpopulation, non-cardiac subpopulation and modified intention-to-treat (mITT) population.

Data from APOLLO demonstrated that almost all patients who received patisiran and placebo experienced adverse events (AEs), similar proportions of patisiran and placebo patients experienced severe and serious AEs, and fewer patisiran group patients discontinued or withdrew due to an AE compared with the placebo group. Diarrhoea was the only serious AE that was reported in ≥2% more patients in the patisiran group than the placebo group (5.4% vs. 1.3%). Thirteen deaths were reported in APOLLO (7 [4.7%] in the patisiran group and 6 [7.8%] in the placebo group), none of which were considered to be related to patisiran. In the Phase 2 OLE, all patients experienced at least one AE, 28% experienced an AE related to the study drug, 12% experienced at least one severe AE and 24.0% experienced at least one serious AE. At the interim data-cut for the Global OLE, 89.6% patients experienced at least one AE, 18% patients experienced at least one severe AE and 26.1% experienced at least one serious AE. In the Phase 2 OLE, there was one death (myocardial infarction) after the patient had completed 24 months of treatment, and 11 deaths were reported in the Global OLE.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic reviews presented in the CS appear to be comprehensive, and the ERG is confident that all relevant patisiran studies for patients with hATTR amyloidosis were included. The quality assessment tools used to appraise the included studies were considered appropriate by the ERG. Most outcomes listed in the NICE scope were presented, with the exception of the effects of amyloid deposits in other organs and tissues (including the eye), and HRQoL for carers.

The ERG is confident that the CS contains the only known studies of patisiran in patients with hATTR amyloidosis. The main source of bias in the one randomised controlled trial (RCT) of patisiran

compared with placebo, APOLLO, was an imbalance in dropouts between the groups. The other three studies use a single-arm design, and the Phase 2 OLE study and the Global OLE study are open-label and are thus susceptible to bias. The Global OLE is an ongoing study, and currently only has data for the first 52 weeks; further data on the long-term efficacy and safety of patisiran are expected.

The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to APOLLO. First, a greater proportion of patients in the patisiran group than the placebo group met the criteria for cardiac involvement. In response to a request for clarification, the company suggested that as hATTR amyloidosis patients with cardiac involvement typically have a worse prognosis than those without, patients in the patisiran group may have had a worse overall prognosis, on average. Second, a greater proportion of placebo group patients discontinued treatment and withdrew from the study compared with the patisiran group patients. Data presented in the CS and the company's clarification response suggest that patients in the placebo group experienced AEs that led to discontinuation and progression of disease, or perceived disease progression.

1.4 Summary of cost effectiveness evidence submitted by the company

The company submitted a *de novo* model-based health economic evaluation to assess the incremental cost-effectiveness of patisiran plus BSC versus BSC alone for the treatment of adult patients with hATTR amyloidosis with polyneuropathy. The incremental health gains, costs and cost-effectiveness of patisiran are evaluated over a 40-year time horizon from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The company's model adopts a state transition approach, with health states defined by polyneuropathy disability (PND) score (from PND 0 [no impairment] to PND IV [confined to a wheelchair or bedridden]) and N-terminal pro b-type natriuretic peptide (NT-proBNP) score (based on a cut-off value of 3,000pg/mL). The population within the model reflects the mITT population enrolled into the APOLLO study. The model parameters were informed by APOLLO, external data from other published studies, a Delphi panel, standard costing sources and assumptions. The model assumes that all patients with hATTR amyloidosis with polyneuropathy are eligible to commence treatment with patisiran, irrespective of NT-proBNP level or PND score and all patients will continue to receive treatment with patisiran indefinitely. Based on the company's model assumptions, patisiran-treated patients are assumed to spend longer in the better PND states and have improved survival compared with BSC.

Based on a re-run of the probabilistic version of the company's model by the ERG, using discount rates of 3.5% and 1.5% for costs and health outcomes and including the Patient Access Scheme (PAS), patisiran is expected to generate an additional 8.11 quality-adjusted life years (QALYs) at an additional cost of [redacted] per patient; the corresponding incremental cost-effectiveness ratio (ICER) for patisiran versus BSC is [redacted] per QALY gained. The deterministic version of the model produces

a slightly higher ICER of [redacted] per QALY gained. The probability that patisiran produces more net benefit than BSC at willingness-to-pay (WTP) thresholds below £100,000 per QALY gained is approximately [redacted]; at WTP thresholds of £200,000 per QALY gained and £300,000 per QALY gained, the probability that patisiran is optimal is approximately [redacted] and [redacted], respectively. The lowest ICER reported within the company's deterministic analyses is [redacted] per QALY gained.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG critically appraised the company's economic analyses and double-programmed the deterministic version of the company's base case model in order to verify its implementation. The ERG's critical appraisal identified a number of issues relating to the company's economic analysis and the evidence used to inform the model. The most pertinent of these include: (i) the inappropriate use of differential discount rates; (ii) the identification of model errors (including inappropriate cycle length conversion); (iii) issues surrounding treatment initiation/discontinuation rules; (iv) issues relating to the company's model structure; (v) concerns regarding the company's assumed mortality assumptions; and (vi) issues relating to the company's HRQoL assumptions.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The ERG does not believe that any relevant studies of patisiran have been excluded from the CS.

Although hATTR is a rare disease, the company was able to conduct an RCT and generate comparative evidence of the effect of patisiran versus BSC.

Clinical advisors to the ERG believe that the APOLLO trial is broadly representative of the population of patients with hATTR amyloidosis with polyneuropathy seen in clinical practice in England.

Clinical advisors to the ERG considered that the structure of the company's health economic model was broadly appropriate and reflected some of the key outcomes associated with hATTR amyloidosis with polyneuropathy. With the exception of the use of differential discount rates, the company's economic analysis is generally in line with the NICE scope.

1.6.2 Weaknesses and areas of uncertainty

The main limitation of the company's clinical evidence review concerns the reporting of outcomes; the literature was not narratively synthesised, and findings were reported by study rather than by outcome. Thus, there is a possibility for outcomes to have been selectively reported. In order to address this issue, the ERG has reported findings by outcome.

The ERG has two concerns relating to the reliability of the clinical evidence from APOLLO:

- A greater proportion of patients in the patisiran group than the placebo group met the criteria for cardiac involvement;
- A greater proportion of placebo group patients discontinued treatment and withdrew from the study compared with the patisiran group.

The other three studies adopted a single,-arm design, and longer-term data from the Phase 2 OLE and Global OLE studies are open-label, and are thus susceptible to bias.

The ERG believes that there is considerable uncertainty surrounding:

- The long-term comparative benefits of patisiran versus BSC in terms of PND and NT-proBNP impacts
- The survival benefit associated with patisiran
- The level of HRQoL experienced by patients who receive patisiran or BSC over time
- The potential impact of introducing a stopping rule for patisiran.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook two broad sets of exploratory analyses using the base case version of the company's model. The first set involved forming an ERG-preferred analysis, which includes: (i) the correction of errors identified within the ERG's critical appraisal; (ii) the application of equal discount rates of 3.5% for health outcomes and costs; (iii) the recalculation of the initial distribution by PND and NT-proBNP score; (iv) the use of general population HRQoL data from Ara and Brazier; and (v) the adjustment of calculations to estimate mortality risk by PND stage for low NT-proBNP states. Additional exploratory analyses were undertaken using the ERG-preferred analysis to explore the impact of altering assumptions regarding health utilities, mortality risks, NT-proBNP change and resource use reductions.

The ERG's preferred ICER for patisiran versus BSC is estimated to be [redacted] per QALY gained using the probabilistic version of the model. The deterministic version of the model yields a lower ICER for patisiran versus BSC of [redacted] per QALY gained. The ERG's additional exploratory analyses led to ICERs ranging from [redacted] to [redacted] per QALY gained. The ERG notes that the assumptions regarding treatment-dependent health utilities, PND-related mortality and NT-proBNP≥3,000pg/mL changes without patisiran treatment have a significant impact upon the ICER.

2 BACKGROUND

This report provides a review of the evidence submitted by the company (Alnylam Pharmaceuticals) in support of patisiran for treating adults with hereditary transthyretin-related amyloidosis (hATTR) with polyneuropathy. It includes evidence presented within the company's submission (CS) received on 20th August 2018,[1] responses to clarification questions provided by the company on 20th September 2018,[2] and responses to additional follow-up clarification questions provided by the company on 27th September 2018.[3]

2.1 Critique of company's description of underlying health problem

The CS (Section 6.1)[1] provides a good and comprehensive description of hATTR amyloidosis. As described in the CS, hATTR amyloidosis is an ultra-rare multi-systemic disease. There is relatively little information in the literature on the incidence and prevalence of hATTR amyloidosis. The CS states that based on data provided by the National Amyloidosis Centre (NAC), in 2018 there were 150 patients in the UK with hATTR amyloidosis; the CS estimates that 112 of these patients were living in England. The incidence of hATTR amyloidosis in England was estimated to be 0.0001% (CS,[1] page 39).

hATTR amyloidosis is an autosomal dominant disease caused by a genetic mutation in the transthyretin (TTR) gene. There are over 120 TTR mutations. Carriers are born with the circulating variant protein but do not experience amyloid deposition or symptomatic disease until adulthood. There is an association between the mutation and whether a patient presents with polyneuropathy or cardiomyopathy, although patients can present with a mixture of symptoms and phenotypes. The most common genetic mutations found in patients in the UK include Val122ll (39%), Thr60Ala (25%) and Val30Met (17).[1]

TTR is a transport protein which is mainly synthesised in the liver and choroid plexus of the brain, and which circulates as a homotetramer in plasma and cerebrospinal fluid. TTR may aggregate to form amyloid fibrils. In TTR amyloidosis, these fibrils are deposited and accumulate in multiple tissues and organs, resulting in symptomatic disease.[1]

Clinical advice to the Evidence Review Group (ERG) suggests that diagnosis following onset of symptoms is difficult in the absence of a family history and it is not known what proportion of individuals with a mutation will go on to develop the disease.

Several scoring systems are available for classifying the disease, including the familial amyloidotic polyneuropathy (FAP) staging system based on peripheral and autonomic neuropathy disability, the polyneuropathy disability (PND) score and the Gillmore staging system for hATTR patients with

cardiomyopathy using the biomarkers N-terminal pro b-type natriuretic peptide (NT-proBNP; cut-off 3,000pg/mL) and estimated glomerular filtration rate (eGFR; cut-off 45mL/min/1.73m^2).[4, 5] No staging or disability scoring system covers all aspects of the disease. Clinical advice received by the ERG suggests that although the FAP staging system is mainly used to classify patients with hATTR amyloidosis in the UK and is the system reflected by the license for patisiran, staging is mainly done for academic purposes and is not used to assess whether treatments are working in clinical practice.

Although patients may present with predominantly polyneuropathy or predominantly cardiomyopathy, most patients will experience symptoms of both over the course of their disease. Early neurological symptoms include painful or abnormal sensations in the feet and hands and an inability to sense temperature. Disease progression results in motor weakness, decreased pain sensation, generalised weakness, an inability to perform activities of daily living, weakness and wasting of the body, and loss of ambulation. Other symptoms include orthostatic hypotension, impotence, severe gastro-intestinal symptoms, bladder dysfunction, recurrent urinary tract infections and cardiac arrhythmias. Disease progression can be rapid and may lead to death as a consequence of gastrointestinal (GI) complications.[1]

Cardiac infiltration with amyloid causes thickening of ventricular walls, interventricular septum, and cardiomyopathy leading to heart failure. Patients with hATTR have a reduced life expectancy (3 to 15 years from onset of symptoms depending on the TTR mutation and clinical manifestation) and typically die from heart failure or complications of autonomic neuropathy resulting in severe malnutrition and wasting. Factors associated with reduced life expectancy include: higher age; the presence of Val122Ile or Thr60Ala mutations; malnutrition leading to weight loss; peripheral neuropathy; cardiac biomarker levels (NT-proBNP levels $\geq$3000pg/mL).[1]

The natural history of the disease is characterised by chronically debilitating symptoms that increasingly affect patients' daily lives. These may include progressive muscle atrophy and weakness in the upper and lower body. Impaired balance may affect the ability to walk and the need for walking aids or wheelchairs. Constant pain may affect the ability to sleep at night and be active during the day. Patients may become dizzy or faint with the potential for serious injury. Constipation, diarrhoea and faecal incontinence may affect patient's willingness to leave their homes. Patients may experience shortness of breath and fatigue.

2.2 Critique of company's overview of current service provision

The CS[1] (Sections 8.1, 8.2 and 8.3) provides a good overview of current service provision. The CS states correctly that at the time of the submission, no National Institute for Health and Care Excellence (NICE), National Health Service (NHS) England or other national guidance documents on the

management of hATTR amyloidosis were available, and that no disease-modifying pharmacological treatments are approved for use in the UK.

The NAC provides specialist diagnostic and management advice for amyloidosis patients in England. In general, treatment is provided at local secondary care facilities with primary care support.[1] Current treatment for patients with hATTR amyloidosis may involve symptomatic treatment, and disease-modifying or stabilising therapy. Clinical advice to the ERG is that orthotopic liver transplantation is rarely performed in the UK.

Given the lack of treatment options, current service provision principally consists of symptom management represented by best supportive care (BSC) administered on an individual patient basis (CS,[1] Section 8.2.1).[1] Table 1 summarises the types of symptomatic treatments used for hATTR amyloidosis listed in the guideline reported by Ando *et al*.[4]

Table 1: BSC - treatments for clinical symptoms of hATTR amyloidosis with polyneuropathy (reproduced from Ando *et al*, 2013)

Symptom	Treatment
Arrhythmia	Pacemaker implantation, pharmacotherapy
Cardiac failure	Diuretics, angiotensin converting enzyme inhibitors, blood thinners, heart transplantation
Orthostatic hypotension	Droxidopa, midodrine, amezinium metisulfate, fludrocortisone, plastic stocking, abdominal belt, elevating head
GI disorders (not severe)	Polycarbophil calcium, metoclopramide
Severe diarrhoea	Loperamide
Neuropathic pain	Pregabalin, gabapentin, amitriptyline, duloxetine
Carpal tunnel syndrome	Surgery
Dry mouth	Potassium dihydrogen phosphate, cevimeline
Hypoglycaemia	Glucose loading
Renal failure	Haemodialysis
Urinary incontinence	Distigmine
Anaemia	Erythropoietin, iron
Hypothyroidism	Levothyroxine
Ocular amyloidosis	Vitrectomy, trabeculectomy

GI – gastrointestinal

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[6] and addressed in the CS[1] is presented in Table 2.

Table 2: Company's statement of the decision problem (reproduced from CS, Table A1)

	Final scope issued by NICE	Variation from scope in the CS	Rationale for variation from scope
Population	People with hereditary transthyretin-related amyloidosis.	Since the NICE scoping, the CHMP has issued its positive opinion with the final indication statement	The population addressed in the submission and the CE model corresponds to final CHMP indication as well as to the population studied in the pivotal registration-enabling APOLLO trial of adult patients with hATTR amyloidosis. This population reflects the presentation prevalent in the UK. The change from the scope merely reflects the final CHMP approved indication which was not yet known at the time of the scoping conclusion.
Intervention	Patisiran	None	N/A
Comparator(s)	Established clinical management without patisiran.	None	N/A
Outcomes	• Neurological impairment • Symptoms of polyneuropathy • Cardiac function • Autonomic function (including the effects on the GI system and postural hypotension) • Weight loss • Effects of amyloid deposits in other organs and tissues (including the eye) • Serum transthyretin • Motor function • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	None	N/A
Subgroups to be considered	None specified	None	N/A

	Final scope issued by NICE	Variation from scope in the CS	Rationale for variation from scope
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	None	N/A
Cost to the NHS and PSS, and value for money	• Cost effectiveness using incremental cost per quality-adjusted life-year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise.	None	N/A
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements	None	N/A

CS – company's submission; NICE – National Institute for Health and Care Excellence; CHMP - Committee for Medicinal Products for Human Use; hATTR – hereditary ATTR amyloidosis; GI – gastrointestinal; NHS – National Health Service; PSS – Personal Social Services; N/A – not applicable

3.1 Population

The population defined in the NICE scope relates to people with hATTR amyloidosis. The decision problem addressed by the CS[1] relates to adult patients with hATTR amyloidosis with Stage 1 or Stage 2 polyneuropathy. This reflects a deviation from the final NICE scope; however, the population addressed in the decision problem is in line with both the APOLLO trial[7] (the main source of clinical evidence within the CS) and the marketing authorisation for patisiran.[8] The ERG notes that in APOLLO, a very small proportion of patients (1 patient in the placebo group only) had FAP stage 3 disease at baseline. The CS does not contain any evidence relating to the use of patisiran for the treatment of patients with predominantly cardiac forms of hATTR in the absence of polyneuropathy.

3.2 Intervention

The intervention under appraisal is patisiran (Onpattro®). The draft Summary of Product Characteristics (SmPC)[8] states that patisiran is a double-stranded small interfering ribonucleic acid (siRNA) that specifically targets a genetically conserved sequence in the 3' untranslated region of all mutant and wild-type TTR messenger ribonucleic acid (mRNA). Patisiran is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR protein in the circulation. Through RNA interference (RNAi), patisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in a reduction of serum TTR protein.[8] The CS[1] highlights that there are currently no effective disease-modifying therapies for hATTR amyloidosis, hence the anticipated place of patisiran is as a first-line treatment for adult patients with hATTR amyloidosis with Stage 1 or Stage 2 polyneuropathy (in combination with BSC).

Patisiran is available as a single vial containing patisiran sodium equivalent to 10mg patisiran formulated as lipid nanoparticles.[8] Patisiran is administered by intravenous (IV) infusion once every three weeks at a dose of 0.3mg/kg; for patients weighing ≥100kg, the maximum recommended dose is 30mg. This dosing regimen is generally in line with the regimen given in the APOLLO trial,[7] except for the maximum dose and the weight at which this applies (see Section 4.2.1). The list price for a single vial of patisiran is £7,676.47.[1] A Patient Access Scheme (PAS) has been proposed by the company involving a simple price discount; including the PAS, the price per vial of patisiran is [redacted]. The draft SmPC advises the use of Vitamin A supplementation at a dose of approximately 2,500 international units (IU) per day. The draft SmPC also recommends that each of the following premedications should be given at leafst 60 minutes prior to patisiran administration to reduce the risk of infusion-related reactions (IRRs):

- Intravenous corticosteroid (dexamethasone 10mg, or equivalent)
- Oral paracetamol (500mg)
- Intravenous H1 blocker (diphenhydramine 50mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50mg, or equivalent)

The draft SmPC[8] does not explicitly specify when patients should discontinue treatment with patisiran. The CS[1] (page 27) states that *"It is expected that patients will be treated with patisiran for the duration of their lives, subject to the clinical judgement of the treating physician."* The ERG notes that there is no randomised controlled evidence regarding the effectiveness of patisiran for the treatment of patients with FAP Stage 3 disease. According to the CS (Table C4, pages 77-78), sixteen (7.6%) patients in the Global open-label extension (OLE) study were in FAP Stage 3 at study entry.

The draft SmPC states that there are no data on the use of patisiran in pregnant women. The draft SmPC states that it is unclear whether patisiran is excreted in human milk. In addition, there are no data on the effects of patisiran on human fertility.

Contraindications to patisiran include severe hypersensitivity (e.g. anaphylaxis) to the active substance or any of the excipients listed in the SmPC.[8]

3.3 Comparators

The final NICE scope[6] defines the comparator for the appraisal as *"established clinical management without patisiran."* The comparator within the company's decision problem is defined as BSC. The ERG notes that other pharmacological treatments may be used for the treatment of hATTR, including tafamidis and diflusinal. However, tafamidis is not currently available in England due to a negative Advisory Group for National Specialised Services (AGNSS) recommendation. In addition, whilst diflunisal is sometimes used off-label, the CS highlights that treatment is contraindicated in patients with severe heart failure, GI bleeding, or hepatic or renal failure, hence this drug may not be an option for many hATTR patients. The ERG also notes that the APOLLO trial[7] did not define a standardised BSC regimen, hence trial outcomes may be subject to variations in the care delivered between participating centres. The company's economic analysis assumes that BSC is comprised of a interventions targeting a variety of symptoms of hATTR amyloidosis, based on guidelines reported by Ando *et al*[4] (see Table 1).

3.4 Outcomes

The final NICE scope[6] lists the following outcomes:

- Neurological impairment
- Symptoms of polyneuropathy
- Cardiac function
- Autonomic function (including the effects on the GI system and postural hypotension)
- Weight loss
- Effects of amyloid deposits in other organs and tissues (including the eye)

- Serum transthyretin
- Motor function
- Mortality
- Adverse effects of treatment
- Health-related quality of life (HRQoL) for patients and carers

The CS[1] includes evidence relating to all of these outcomes except for effects of amyloid deposits in other organs and tissues (including the eye), and HRQoL for carers.

3.5 Economic analysis

The CS[1] reports the methods and results of a *de novo* model-based health economic analysis to assess the incremental cost-effectiveness of patisiran plus BSC versus BSC alone for the treatment of adult patients with hATTR amyloidosis with polyneuropathy. The company's health economic analysis is detailed and critiqued in Chapter 5.

3.6 Subgroups

The APOLLO trial[7] included pre-specified subgroup analyses relating to the cardiac subgroup, which consisted of patients with left ventricular (LV) wall thickness of ≥1.3cm, excluding those with other medical conditions (e.g. hypertension) that may contribute to LV wall thickening (CS,[1] page 78). Clinical data relating to this subgroup are summarised in Section 4.2.4. In addition, the primary outcome, change from baseline to 18 months on the Modified Neuropathy Impairment Score +7 (mNIS+7), was examined in several patient subgroups, including: age (<65; ≥65 years); sex (male; female); race (white; non-white); region (North America; Western Europe; rest of world), Neuropathy Impairment Score (NIS; <50; ≥50); genotype (Val30Met; other); genotype class (early onset Val30Met; all other mutations); previous tetramer stabiliser use (yes; no), and FAP stage (1; 2 & 3). The company's health economic analysis does not include any subgroup analyses.

3.7 Special considerations

Table A1 of the CS[1] states that there are no equality issues relating to the use of patisiran for the treatment of hATTR amyloidosis.

Section 8.5 of the CS states that patisiran is the first approved disease-modifying drug treatment for hATTR amyloidosis in the UK and that the technology represents a step-change in the management of hATTR amyloidosis. The ERG notes that whilst not routinely available, tafamidis is also a disease-modifying treatment. The CS also notes that the Medicines and Healthcare products Regulatory Agency (MHRA) awarded patisiran a Promising Innovative Medicine designation in January 2018.

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS for patisiran for treating hATTR amyloidosis. Section 4.1 provides a critique of the company's systematic review. Section 4.2 provides a summary of the clinical effectiveness and safety results together with a critique of the included studies. Sections 4.3 to 4.5 of the template (relating to indirect comparisons and additional work undertaken by the ERG) are not applicable. Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

The company undertook two systematic literature reviews (SLRs) to identify all relevant studies reporting on the safety and efficacy of current treatments for: (1) hATTR amyloidosis with polyneuropathy; and (2) hATTR amyloidosis with cardiomyopathy; only studies including patisiran were reported in the CS.[1] Two separate reviews were conducted for historical reasons, as until recently, these were conceptualised as two distinct diseases.[1, 2] Both randomised controlled trials (RCTs) and non-RCTs were included. The systematic review methods are detailed in Section 9.1 of the CS and CS Appendix 1.[1] A systematic review was not undertaken for studies of the comparator listed in the NICE scope[6] (established clinical management without patisiran).

4.1.1 Searches

The ERG considers the sources selected and searched by the company to be comprehensive and relevant. The company searched five electronic bibliographic databases: MEDLINE (via PubMed); EMBASE (via Elsevier); the Cochrane library (which includes the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Health Technology Assessment database [via Wiley]); EconLit (via the American Economics Association), and PsycINFO (via the American Psychological Association). The company searched multiple conference abstract sources either via Embase or manually (International Symposium on Amyloidosis; European Congress on Hereditary ATTR Amyloidosis; European Society of Cardiology Congress; Congress of the European Academy of Neurology; American Neurological Association Annual Meeting; American Academy of Neurology Annual Meeting; Peripheral Nerve Society Annual Meeting; International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and European Meetings; International Congress on Neuromuscular Diseases; American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting) covering the period from 2015 to July 2018 and excluding abstracts published prior to 2015. The ERG has reviewed all the pre-2015 abstracts and found that no relevant records were excluded. The company searched two clinical trials registers in the SLR update (clinicaltrials.gov and WHOICTRP). Supplementary searches by the company covered multiple health technology assessment websites (United States [US] Food and Drug Administration [FDA] Advisory

Committees, the European Public Assessment Reports [EPARs], NICE, the Scottish Medicines Consortium [SMC], the All Wales Medicines Strategy Group [AWMSG], and the Canadian Agency for Drugs and Technologies in Health [CADTH]) (CS,[1] Appendix 1, page 3).

The company performed two SLR searches to identify all clinical and safety studies of patisiran and its comparators for adult patients with hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy. Prior to the separate searches carried out in January 2018, the only term used and applied was hATTR combined with polyneuropathy (May 2017). Subsequent search updates were undertaken in January 2018 and again in July 2018.

A separate search for hATTR amyloidosis with cardiomyopathy covering all years was performed to identify clinical effectiveness, economic and quality of life studies. The translation of the search between PubMed Medline (via NIH) and Embase (via Ovid) shows minor inconsistencies. First, restrictions were applied to limit the number of records retrieved in the Embase strategy by applying proximity indicators (ADJ4) as opposed to the Boolean operator 'AND' used in the Medline search strategy which would potentially double the number of records retrieved in that statement alone. Field limiting searching was applied in Medline to search within title and abstract (tiab) fields whereas multiple fields were searched in Embase (.mp). The impact of the inconsistencies would result in fewer records being retrieved.

The ERG agrees with the broad structuring of the company's search strategies to retrieve all clinical, economic, and HRQoL studies without restrictions made to interventions, comparators or outcomes according to the PICOS criteria (population, intervention, comparator, outcomes and study design). The population terms for polyneuropathy and the sources used were considered to be comprehensive and the ERG believes it is unlikely that studies relevant to the decision problem have been missed. The company applied publication design filters to remove non-relevant article types (e.g. non-systematic literature review) by adapting a validated filter[9] for retrieving systematic reviews and meta-analyses in Medline and Embase. The validity of this approach is unclear.

The ERG set up Google Alerts to monitor ongoing news releases pertaining to patisiran. The release of data investigating the effect of patisiran on cardiac disease[10] was identified via these alerts.

4.1.2 Inclusion criteria

The company's inclusion criteria for the reviews of clinical effectiveness and safety, economic analyses and HRQoL studies are presented in Table 3.[1]

Table 3: Study inclusion criteria (reproduced from CS, Table C1)

	hATTR amyloidosis with polyneuropathy SLR	hATTR amyloidosis with cardiomyopathy SLR
Inclusion criteria		
Population	• Populations or subgroups enrolling at least 80% patients per treatment arm with hATTR amyloidosis with polyneuropathy	• Patients with hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis*
Interventions	• Any treatments	• Any treatments
Comparators	• Any	• Any
Outcomes	• From RCTs: safety and efficacy outcomes, patient-reported outcomes • From single-arm studies: safety and effectiveness outcomes • From observational studies: clinical effectiveness, safety, patient-reported outcomes • From economic studies: costs, cost-effectiveness, and resource use	• From RCTs: safety and efficacy outcomes, patient-reported outcomes • From single-arm studies: safety and effectiveness outcomes • From observational studies: clinical effectiveness, safety, patient-reported outcomes • From economic studies: costs, cost-effectiveness, and resource use
Study design	• RCTs and non-randomised controlled trials • Open-label extensions • Observational studies (prospective, cross-sectional, and retrospective [i.e., chart reviews, registries, surveys, etc.]) of clinical effectiveness and safety • Single-arm trials • Cost-effectiveness, cost-utility, or cost-minimisation studies • Healthcare resource use studies • Utility assessments or patient-reported outcome studies	• RCTs and non-randomised controlled trials • Open-label extensions • Observational studies (prospective, cross-sectional, and retrospective [i.e. chart reviews, registries, surveys, etc.]) of clinical effectiveness and safety • Single-arm trials • Cost-effectiveness, cost-utility, or cost-minimisation studies • Healthcare resource use studies • Utility assessments or patient-reported outcome studies
Language restrictions	None	None
Search dates	Original SLR: 30 May 2017; SLR Update: 10 January 2018	28 January 2018

	hATTR amyloidosis with polyneuropathy SLR	hATTR amyloidosis with cardiomyopathy SLR
Exclusion criteria		
Population	• Not hATTR amyloidosis (such as wtATTR amyloidosis) • hATTR amyloidosis not presenting with predominant polyneuropathy or • hATTR amyloidosis in which polyneuropathy is attributable to another cause • Mixed populations or subgroups with <80% adult hATTR amyloidosis with polyneuropathy • hATTR amyloidosis patients who have undergone OLT	• hATTR amyloidosis patients who have undergone OLT
Interventions	N/A	N/A
Comparators	• Dose-finding clinical trials (i.e., studies in which all treatment arms are different doses of the same agent)	• Dose-finding clinical trials (i.e., studies in which all treatment arms are different doses of the same agent)
Outcomes	• Pharmacodynamic/pharmacokinetic studies or non-clinical studies (such as gene expression or protein expression studies)	• Pharmacodynamic/pharmacokinetic studies or non-clinical studies (such as gene expression or protein expression studies)
Study design	• Letters, literature reviews, expert opinion articles, etc.	• Letters, literature reviews, expert opinion articles, etc.
Language restrictions	• None	• None
Search dates	Original SLR and rescreen: 30 May 2017 SLR Update: 10 January 2018	January 28, 2018

hATTR - hereditary transthyretin-mediated amyloidosis; NA - not applicable; OLT - orthotopic liver transplantation; RCT - randomised controlled trial; SLR - systematic literature review; wtATTR - wild-type transthyretin-mediated amyloidosis.

**May include patients with ATTR with primary cardiomyopathy (hereditary or wild type), hATTR with primary polyneuropathy who also have cardiomyopathy, or ATTR with cardiomyopathy alone (hereditary or wild type)*

The inclusion criteria partially reflect the decision problem. One key difference is that separate reviews have been undertaken for hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy, whereas the decision problem relates to people with hATTR amyloidosis overall. In response to a request for clarification from the ERG (see clarification response,[2] question A3), the company stated that the population was amended to hATTR amyloidosis in adults with polyneuropathy to reflect the approved patisiran indication.[2] Any intervention and any comparator have been specified in the inclusion criteria, however patisiran and established clinical management without patisiran were specified as the intervention and comparator in the NICE scope.[6] Specific outcomes are not listed in the company's inclusion criteria for the reviews, hence it is difficult to comment on the extent to which the outcomes listed in the NICE scope[6] have been included in the reviews. The exclusion criteria appear to be consistent with the NICE scope.[6]

No details are reported regarding the number of reviewers who screened study titles and abstracts for inclusion. The process of full text screening and decision-making was also not reported in the CS.[1]

Three Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams are presented (Figures 3 and 4, pages 62-63 CS),[1] referring to a total of 69 articles included in the clinical review of hATTR amyloidosis with polyneuropathy and 19 articles included in the clinical review of hATTR amyloidosis with cardiomyopathy. All of the articles that met the inclusion criteria in the hATTR amyloidosis with cardiomyopathy systematic review were either out of scope or were duplicates from the hATTR amyloidosis with polyneuropathy review. Five studies are listed in CS Table C2 (page 65), all of which relate to studies of patisiran.[1] A list of excluded studies for each of the reviews is presented within two separate documents embedded in CS Appendix 1, and reasons for study exclusion are given in Figure 3 (CS, page 62); however, some of these do not match up with the inclusion and exclusion criteria in CS Table C1 (pages 59-60). For example, studies have been excluded for being observational studies of <50 patients, natural history (NH) study outside US or Europe, language (in Table C1, pages 59-60, CS, language restrictions are listed as "none"), or for being reported in an abstract from earlier than 2015.[1] In response to a request for clarification from the ERG (see clarification response,[2] question A15), the company highlighted that: observational studies of <50 patients were natural history (NH) studies and were outside the scope of the CS; the exclusion of NH studies outside of the US or Europe was part of the original search (although no justification was provided); the language restriction was dropped for the SLR update search, and the exclusion of abstracts published prior to 2015 was part of the search algorithm and the company believes that the exclusion of abstracts published >2 years prior to the search is common practice in systematic reviewing.[2] The ERG checked all excluded pre-2015 abstracts and found that none were relevant to the decision problem.

4.1.3 Critique of data extraction

Data were extracted by one investigator and checked by a second, with any disagreements resolved by a third investigator (CS Appendix 1, page 4). The CS does not state how many disagreements required the involvement of a third investigator. The extractions were used as the basis for evidence tables, and the data presented in the clinical effectiveness section of the CS appear to be comprehensive and appropriate.

4.1.4 Critique of quality assessment

Quality assessment of the four studies included in the company's SLR was conducted using two different methods as one included study was an RCT (APOLLO),[11] whilst the other three studies adopted an observational design. The CS states that the quality assessment of the included studies was conducted independently by two reviewers, with disagreement resolved by a third reviewer.[1]

The CS states that the APOLLO RCT[11] was assessed using a quality assessment tool adapted from the Centre for Reviews and Dissemination (CRD) guidance on undertaking systematic reviews in health care.[12] The table used was populated with criteria adapted from the Cochrane Risk of Bias tool; this is widely recognised as the most robust quality assessment tool for the assessment of RCTs. The remaining three studies were observational studies (Phase 2 dose escalation study, Phase 2 OLE, and Global OLE; see CS,[1] Appendix 1); these studies were quality assessed using a tool adapted from the Critical Appraisal Skills Programme (CASP): Making sense of a cohort study.[13] The ERG notes that the CASP checklist was adapted, and included only seven of the twelve questions applied to each of the three included studies. No justification for either method of critical appraisal is presented in the CS. As part of their clarification response[2] (question A16), the company highlighted that the NICE Highly Specialised Technologies (HST) interim company evidence submission template (May 2017), provides a suggested format for the critical appraisal of both RCT and observational studies, which excludes the questions identified by the ERG as missing. Therefore this has been applied by the company, and accounts for the missing questions.[2]

No overall assessment of the risk of bias for each study or narrative synthesis of the critical assessments was provided, and no attempt was made to integrate the quality assessment into the reporting of the findings. Although quality has been assessed, the overall impact of the quality of the included studies on the results is unclear.

4.1.5 Critique of evidence synthesis

The CS does not include any formal evidence synthesis.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The CS includes four studies that examine the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy: APOLLO,[11] a pivotal RCT; the Phase 2 dose-escalation study,[14] an open-label dose escalation study; the Phase 2 OLE,[15] an open-label extension of the Phase 2 dose-escalation study; and the Global OLE study,[16] an open-label extension of the Phase 2 OLE and APOLLO.[1] The study characteristics of these four studies are presented in Table 4.

The pivotal study, APOLLO, was a Phase III, multicentre, randomised, double-blind, placebo-controlled trial (CS[1] page 66; clinical study report (CSR);[7] Adams *et al*. 2017;[17] Adams *et al*. 2018[11]). The CS states that APOLLO was conducted in 19 countries: France, the US, Taiwan, Spain, Japan, Germany, Mexico, Portugal, South Korea, Sweden, Bulgaria, Italy, Canada, Turkey, Cyprus, Brazil, the Netherlands, United Kingdom and Argentina. Two patients enrolled in APOLLO were from the UK (see clarification response,[2] question A23).

The Phase 2 dose escalation study (Suhr *et al*. 2015[14]) was a Phase II, international, multicentre, open-label, multi-dose, dose escalation trial (CS[1] page 70). Patients were enrolled across seven countries: Brazil, France, Germany, Portugal, Spain, Sweden and the US.[14] None of the patients in the Phase 2 dose escalation study were from the UK (see clarification response,[2] question A23).

The Phase 2 OLE study was a single-arm open-label extension of the Phase 2 dose escalation study (CS[1] page 70; Adams *et al*. 2017;[15] Adams *et al*. 2017[17]). Patients from the Phase 2 dose escalation study were eligible to roll over into the Phase 2 OLE. The CSR[18] (page 64) lists seven countries in which the Phase 2 OLE was conducted: Brazil, France, Germany, Portugal, Spain, Sweden and the US. None of the patients in the Phase 2 OLE study were from the UK (see clarification response,[2] question A23).

The Global OLE is an ongoing single-arm open-label extension (CS[1] page 70; Partisano *et al*. 2017[16]). The CS states that patients from both the Phase 2 OLE and APOLLO were eligible to enrol on the Global OLE (page 71; Table S6, Appendix 1);[1] however, the Partisano *et al*. 2017 abstract[16] states that patients were enrolled from the Phase 2 OLE, with no mention of patients enrolling from APOLLO. In response to a request for clarification on this point (see clarification response,[2] question A17), the company confirmed that all patients enrolled in the Global OLE had previously participated in either the Phase 2 OLE or APOLLO.[2] According to clinicaltrials.gov, 45 study sites are operational or planned, across 26 countries: the US, Argentina, Australia, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, Turkey and United Kingdom (1 site).[19]

Table 4: Study characteristics of trials reported in the clinical effectiveness section of the CS

Study	Location (sites)	Design	Population	Interventions	Comparator	Primary outcome measure	Secondary outcome measures	Duration
APOLLO[1, 11] (NCT01960348)	46 sites (including 44 academic hospitals) in 19 countries	Phase III multicentre randomised double-blind trial	225 adult patients aged 18-85 years with diagnosis of hATTR amyloidosis with polyneuropathy.	Patisiran IV 0.3mg/kg Q3W, max dose 32.1 mg (if ≥105 kg)[7] (n=148)	Placebo IV (normal saline 0.9%) Q3W (n=77)	Difference in change from baseline in mNIS+7 score at 18 months	QoL; disability; ambulation; nutritional status (mBMI); autonomic symptoms; neurological symptoms; cardiac measures; pharmacodynamic biomarkers; rapid disease progression; MRN; FAP stage and PND score.	18 months
Phase 2 dose-escalation study[1, 14] (NCT01617967)	10 sites in seven countries[20]	Phase II multicentre open-label multi-dose dose escalation trial	29 adults aged ≥18 years with biopsy proven ATTR amyloidosis and mild-to-moderate neuropathy.	Patisiran IV 0.01 to 0.3mg/kg Q3W or Q4W (2 doses) (n=29)	None	Safety and tolerability of multiple ascending doses of patisiran.	Characterise the plasma and urine PK of patisiran; assess preliminary evidence of PD effect of patisiran on serum total TTR levels.	208 days[2]
Phase 2 OLE[1, 15, 17] (NCT01961921)	Nine sites in seven countries[17]	Phase II single-intervention open-label extension	27 adults who had previously participated in the Phase 2 dose escalation study and had received and tolerated 2 doses of patisiran; cardiac subgroup	Patisiran IV 0.3mg/kg Q3W (n=27)	None	Safety and tolerability of up to 2 years of patisiran	PD effect of long-term dosing of patisiran on serum TTR; neurologic impairment (mNIS+7); QoL; disability; motor function ADLs; nutritional status (mBMI) (CSR, p.24)[18]	24 months (additional to the duration of The Phase 2 dose-escalation study; CSR, p.25)[18]
Global OLE[1, 16] (NCT02510261)	45 study sites, in 26 countries[19]	Phase III single-intervention open-label extension	211 patients with hATTR amyloidosis with polyneuropathy amyloidosis who participated in the Phase 2 OLE or APOLLO. (25 patients from the Phase 2 OLE)[16]	Patisiran IV 0.3 mg/kg Q3W	None	Safety and tolerability of long-term dosing of patisiran (proportion of patients who discontinue patisiran due to AEs)	Neurologic impairment; QoL; autonomic function; serum TTR lowering; nutritional status; disability; motor function.[19]	36 months

ADL - activity of daily living; AE - adverse event; CSR - clinical study report; FAP - familial amyloidotic polyneuropathy; IV – intravenous; mBMI - modified body mass index; mNIS+7 - modified neuropathy impairment score +7; MRN - magnetic resonance neurography; NR - not reported; OLE – open-label extension; PD - pharmacodynamics; PK - pharmacokinetics; PND - polyneuropathy disability Q3W - every 3 weeks; Q4W - every 4 weeks; QoL - quality of life; TTR - transthyretin.

Patients

APOLLO

Key eligibility criteria[17] were as follows (taken from CS[1] Table C3):

- Adults aged 18-85 years (inclusive) with a diagnosis of hATTR amyloidosis with documented mutation
- NIS of 5-130 and a PND score ≤IIIb
- Nerve conduction studies (NCS) sum of sensory nerve action potential, tibial compound muscle action potential (CMAP), ulnar CMAP, and peroneal CMAP of ≥2 points;
- Karnofsky performance status requirements ≥60%
- Absolute neutrophil count ≥1500 cells mm^3 and platelet count ≥50,000 cells mm^3
- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 upper limit of normal (ULN), total bilirubin within normal limits, international normalized ratio (INR) ≤2.0 (patients on anticoagulant therapy up to INR ≤3.5 and those with total bilirubin ≤2 ULN were eligible if the elevation was secondary to documented Gilbert's syndrome and the patient had ALT and AST levels within normal ranges)
- Serum creatinine ≤2 x ULN
- No active hepatitis B or hepatitis C by serology
- Negative pregnancy test as appropriate and no breastfeeding
- Anticipated survival ≥2 years[11]
- Birth control: Female and male patients of child-bearing age or with partners of such age agreed to use 2 methods of birth control during the study and for 75 days after the last dose
- Willingness to comply with protocol schedule; written informed consent.

Exclusion criteria can be found in CS[1] Table C3. Key criteria include: prior or planned liver transplant; known cause of neuropathy; primary amyloidosis or leptomeningeal amyloidosis; type I diabetes; type II diabetes for ≥5 years; major surgery within the past three months or planned during the study period; current antiviral or antimicrobial therapy for an active infection; malignancy ≤2 years ago, except successfully treated basal/squamous cell carcinoma of the skin or carcinoma in situ of the cervix; New York Heart Association (NYHA) heart failure classification of >2; acute coronary syndrome ≤3 months ago; uncontrolled cardiac arrhythmia or unstable angina; participation in a clinical study with antisense oligonucleotide (3-month washout period prior to APOLLO study drug administration); current tafamidis, doxycycline, or taurosodeoxycholic acid (TUDCA; 14-day washout period); anticipated survival <2 years.

Initially, 225 patients were randomised (patisiran n=148; placebo n=77) and received at least one dose of the study drug.[11] Of these, 193 patients (patisiran n=138; placebo n=55) completed the study. Of the

148 patients randomised to the patisiran arm, 11 (7%) discontinued, and of the 77 patients assigned to placebo, 29 (38%) discontinued. The APOLLO CSR reports that for the majority of patients in the placebo group, reasons for withdrawal of consent were that they "felt worsening of disease" or "felt disease progression" (CSR,[7] page 101).

Demographic and clinical characteristics were generally comparable between the patisiran and placebo groups at baseline, although the ERG notes that there was a greater proportion of patients in the cardiac subpopulation in the patisiran group than the placebo group (60.8% versus 46.8%; see CS[1] Table C4, page 78). In response to a request for clarification[2] (question A21), the company attributed this difference to chance, and suggested that it could have impacted on several outcomes including HRQoL, gait speed, cardiac assessments, biasing them against patisiran due to the worse prognosis of patients with cardiac involvement.[2] However, the company notes that the impact of this imbalance on mNIS+7, the primary outcome, is likely to have been minimal, as the mNIS+7 is a measure of neuropathy rather than cardiomyopathy.[2]

Phase 2 dose escalation study

Key eligibility criteria for the Phase 2 dose-escalation study were as follows (from CS,[1] Appendix 1, Table S4):

- Adults ≥18 years with biopsy proven ATTR amyloidosis and mild-to-moderate neuropathy
- Karnofsky performance status ≥ 60 %
- Body mass index (BMI) between 17 and 33 kg/m^2
- Adequate liver and renal function (AST and ALT ≤2.5 ULN, total bilirubin within normal limits, albumin >3 g/dL, INR ≤1.2, serum creatinine ≤1.5 ULN)
- Seronegativity for hepatitis B and hepatitis C viruses.

Exclusion criteria can be found in CS,[1] Appendix 1, Table S4.

All 29 enrolled patients received study treatment, and 26 patients completed the study.[14] Following the protocol-related discontinuation of one patient in the 0.01mg/kg Q4W dose group, an additional patient was enrolled into this cohort.[14]

Phase 2 OLE

Inclusion and exclusion criteria are not provided in the CS (reference is made to Table S3; however, Table S3 is a list of excluded unpublished studies). Inclusion criteria listed on clinicaltrials.gov[21] are:

- Previously received and tolerated ALN-TTR02 (patisiran) in Study ALN-TTR02-002
- Adequate Karnofsky performance status, liver function, and renal function.

Exclusion criteria provided on clinicaltrials.gov[21] for the Phase 2 OLE are:

- Pregnant or nursing
- Has had a liver transplant
- Has a NYHA heart failure classification >2
- Has unstable angina
- Has uncontrolled clinically significant cardiac arrhythmia.

Of the 27 patients enrolled, none were lost to follow-up at the end of the study (24-month follow-up; CS,[1] Appendix 1, Table S5).

Global OLE study

Inclusion and exclusion criteria are not provided in the CS (reference is made to Table S3; however, Table S3 is a list of excluded unpublished studies). Inclusion criteria listed on clinicaltrials.gov[19] are:

- Have completed a patisiran study (i.e., completed the last efficacy visit in the parent study) and, in the opinion of the investigator, tolerated study drug
- Be willing and able to comply with the protocol-required visit schedule and visit requirements and provide written informed consent.

Exclusion criteria provided on clinicaltrials.gov[19] for the Global OLE study are:

- Any new or uncontrolled condition that could make the patient unsuitable for participation.

None of the 25 patients enrolled from the Phase 2 OLE were lost to follow-up at the end of the study (36-month follow-up; CS,[1] Appendix 1, Table S6). Partisano *et al*.[16] state that 25 patients from the Phase 2 OLE had enrolled into the Global OLE. CS Appendix 1 (Table S6) states that 25 patients had enrolled; however, CS Table C2 states that 27 patients had enrolled into the Global OLE.[1]

Baseline characteristics of patisiran studies

Table 5 presents the baseline characteristics of the patients enrolled into the four patisiran studies included in the CS.

Table 5: Baseline characteristics of patisiran studies (reproduced from CS, Table C4)

Study	APOLLO[7, 11]		Phase 2[14]	Phase 2 OLE[1, 15, 17]	Global OLE[16, 22]
Study design	RCT		Phase 2, single-arm, interventional, dose escalation	Phase 2 study OLE	Global OLE (APOLLO and Phase 2 OLE patients)
Population (n)	Patisiran n=148	Placebo n=77	29	27	211
Age, median (range), years	62 (24–83)	63 (34–80)	mean: 56 (15.6)	64.0 (29–77)	65 (26–81)
Male, n (%)	109 (74)	58 (75)	20 (69) -	18 (67)	156 (73.9)-
Median years since diagnosis (range)	1.3 (0.0–21.0)	1.4 (0.0–16.5)	-	-	--
Mean NIS, mean (SD)	60.50 (34.512)	57.02 (32.042)	-	34.8 (range: 4.0–93.4)	64 (range: 0–162)
Mean NIS+7	80.93 (41.507)	74.61 (37.041)	-	53.0 (range: 2.0–122.5)	77 (range: 3–199)-
PND score, n (%)					
0	-	-	-	-	1 (0.5)
I	36 (24)	20 (26)	-	15[a] (55.6)[b]	49 (23.2)
II	43 (29)	23 (30)	-	9 (33.3)[b]	58 (27.5)
IIIA	41 (28)	22 (29)	-	2 (7.4)[b]	42 (19.9)
IIIB	28 (19)	11 (14)	-	1 (3.7)[b]	45 (21.3)
IV	0	1 (1)	-	-	16 (7.6)
FAP stage, n (%)					
0	0	0	-	-	
I	67 (45)	37 (48)	25 (86.2)	24 (88.9)[b]	92 (43.6)
II	81 (55)	39 (51)	4 (13.8)	3 (11.1)[b]	103 (48.8)
III	0	1 (1)	-	-	16 (7.6)
Mutation, n (%)					
Val30Met	56 (38)	40 (52)	22 (75.9)	20	98 (46.4)
non-Val30Met	92 (62)	37 (48)	7 (24.1)	7	113 (53.6)
Previous stabiliser use, n (%)	78 (53)	41 (53)	Diflunisal: 7 (24.1) Tafamidis: 14 (48.3)	Concurrent use: Diflunisal: 7 Tafamidis: 13 ---- Current use: Diflunisal: 2 (7.4)[b] Tafamidis: 12 (44.4)[b]	Diflunisal: 3 (1.4) Tafamidis: 13 (6.2)
Cardiac subpopulation, n (%)	90 (60.8)	36 (46.8)	-	11 (40.7)[b]	-

FAP - Familial Amyloidotic Polyneuropathy; NIS - neuropathy impairment score; NIS+7 - neuropathy impairment score +7; OLE – open-label extension; PND - Polyneuropathy Disability; RCT - randomised controlled trial; SD - standard deviation
[a] From Adams et al. 2017[15]; [b] Percentage calculated by the ERG

The demographics and baseline characteristics of the patients in the patisiran studies are consistent with the population of patients with hATTR amyloidosis with polyneuropathy who are typically seen in clinical practice in England. Within APOLLO, participants were generally similar across treatment arms at baseline. However, compared with patients in the placebo arm (n=77), patients in the patisiran arm (n=148) had a higher mean NIS+7 score (80.93 vs. 74.61), a smaller proportion of patisiran patients had Val30Met mutations (38% vs. 52%) and, related to this, a greater proportion were in the cardiac subpopulation (60.8% vs. 46.8%).

Across the studies, patients in the Phase 2 dose escalation study were slightly younger than patients in the patisiran and placebo arms of APOLLO (mean age 56 and 62 years, respectively), the Phase 2 OLE study (mean age 64 years) and the Global OLE (mean 65 years). A slightly smaller proportion of the sample was male in the Phase 2 study (69%) and Phase 2 OLE (67%) compared with the patisiran and placebo arms of APOLLO (74% and 75%, respectively) and the Global OLE (73.9%). Mean NIS and mean NIS+7 were considerably lower in the Phase 2 OLE (34.8 and 53.0) compared with the patisiran arm (60.50 and 80.93) and the placebo arm (57.02 and 74.61) of APOLLO, and the Global OLE (64 and 77). Similarly, the Phase 2 OLE contained a greater proportion of patients with PND I (55.6%) than the patisiran and placebo arms of APOLLO (24% and 26%, respectively). The Global OLE (23.2%), and the Phase 2 study and Phase 2 OLE contained a greater proportion of patients with FAP stage I (86.2% and 88.9%, respectively) than the patisiran and placebo arms of APOLLO (45% and 48%, respectively) and the Global OLE study (43.6%). This suggests that the patients in the Phase 2 study and the Phase 2 OLE had less advanced disease compared with those in APOLLO and the Global OLE. The Global OLE contained a greater proportion of patients in the higher PND and FAP stages than patients in both arms of APOLLO, the Phase 2 study and the Phase 2 OLE; this suggests that the patients enrolled in the Global OLE had more advanced disease than at enrolment in APOLLO and the Phase 2 OLE. This suggests that patients' disease has progressed overall, over the time period of APOLLO and the Phase 2 OLE study, despite treatment, although a proportion of these patients will have received placebo in APOLLO. Clinical advice received by the ERG suggested that this was reasonable. A greater proportion of patients in the Phase 2 study had a Val30Met mutation (75.9%) than in the patisiran (38%) and placebo (52%) arms of APOLLO, and the Global OLE (46.4%). Although only 12 of the 29 patients enrolled into the Phase 2 study received a dose very similar to the licensed dose (0.3mg/kg every 3 weeks), Suhr *et al*. 2015[14] reported baseline characteristics by treatment dose, and baseline characteristics were similar to those of the overall study sample.

Intervention

Patients in the patisiran arm of APOLLO received 0.3mg/kg by IV infusion (over 70 minutes; 1mL/min for the first 15 minutes and then 3mL/min thereafter) every 3 weeks for 18 months (CS,[1] page 66; Adams *et al*. 2017[17]). The dosing schedule matches the license, except that the maximum licensed dose

is 30mg for patients that weigh ≥100kg; in APOLLO, patients were dosed according to an assumed weight of 104kg if they weighed ≥105kg (i.e. a maximum dose of 31.2mg).[7] Patients with protocol-defined rapid disease progression at 9 months (≥24-point increase in mNIS+7) and FAP stage progression relative to baseline (confirmed by an external adjudication committee) had the option of discontinuing the study drug (patisiran or placebo). There is no detail reported in the CS[1] or CSR[7] as to who made this decision, however the company's clarification response[2] (question A25) states that the patient's treating physician gave the patient the option of discontinuing the study drug. The concurrent use of any investigational agent other than patisiran (e.g. tafamidis, doxycycline, TUDCA) was prohibited, and if tafamidis, doxycycline or TUDCA were used prior to screening, a washout period of 14 days was required (this was 3 days for diflunisal).

In the Phase 2 dose escalation study, patients received doses of patisiran ranging from 0.01mg/kg to 0.3mg/kg, every 4 weeks or every 3 weeks (CS[1] page 70; Suhr *et al*. 2015[14]), administered IV over 60 minutes (3.3mL/min) or 70 minutes (1.1mL/min for 15 minutes, then 3.3mL/min for the remainder of the dose). Only one of the administered dosing regimens (0.3mg/kg every 3 weeks) is consistent with the licensed dose, with the exception that no maximum dose was stated (CS,[1] page 70; Suhr *et al*. 2015[14]). Twelve patients received patisiran 0.3mg/kg, every 3 weeks; each patient received two doses in total. Of these 12 patients, one was concurrently using diflunisal and seven were concurrently using tafamidis. One of the 12 patients receiving patisiran 0.3mg/kg every 3 weeks withdrew from the study due to an adverse event (AE).[14]

All Phase 2 OLE patients received 0.3mg/kg patisiran every 3 weeks, for up to 24 months (CS,[1] page 70; Adams *et al*. 2017;[15] Adams *et al*. 2017[17]), administered as an IV infusion over 70 minutes (CSR,[18] page 29). The time between the last dose of patisiran in the Phase 2 dose escalation study and the first dose in the Phase 2 OLE study ranged from 169 to 512 days, and patients received patisiran for a mean (SD) of 24.7 (0.21), range 19-25 months; all except one patient received 24 months of treatment (CSR,[18] page 73).

Patients in the Global OLE received 0.3mg/kg patisiran every 3 weeks (CS,[1] Appendix 1, Table S6).

Ongoing studies

The Global OLE, which recruited patients from APOLLO and the Phase 2 OLE, is currently ongoing, with an estimated completion date of July 2019 (CS,[1] page 28). The CS[1] and Suhr *et al*. 2018 abstract[22] report data from the 52-week measurement point of the Global OLE, and patients in the Global OLE may receive patisiran for up to 5 years in total (including the time on patisiran in APOLLO or the Phase 2 OLE, see CS,[1] page 28 and Suhr *et al*. 2018[22]). Outcome assessments will be made annually until

study completion.[22] This study is expected to provide data on the long-term safety and efficacy of patisiran (CS,[1] page 28).

Data are also available from the ongoing Expanded Access Protocol (Compassionate Use Programme; NCT02939820),[23] which enables adult hATTR amyloidosis patients who meet the eligibility criteria, and who have not previously participated in an interventional study of RNAi therapeutics for hATTR amyloidosis within the last 12 months, to receive patisiran (CS,[1] page 28). Patisiran is also included in the Early Access to Medicines Scheme (EAMS), through which evidence on its efficacy and safety will be available (CS,[1] pages 28-29). The company does not anticipate any additional evidence to be released from either the Expanded Access Protocol or the EAMS within the next 12 months (CS,[1] page 29).

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that APOLLO, the Phase 2 dose escalation study, the Phase 2 OLE and Global OLE are the only relevant studies in this patient population, and that no relevant studies have been omitted from the CS.

4.2.3 Summary and critique of the company's quality assessment

The company provided a critical appraisal of the validity of the included studies based on two different methodological assessment tools. The APOLLO RCT[11] was assessed using a quality assessment table from the CRD guidance on undertaking reviews in health care[12] (see CS,[1] pages 80-81), which was adapted from the Cochrane Risk of Bias tool.[24] As noted in Section 4.1.4, this is the suggested format in the NICE HST interim company evidence submission template (May 2017). A summary of the risk of bias in the APOLLO RCT undertaken by the company alongside the ERG's independent quality assessment is presented in Table 6.

Table 6: Company and ERG quality assessment of APOLLO RCT (adapted from CS, Table C5)

Study question	Company quality assessment (yes/no/not clear/NA)	ERG quality assessment (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Yes - Conducted using an interactive response system	Yes - Conducted using an interactive response system, and stratified.
Was the concealment of treatment allocation adequate?	Yes - Conducted using an interactive response system	Yes - Conducted using an interactive response system
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes - Demographics and clinical characteristics were generally balanced between the patisiran and placebo treatment arms.	Yes generally – a significant difference between the groups was found for TTR genotype only.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes - Patients and study personnel who monitored patients during infusions and performed clinical assessments were blinded to the study treatment. Unblinded personnel and pharmacists prepared the drug for administration but were not involved in patient management or safety or efficacy assessments. Details of patients who discontinued study drug at 9 months due to rapid disease progression remained blinded throughout the study.	Yes - Patients and care providers, and those who performed clinical assessments were blinded to the study treatment.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes, for overall study - A larger proportion of patients withdrew in the placebo group. Data not specifically presented for cardiomyopathy subgroup. No adjustment was made.	Yes – a large proportion (38%) of the placebo group discontinued, compared to7% in the treatment group. No adjustment was made.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No - Outcomes reported as stated a priori, clearly stated exploratory subgroup analysis performed on cardiac subgroup	No – extensive list of outcomes specified *a priori*.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes - ITT method used and appropriate. Missing data imputed using pre-specified algorithm where appropriate.	Yes - ITT method used and appropriate. Missing data imputed using pre-specified algorithm where appropriate.

NA - not applicable; ITT - intent-to-treat; TTR - transthyretin

A summary of the risk of bias in the Phase 2 dose escalation, study[14] Phase 2 OLE,[15, 17] and Global OLE[16] undertaken by the company alongside the ERG summary is presented in Table 7.

Table 7: Company and ERG quality assessment for the observational studies (adapted from CS, Tables S7-S9)

	Phase 2 dose escalation study (Suhr *et al.* 2015)[14]		**Phase 2 OLE (Adams *et al.* 2017; Adams *et al.* 2017)[15, 17]**		**Global OLE (Partisano *et al.* 2017)[16]**	
	Company quality assessment (yes/no/not clear/NA)	**ERG quality assessment (yes/no/not clear/NA)**	**Company quality assessment (yes/no/not clear/NA)**	**ERG quality assessment yes/no/not clear/NA)**	**Company quality assessment (yes/no/not clear/NA)**	**ERG quality assessment (yes/no/not clear/NA)**
Was the cohort recruited in an acceptable way?	Yes - Phase 2 single intervention dose-escalation study. Patients were recruited according to specific inclusion and exclusion criteria	Yes – Patients were recruited according to inclusion and exclusion criteria.	Yes - Single-arm OLE of the Phase 2 dose escalation study for which patients were recruited according to specific inclusion and exclusion criteria	Yes – recruited from the Phase 2 study, and therefore according inclusion and exclusion criteria.	Yes - Global extension OLE of single-arm OLE of the Phase 2 study for which patients were recruited according to specific inclusion and exclusion criteria	Yes – recruited from the Phase 2 OLE, and therefore according inclusion and exclusion
Was the exposure accurately measured to minimise bias?	Yes - Interventional study where exposure was controlled and monitored. IV administration by study personnel.	Yes – exposure controlled and monitored, dose administered by IV.	Yes - Prospective interventional study	Yes – exposure controlled and monitored, dose administered by IV.	Yes - Prospective interventional study	Yes – exposure controlled and monitored, dose administered by IV.
Was the outcome accurately measured to minimise bias?	Yes - Prospective outcome assessment.	Yes – *a priori* outcomes provided and reported	Yes - Prospective outcome assessment	Yes – *a priori* outcomes provided and reported	Yes - Prospective outcome assessment	Yes – *a priori* outcomes provided and reported
Have the authors identified all important confounding factors?	Yes - Baseline characteristics of patients reported by dose and overall	Yes – baseline characteristics presented and assessed.	Yes - Assessed use of stabilisers at baseline	Yes – baseline characteristics presented and assessed.	Yes - Assessed use of stabilisers at baseline	Yes – baseline characteristics presented and assessed.

	Phase 2 dose escalation study (Suhr *et al.* 2015)[14]		Phase 2 OLE (Adams *et al.* 2017; Adams *et al.* 2017)[15, 17]		Global OLE (Partisano *et al.* 2017)[16]	
	Company quality assessment (yes/no/not clear/NA)	**ERG quality assessment (yes/no/not clear/NA)**	**Company quality assessment (yes/no/not clear/NA)**	**ERG quality assessment yes/no/not clear/NA)**	**Company quality assessment (yes/no/not clear/NA)**	**ERG quality assessment (yes/no/not clear/NA)**
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes - Some control through inclusion/exclusion criteria. Difficult to control in analysis due to small sample size	Unclear – not controlled for in the analysis.	Yes - Subgroup analysis of stabiliser use	Unclear if confounding factors have been controlled for in the analysis.	Unclear - Subgroup analysis by stabiliser use not reported	Unclear if confounding factors have been controlled for in the analysis.
Was the follow-up of patients complete?	Yes - 26/29 patients completed the study and information on patients who did not complete study is documented.	Yes - 26/29 patients completed the study and information on patients who did not complete study is documented.	Yes - Complete follow-up on 26/27 patients over two years; patient that was lost to follow-up at 20 months died of gastroesophageal cancer. Patient final assessments missing for some outcomes.	Yes – follow up reported for most patients; explanations for those lost to follow up.	Unclear - 24/25 patients completed 36 months follow-up, reason for withdrawal of 1 patient not reported	Unclear – withdrawal of one patient at follow up not reported.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes - P values reported to three decimal places	Yes – *p*-values, mean and SD reported	Yes - P values were reported to two decimal places.	Yes – *p*-values, mean and SD reported	NA – *p*-values and CIs not reported	Unclear – not reported

CI - confidence interval; IV – intravenous; NA - not applicable; SD - standard deviation; OLE – open-label extension

APOLLO[11] and the three observational studies[14-16] were assessed by both the company (CS,[1] pages 80-81; CS Appendix 1, pages 17-18) and the ERG. For APOLLO, the company's critical appraisal and the ERG's critical appraisal were similar. The ERG concludes that there is a moderate risk of bias for APOLLO. Both the company and the ERG noted that there were unexpected imbalances in drop-outs between groups, in that a significant number of participants had dropped out of the placebo arm (a large proportion of these withdrew from the study). The withdrawals were not clearly explained, but appear to be due to worsening of symptoms. Missing data were imputed using a pre-specified algorithm where appropriate.[1]

Across the Phase 2,[14] the Phase 2 OLE,[15] and the Global OLE[16] studies, the primary difference in the findings of the critical appraisals performed by the company and the ERG was that the ERG was unclear if confounding factors were controlled for in the analysis. The ERG assessed that it was unclear whether confounding factors were controlled for in the Phase 2, the Phase 2 OLE, and the Global OLE studies, due to lack of information presented. This finding was contrary to the company's conclusion for the Phase 2, and Phase 2 OLE studies, but was aligned with the company's assessment of the Global OLE study.[1] Overall, the ERG assessed the Phase 2 and Phase 2 OLE studies to be at a moderate risk of bias. The ERG concluded that the Global OLE may be at high risk of bias due to a number of the quality assessment domains being unclear; this appears to match the company's assessment. However, as the company did not provide further narrative synthesis of the critical appraisal assessments, or an indication of the overall assessment of risk of bias,[1] this cannot be compared directly to the ERG's assessment.

4.2.4 Summary and critique of results

The outcomes stated in the decision problem addressed by the company (CS,[1] page 23) included: neurological impairment; symptoms of polyneuropathy; cardiac function; autonomic function; weight loss; effects of amyloid deposits in other organs and tissues; serum TTR; motor function; mortality; adverse effects of treatment, and HRQoL. All of these outcomes are reported in the CS[1] (pages 82-109). The CS[1] includes evidence relating to all of the outcomes specified in the final NICE scope,[6] except for effects of amyloid deposits in other organs and tissues (including the eye), and HRQoL for carers. The ERG have considered key outcomes in this section; for full consideration of the outcomes, see CS pages 82-109.

Critique of endpoints

The primary efficacy endpoint was the difference between the patisiran and placebo groups in the change from baseline of mNIS+7 score at 18 months. Other continuous outcomes are also analysed and discussed in terms of change from baseline. Although it is common for clinical trialists to analyse change from baseline, the ERG has a preference in linear models for analysing raw follow-up data

adjusted for baseline responses using analysis of covariance. The purpose of a parallel group study is to compare the treatment groups and not to make within patient comparisons. There are various problems associated with change from baseline, including:

- The baseline value should not be used as an inclusion/exclusion criterion for a study, otherwise regression to the mean may be strong,
- If the variable is used as an inclusion/exclusion criterion for a study then a second post-screening baseline value should be measured and used in subsequent analysis; in the case of APOLLO, the baseline value for mNIS+7/NIS+7 was calculated as the average of the screening/baseline and baseline visits
- The post-treatment value must be linearly related to the pre-treatment value
- The result should not be baseline-dependent.

In addition, clinical trials should be analysed according to the way in which they were randomised, which means adjusting for any stratification factors. It was unclear from the description in the CS how the primary analysis was performed; the ERG requested an analysis of the primary endpoint (change from baseline at 18 months in mNIS+7) adjusted for the stratification factors and baseline mNIS+7 (clarification question A39). However, the APOLLO CSR[7] provided more information and stated that the primary analysis was as requested with the addition of region (North America, Western Europe, and Rest of World) as a factor in the model; analysis of covariance effectively cancels out the change score and gives the required results even if the slope of the post-treatment value on pre-treatment value is not 1.0. Nevertheless, there is considerable discussion within the CS regarding within-group differences in spite of the only meaningful comparison being that between groups.

The company performed several subgroup analyses. The ERG considers that an assessment of differential treatment effects is best done using formal interaction tests to account for patient characteristics that may be correlated with the subgroup. Patients were dichotomised according to whether they were <65 or ≥65 years of age at randomisation. The ERG could find no rationale for this grouping, which assumes that there is a discontinuity in treatment effect for patients aged 65 years; the ERG has a preference for modelling such data as continuous variables and not assuming linearity. In spite of these reservations and the treatment effect being in favour of patisiran in all subgroups, the ERG could not rule out the possibility of heterogeneous treatment effects.

Although the subgroup of patients with cardiac amyloid involvement was a pre-specified subgroup, it was not a stratified subgroup and loses the protection of the randomisation. Indeed, there is an imbalance in the proportion of patients allocated to each treatment and it is not known whether there is an

imbalance in known and unknown prognostic factors. The ERG has a preference for using formal interaction tests to assess whether treatment effects vary according to cardiac amyloid involvement.

Results across included endpoints

mNIS+7

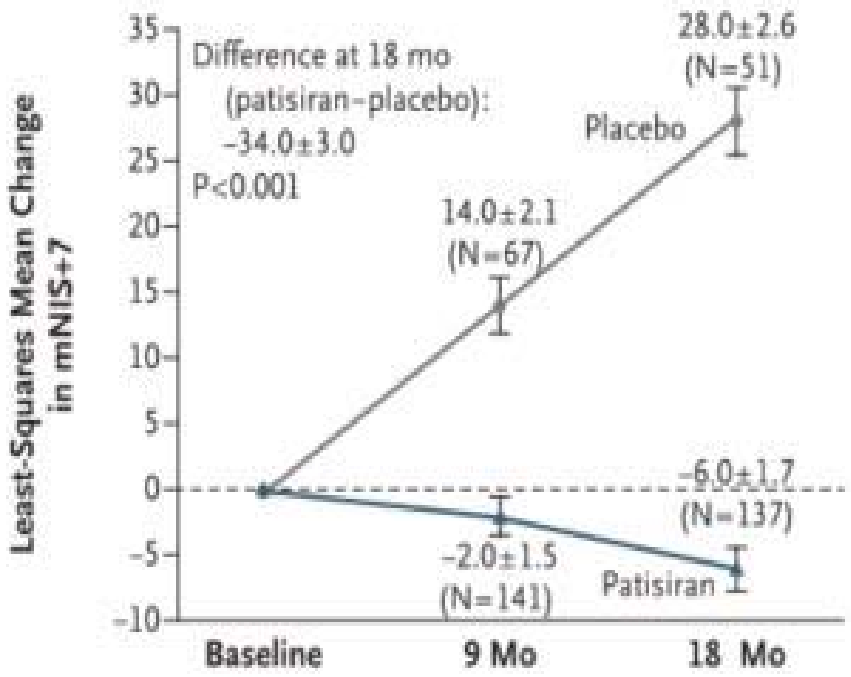
The mNIS+7 is a 304-point composite measure of neurological impairment, which includes: lower limb, upper limb and cranial nerve function; small and large nerve fibre function; touch pressure and heat pain; and autonomic function (postural hypotension).[1] Within their clarification response[2] (question A29), the company reported that a difference of 2 points on the mNIS+7 is considered to indicate a clinically important difference.

APOLLO

The primary outcome of the APOLLO trial was the difference between the patisiran and placebo arms in change from baseline in mNIS+7 score at 18 months, analysed using the mixed model repeat measurement (MMRM) method in the modified intention-to-treat (mITT) population (CS, page 82).[1] On the mNIS+7, a decrease from baseline suggests a reduction in neurological impairment and improvement of neuropathy, and an increase from baseline suggests an increase in neurologic impairment and worsening of neuropathy (CS,[1] page 82). Mean and standard error values are reported in the CS;[1] for brevity, standard errors are not reported in the text, but are available in the tables.

The least squares mean (LSM) change in mNIS+7 from baseline at 18 months was -6.0 in the patisiran group and 28.0 in the placebo group (LSM difference between groups: -34.0 points, $p<0.001$) (see Figure 1).[1] The LSM change in mNIS+7 from baseline at 9 months was -2.0 in the patisiran group and 14.0 the placebo group (LSM difference between groups: -15.98, 95% CI -20.70, -11.27).[1] Similar results were reported in the per protocol population (CSR,[7] page 104).

Figure 1: Mean change from baseline in the mNIS+7 in the patisiran and placebo arm (reproduced from CS, Figure 6)



Additionally, a pre-specified analysis considered the number of patients with an improvement from baseline in nMIS+7 of <0 points at 18 months (CS,[1] page 86). Expressed as a proportion, this was 56% for the patisiran group and 4% in the placebo group (OR: 39.9, 95% CI: 11.0, 144.4, p<0.001) (CS,[1] page 86).

Phase 2 dose escalation study

mNIS+7 was not reported in the Phase 2 dose-escalation study.[14]

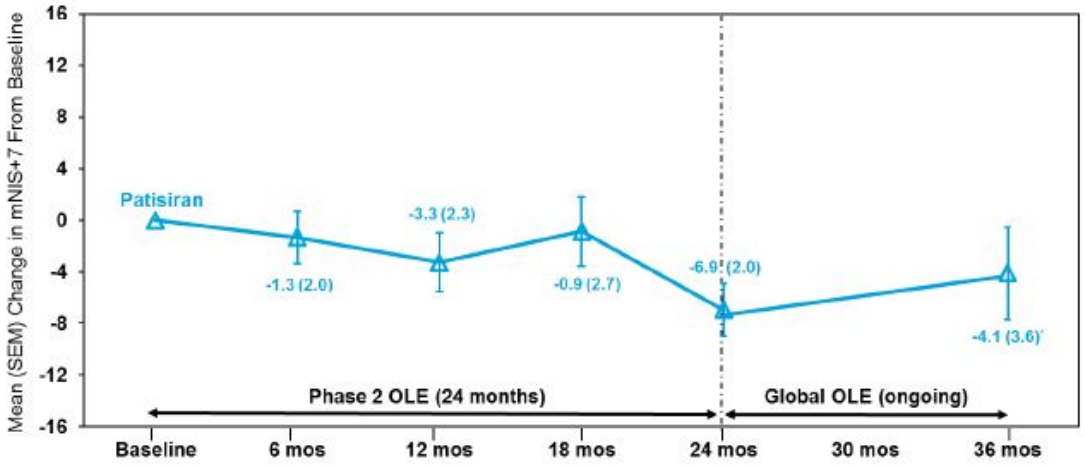
Phase 2 OLE

Mean change from baseline to 24 months in mNIS+7 in the Phase 2 OLE was -7.0 (n=26) (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[15]), and 74% of patients had no change or an improvement in mNIS+7 at 24 months relative to baseline (CS, page 95;[1] Adams *et al*. 2017[15]).

Global OLE

Mean change from baseline at 36 months was -4.1 in the Global OLE study (see Figure 2). CS[1] Appendix 1 (Table S12) and the Berk *et al*. 2018 conference paper[25] note that the mean mNIS+7 score at 36 months was 48.49.

Figure 2: Mean change in mNIS+7 over 36 months (reproduced from CS, Figure 17)



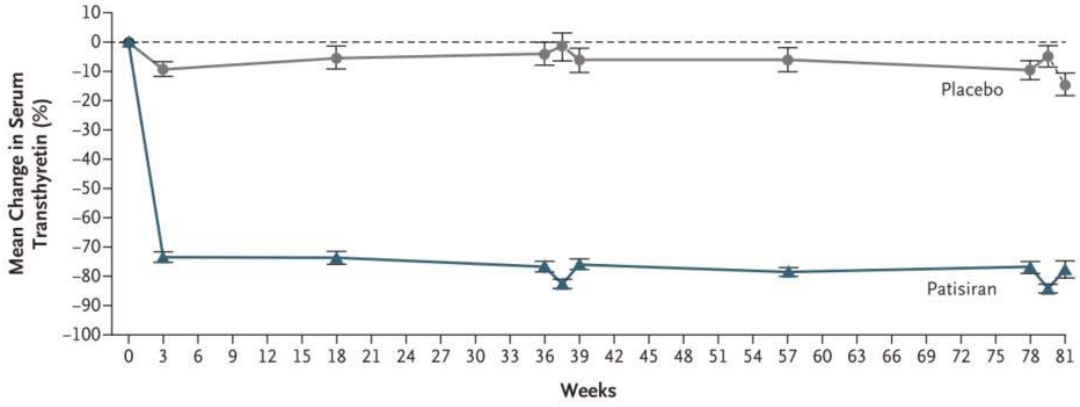
TTR knockdown

During the clarification process, the company reported that a TTR reduction of ≥80% is considered to indicate a clinically important difference, as this level of reduction is predicted to lead to the halting or reversal of neuropathy progression.[2]

APOLLO

The median serum TTR knockdown in the patisiran group over 18 months was 81% (range -38 to 95); this was similar across age, sex and genotype (CS,[1] page 93; Adams *et al*. 2018[11]). The mean maximal serum TTR knockdown from baseline over 18 months for patisiran was 87.8%. In the patisiran group, the mean serum TTR knockdown from baseline was 82.6% and 84.3% at 9 months and 18 months, respectively. In the placebo group, the mean percent reduction was 1.5% and 4.8% at 9 months and 18 months, respectively (see Figure 3; CS,[1] page 93 and Table C6, page 98;[1] CSR;[7] Coelho *et al*. 2018[26]). The mean TTR percent knockdown in the patisiran group was 73.5% from day 22, and this was maintained throughout the study, whereas in the placebo group the mean percent TTR knockdown was 9.3% at day 22, and the overall mean percent TTR knockdown was 5.7% over 18 months (see Figure 3; CS,[1] pages 93-94; CSR;[7] Coelho *et al*. 2018[26]). It is unclear why there was a reduction in TTR in the placebo group, although there is a possibility that this might reflect a regression to the mean. The baseline in APOLLO was defined as the average of the screening and pre-treatment values, although screening values should not normally be part of the baseline.

Figure 3: Mean serum TTR knockdown in patients at baseline, 9 and 18 months (CS, Figure 16)



Note: Bars indicate standard error. The nadirs seen at 9 and 18 months correspond to the pre-dose and post-dose assessments for those time points. Source: Adams et al. 2018[11]

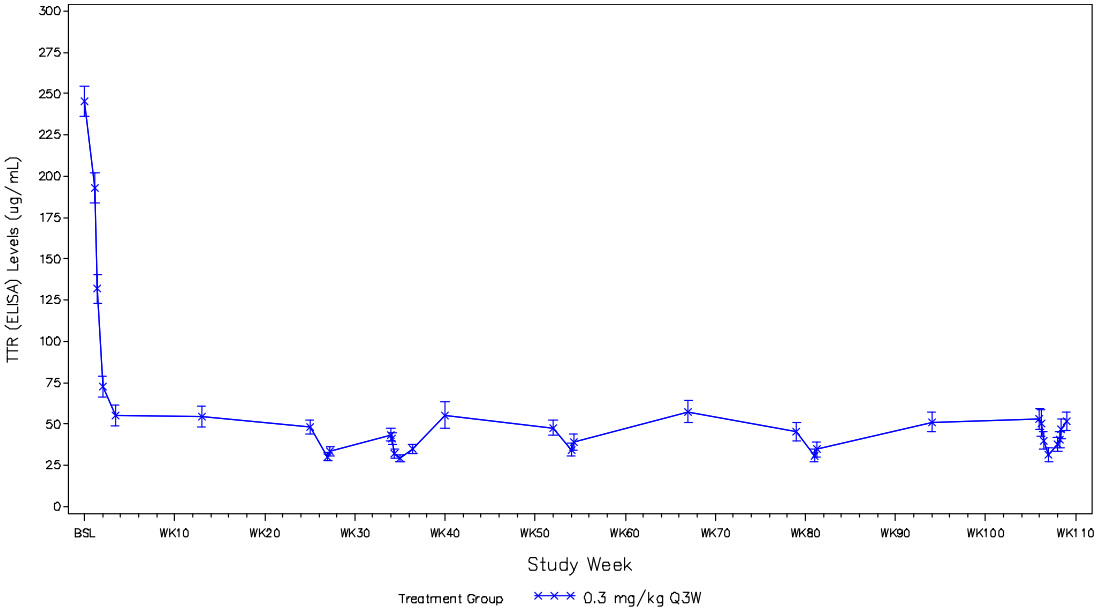
Phase 2 dose escalation study

In patients treated with the 0.3mg/kg Q3W dose of patisiran (n=12), there was a significant mean reduction in serum TTR levels from baseline at nadir after the first and second dose (CS, page 95) of 83.8% and 86.7%, respectively (CS,[1] Appendix 1, Table S10; Suhr *et al*. 2015[14]). The maximum serum TTR knockdown was 94.2% after the first dose, and 96.0% after the second dose (CS,[1] Appendix 1, Table S10; Suhr *et al*. 2015[14]).

Phase 2 OLE

In the Phase 2 OLE, mean serum TTR knockdown at 24 months was 82%, and mean maximal serum TTR knockdown was 93% (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[15]). Following a request for clarification[2] (question A45), the company provided data on absolute mean TTR levels over time and through week 109 (21-day follow-up visit), excluding the week 114 assessment, as it was only performed on two patients (see Figure 4).

Figure 4: Absolute mean (± SE) TTR levels over time in the Phase 2 OLE (reproduced from company's clarification response, Figure 3)



Cardiac outcomes

During the clarification process, the company reported that a change of 30% and 300ng/L in NT-proBNP level is considered to indicate a clinically important difference, as this level of change in response to therapy has been found to predict survival in large, independent studies within the cardiac amyloidosis literature.[2] In addition, the company highlighted that NT-proBNP levels above ~3,000pg/mL have been associated with poor short-term survival in patients with hATTR amyloidosis.[2]

Cardiac outcomes were only reported for the cardiac subpopulations of APOLLO and the Phase 2 OLE in the CS; however, some data on cardiac outcomes in overall and non-cardiac populations in APOLLO have recently been published by Solomon *et al*. 2018.[10] In the mITT population in APOLLO (consisting of all patients randomised, who received at least one dose of study drug), the effects of patisiran relative to placebo on echocardiographic outcomes were similar to those in the cardiac subpopulation.[10] Difference in LSM change from baseline at 18 months between the patisiran and placebo groups in the mITT population was -0.066 for LV wall thickness (mm) (p=0.0239), -0.05 for LV relative wall thickness (p=0.0168), -0.59 for global longitudinal strain (%) (p=0.1496), 0.37 for cardiac output (L/min) (p=0.0097), 5.30 for LV end-diastolic volume (mL) (p=0.0670) and -11.00 for LV mass (g) (p=0.1337).[10] In the mITT population of APOLLO, NT-proBNP levels were also reduced significantly from baseline to 18 months in the patisiran group relative to placebo (ratio fold change 0.47, 95% CI 0.39, 0.56).[10]

Solomon *et al*. 2018[10] also report that among the non-cardiac subpopulation (all patients other than the cardiac subpopulation), NT-proBNP was reduced in the patisiran group relative to placebo from

baseline to 18 months by 51% (ratio of fold-change 0.49, 95% CI 0.38, 0.63), which was similar to the cardiac subpopulation.[10] There was also an increase of 0.283m/s (95% CI 0.156, 0.409) in 10-metre walk test (10MWT) gait speed from baseline at 18 months in the patisiran group relative to the placebo group among the non-cardiac subpopulation.[10]

HRQoL

As part of their clarification response[2] (question A29), the company reported that a minimal clinically important difference (MCID) for the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) has not been reported in the literature, however there is evidence that this measure can clearly distinguish between FAP stages.[2]

APOLLO

The change from baseline to 18 months in Norfolk QoL-DN total score was the key secondary endpoint in APOLLO (CS,[1] page 87). A decrease in score represents improvement, and an increase suggests worsening, with scores ranging from -4 to 136 (CS,[1] page 87). The LSM change from baseline to 18 months in Norfolk QoL-DN was -6.7 in the patisiran group and 14.4 in the placebo group (LSM difference between groups: -21.1, 95% CI -27.2 to -15.0, $p<0.001$).[1] In a *post hoc* binary analysis, improvement on the Norfolk QoL-DN score at 18 months was demonstrated in 51% (95% CI: 43% to 59%) of patients in the patisiran group and 10% (95% CI: 4% to 17%) of patients in the placebo group (OR 10.0, 95% CI: 4.4, 22.5, $p<0.001$; CS,[1] page 90).

The CS[1] reports overall improvement in quality of life as assessed by the EuroQol-5 Dimensions (EQ-5D) 5-Level (5L) questionnaire (mapped to the 3-Level (3L) using van Hout *et al.* 2012[27]) in the patisiran group relative to the placebo group at 9 and 18 months (LSM difference between groups: 0.09 points, 95% CI: 0.05, 0.14, and 0.20 points, 95% CI: 0.15, 0.25, respectively, $p=1.40\text{x}10^{-12}$; CS,[1] page 95). The CSR[7] reports a LSM change from baseline to 18 months of 0.01 in the patisiran group and -0.20 in the placebo group (page 138). Similarly, the CS reports overall improvement in the EuroQoL visual analogue scale (EQ-VAS) in the patisiran group compared with the placebo group at 9 and 18 months (LSM difference between groups: 5.4 points, 95% CI: 0.5, 10.3, and 9.5 points, 95% CI: 4.3, 14.8, respectively, $p=0.0004$; CS,[1] page 95).

Phase 2 dose escalation study

HRQoL was not reported in the Phase 2 study.[14]

Phase 2 OLE

Mean change in EQ-5D score from baseline to 24 months score was -0.01 in the Phase 2 OLE (CS,[1] Appendix 1, Table S11). Mean EQ-5D score at 24 months was 0.76 (CSR,[7] page 94).

Global OLE

HRQoL was not reported in the Global OLE.[16, 25]

Secondary and exploratory outcomes

Table 8 reports on additional secondary and exploratory outcomes examined by the four studies and reported in the CS.[1] During the clarification process, the company reported the MCIDs for key outcome measures in APOLLO.[2] As part of this clarification response, the company stated that any change in PND score is clinically meaningful, increases of 0.05m/s and 0.10m/s represent a small meaningful change in gait speed and a substantial clinically meaningful change, respectively, on the 10MWT, and a change in grip strength of 4.7-6.2kg is considered clinically meaningful, with no MCID reported in the literature for Composite Autonomic Symptom Score-31 (COMPASS-31) or Rasch-built Overall Disability Scale (R-ODS).[2]

Table 8: Additional secondary and exploratory outcomes

Outcome	Measure	APOLLO (18 months)		Phase 2 dose escalation study	Phase 2 OLE (24 months)	Global OLE (36 months)
		Patisiran	Placebo			
Motor strength	**NIS-W (0-192)[a]**	LSM (SE) change from BL: 0.1 (1.3) points; LSM difference between groups (SE): -17.9 (2.3) points (p<0.001)	LSM (SE) change from BL: 17.9 (2.0) points	NR	Mean (SEM) change from BL: 1.2 (1.4) points	NR
Disability	**R-ODS score (range 0-48)[b]**	LSM (SE) change from BL: 0.0 (0.6) points; LSM difference between groups (SE): 9.0 (1.0) points (p<0.001)	LSM (SE) change from BL: -8.9 (0.9) points	NR	Mean (SEM) change from BL: -1.8 (0.8) points	NR
Gait speed	**10MWT (m/s)[b]**	LSM (SE) change from BL: 0.08 (0.02) m/s; LSM difference between groups (SE): 0.31 (0.04) m/s (p<0.001)	LSM (SE) change from BL: -0.24 (0.04) m/s	NR	Mean (SEM) change from BL: 0.3 (0.4) m/s	NR
Nutritional status	**mBMI (kg/m^2 x albumin g/L)[b]**	LSM (SE) change from BL: -3.7 (9.6) kg/m^2 x albumin g/L; LSM difference between groups (SE): 115.7 (16.9) kg/m^2 x albumin g/L	LSM (SE) change from BL: -119.4 (14.5) kg/m^2 x albumin g/L	NR	Mean (SEM) change from BL: -60.8 (34.9) kg/m^2 x albumin g/L	NR
Autonomic neuropathy symptoms	**COMPASS-31 (0-100)[a]**	LSM (SE) change from BL: -5.3 (1.3) points; LSM difference between groups (SE): -7.5 (2.2) points	LSM (SE) change from BL: 2.2 (1.9) points	NR	Mean (SEM) change from BL: 1.3 (1.8) points	NR

Outcome	Measure	APOLLO (18 months)		Phase 2 dose escalation study	Phase 2 OLE (24 months)	Global OLE (36 months)
		Patisiran	Placebo			
Neuropathy	**NIS+7**	[redacted]		NR	NR	NR
Stage	**PND score (stable or improved)**	[redacted]	[redacted]	NR	NR	NR
	PND score (improved)	[redacted]	[redacted]	NR	NR	NR
	PND score (stable)	[redacted]	[redacted]	NR	NR	NR
	PND score (worsened)	[redacted]	[redacted]	NR	NR	NR
	FAP stage (stable or improved)	[redacted]	[redacted]	NR	NR	NR
Large fibre function	**NCS ∑5 + VDT + QST-BSA$_{TP}$**	[redacted]		NR	NR	NR
Small fibre function	**QST-BSA$_{HP}$ + HRdB + postural BP**	[redacted]		NR	NR	NR
Grip strength	**Kg**	[redacted]		NR	Mean (SEM) change from BL: 1.5 (1.2) kg	NR
Blood pressure	**Postural BP (0-2 points)**	NR	NR	NR	Mean (SEM) change from BL: -0.1 (0.1) points	NR

10MWT - 10-metre walk test; BL - baseline; BP - blood pressure; CI - confidence interval; COMPASS-31 - Composite autonomic symptom score-31; FAP - familial amyloidotic polyneuropathy; HRdB - heart rate variability with deep breathing; LSM - least squares mean; mBMI - modified body mass index; NIS+7 - modified neuropathy impairment score +7; NCS – nerve conduction studies; NIS-W - Neuropathy Impairment Score - Weakness; NR - not reported; OLE – open-label extension; PND - polyneuropathy disability; QST-BSA HP - quantitative sensory testing heat pain by body surface area; QST-BSA TP - quantitative sensory testing touch pressure by body surface area; R-ODS - Rasch-built Overall Disbility Scale; SE - standard error; SEM - standard error of the mean; VDT - vibration detection threshold..

[a] *A decrease from baseline on this measure represents an improvement*

[b] *An increase from baseline on this measure represents an improvement*

[c] *Percentage calculated by the ERG*

Some outcomes from APOLLO were reported in the summary of methods in the CS (Section 9.4.1, page 69), for which no results were reported. Results for these outcomes were provided in the company's response to clarification question A31;[2] these results are reproduced in Table 9.

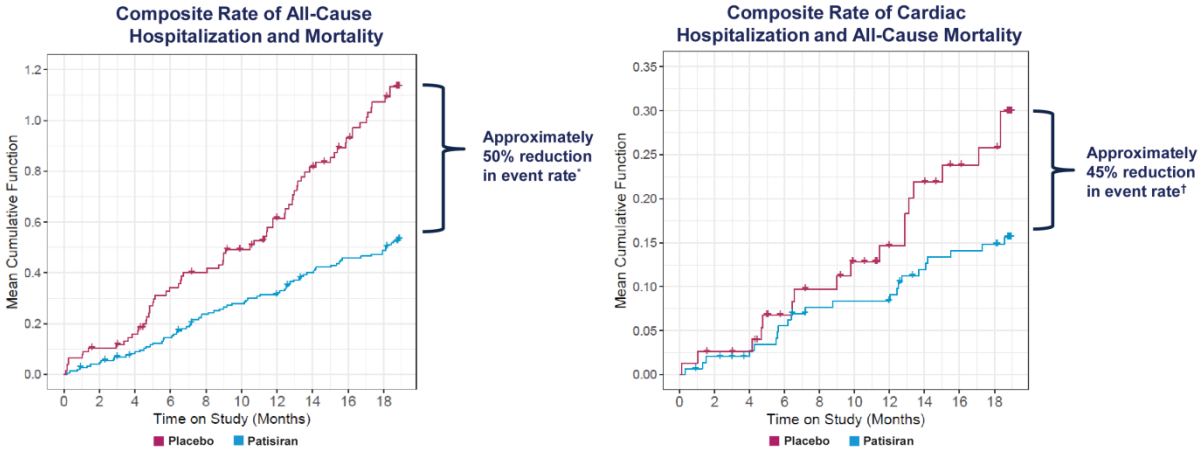
Table 9: Exploratory endpoint results in APOLLO (reproduced from company's clarification response, question A31)

Outcome	Placebo	Patisiran
Quantitative sensory testing (80 points max. possible score)		
LS mean (95% CI) change from baseline	7.0 (4.1, 9.9)	-6.0 (-8.0, -4.1)
LS mean (95% CI) difference (patisiran - placebo)	-	-13.05 (-16.3, -9.8)
Rapid disease progression at 9 months, n patients	6	1
Dermal amyloid burden, %		
Distal thigh		
LS mean (95% CI) change from baseline	0.996% (-2.640, 4.633)	0.044% (-2.358, 2.446)
LS mean (95% CI) difference (patisiran - placebo)		-0.953% (-5.104, 3.198)
Distal leg		
LS mean (95% CI) change from baseline	2.152% (-2.451, 6.755)	0.011% (-3.029, 3.051)
LS mean (95% CI) difference (patisiran - placebo)		-2.141% (-7.492, 3.211)
Magnetic resonance neurography	Performed only on 2 patients in placebo group and 10 patients in the patisiran group who volunteered for serial scans; given the small number of patients, no conclusions can be drawn	
TTR		
Mean±SE percent reduction from baseline	4.8±3.38	84.3±1.48
	See additional TTR results reported in CS pages 93–94, including Figure 16	
Retinol binding protein		
Mean±SE percent reduction from baseline	0.48%±1.637	45.31%±1.854
Vitamin A		
Mean±SE percent reduction from baseline	0.1%±1.79	62.4%±1.19

Note: unless specified otherwise, results are at 18 months.
CI - confidence interval; LS - least square; SE - standard error; TTR - transthyretin
Source: Alnylam, data on file (APOLLO CSR)[7]

The company's clarification response,[2] (question A34) also provided data on hospitalisation and mortality for patisiran versus placebo in APOLLO at 18 months. The company reported an approximately 50% reduction in the event rate of all-cause hospitalisation and mortality for patisiran compared with placebo after 18 months (see Figure 5). These data are not used in the company's health economic model (see Chapter 5).

Figure 5: Composite rate of hospitalisation and mortality in APOLLO (reproduced from company's clarification response, question A34)



Safety and tolerability

This section provides the main safety evidence for the use of patisiran in people with hATTR amyloidosis. The CS reports safety data from APOLLO, the Phase 2 dose escalation study, the Phase 2 OLE and the Global OLE. The safety population in APOLLO consisted of patients who received at least one dose of the study drug (n=225; see CS,[1] page 100). Data on adverse events (AEs) are summarised in Table 10. Treatment-related AEs were those considered by the investigator to be possibly or definitely related to patisiran (APOLLO CSR, page 203;[7] Phase 2 OLE CSR, page 132[18]).

Table 10: Adverse event summary from the APOLLO trial, safety population (n=225) (adapted from CS Tables C7 and Table C9, and CS Appendix 1 Tables S13, S14 and S15)

AE	APOLLO		Phase 2 OLE (n=25) n (%)[e]	Global OLE[22] n (%)
	Patisiran (n=148) n (%)	Placebo (n=77) n (%)		
Any adverse event	143 (96.6)	75 (97.4)	25 (100.0)	189 (89.6)
Severe adverse event	42 (28.4)	28 (36.4)	3 (12.0)	38 (18.0)
Serious adverse events	54 (36.5)	31 (40.3)	6 (24.0)	55 (26.1)
[redacted]	[redacted]	[redacted]	7 (28.0)	59 (28.0)
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	0	2 (0.9)
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
Serious treatment-related AEs	0	2 (4.1)	0	2 (0.9)

AE	APOLLO		Phase 2 OLE (n=25) n (%)[e]	Global OLE[22] n (%)
	Patisiran (n=148) n (%)	Placebo (n=77) n (%)		
Discontinuation due to AE	7 (4.7)	11 (14.3)	NR	NR
Withdrawals due to AE	7 (4.7)	9 (11.7)	0	16 (7.6)
Withdrawals due to treatment-related AE	0	1 (2.0)	0	1 (0.5)
Death	7 (4.7)	6 (7.8)	0	11 (5.2)
Death due to a treatment-related adverse event	0	0	NR	NR
AEs occurring in ≥10% patients in either group[11]				
Diarrhoea	55 (37)	29 (38)	6 (22.2)	NR
Oedema, peripheral	44 (30)	17 (22)	3 (11.1)	NR
Fall	25 (17)	22 (29)	NR	NR
Nausea	22 (15)	16 (21)	5 (18.5)	NR
Infusion-related reaction	28 (19)	7 (9)	6 (22.2)	NR
Constipation	22 (15)	13 (17)	NR	NR
Urinary tract infection	19 (13)	14 (18)	6 (22.2)	NR
Dizziness	19 (13)	11 (14)	NR	NR
Fatigue	18 (12)	8 (10)	NR	NR
Headache	16 (11)	9 (12)	NR	NR
Cough	15 (10)	9 (12)	NR	NR
Vomiting	15 (10)	8 (10)	6 (22.2)	NR
Asthenia	14 (9)	9 (12)	NR	NR
Insomnia	15 (10)	7 (9)	4 (14.8)	NR
Nasopharyngitis	15 (10)	6 (8)	6 (22.2)	NR
Pain in extremity	10 (7)	8 (10)	NR	NR
Muscular weakness	5 (3)	11 (14)	NR	NR
Anaemia	3 (2)	8 (10)	3 (11.1)	NR
Syncope	3 (2)	8 (10)	NR	NR
Pyrexia	NR	NR	4 (14.8)	NR
Flushing	NR	NR	7 (25.9)	NR
Wound	NR	NR	6 (22.2)	NR
Musculoskeletal pain	NR	NR	3 (11.1)	NR
Osteoporosis	NR	NR	3 (11.1)	NR
Neuralgia	NR	NR	4 (14.8)	NR
Cataract	NR	NR	3 (11.1)	NR
Macular degeneration	NR	NR	3 (11.1)	NR
Bronchitis	NR	NR	3 (11.1)	NR
Infusion site extravasation	NR	NR	3 (11.1)	NR
Serious AEs ≥2% in any treatment group				
At least one SAE	54 (36.5)	31 (40.3)	NR	NR
[redacted]			NR	NR
[redacted]			NR	NR
[redacted]			NR	NR
[redacted]			NR	NR
[redacted]			NR	NR
[redacted]			NR	NR
[redacted]			NR	NR
Cardiac				
Cardiac failure	3 (2.0)	2 (2.6)	NR	NR
Cardiac failure congestive	3 (2.0)	2 (2.6)	NR	NR

AE	APOLLO		Phase 2 OLE (n=25) n (%)[e]	Global OLE[22] n (%)
	Patisiran (n=148) n (%)	Placebo (n=77) n (%)		
Orthostatic hypertension	3 (2.0)	1 (1.3)	NR	NR
Atrioventricular block complete	3 (2.0)	0	NR	NR
Gastrointestinal				
Diarrhoea	8 (5.4)	1 (1.3)	NR	NR
Dehydration	1 (0.7)	3 (3.9)	NR	NR
Vomiting	1 (0.7)	3 (3.9)	NR	NR
Constipation	0	2 (2.6)	NR	NR
Metabolic				
Hyponatremia	0	2 (2.6)	NR	NR
Hereditary neuropathic amyloidosis	0	2 (2.6)	NR	NR
Respiratory				
Pneumonia	3 (2.0)	3 (3.9)	NR	NR
Pneumonia aspiration	0	2 (2.6)	NR	NR
Renal/genitourinary				
Acute kidney injury	1 (0.7)	4 (5.2)	NR	NR
Urinary tract infection	0	4 (5.2)	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	NR	NR	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
[redacted]	[redacted]	[redacted]	NR	NR
Cardiac AEs[c]				
Cardiac disorders AEs	42 (28)	28 (36)	NR	NR
Cardiac disorders SAEs	20 (14)	10 (13)	NR	NR
Cardiac arrhythmias	28 (19)	22 (29)	NR	NR
Torsades de Pointes SMQ	8 (5.4)	14 (18.2)	NR	NR
Cardiac failure SMQ (narrow)[d]	14 (9)	8 (10)	NR	NR
Cardiac mortality	7 (5)	6 (8)	NR	NR

AE - adverse event; IRR - infusion related reaction; NR - not reported; OLE - open-label extension; SMQ - standardised MedDRA query Drug Related Hepatic Disorders.

[a] Calculated by the ERG; [b] Considered unlikely or not related to study drug; [c] In the mITT population in APOLLO; [d] Events included in Cardiac Failure SMQ: congestive cardiac failure, acute and chronic cardiac failure, pulmonary oedema, cardiogenic shock, right ventricular failure (CS, page 103);[1] [e] These figures are from the CS, and differ from those presented in the CSR, which used the safety population (n=27)[18]

Adverse events and treatment-related adverse events

The majority of patients in the patisiran arm (97%) and the placebo arm (97%) of APOLLO experienced at least one AE (see Table 10; CS,[1] page 100). [redacted] Adams *et al.* 2018[11] report a higher incidence of oedema (30% and 22%, respectively) and infusion-related reactions (19% and 9%, respectively) in the patisiran arm

compared with the placebo arm. Clinician advice to the ERG suggests that oedema could be a side effect of the steroids required for patisiran administration, and/or a manifestation of cardiac failure due to the disease.

[redacted]

The ERG requested clarification on why there is a high number of treatment-related AEs in the placebo group of APOLLO (see clarification response,[2] question A37). In their response, the company suggested that this may be due to blinding of the investigators to the study drug (patisiran or placebo), and the possibility that patients may have been manifesting disease symptoms that were recorded as AEs.[2]

In the Phase 2 dose escalation study, treatment-emergent AEs (not defined in the CS[1] or the Suhr *et al*. 2015 publication[14]) experienced by patients on the patisiran IV 0.3mg/kg every 3 weeks dose (n=12) were: leucocytosis, neutrophilia, asthenia, pyrexia, facial erythema, nausea/vomiting, dry mouth and dysphagia (1 patient [8.3%] each event) (CS, Appendix 1, Table S13 and Suhr *et al*[14]).

In the Phase 2 OLE, all 25 patients experienced at least one AE, seven (28%) experienced an AE related to the study drug, and three (12%) experienced at least one severe AE, none of which were related to patisiran (CS,[1] Table C9, page 108). AEs reported in >10% of patients were: anaemia (11.1% patients); peripheral oedema (11.1% patients); insomnia (14.8% patients); pyrexia (14.8% patients); flushing (25.9% patients); wound (22.2% patients); diarrhoea (22.2% patients); vomiting (22.2% patients); nausea (18.5% patients); musculoskeletal pain (11.1% patients); osteoporosis (11.1% patients); neuralgia (14.8% patients); cataract (11.1% patients); macular degeneration (11.1% patients); urinary tract infection (22.2% patients); nasopharyngitis (22.2% patients); bronchitis (11.1% patients); infusion related reaction (22.2% patients), and infusion site extravasation (11.1% patients) (CS[1] Appendix 1, Table S14; Adams *et al.* 2017 [15]). Seven patients (25.9%) reported experiencing 10 serious adverse events (SAEs), none of which were thought to be related to patisiran (CS,[1] Appendix 1, Table S14).

In the Global OLE, 189 (89.6%) patients experienced AEs. Fifty-nine (28%) patients experienced AEs related to the study drug by, 38 (18%) experienced severe AEs, and two (0.9%) experienced severe AEs considered related to patisiran (CS[1] Table C9, page 108; Suhr *et al.* 2018[23]).

Serious adverse events and AEs leading to discontinuation

SAEs were reported in the APOLLO CSR[7] as being AEs that resulted in death, immediate risk of death, hospitalisation or disability/incapacity, was a congenital abnormality or birth defect, or an important medical event requiring intervention to prevent death, disability or hospitalisation. The proportion of patients in APOLLO experiencing an SAE was similar in the patisiran (36%) and placebo (40%) groups, [redacted] CS,[1] page 100). The proportion of patients with an adverse event that led to discontinuation of the study treatment was lower in the patisiran group (5%) than in the placebo group (14%), as was the proportion of patients with severe adverse events (28% and 36% in the patisiran and placebo groups, respectively; CS, page 100).[1]

In terms of SAEs with a frequency of ≥2% in any treatment group in APOLLO, [redacted] Diarrhoea was the only SAE that was reported in ≥2% more patients in the patisiran group (5.4%) than the placebo group (1.3%) (CS,[1] page 101).

The CS (Table C9,[1] page 108) states that in the Phase 2 OLE study, six patients (24.0%) experienced at least one SAE; however, the Adams *et al*. 2017 conference publication[17] states that 10 SAEs were reported by seven patients (26%). No patients were reported to experience adverse events leading to withdrawal (CS,[1] Table C9, page 108).

In the Global OLE, SAEs were reported in 26.1% patients, SAEs considered to be related to patisiran were reported in two (0.9%) patients, AEs leading to study withdrawal in 7.6% patients and study drug related AEs leading to withdrawal from the study in one patient (0.5%) (CS,[1] Table C9, page 108).

Death

Thirteen deaths were reported in APOLLO: 7 (5%) deaths occurred in the patisiran group and 6 (8%) occurred in the placebo group (CS,[1] page 100). The CS states that no deaths were considered to be related to patisiran (page 100).[1] According to the CS[1] (Table C9, page 108), there were no deaths reported in the Phase 2 OLE; however, the Adams *et al*. 2017 conference publication[17] reports one death due to myocardial infarction after the patient had completed 24 months of treatment. Eleven deaths (5.2% patients) were reported in the Global OLE (CS[1] Table C9, page 108; Suhr *et al.* 2018[23]).

Infusion-related reactions

[redacted]

Forty-six IRRs were reported in six patients (22.2%) in the Phase 2 OLE; all were mild, considered to be possibly or definitely related to the study drug and all were resolved (CSR,[7] page 136).

Hepatic disorders

[redacted]

Cardiac events

Cardiac safety in APOLLO was considered using the mITT population, and the frequency of events was generally similar in the patisiran and placebo groups (CS,[1] page 102). With respect to individual events, these were either similar in the patisiran and placebo groups, or were more frequent in the placebo group (see Table 10): cardiac disorders AEs (28% and 36% in the patisiran and placebo groups, respectively); cardiac disorders SAEs (14% and 13%, respectively); cardiac arrhythmias (19% and 29%, respectively); Torsades de Pointes SMQ (suspected, not confirmed; 5.4% and 18.2%, respectively); cardiac failure SMQ (including congestive cardiac failure, acute and chronic cardiac failure, pulmonary

oedema, cardiogenic shock, right ventricular failure; 9% and 10%, respectively), and deaths (5% and 8%) (CS,[1] page 102).

Subgroups

A pre-specified subgroup analysis of patients with cardiac involvement was conducted in the APOLLO trial and Phase 2 OLE (CS,[1] page 78). This represented 56% of patients in the APOLLO trial (126 patients):[10] 60.8% and 46.8% of patients in the patisiran and placebo arms, respectively (CS, page 92). As patients in the UK predominantly carry mutations associated with a mixed phenotype (consisting of both polyneuropathy and cardiomyopathy symptoms), the CS (page 78) states that the cardiac subpopulation is reflective of the UK population. Clinical advice received by the ERG concurred with this view. The APOLLO cardiac subpopulation consisted of patients with LV wall thickness of ≥1.3cm, excluding those with other medical conditions (e.g. hypertension) that may contribute to LV wall thickening (of which there were 55 in APOLLO) (CS,[1] page 78). The Phase 2 OLE cardiac subpopulation consisted of those with LV wall thickness of ≥1.3cm, with no history of hypertension or aortic valve disease (CS,[1] page 79). Among the APOLLO cardiac subpopulation, the mean age was 61 years (inter-quartile range (IQR) 54-67), and most were male (78%), white (62%) and carrying a non-Val30Met genotype, with a median time from diagnosis of 1.4 years (IQR 0.0-21.0).[10] The Solomon *et al*. 2018 paper[10] reports that there were no demographic differences between the groups apart from that a higher proportion of patients in the placebo arm were Asian compared with the patisiran arm (50.0% vs. 25.6%). The ERG also notes that there was a slightly greater proportion of males in the placebo arm (83.3% vs. 75.6%), white patients in the patisiran arm (70.0% vs. 44.4%), patients with the Val30Met genotype in the placebo arm (33.3% vs. 24.4%) patients in FAP stage 1 in the patisiran arm (46.7% vs. 36.1%), patients in FAP stage 2 in the placebo arm (63.9% vs. 53.3%), and proportion who have a cardiac implant device (mainly pacemaker) in the placebo arm (25.0% vs. 14.4%), according to data presented in Solomon *et al.* 2018.[10] In the Phase 2 OLE cardiac subgroup, the mean age was 64 years (range 29 to 77), and most were male (73%), most had FAP stage 1 (82%), a PND score of II (46%) and most were carrying a Val30Met genotype (73%).[17]

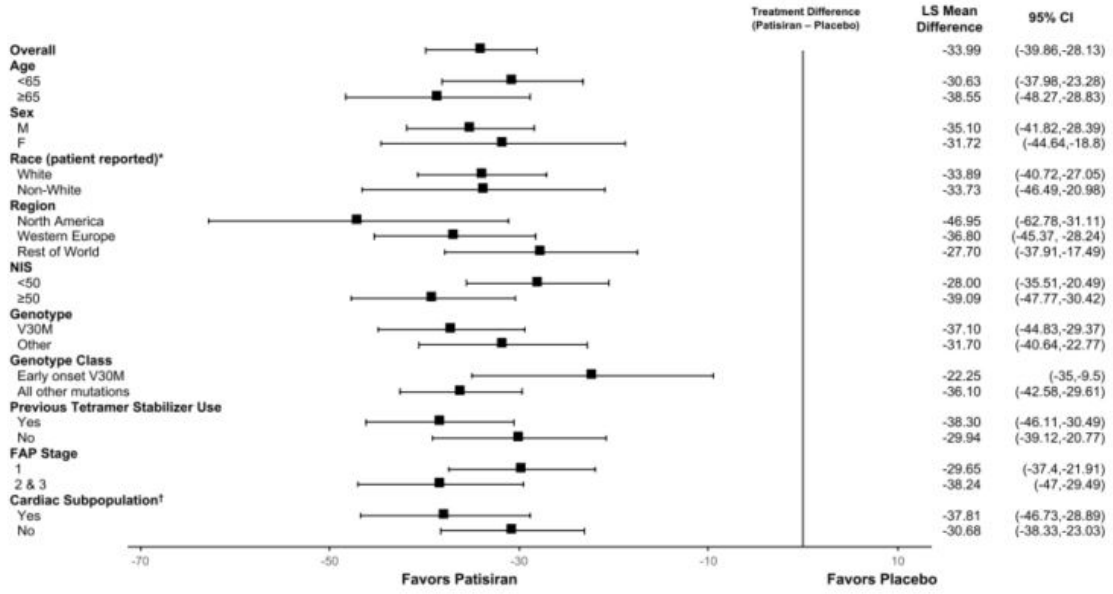
In APOLLO, compared with the population of patients outside the cardiac subtype, a higher proportion of patients in the cardiac subpopulation were NYHA Class II (60.3% vs. 38.1%), had a non-Val30Met genotype (73.0% vs. 37.4%), and had greater signs of cardiac dysfunction at baseline.[10] Genotypes that were more prevalent in the cardiac subpopulation than the other patients in APOLLO included Ala97Ser (15.9%), Thr60Ala (9.5%) and Ser50Arg (7.9%).[10]

mNIS+7

The improvement in the patisiran group relative to the placebo group in APOLLO (reported on page 46 of this report) was apparent regardless of subgroups based on age, race, underlying mutation

(Val30MET and other), previous stabiliser use, FAP stage at baseline and cardiac subpopulation (see Figure 6), as well as for all components of the mNIS+7 (CS,[1] page 83), although the actual effect may differ quantitatively in some subgroups, including region, NIS, genotype and cardiac subgroup.

Figure 6: Change from baseline to 18 months on the mNIS+7 in patient subgroups (reproduced from CS, Figure 7)



In the cardiac subgroup of the Phase 2 OLE (n=11), mean change in mNIS+7 score from baseline to 24 months was -10.0 (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[17]). This appears numerically superior to the improvement observed in the Phase 2 OLE population overall (mean -7.0); however, this is not commented upon in the CS.

TTR knockdown

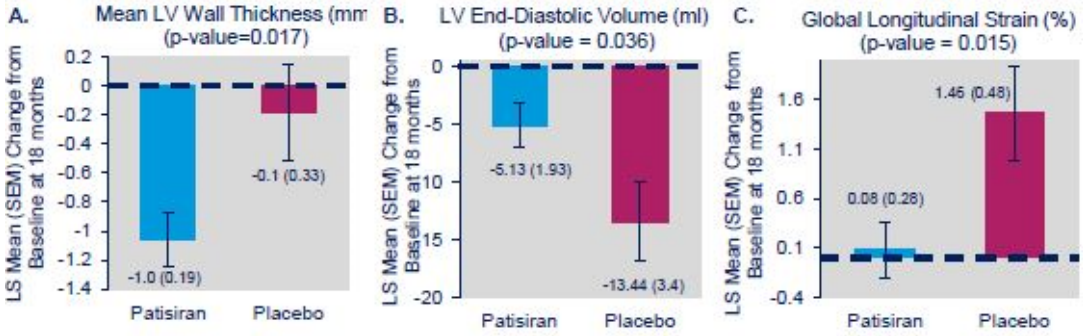
TTR knockdown was not reported in the cardiac subpopulation for either APOLLO or the Phase 2 OLE.

Cardiac outcomes

In the cardiac subpopulation of APOLLO, at 18 months, those in the patisiran group had significantly greater improvement compared with the placebo group in LV wall thickness (LSM difference from baseline between groups -0.9mm, *p*=0.02), LV end-diastolic volume (LSM difference from baseline between groups not reported) and global longitudinal strain (LSM difference from baseline between groups -1.37%, *p*=0.02) (Figure 7; CS,[1] page 92; Adams *et al*. 2018[11]). The between-group difference in mean change from baseline at 18 months in the APOLLO trial is reported as -15.75 g (*p*=0.15) and 0.43% (*p*=0.78) for LV mass and LV ejection fraction.[1] In addition, the Solomon *et al*. 2018 paper[10] reports reductions in interventricular septum wall thickness (relative treatment effect not reported), posterior wall thickness (relative treatment effect not reported), relative wall thickness (-0.05, *p*=0.0168), and increases in cardiac output (0.38 L/min, *p*=0.044) and LV end-diastolic volume (8.31, *p*=0.036) for patisiran versus placebo. There was a trend towards a reduction relative to placebo for LV mass (mean change -15.1g, 95% CI -25.8g, -4.4g) and no differences in LV ejection fraction (LSM change 0.43, *p*=0.7852) or left atrial volume (LSM change -0.95, *p*=0.7306) between the treatment

groups.[10] At 24 months in the Phase 2 OLE, the mean change from baseline is reported as being -0.08, 0.63 and 0.85 for LV wall thickness (mm), ejection fraction and average peak longitudinal strain, respectively (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[17]).

Figure 7: Echocardiographic parameters following 18 months of treatment with patisiran (reproduced from CS, Figure 15)



LS - least square; LV - left ventricular; SEM - standard error of the mean
Source: Solomon et al. 2018[28]

In APOLLO, NT-proBNP levels decreased in the patisiran group, but increased in the placebo group from baseline to 18 months. The CS[1] (page 93) reports an adjusted geometric mean ratio for NT-proBNP levels at 18 months relative to baseline of 0.89 in the patisiran group and 1.97 in the placebo group (ratio 0.45, 95% CI 0.50-0.80, p<0.001).[1, 10] The CS states that this represents a 55% (significant) difference in favour of patisiran, and this is also stated in the recent paper by Solomon *et al*. 2018.[10] The between-group difference in mean change from baseline to 18 months for NT-proBNP is reported as -370.2 (p=0.7.74x10^{-8}).[1] There was a decrease from baseline of NT-proBNP ≥30% and ≥300pg/mL at month 18 among 31.6% of patients in the patisiran group and 0% of patients in the placebo group; conversely, there was an increase from baseline of NT-proBNP ≥30% and ≥300pg/mL at month 18 among 21.1% of patients in the patisiran group and 58.3% of patients in the placebo group.[10] The mean (SEM) change from baseline to 24 months in NT-proBNP levels in the Phase 2 OLE was -49.6 (170.83) (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[17]). Clinical advice received by the ERG suggests that NT-proBNP results are more important outcomes than structural changes seen on cardiac imaging, as the latter will be much slower to evolve.

The CS[1] (page 93) reports a lack of precision in troponin I values (90.2% of values were reported as <0.1µg/L, which were all imputed to 0.1µg/L for the analysis), which precluded an accurate assessment of the effect of patisiran on troponin I. The between-group difference in mean change from baseline at 18 months for troponin I in APOLLO is reported as 0.004 (p=0.87) in Table C6 of the CS,[1] and as -0.09 (0.08) at 24 months in the Phase 2 OLE (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[17]).

HRQoL

In the cardiac subpopulation of APOLLO, patients in the patisiran group had significantly improved quality of life from baseline to 18 months according to the Norfolk QoL-DN compared with patients in the placebo group (LSM change: 20.4 vs. -2.6; LSM difference between groups: -23.0, p=1.65x10^{-6}; CS,[1] page 88; Merlini *et al*. 2018[29]). The CS[1] (Table C6, page 99) reports that a greater proportion of patients in the patisiran arm had improved quality of life according to the Norfolk QoL-DN at 18 months compared with the placebo group, although the percentages for each group were not presented (OR 10.0, 95% CI 4.4, 22.5, p=1.95x10^{-10}).

In the cardiac subgroup of the Phase 2 OLE, the mean change from baseline to 24 months in EQ-5D was -0.07 (CS,[1] Appendix 1, Table S11; Adams *et al*. 2017[17]).

Secondary and exploratory outcomes

Table 11 reports on additional secondary and exploratory outcomes reported for the cardiac subpopulation examined by the four studies and reported in the CS.

Table 11: Additional secondary and exploratory outcomes reported for the cardiac subpopulation

Outcome	Measure	Study				
		APOLLO (18 months)		Phase 2 study	Phase 2 OLE (24 months) (n=11)	Global OLE (36 months)
		Patisiran	Placebo			
Motor strength	**NIS-W (0-192)[a]**	NR	NR	NR	NR	NR
Disability	**R-ODS score (range 0-48)[b]**	Between-group difference in mean change from BL: 9.0, $p=4.07x10^{-16}$	NR	NR	Mean (SEM) change from BL: -4.0 (1.5) points	NR
Gait speed	**10MWT (m/s)[b]**	Between-group difference in mean change from BL: 0.35 m/s, $p=7.42x10^{-9}$	NR	NR	Mean (SEM) change from BL: 0.3 (0.05) m/s	NR
Nutritional status	**mBMI (kg/m^2 x albumin g/L)[b]**	NR	NR	NR	Mean (SEM) change from BL: -57.0 (73.0) kg/m^2 x albumin g/L[c]	NR
Autonomic neuropathy symptoms	**COMPASS-31 (0-100)[a]**	NR	NR	NR	Mean (SEM) change from BL: 0.4 (3.4) points	NR
Neuropathy	**NIS+7**	NR	NR	NR	NR	NR
Stage	**PND score (stable or improved)**	NR	NR	NR	NR	NR
	PND score (improved)	NR	NR	NR	NR	NR
	PND score (stable)	NR	NR	NR	NR	NR
	PND score (worsened)	NR	NR	NR	NR	NR
	FAP stage (stable or improved)	NR	NR	NR	NR	NR
Large fibre function	**NCS ∑5 + VDT + QST-BSA TP**	NR	NR	NR	NR	NR
Small fibre function	**QST-BSAHP + HRdB + postural BP**	NR	NR	NR	NR	NR
Grip strength	**kg**				Mean (SEM) change from BL: -1.2 (1.7) kg[c]	
Blood pressure	**Postural BP (0-2 points)**	NR	NR	NR	NR	NR

10MWT - 10-metre walk test; BL - baseline; BP - blood pressure; CI - confidence interval; COMPASS-31 - Composite autonomic symptom score-31; FAP - familial amyloidotic polyneuropathy; HRdB - heart rate variability with deep breathing; mBMI - modified body mass index; NIS+7 - modified neuropathy impairment score +7; NCS – nerve conduction studies; NIS-W - Neuropathy Impairment Score - Weakness; NR - not reported; OLE – open-label extension; PND - polyneuropathy disability; QST-BSA HP - quantitative sensory testing heat pain by body surface area; QST-BSA TP - quantitative sensory testing touch pressure by body surface area; R-ODS - Rasch-built Overall Disbility Scale; SEM - standard error of the mean; VDT - vibration detection threshold.

[a] A decrease from baseline on this measure represents an improvement; [b] An increase from baseline on this measure represents an improvement; [c] Data reported in Adams et al. 2017[17] – not reported in the CS

Safety and tolerability

The CS reports that the safety profile of patients in the cardiac subpopulation of APOLLO (patisiran n=90; placebo n=36) was similar to that of the APOLLO safety population (CS,[1] page 103). Eighty-six (95.6%) patients in the patisiran group and 35 (97.2%) patients in the placebo group experienced an AE (CS[1] Table C7, page 105; Adams *et al.* 2017[30]). The CS reports that 31 (34.4%) patients in the patisiran group and 13 (36.1%) patients in the placebo group experienced SAEs, although the Adams *et al*. 2017 conference presentation[30] reports that 18 (50.0%) patients in the placebo arm experienced SAEs. Similar proportions of patients in the patisiran and placebo arms of the APOLLO cardiac subpopulation experienced cardiac disorders system organ class AEs (32.2% and 36.1%, respectively) and SAEs (14.4% and 11.1%, respectively) (CS[1] page 103; Adams *et al.* 2017[30]). SAEs experienced by the cardiac subpopulation included cardiac disorders (14.4% and 11.1%) in the patisiran and placebo groups, respectively), cardiac arrhythmias (18.9% and 30.6%, respectively) and Torsades de Points (unconfirmed; 7.8% and 13.9%, respectively) (CS[1] page 103; Adams *et al.* 2017[30]). According to the Solomon *et al*. 2018 publication,[10] a larger proportion of patients in the patisiran group of the APOLLO cardiac subpopulation experienced cardiac failure AEs compared with the placebo group (11.1% and 5.6%, respectively).

All (100%) patients in the cardiac subgroup of the Phase 2 OLE experienced at least one AE, three patients (27.3%) reported SAEs, none of which were considered to be related to patisiran, and one patient died (CSR,[18] page 143). The CS[1] (Appendix 1, Table S14) reports AEs which occurred in >20% patients in the cardiac subpopulation of the Phase 2 OLE (n=11). These were: insomnia (27.3% patients), pyrexia (27.3% patients), flushing (36.4% patients), wound (27.3% patients), diarrhoea (18.2% patients), cataract (27.3% patients), urinary tract infection (27.3% patients), nasopharyngitis 45.5% patients) and infusion site extravasation (27.3% patients) (CS[1] Appendix 1, Table S14; Adams *et al.* 2017[21]). One IRR (9.1%) was also reported.[17] Three patients (27%) in the cardiac subgroup experienced SAEs not considered to be related to patisiran (CS[1] Appendix 1, Table S14; Adams *et al.* 2017[30]).

4.3 Critique of the trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to patisiran for hATTR amyloidosis is based on APOLLO,[11] a Phase III RCT, a Phase II single-arm study reported by Suhr *et al*. 2015,[14] a Phase 2 OLE study[15, 17] and a Global OLE,[16] which is a single-arm open-label extension of both APOLLO and the Phase 2 OLE. The ERG is confident that no relevant studies (published or unpublished) of patisiran for hATTR amyloidosis are likely to have been missed. A systematic review of studies relating to BSC, listed as the comparator in the NICE scope,[6] was not presented in the CS.[1]

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is content that the relevant population and intervention have been included in the CS, that is, patients with hATTR amyloidosis treated with patisiran. The company did not present a systematic review of the comparator, BSC. The CS[1] includes evidence relating to all of the outcomes specified in the final NICE scope,[6] except for effects of amyloid deposits in other organs and tissues (including the eye), and HRQoL for carers.

In the APOLLO study, the primary outcome was the difference between the patisiran and placebo groups in change from baseline mNIS+7 score at 18 months. There was a significant difference between the groups in change from baseline on mNIS+7 score at 18 months in favour of patisiran; patients in the placebo group worsened, and those in the patisiran group slightly improved (LSM difference between groups: -34.0 points, $p<0.001$).

Mean TTR knockdown over 18 months in APOLLO was 87.8% in the patisiran group and 5.7% in the placebo group. There was a significant mean reduction in serum TTR levels from baseline at nadir after the first (83.8%) and second (86.7%) dose of patisiran, among patients treated with the 0.3mg/kg Q3W dose. Mean serum knockdown at 24 months in the Phase 2 OLE study was 82%. Clinical advice received by the ERG suggests that this indicates a clinically meaningful impact of patisiran on hATTR amyloidosis.

HRQoL assessed using the Norfolk QoL-DN was a key secondary endpoint in APOLLO. There was a significant difference between the groups in change from baseline on Norfolk QoL-DN score at 18

months in favour of patisiran; patients in the placebo group worsened, and those in the patisiran group slightly improved (LSM difference between groups: -21.1, 95% CI -27.2 to -15.0, $p<0.001$).

Cardiac outcomes were shown to be improved on most outcomes in the patisiran group compared with placebo (relative to baseline) at 18 months in APOLLO, including LV wall thickness (LSM difference from baseline between groups 0.9mm, $p=0.02$), LV end-diastolic volume (LSM difference from baseline between groups not reported), global longitudinal strain (LSM difference from baseline between groups 1.37%, $p=0.02$), interventricular septum wall thickness (relative treatment effect not reported), posterior wall thickness (relative treatment effect not reported), relative wall thickness (0.05, $p=0.0168$), and cardiac output (0.38L/min, $p=0.044$), among the cardiac subpopulation. Results from the non-cardiac subpopulation and mITT population were broadly similar.

The primary outcome of the Phase 2 dose escalation study was the safety and tolerability of multiple ascending doses of patisiran, and the primary outcomes of the Phase 2 OLE and Global OLE studies were the safety and tolerability of up to 2 years' treatment with patisiran, and of long-term dosing of patisiran, in terms of the proportion of patients who discontinue patisiran due to AEs, respectively. Data from APOLLO demonstrated that almost all patients who received patisiran and placebo experienced AEs, similar proportions of patisiran and placebo patients experienced severe and serious AEs, and fewer patisiran group patients discontinued or withdrew due to an AE compared with the placebo group. Diarrhoea was the only serious AE that was reported in ≥2% more patients in the patisiran group than the placebo group (5.4% vs. 1.3%). Thirteen deaths were reported in APOLLO (7 [4.7%] in the patisiran group and 6 [7.8%] in the placebo group), none of which were considered to be related to patisiran.

In the Phase 2 OLE, all patients experienced at least on AE, 28% experienced an AE related to the study drug, 12% experienced at least one severe AE and 24.0% experienced at least one serious AE. At the interim data-cut of the Global OLE, 89.6% patients experienced at least one AE, 18% patients experienced at least one severe AE and 26.1% experienced at least one serious AE. In the Phase 2 OLE, there was one death (myocardial infarction) after the patient had completed 24 months of treatment, and 11 deaths were reported in the Global OLE.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to APOLLO. First, a greater proportion of patients in the patisiran group (60.8%) than the placebo group (46.8%) met the criteria for cardiac involvement. As part of their clarification response,[2] the company suggested that hATTR amyloidosis patients with cardiac involvement typically have a worse prognosis than those without cardiac involvement, therefore patients in the patisiran group may have had a worse prognosis overall, on average, because of the higher proportion of those with cardiomyopathy.[2] Second,

a greater proportion of placebo group patients discontinued treatment compared with the patisiran group (38% and 7%, respectively), and withdrew from the study (29% and 7%, respectively). Data presented in the CS and the company's clarification response suggest patients in the placebo group experienced AEs that led to discontinuation and progression of disease, or perceived disease progression.[1, 2] The other three studies adopted a single-arm design, and the Phase 2 OLE study and Global OLE study are open-label and thus susceptible to bias.

5 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of patisiran for the treatment of adult patients with hATTR amyloidosis with polyneuropathy. Section 5.1 presents a critique of the company's review of existing health economic analyses. Section 5.2 summarises the methods and results of the company's model. Sections 5.3 and 5.4 present a detailed critique of the model and additional exploratory analyses undertaken by the ERG. Sections 5.5 and 5.6 present a brief discussion of the company's budget impact estimates and wider impact beyond the NHS and PSS. Section 5.7 presents a discussion of the available economic evidence.

5.1 Company's review of published cost-effectiveness studies

The CS includes systematic reviews of existing health economic studies and HRQoL valuation studies (see CS,[1] Sections 10.1.3 and 11.2). A summary and critique of the company's search strategies have previously been provided in Section 4.1. The ERG notes that the company's searches and inclusion criteria for the review were not restricted by intervention; however, the CS excluded all HRQoL valuation studies and health economic studies unless they specifically included patisiran. As such, the only HRQoL studies discussed in the CS relate to APOLLO[15, 30-32] and no economic evaluation studies were included in the company's review. In response to a request for clarification from the ERG (see clarification response,[2] question B1), the company stated that *"studies that were not of patisiran were excluded from the submission because they were outside the NICE scope; however, all non-patisiran studies were included in the SLRs."* The ERG notes that there are other studies reporting HRQoL estimates besides APOLLO which could have been used to inform the utility values in company's health economic model.[33, 34]

Further, whilst the company's clarification response states that their systematic searches did not identify health economic studies of treatments for hATTR amyloidosis, other sections of the CS refer to the previous AGNSS report of tafamidis for TTR-FAP.[33] According to the company's clarification response[2] (question B2), this report was identified independently from the systematic search process. The ERG consider that this model should have been discussed within the company's review of existing economic models, particularly with reference to issues around the model structure and assumptions. The ERG also notes that in July 2018, the Institute for Clinical and Economic Review (ICER) published an evaluation report which includes model-based economic analyses of patisiran and inotersen for the treatment of hATTR amyloidosis;[35] this evidence review was published after the cut-off date for the company's searches, but before the completion of the CS. The ERG believes that it is reasonable that the CS does not refer to the ICER review, but notes that the structure and assumptions of the model are different to those implemented within the company's model. These studies are discussed further in Section 5.3.

5.2 Description of company's health economic analysis

5.2.1 Model scope

As part of its submission to NICE,[1] the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's model is summarised in Table 12. The company's model assesses the incremental cost-effectiveness of patisiran versus BSC in patients with hATTR amyloidosis with polyneuropathy from the perspective of the NHS and PSS over a 40-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Unit costs are valued at 2016/17 prices. Costs and health outcomes are discounted at differential rates of 3.5% per annum and 1.5% per annum, respectively. The ERG considers the use of a lower discount rate for health outcomes to be inappropriate; this issue is discussed in further detail in Section 5.3.

Table 12: Summary of company's model scope

Population	Patients with hATTR amyloidosis with polyneuropathy (reflective of the APOLLO trial population*)
Time horizon	40 years (lifetime)
Intervention	Patisiran (plus BSC)
Comparator	BSC
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for costs; 1.5% for health outcomes
Price year	2016/17

hATTR - Hereditary transthyretin amyloidosis; BSC - best supportive care; QALY - quality-adjusted life year; PSS - Personal Social Services
** Patient age and gender distribution based on subgroup of the mITT APOLLO population with non-Val30Met (non-V30M) mutations of the transthyretin gene*

Population

The population within the model reflects the mITT population enrolled into the APOLLO study.[7] At model entry, patients are assumed to have a mean age of 58.80 years and 70.5% of the modelled cohort is assumed to be male, based on the mITT APOLLO population with non-Val30Met (non-V30M) mutations of the transthyretin gene.[3]

Comparator

BSC is assumed to be comprised of symptomatic management, based on the list of interventions set out in the 2013 guidelines for transthyretin-related hereditary amyloidosis reported by Ando *et al*[4] (see Table 1). The CS[1] notes that patients in the placebo arm of APOLLO were not prescribed a BSC regimen specifically in line with the recommendations of Ando *et al*;[4] the APOLLO CSR[7] notes that there may have been differences in regional practice and standard of care.

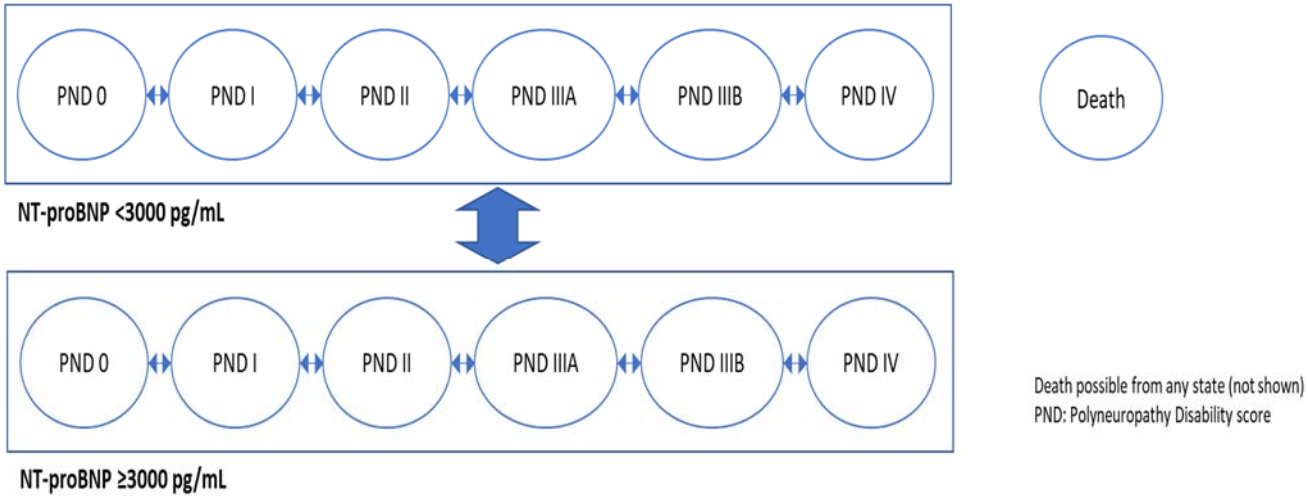
Intervention

The intervention included in the model is patisiran administered by IV infusion. The model assumes that patisiran is given alongside BSC. Patisiran is assumed to be given at a dose of 0.3mg/kg (or up to a maximum dose of 30mg for patients with a body mass ≥100kg) once every three weeks. Within the model, acquisition cost calculations are based on the distribution of body mass amongst patients in APOLLO.[7] This distribution suggests a mean of [redacted] vials of patisiran per patient per administration (including wastage). The company's model does not include any continuation/discontinuation rules - all patients are assumed to initiate patisiran treatment irrespective of baseline PND score or NT-proBNP score and all patients are assumed to continue to receive patisiran indefinitely (until death) irrespective of PND score or NT-proBNP score. The ERG notes that according to the draft SmPC,[8] patisiran is indicated for the treatment of hATTR amyloidosis in adult patients with Stage 1 or 2 polyneuropathy (i.e. PND score I-III, see Table 13).

5.2.2 Model structure and logic

The general structure of the company's model is presented in Figure 8. The model adopts a Markov approach with a structure which is comprised of 12 alive health states based on PND score (from PND 0 [no impairment] to PND IV [confined to a wheelchair or bedridden]) and NT-proBNP score (based on a cut-off value of 3,000pg/mL). The model also includes an additional state for death. The ERG notes that the diagrammatic representation of the company's model structure reported in the CS[1] (Figure 8) suggests that patients may progress only to adjacent health states (better or worse); however, this does not reflect the implemented model. With the exception of the BSC group during the extrapolation period, patients have a non-zero probability of transiting from any alive health state to any other health state during each model cycle. The PND scoring system used to characterise the model health states is summarised in Table 13.

Figure 8: Company's model structure (reproduced from CS, Figure 26)



PND - polyneuropathy disability; NT-proBNP - N-terminal pro b-type natriuretic peptide

Table 13: PND score state descriptions and corresponding FAP stages

PND score	PND state description[36]	Corresponding FAP stage
0	No impairment	Not included in staging system
I	Sensory disturbances but preserved walking capability	Stage I
II	Impaired walking capability but ability to walk without a stick or crutches	Stage II
IIIA	Walking only with the help of one stick or crutch	Stage II
IIIB	Walking with the help of two sticks or crutches	Stage II
IV	Confined to a wheelchair or bedridden	Stage III

PND – polyneuropathy disability; FAP – familial amyloidotic polyneuropathy

Patients can enter the model in any alive health state except for PND 0, based on two factors: (i) the initial distribution of PND score in APOLLO and (ii) the probability of NT-proBNP≥3,000pg/mL within APOLLO.[7] The incremental health gains, costs and cost-effectiveness of patisiran versus BSC are modelled over a time horizon of 40 years using 6-monthly cycles. Half-cycle correction is applied to account for the timing of events.

The risk of death during each model cycle is assumed to increase according to advancing PND score, and an additional mortality risk is applied to those patients with an NT-proBNP score ≥3,000pg/mL. This additional mortality risk for NT-proBNP is assumed to be proportional to the risk for the same PND state without an NT-proBNP score ≥3,000pg/mL (mortality risks for all low NT-proBNP states are inflated by a single hazard ratio [HR]). The approach used to estimate mortality risks in each health state is based largely on external data[5, 37, 38] rather than the APOLLO trial.

Within each treatment group, the probability that a patient occupies a particular health state at any time *t* (excluding mortality adjustments) is governed by two transition matrices: one matrix corresponds to the observed period in APOLLO (three 6-month cycles, up to 18 months), whilst the second matrix relates to the extrapolation period (remaining 77 cycles, beyond 18 months). Within both the patisiran and BSC groups, transition probabilities applied during the observed period were estimated using sample patient count data from the intervention and control groups of APOLLO and "non-informative" prior probabilities for transitions between all alive health states. During the extrapolation period, the approach used to derive transition probabilities is different between the two treatment groups. Within the patisiran group, the same matrix applied during the observed period is used in all cycles within the extrapolation period. In contrast, the transition matrix applied to the BSC group during the extrapolation period assumes only that patients can either stay in their current health state or progress to the next worst PND state during each cycle; this matrix is based on the probability that a patient's PND state worsened between baseline and month 18 in the placebo group of APOLLO and the estimated

probability of crossing the NT-proBNP threshold of ≥3,000pg/mL during any given 6-month cycle. No priors were included in this matrix. As a consequence of this approach, patients receiving BSC cannot transit to an improved health state during the extrapolation period. However, while no PND improvements were observed within the placebo group of APOLLO, the health state of BSC-treated patients can improve as a consequence of the inclusion of "non-informative" prior information during the observed period.

Utility values by PND score, treatment group and time were estimated using an ordinary least squares (OLS) regression model fitted to EQ-5D-5L data collected in APOLLO (mapped to the EQ-5D-3L using Van Hout *et al*[27]). NT-proBNP score was not included in the regression model. In addition, a disutility related to the impact of the final stages of the disease on caregivers is applied for patients in the PND IV state. The model includes two different types of utility "caps" which are used to constrain a possible infinite growth or decrease in the utilities for patisiran and BSC patients, respectively; these were based on the maximum and minimum observed EQ-5D estimates in any group at any timepoint in APOLLO. A second constraint is also applied to ensure that the projected utility never exceeds the estimated HRQoL of the corresponding age- and sex-matched general population in England.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) premedications given prior to patisiran administration; (iv) health care resource use conditional on model health state (per cycle polyneuropathy-related and cardiomyopathy-related costs and one-off polyneuropathy-related costs), (v) SAEs, and (vi) end-of-life costs. The model assumes that over time, an increasing proportion of patients discontinue patisiran and therefore do not subsequently incur drug acquisition, administration or premedication costs.

Incremental cost-effectiveness is calculated in a pairwise fashion based on the difference in costs divided by the difference in QALYs for patisiran and BSC.

Key structural assumptions employed in company's model

The company's model employs the following key assumptions:

- All patients with hATTR amyloidosis with polyneuropathy are eligible to commence treatment with patisiran, irrespective of NT-proBNP level or PND score (excluding PND 0). This includes the small proportion of APOLLO patients with a baseline PND IV score (FAP Stage 3) who would not be eligible for patisiran treatment according to the draft SmPC.[8]
- All patients with hATTR amyloidosis with polyneuropathy will continue to receive treatment with patisiran, irrespective of PND score or NT-proBNP score.

- Mortality risk is assumed to increase with advancing PND score. Mortality risk is also assumed to increase for patients with NT-proBNP≥3,000pg/mL and is assumed to be proportional to that for a patient with a given PND score and NT-proBNP<3,000pg/mL. The model does not explicitly capture mortality as a consequence of wasting, although this is likely to be correlated with advanced PND scores.
- The trajectory of PND progression/improvement for patients receiving patisiran observed in APOLLO is assumed to be maintained indefinitely.
- The trajectory of patients who discontinue patisiran treatment is assumed to be reflected in the patisiran matrices – these patients do not follow a different matrix after stopping treatment, hence the matrix reflects the average outcomes based on the amount of patisiran received in APOLLO.
- During the extrapolation period, the rate of worsening of PND score for patients receiving BSC is assumed to be maintained indefinitely, based on data from APOLLO. Patients are assumed to be able to progress only to the next worst health state during each extrapolation cycle. In addition, NT-proBNP score in APOLLO is assumed to be gamma distributed; the rate of increase in NT-proBNP score is assumed to be equivalent for all patients and is assumed to be constant with respect to time.
- HRQoL for patients with hATTR amyloidosis with polyneuropathy is assumed to be dependent on PND score, treatment group and time. The company's model assumes that HRQoL for patisiran-treated patients in each PND state will improve at a constant rate up to a maximum ceiling value for that PND state, based on the maximum of the mean observed EQ-5D score and its IQR for that state observed in both arms of APOLLO. In addition, a further cap is applied to ensure that the projected HRQoL for each state does not exceed that of the age-and sex-matched general population in England.
- HRQoL for BSC-treated patients in each PND state is assumed to worsen at a constant rate to a minimum floor value, based on the minimum of the mean observed EQ-5D score and its IQR for that state observed in both arms of APOLLO. In addition, a further cap is applied to ensure that the modelled HRQoL for each state does not exceed that of the age-and sex-matched general population in England. The consequence of these assumptions is that the level of HRQoL associated with any health state is different between patisiran- and BSC-treated patients for all timepoints except baseline.
- A caregiver disutility of -0.01 is applied to the PND IV state, based on an estimate used in the tafamidis AGNSS evaluation.[33]
- Polyneuropathy-related health care resource use is assumed to increase according to advancing PND score. The model also assumes that additional cardiomyopathy-related resources are required for the treatment of patients with NT-proBNP≥3,000pg/mL.

- Whilst the CS[1] states that patisiran may be given via a homecare service, the model assumes that patisiran will be administered in a day case setting for all patients.
- The costs associated with SAEs are assumed to apply indefinitely, including after discontinuation of patisiran treatment. The risk of SAEs is assumed to be independent of PND and NT-proBNP scores.
- Health care resource use is assumed to be reduced for patisiran-treated patients compared with BSC-treated patients, independent of PND and NT-proBNP scores. This reduction is assumed differ between polyneuropathy-related and cardiomyopathy-related resource use, and is assumed to be constant with respect to time.

5.2.3 Evidence used to inform the company's model parameters

Table 14 summarises the evidence sources used to inform the model's parameters. These are discussed in more detail in the following sections.

Table 14: Summary of evidence used to inform the company's model parameters

Parameter group	Source
Initial health state distribution and patient characteristics	PND score distribution and probability of NT-proBNP≥3,000pg/mL taken from APOLLO. Age, sex, and body weight distribution were based on the subgroup of patients with non-Val30Met (non-V30M).[7]
Transition matrix – observed period (18 months), patisiran	Based on observed patient count data from patisiran group of APOLLO.[7] Includes priors.
Transition matrix – extrapolated period (beyond 18 months), patisiran	
Transition matrix – observed period (18 months), BSC	Same as observed matrix for patisiran detailed above. Includes priors.
Transition matrix – extrapolation period (beyond 18 months), BSC	Estimated using probability of PND worsening in placebo group in APOLLO[7] and assumptions regarding NT-proBNP increase from Ruberg and Berk.[39] Does not include priors.
HRQoL – general population (both groups)	Kind *et al*.[40]
HRQoL – baseline, by PND state (both groups)	Regression model fitted to APOLLO data including PND score and time*treatment covariate.[1]
HRQoL – maximum, by PND state (patisiran)	Based on maximum mean/IQR utility value observed in each PND state in both treatment groups in APOLLO[7]
HRQoL – minimum, by PND state (BSC)	Based on minimum mean/IQR utility value observed in each PND state in both treatment groups in APOLLO[7]
HRQoL – carer disutility	AGNSS tafamidis report[33]
Mortality – general population	Life tables[38]
Mortality – HR PND 0-II versus general population	HR estimated using life tables,[38] distribution of patients by PND and NT-proBNP groups from APOLLO,[7] mean OS from Suhr *et al*[37] and weighted average of HRs for V122I group and non-V122I group in Gillmore *et al*[5]
Mortality – HR PND III versus PND 0-II	Estimates based on distribution of patients by NT-proBNP groups from APOLLO,[7] mean OS from Suhr *et al*[37] and weighted average of HRs for V122I group and non-V122I group in Gillmore *et al*[5]
Mortality – HR PND IV versus PND 0-II	
Mortality – HR NTproBNP≥3,000 versus NT-proBNP<3,000 versus	Weighted mean of HRs for V122I group and non-V122I group in Gillmore *et al*[5]
Relative dose intensity (RDI)	APOLLO[7]
SAE incidence	Based on events occurring in ≥2% patients in APOLLO[7]
Drug acquisition cost - patisiran	Manufacturer[1]
Drug administration cost - patisiran	NHS Reference Costs 2016/17[41]
Premedication costs - patisiran	eMIT[42] and MIMS[43]
Time to treatment discontinuation	Log normal model fitted to data from APOLLO[7]
Costs – polyneuropathy one-off	Estimates derived from company's Delphi panel;[1] unit costs taken from various sources including NHS Reference Costs 2016/17,[41] PSSRU,[44] eMIT,[42] and MIMS[43]
Costs – polyneuropathy per cycle	
Costs – cardiomyopathy per cycle	
Costs – reduction in resource use due to patisiran	Company's Delphi panel[1]
Costs – serious AEs	NHS Reference Costs 2016/17[41]

AE – adverse event; AGNSS – Advisory Group for National Specialised Services; BSC – best supportive care; eMIT – electronic market information tool; HR – hazard ratio; HRQoL – health-related quality of life; IQR – interquartile range; MIMS – Monthly Index of Medical Specialities; NT-proBNP- N-terminal pro b-type natriuretic peptide; OS – overall survival; PND – polyneuropathy disability; pg/mL – nanogram/millilitre; PSS – Personal Social Services; PSSRU - Personal Social Services Research Unit; RDI – Relative dose intensity

Initial patient characteristics at model entry

The model assumes that patients enter the model aged 58.8 years and approximately 70.5% of the modelled cohort is assumed to be male. The ERG notes that these parameters reflect a subgroup of the mITT APOLLO population with non-Val30Met (non-V30M) mutations of the transthyretin gene.[3]

The initial distribution of patients at model entry is defined according to baseline PND score (0-IV) and the mean probability that a patient has an initial NT-proBNP score ≥3,000pg/mL in APOLLO (assuming a constant proportion of NT-proBNP ≥3,000pg/ml and <3,000pg/ml in each PND state). These values are based on the overall mITT population of APOLLO.[7]

Health state transitions

For both treatment groups, the transition matrices for the observed period were calculated directly using the observed PND count data observed within APOLLO.[7] These data relate to PND transitions observed between baseline and 18 months; the company did not make use of the PND count data at the 9-month assessment visit. The company also included a "non-informative prior distribution" of 1/12 to all surviving transitions in each matrix (implying an equal probability of transitioning between health states of 0.083, with an equivalent weight of 1 patient transitioning across 12 health states). The transition matrix applied in the patisiran group during the observed period is shown in Table 15; the matrix applied in the BSC group during the observed period is shown in Table 16. The shaded cells in the matrices represent transitions for which no observed data are available from APOLLO, hence these transitions are informed only by priors. These matrices are applied to the first three 6-month cycles (up to 18 months). The observed patient count data (excluding priors) are provided in Appendix 1.

Table 15: Per-cycle transition probabilities, patisiran group, observed period and extrapolation (cycles 1-80), N contributing data = 134 patients

From \ to state		NT-proBNP<3000pg/mL						NT-proBNP≥3000pg/mL					
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
NT-proBNP <3000pg/mL	PND 0	0.69	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
	PND I				0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00
	PND II	0.00						0.00	0.00	0.00	0.00	0.00	0.00
	PND IIIA	0.00					0.00	0.00	0.00	0.00	0.00	0.00	
	PND IIIB	0.00	0.00					0.00	0.00	0.00	0.00		
	PND IV	0.03	0.03	0.03	0.03	0.03	0.69	0.03	0.03	0.03	0.03	0.03	0.03
NT-proBNP ≥3000pg/mL	PND 0	0.03	0.03	0.03	0.03	0.03	0.03	0.69	0.03	0.03	0.03	0.03	0.03
	PND I	0.00	0.00		0.00		0.00	0.00			0.00	0.00	0.00
	PND II	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01		0.01	0.01	0.01
	PND IIIA	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01		0.01	
	PND IIIB	0.01	0.01	0.01	0.01		0.01	0.01	0.01	0.01	0.01	0.62	
	PND IV	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.69

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre
Shaded cells represent transitions for which no observed data are available from APOLLO, hence these transitions are informed only by priors

Table 16: Per-cycle transition probabilities, BSC group, observed period (cycles 1-3), N contributing data = 51 patients

From \ to state		NT-proBNP<3000pg/mL						NT-proBNP≥3000pg/mL					
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
NT-proBNP <3000pg/mL	PND 0	0.69	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
	PND I	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00
	PND II	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]	0.00	0.00	0.00
	PND IIIA	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	PND IIIB	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00	0.00	0.00
	PND IV	0.03	0.03	0.03	0.03	0.03	0.69	0.03	0.03	0.03	0.03	0.03	0.03
NT-proBNP ≥3000pg/mL	PND 0	0.03	0.03	0.03	0.03	0.03	0.03	0.69	0.03	0.03	0.03	0.03	0.03
	PND I	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.63	[redacted]	0.01	0.01	0.01
	PND II	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.63	0.01	[redacted]	0.01
	PND IIIA	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.63	0.01	[redacted]
	PND IIIB	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.69	0.03
	PND IV	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.69

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre
Shaded cells represent transitions for which no observed data are available from APOLLO, hence these transitions are informed only by priors

Within the extrapolation period, the approach used to derive transition probabilities differs between the two treatment groups. Within the patisiran group, the observed matrix (shown previously in Table 15) is also applied to all model cycles after 18 months. Conversely, within the BSC group, the transition matrix applied in the extrapolation period was estimated using two sources: (i) the probability of a patient's PND score worsening between baseline and 18 months in the placebo group of APOLLO, and (ii) the probability that a patient will have transitioned from NT-proBNP<3,000pg/mL to NT-proBNP≥3,000pg/mL over 18 months, based on the company's "gamma function method." According to Table 34 of the CSR for APOLLO,[7] the PND score for [redacted] of 55 patients in the placebo group worsened between baseline and 18 months. The company converted this 18-month probability of PND worsening of [redacted] to a 6-month probability of [redacted], assuming a constant event rate.[45] This probability is applied to the company's BSC extrapolation period matrix to determine the probability of transiting from any PND state to the next worst PND state. Within this matrix, transitions by more than one state are assumed not to be possible.

The model also applies an estimated probability of transiting from a low NT-proBNP score (<3,000pg/mL) to a high NT-proBNP score (≥3,000pg/mL). The approach taken by the company adopted the following calculation steps:

1. The mean NT-proBNP score observed in the mITT population of APOLLO ([redacted]) and the proportion of patients with an NT-proBNP≥3,000pg/mL ([redacted]) were calculated.
2. Assuming the NT-proBNP score follows a gamma distribution, the Excel Solver add-in was used to estimate the parameters of a gamma distribution which match the observed mean NT-proBNP score and the proportion of patients with NT-proBNP≥3,000pg/mL in APOLLO.
3. The company assumed that all patients experience an increase in NT-proBNP score of 1,816pg/mL during each 6-month period. This was based on a study reported by Ruberg and Berk[39] and relates to a patient population of hATTR amyloidosis patients with the Val122Ile mutation (n=11) or wtATTR amyloidosis (n=18). The company estimated the 18-month NT-proBNP score for the cohort to be 6,711pg/mL (calculated as 1,263 + 3 x 1,816).
4. The parameters of the estimated distribution for NT-proBNP score at 18-months were then calculated using the estimated mean, assuming a gamma distribution with the same variance as the baseline distribution. Transition probabilities between NT-proBNP<3,000pg/mL and the NT-proBNP≥3,000pg/mL states were then calculated as follows:
    (a) The probability that a patient has an NT-proBNP<3,000pg/mL at 18-months was calculated directly using the cumulative distribution function (CDF) for the NT-proBNP distribution at 18 months.
    (b) The probability that a patient transitions from NT-proBNP<3,000pg/mL to NT-proBNP≥3,000mg/mL was calculated based on the estimated proportion of patients

who cross the NT-proBNP cut-off between baseline and 18 months divided by the proportion of patients who previously had NT-proBNP score <3,000pg/mL at baseline.

(c) The probability of transiting from NT-proBNP ≥3,000pg/mL to NT-proBNP<3,000pg/mL was calculated using a similar equation to (b), however, the ERG notes that using the company's method, irrespective of the assumed variance, this value can only ever be zero.

Table 17: Gamma function method parameters (NT-proBNP transitions)

Parameter	Value	Source
Mean NT-proBNP at baseline (pg/mL)	[redacted]	APOLLO (both treatment groups)[7]
Probability NT-proBNP ≥3,000pg/mL at baseline	[redacted]	APOLLO (both treatment groups)[7]
Estimated variance	9,649,355	Calculated using Excel Solver add-in
Increase in NT-proBNP score over each 6-month period (pg/mL)	1,816	Ruberg and Berk[39]
Probability of transition from NT-proBNP<3,000pg/mL to ≥3,000pg/mL in 6 months	0.54	Based on company's estimated baseline and 18-month gamma distributions
Probability of transition from NT-proBNP≥3,000pg/mL to <3,000pg/mL in 6 months	0.00	Based on company's estimated baseline and 18-month gamma distributions

NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre

Based on these two transition probabilities, the company generated a transition matrix for BSC in the extrapolation period (see Table 18). During this period, BSC-treated patients can only remain in their current PND state or progress to the next worst PND state, with or without switching to the NT-proBNP≥3,000pg/mL states. The company did not apply any form of prior distribution within this matrix, hence regression to a better health state or worsening by more than one health state is not believed to be possible.

Table 18: Per-cycle transition probabilities, BSC group, extrapolation period (cycles 4-80), N contributing data = 55 patients

From \ to state		NT-proBNP<3000pg/mL						NT-proBNP≥3000pg/mL					
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
NT-proBNP <3000pg/mL	PND 0	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	PND I	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00
	PND II	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00
	PND IIIA	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00
	PND IIIB	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]
	PND IV	0.00	0.00	0.00	0.00	0.00	[redacted]	0.00	0.00	0.00	0.00	0.00	[redacted]
NT-proBNP ≥3000pg/mL	PND 0	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	PND I	0.00	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00
	PND II	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00	0.00
	PND IIIA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]	[redacted]	0.00
	PND IIIB	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]	[redacted]
	PND IV	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre
Shaded cells represent transitions which are believed to be impossible

Mortality risk according to PND score and NT-proBNP score

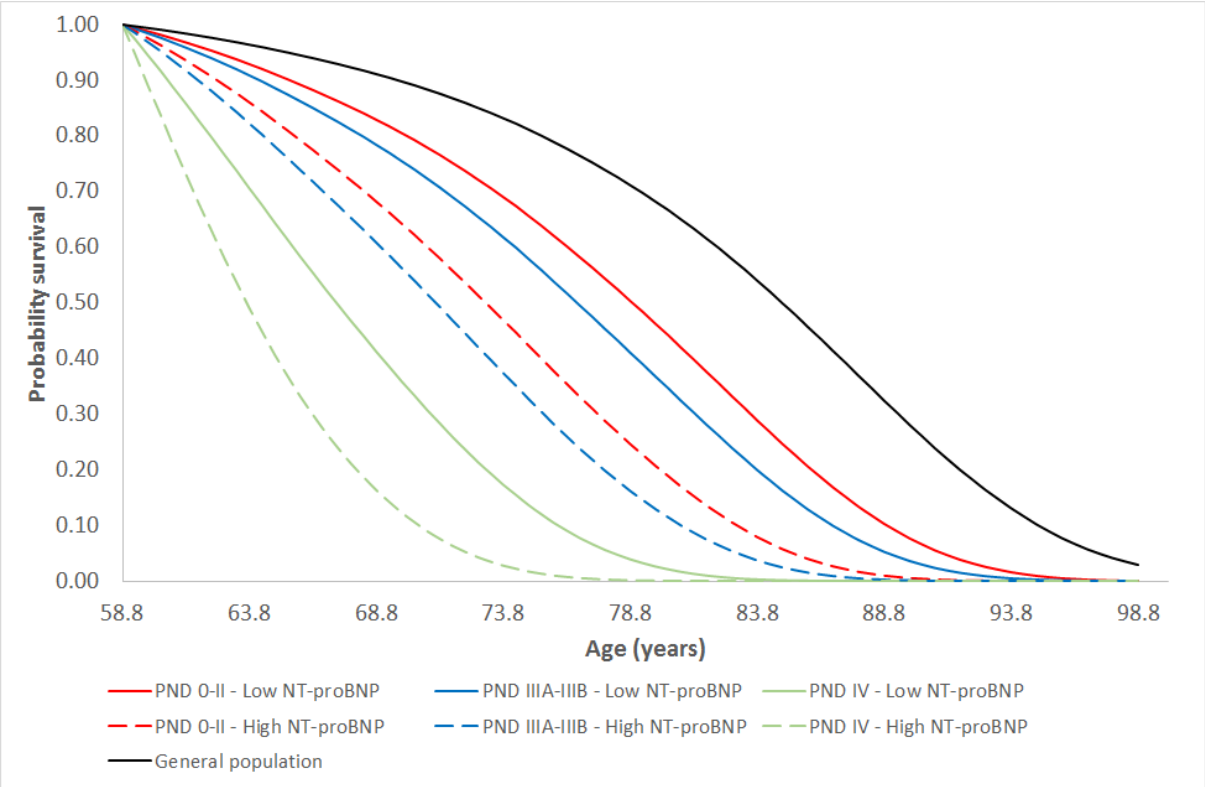
The model does not use mortality data from APOLLO. Instead, mortality risk is modelled using a series of HRs applied to general population life tables for England.[38] As the patient's PND score increases, or if their NT-proBNP score exceeds 3,000pg/mL, more HRs are combined to estimate the overall HR applied to the general population baseline risk. The HRs used in the company's model are summarised in Table 19; these were taken or estimated from two studies (Gillmore *et al*[5] and Suhr *et al*[37]). The study reported by Gillmore *et al*[5] is a retrospective analysis of 869 patients with cardiac ATTR amyloidosis who were routinely followed up at the UK NAC which was undertaken to define a new staging system for cardiac transthyretin amyloidosis. The study reported by Suhr *et al*[37] is a prospective and retrospective analysis of prognostic factors for survival in 27 patients with FAP that had symptomatic onset before the age of 50 who were treated at a single department in Sweden. The resulting survival models for each health state, generated through reference to a general population baseline assuming no change in health state, are shown in Figure 9. The company's overall survival (OS) predictions for the patisiran and BSC groups are shown in Figure 10. The subsequent text briefly explains the approach used by the company to estimate these HRs.

Table 19: Hazard ratios applied to each PND state and NT-proBNP group (applied to general population mortality as baseline)

Index	PND, NT-proBNP groups	HR applied in state	HR derivation	Calculation rationale
A	PND 0-II, NT-proBNP<3,000pg/mL	2.01	=2.01	Calculated using HR for PND 0-II, NT-proBNP<3,000pg/mL versus general population
B	PND IIIa and IIIb, NT-proBNP<3,000pg/mL	2.62	=2.01*1.30	Calculated using (A) multiplied by HR for PND III, NT-proBNP<3000pg/mL versus PND 0-II, NT-proBNP<3,000pg/mL
C	PND IV, NT-proBNP<3,000pg/mL	9.53	=2.01*4.73	Calculated using (A) multiplied by HR for PND IV, NT-proBNP<3000pg/mL versus PND 0-II, NT-proBNP<3,000pg/mL
D	PND 0-II, NT-proBNP≥3,000pg/mL	4.12	=2.01*2.04	Calculated using (A) multiplied by HR for NT-proBNP≥3,000pg/ml groups
E	PND IIIa and IIIb, NT-proBNP≥3,000pg/mL	5.35	=2.01*1.30*2.04	Calculated using (B) multiplied by HR for NT-proBNP≥3,000pg/ml groups
F	PND IV, NT-proBNP≥3,000pg/mL	19.49	=2.01*4.73*2.04	Calculated using (C) multiplied by HR for NT-proBNP≥3,000pg/ml groups

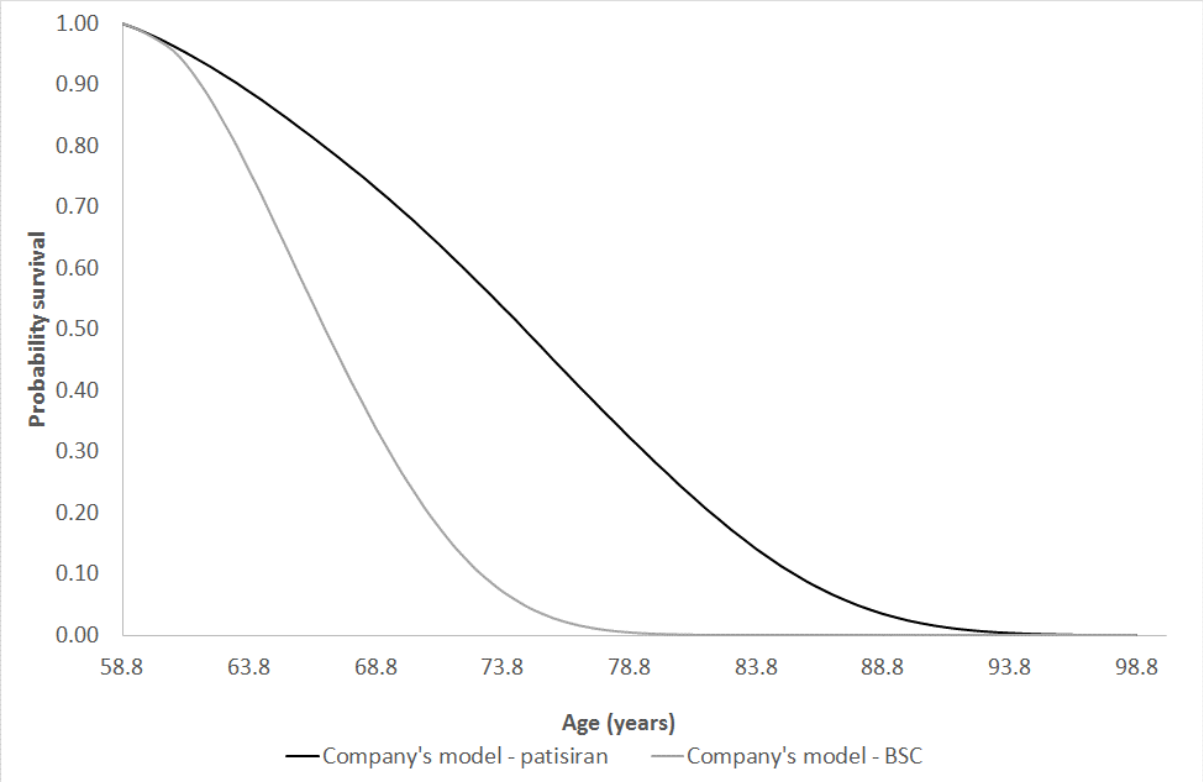
PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre; HR – hazard ratio

Figure 9: Overall survival by PND score and NT-proBNP score (≥3,000pg/mL or <3,000pg/mL), assumes patients do not change PND score or NT-proBNP score (generated by ERG using company's model)



PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide

Figure 10: Overall survival by treatment group



[i] Hazard ratio PND 0-II versus general population (NT-proBNP<3,000pg/mL)

The HR for PND 0-II versus general population mortality risk was estimated by using the Excel Solver add-in to crudely calibrate an HR-adjusted life table-based survival model which produces a mean survival gain that is equivalent to the estimated mean survival of patients with Stage I cardiac transthyretin amyloidosis in the study reported by Gillmore *et al*.[5] The company first estimated a mortality risk function for the general population with a starting age of 73 years (based on Gillmore *et al*[5]) and weighted this by the proportion of males and females (also based on Gillmore *et al*[5]). Based on the distribution of patients in PND I-II and III-IV in APOLLO[7] and the estimated HR for death for PND III-IV versus PND I-II from Suhr *et al*[37] (which includes further adjustment for NT-proBNP score, see Sections [ii]-[iv] below), the company then estimated the necessary HR for PND I-II versus general population mortality risk which, when applied to this survival model, produces a mean lifetime survival of 7.72 years (equivalent to the company's estimated mean survival from Gillmore *et al*[5]). The estimated HR was 2.01; this estimate is applied to the general population death probability during each cycle.

[ii] Hazard ratio for PND III versus PND 0-II (NT-proBNP<3,000pg/mL)

The company estimated a hazard rate for patients with PND IIIa and IIIb based on the estimated mean OS for PND III patients reported in Suhr *et al*[37] This rate was then inflated by assuming an increased mortality risk for patients with NT-proBNP≥3,000pg/mL, based on the HR for patients with Stage 2 versus Stage 1 cardiac transthyretin amyloidosis in Gillmore *et al*,[5] assuming the distribution of PND scores in APOLLO. The same approach was also used to estimate the hazard rate for patients with PND I-II. The HR for PND III versus PND 0-II was then calculated as the ratio of hazard rates for PND III versus PND I-II. This produced an estimated HR of 1.30, which is combined with the HR for patients with PND I-II (HR=2.01, see calculation set [i]), and produces a composite HR for PND III versus general population mortality risk of 2.62.

[iii] Hazard ratio for PND IV versus PND 0-II (NT-proBNP<3,000pg/mL)

The HR for PND IV versus PND 0-II was calculated using the same rationale described for the PND III group (see calculation set [ii]), resulting in an estimated HR of 4.7. This HR is combined with the HR for PND 0-II (HR=2.01, see calculation set [i]), which leads to a composite HR for PND IV versus the general population mortality risk of 9.53.

[iv] Hazard ratio for NT-proBNP≥3,000pg/mL versus NT-proBNP<3,000pg/mL

For the patients with NT-proBNP≥3,000pg/mL, an additional HR is applied to the HRs described in calculation sets [i]-[iii] described above, irrespective of the patient's PND-related mortality risk. An HR of 2.04 was calculated as the weighted mean of the HR for death for patients with Stage 2 versus Stage 1 cardiac transthyretin amyloidosis for the two subgroups in the Gillmore *et al* study.[5] This increased risk is combined with the HRs for patients with the same PND score and with low NT-

proBNP. This results in composite HRs (versus general population mortality risk) of 4.12, 5.35 and 19.49 for groups PND 0-II, PND III and PND IV, respectively.

Health-related quality of life

HRQoL outcomes within the company's model are based on EQ-5D-5L data collected in APOLLO.[7] Within the trial, the EQ-5D-5L questionnaire was administered at baseline, 9 months and 18 months. Table 20 summarises the observed EQ-5D-5L estimates by PND score; as shown in the table, the raw data indicate a general trend of lower HRQoL in more advanced PND states.

Table 20: Mean (IQR) UK EQ-5D statistics by APOLLO treatment group, study visit, and PND score (reproduced from company's clarification response, question B12)

PND state	Baseline		Month 9		Month 18	
	Placebo	Patisiran	Placebo	Patisiran	Placebo	Patisiran
Overall	[redacted]					
PND 0						
PND I	[redacted]					
PND II	[redacted]					
PND IIIA	[redacted]					
PND IIIB	[redacted]					
PND IV	[redacted]					

PND – polyneuropathy disability; IQR – interquartile range
Figures in parentheses represent 95% CIs

The company undertook a regression analysis using these data to estimate a relationship between PND score and HRQoL, including covariates and interaction terms for NT-proBNP (<3000pg/mL or ≥3000pg/mL), treatment group (patisiran or BSC) and time (months). A forward selection process was used to identify the final regression model. The final model included only two terms: (i) treatment group and (ii) a categorical variable denoting PND score multiplied by time.[2] The parameters of the company's model are shown in Table 21. Within the patisiran group of the company's model, health utility in all PND states (irrespective of NT-proBNP score) increases by [redacted] per month until the modelled health utility reaches either the ceiling value for that health state (calculated as the highest mean/IQR utility

value observed in either treatment group in APOLLO at any timepoint), or the estimated health utility for the general population. Within the BSC group, health utility is assumed to decrease by [redacted] each month until the modelled health utility reaches the floor value for that health state (calculated as the lowest mean/IQR utility value observed in either treatment group in APOLLO at any timepoint); an additional constraint is applied to ensure that the modelled utility in the BSC group does not exceed that of the general population.

Table 21: Estimated HRQoL parameters and maximum/minimum values applied in the company's model

Parameter	Regression mean	SE	Assumed maximum cap (patisiran)*	SE	Assumed minimum cap (BSC)*	SE
[redacted]						

PND – polyneuropathy disability; BSC – best supportive care; SE – standard error
** The CS includes a transcription error relating to the maximum and minimum utility values. The table presents the values which are used in the company's model rather than the incorrect values presented in the CS*

The company's model applies a disutility score for caregivers of 0.01 of patients with PND IV. This estimate was taken from a previous model of treatments for Alzheimer's disease.[46]

Resource and costs

The model accounts for direct costs related to the treatment of the hATTR amyloidosis throughout patient's life, with or without patisiran. These costs include: (i) cost related to patisiran treatment (drug acquisition, patisiran administration and premedications); (ii) health care resources used for the treatment of the polyneuropathy (per-cycle and one-off costs) and cardiomyopathy symptoms (per-cycle costs only); (iii) SAEs and (iv) end-of-life care for patients who are near death. The costs applied in the model are summarised in Table 22.

Table 22: Summary of cost inputs applied in company's model

Cost component		Patisiran	BSC
Drug treatment (per cycle)	Drug acquisition (without PAS) – patisiran	[redacted]	n/a
	Drug acquisition (with PAS) – patisiran	[redacted]	n/a
	Drug administration - patisiran	£2,695.89	n/a
	Premedication - patisiran	n/a	n/a
Costs due to polyneuropathy (per-cycle)	PND 0	[redacted]	[redacted]
	PND I		
	PND II		
	PND IIIA		
	PND IIIA		
	PND IV		
Costs due to cardiomyopathy (per cycle)	NT-proBNP <3,000pg/mL		
	NT-proBNP ≥3,000pg/mL		
One-off polyneuropathy costs	PND I	[redacted]	[redacted]
	PND II		
	PND IIIA		
	PND IIIA		
	PND IV		
AEs (per event*)	Diarrhoea	£916.80	£916.80
	Cardiac failure	£508.72	£508.72
	Cardiac failure congestive	£553.58	£553.58
	Orthostatic hypotension	£617.11	£617.11
	Pneumonia	£819.09	£819.09
	Atrioventricular block complete	£502.83	£502.83
	Acute kidney injury	£978.32	£978.32
	Dehydration	£727.25	£727.25
	Vomiting	£916.80	£916.80
	Urinary tract infection	£1,123.22	£1,123.22
	Constipation	£916.80	£916.80
	Hereditary neuropathic amyloidosis	£0.00	£0.00
	Hyponatremia	£727.25	£727.25
	Pneumonia aspiration	£819.09	£819.09
End-of-Life costs	-	£5,765.76	£5,765.76

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; PAS – Patient Access Scheme; AE – adverse event

** The same incidence is applied during each cycle*

Based on its list price, the cost per 10mg vial of patisiran is £7,676.47. The company has proposed a PAS which takes the form of a simple price discount of [redacted]; the cost per vial of patisiran including this discount is [redacted]. The acquisition cost of patisiran per 6-month treatment period is estimated as a function of the cost per vial, the distribution of patients' body weight in APOLLO, the number of administrations during the period and the relative dose intensity (RDI) in APOLLO (estimated to be

0.97). Including the PAS, the acquisition for patisiran per 6-month model cycle is estimated to be [redacted] per patient.

Patisiran is given as an IV infusion; the unit costs of patisiran administration were taken from the NHS Reference Costs 2016/17[41] and are assumed to be equivalent to the cost of an IV chemotherapy infusion (cost = £310 per attendance – "Deliver more complex parenteral chemotherapy at first attendance, day case and regular day/night [SB13Z]").

The model includes the costs of premedications given prior to patisiran administration. These include corticosteroids, paracetamol, IV H1 blockers and IV H2 blockers. Unit costs for these drugs were obtained from eMIT (2018) or MIMS.[41-43] The costs of vitamin A supplements (advised within the draft SmPC[8]) are not included in the model.

Within the company's model, the total costs of drug acquisition, administration and premedications are assumed to reduce over time, based on a separate parametric (log normal) function used to model time to treatment discontinuation. This function was selected based on the comparison of goodness-of-fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC] statistics).

BSC costs are assumed to differ between the model health states, based on resource use estimates derived from a Delphi panel study held with clinical experts (detailed in Appendix 3 of the CS[1]). The model includes three separate groups of costs: (i) per-cycle polyneuropathy-related costs; (ii) per-cycle cardiomyopathy-related costs, and (iii) one-off polyneuropathy costs (mobility aids e.g. wheelchairs, shower chair, walking aids, kitchen and bathroom adjustments, door openers, rails, ramps, and a homecare bed[1]). For the polyneuropathy-related resources use, average costs by each PND score were derived and applied for both low and high NT-proBNP groups based on the unweighted mean of Delphi panellists' responses. For the cardiomyopathy-related resources, a similar approach was used for each of the NT-proBNP groups, and average costs obtained were applied uniformly to all PND groups. One-off costs were intended to be only applied to patients progressing from lower PND states to higher PND states; however, the ERG notes that there are problems in the implementation of these costs within the company's model (see Section 5.3). PND 0 and I were assumed to not be associated with one-off costs. Within the patisiran group, the model assumes that patisiran will lead to reductions in resource use; these parameters were also elicited as part of the Delphi panel study. Constant reductions in resource use of [redacted] and [redacted] were applied to the polyneuropathy-related costs (per-cycle and one-off) and the cardiomyopathy-related costs, respectively.

The model includes only SAEs occurring in >2% of patients in APOLLO (see Table 22). The company elected to include only SAEs (rather than AEs of any grade) because these would require hospitalisation

or other interventions to manage them, hence they would impact on health care costs and HRQoL.[2] The model assumes that these events occur at a constant rate during all model cycles. Unit costs were taken from NHS Reference Costs 2016/17.[41]

The model includes a once-only cost associated with hospitalisation or care in hospices and palliative care; this cost is applied to all patients at the point of death. The unit cost was taken from NICE Technology Appraisal 451 (ponatinib for treating chronic myeloid leukaemia [CML] and acute lymphocytic leukaemia [ALL]).[47]

5.2.4 Model evaluation methods

The CS[1] presents the results of the model in terms of the incremental cost per QALY gained for patisiran versus BSC. The company's base case incremental cost-effectiveness ratios (ICERs) were generated using the deterministic version of the model. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs) and scenario analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The probabilistic ICER, based on the expectation of the mean, is not presented within the CS. The distributions applied in the company's PSA are summarised in Table 23. The results of the DSAs are presented in the form of a tornado diagram for specified model parameters. Scenario analyses were undertaken to explore the impact of: (i) applying alternative imputation methods to the patient count data used to inform the transition matrices; (ii) removing the caps for maximum/minimum utilities; (iii) applying an alternative distribution for time to treatment discontinuation, and (iv) removing additional mortality risks associated with PND.

Table 23: Distributions used in the company's PSA

Parameter group	Parameter	Distribution	ERG comment
Initial health state distribution	Initial age	Gamma	-
	Proportion of males	Beta	-
	PND groups	Dirichlet	
	Initial NT-proBNP (pg/ml)	Gamma	Only the mean is sampled, rather than alpha and beta parameters
	% of patients above 3,000pg/mL	Beta	Given that the initial NT-proBNP distribution is sampled, it is unclear why this parameter is specified
Effectiveness of treatment	Delta NT-proBNP, extrapolation period, BSC	Normal	Should be bounded by zero
Transition matrices	Observed period (≤18mo), patisiran	Dirichlet	Posterior distributions based on sparse data and "non-informative" prior distributions are unlikely to reflect the beliefs of a reasonable impartial observer
	Extrapolated period (>18mo), patisiran	Dirichlet	
	Observed period (≤18mo), BSC	Dirichlet	
	Extrapolation period (>18mo), BSC	Dirichlet	
HRQoL	General population	Normal	Distributions not bounded by zero. Certain PND utility parameters and patisiran maximum utility exceed 1.0 in some probabilistic samples*
	Baseline (both groups) by PND state	Normal	
	Maximum (patisiran)	Normal	
	Minimum (BSC)	Normal	
	Carer disutility	Gamma	A beta distribution may be more appropriate
Mortality	general population in UK	Fixed	-
	HR PND 0-II versus general population	Gamma	Parameter estimates used to estimate mortality (e.g. population mean OS from Suhr and Gillmore) are assumed to be known with no allowance for uncertainty
	HR PND III versus PND 0-II	Gamma	
	HR PND IV versus PND III	Gamma	
	HR NT-proBNP≥3,000 versus NT-proBNP<3,000	Gamma	
AEs	Serious AE incidence (both groups)	Gamma	A beta distribution would be more appropriate
Resource use and costs	Drug acquisition costs - patisiran	Fixed	-
	Drug administration costs - patisiran	Gamma	-
	Premedication costs - patisiran	Gamma	-
	Polyneuropathy per cycle costs	Various	The per-cycle cost for PND I frequently produces errors due to large SE.* Uncertainty from the Delphi panel is not reflected in the model
	Cardiomyopathy per cycle costs	Various	
	Polyneuropathy one-off costs	Various	
	Polyneuropathy resource use reduction	Beta	
	Cardiomyopathy resource use reduction	Beta	
	SAEs	Gamma	-
	End-of-life costs	Beta/Gamma	-
	Time on treatment function	Multivariate normal	Sampling produces frequently illogical or incorrect samples*

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; mo – month; HRQoL – health-related quality of life; AE – adverse event; PSA – probabilistic sensitivity analysis

** These errors are discussed in further detail in Section 5.3*

5.2.5 Company's model validation and verification

The company consulted with two clinical experts at the NAC (Professor Philip Hawkins and Professor Julian Gillmore) to elicit their views regarding the appropriateness of the model methodology and assumptions. Overall, the clinicians consulted considered the company's model approach and assumptions to be reasonable (see Table 24).

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Table 24: Results of company's clinical validation of model methodology and assumptions (reproduced from CS, Table D11)

CE model assumptions/methodology	NAC clinical expert opinion
Overall	
General design of model	Appropriate; noted that model captures the multi-systemic nature of the disease
Health states defined by PND score and NT-proBNP	Appropriate, considering data limitations in hATTR
Use of observed PND transitions in APOLLO	Agree; prefer this decision vs Pfizer's use of Norfolk TQoL score cut-offs to define FAP stages in their tafamidis submission[33]
UK clinical practice	
0% OLT in England	Agree
Cardiomyopathy mortality	
HR for patients with NT-proBNP ≥3000 pg/mL estimated from HR reported for Stage II patients by Gillmore *et al*. 2017[5]	Reasonable and appropriate
HR estimate for patients with NT-proBNP ≥3000pg/mL estimated as a weighted average of the HR for V122I and other (mixed-genotype) subgroups reported by Gillmore *et al*. 2017[5]	Agree
Polyneuropathy mortality	
Inclusion of mortality due to polyneuropathy	Agree
Mortality due to polyneuropathy estimated from Suhr *et al*. 1994[37]	Appropriate, in the absence of other sources
Extrapolation past 18 months	
PND transitions and NT-proBNP evolution for patisiran extrapolated from observed data in APOLLO patisiran arm	Reasonable
mNIS+7 progression for BSC extrapolated from observed data in APOLLO placebo arm	Agree; noted that extrapolated values were supported by data reported by Adams *et al*. 2015[48]
NT-proBNP evolution for BSC extrapolated from Ruberg & Berk 2012[39]	Appropriate, in the absence of other sources
Face validity	
LY estimates in the BSC arm	The estimated LYs for the BSC arm used in the CE model are within the realm of plausibility; reasonable to say that the model has face validity
HRQoL values by PND score	
Utility values differ within the same PND score for patisiran and BSC	Reasonable to expect different utilities for patisiran and BSC as observed in APOLLO, because PND health states as defined in the model may be capturing autonomic symptoms as well as functional aspects of hATTR, and autonomic symptoms may progress at a different rate than PND score (a functional scale);

CE model assumptions/methodology	NAC clinical expert opinion
	believe HRQoL is driven mainly by autonomic symptoms (diarrhoea, constipation, wasting)
Extrapolation of utilities after 18 months	
Capping change in utilities in patisiran arm after initial 18 months	Agree
Decrease in utilities for BSC arm capped after 18 months	Conservative assumption because autonomic symptoms could worsen without the patient progressing in PND score; however, consider the assumption to be reasonable

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; OLT – orthotopic liver transplant; HR – hazard ratio; hATTR – hereditary ATTR amyloidosis; mNIS+7 – Modified Neuropathy Impairment Score +7; FAP – familial amyloidotic polyneuropathy; HRQoL – health-related quality of life; BSC – best supportive care; TQoL – total quality of life; LY – life year; CE – cost-effectiveness

In addition, the CS[1] states that a number of further verification and validation measures were taken to ensure the credibility of the model:

- All stages of model design, including the main assumptions and data sources were reviewed and discussed by a group of expert UK health economic consultants.
- The CS states that the interim and final results produced by the model were compared with the input data for clinical and economic plausibility. The ERG is unsure what this means.
- The CS (page 197) states that *"Random checks were made on specific elements of the calculation."* The ERG is also unsure what this means.
- The company's model was reviewed during model development and after completion by senior health economic consultants who were not previously involved in the project and whose comments and suggestions were incorporated into the model.
- The model was reviewed following an internal checklist and then cell-by-cell to validate the model both internally and externally.
- The company also compared the modelled mortality predictions against the crude observed mortality rates (excluding censoring) from APOLLO at 18-months follow-up; according to the CS, this exercise suggested that model under-predicts mortality in both treatment groups and, at least at the 18-month timepoint, the model under-predicts the incremental survival advantage of patisiran.[1] The ERG notes that crude mortality rates which do not account for censoring will be underestimates. Although this may reflect the fact that the observed estimates are just one realisation from a predictive distribution of study responses, it may also mean that the modelled survival functions are over-estimated.

5.2.6 Company's results (including PAS)

In line with the analyses presented within the CS,[1] the results presented in this section are based on discount rates of 3.5% and 1.5% for costs and health outcomes, respectively. The ERG does not consider the use of differential discounting to be appropriate; corrected ICERs based on equal discount rates of 3.5% for health outcomes and costs are presented subsequently throughout this report. All results

presented in this section include the company's PAS; results based on the list price of patisiran are presented in Appendix 2.

Central estimates of cost-effectiveness

Table 25 presents the central estimates of cost-effectiveness generated using the company's model, based on discount rates of 1.5% for health outcomes and 3.5% for costs. Based on a re-run of the probabilistic version of the model by the ERG, patisiran is expected to generate an additional 8.11 QALYs at an additional cost of [redacted] per patient; the corresponding ICER for patisiran versus BSC is [redacted] per QALY gained. The deterministic version of the model produces a slightly higher ICER of [redacted] per QALY gained for patisiran versus BSC. The deterministic model suggests that patisiran generates approximately 9.73 additional undiscounted QALYs compared with BSC (not shown in Table 25).

Table 25: Company's base-case cost-effectiveness results – patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, includes PAS

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Probabilistic model*							
Patisiran	NR†	8.42	[redacted]	NR†	8.11	[redacted]	[redacted]
BSC	NR†	0.31	[redacted]	-	-	-	-
Deterministic model							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life years; ICER - incremental cost-effectiveness ratio
**Probabilistic results based on a re-run of the company's model by the ERG*
† Not included in company's PSA VBA sub-routine
‡ Undiscounted

Company's probabilistic sensitivity analysis

Figure 11 presents CEACs for patisiran and BSC. As shown in the figure, the probability that patisiran produces more net benefit than BSC at willingness-to-pay (WTP) thresholds below £100,000 per QALY gained is approximately [redacted]. At WTP thresholds of £200,000 per QALY gained and £300,000 per QALY gained, the probability that patisiran is optimal is approximately [redacted] and [redacted], respectively. The ERG notes that despite the magnitude of the company's base case ICER, the CEACs indicates a non-zero probability that patisiran is cost-effective at very low WTP thresholds; this is a consequence of errors in the company's PSA which are discussed in Section 5.3.

Figure 11: Cost-effectiveness acceptability curves – patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, includes PAS

[redacted]

Company's deterministic sensitivity analyses

Figure 12 presents the results of the company's DSAs in the form of a tornado diagram (change in ICER from baseline). These analyses suggest that the most influential model parameters are the discount rates for health outcomes and costs, the utility regression model interaction term for time*treatment and the mortality HR for the PND 0-II versus the general population. The ERG notes that the ICER is greater than [redacted] per QALY gained across all analyses.

Figure 12: DSA tornado diagram – patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, includes PAS (adapted by the ERG*)

** The tornado diagram presented in the CS was incorrect, the version presented here has been generated by the ERG using the company's model*

Company's scenario analyses

Table 26 presents the results of the company's scenario analyses. As shown in the table, the ICERs generated within the scenario analyses around alternative imputation rules for missing transition data produce ICERs which are higher than the company's base case analysis; the remaining scenarios analyses produce ICERs which are lower than the company's base case.

Table 26: Company's scenario analysis results - patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, includes PAS (generated by the ERG)

Scenario	Inc. LYGs‡	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Scenario 1A – pessimistic imputation of missing transition data (all patients with missing data progress to next worst state)	6.19	7.36	[redacted]	[redacted]
Scenario 1B – optimistic imputation of missing transition data (all patients with missing data regress to next best state)*	7.70	8.46	[redacted]	[redacted]
Scenario 2 – no utility constraint†	7.41	10.61	[redacted]	[redacted]
Scenario 3 – exponential ToT function	7.41	8.30	[redacted]	[redacted]
Scenario 4 – no additional mortality risk associated with PND	3.61	11.17	[redacted]	[redacted]

LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PND – polyneuropathy disability; ToT – time on treatment

** The results for this scenario appear to be incorrect in the CS*

† Assumes minimum utility for BSC equal to -1.0; ‡ Undiscounted

5.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[49, 50]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.
- Replication of the base case results, PSA, DSA and scenario analyses presented within the CS.[1]
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.1 Model verification

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. As shown in Table 27, the ERG's results are identical to those generated using the company's model. During the process of rebuilding the model, the ERG identified several minor programming errors as well as conceptual issues relating to the model structure and its use of evidence; these are detailed in Section 5.3.3. Overall, the ERG is satisfied that the company's deterministic base case analyses have been implemented without significant error.

Table 27: Comparison of company's base case model and ERG's rebuilt model results, health outcomes and costs discounted at rates of 1.5% and 3.5%, respectively, including PAS*

Model outcome	Company's model			ERG's rebuilt model		
	Patisiran	BSC	Incremental	Patisiran	BSC	Incremental
LYGs	13.73	7.78	5.95	13.73	7.78	5.95
QALYs	8.52	0.22	8.30	8.52	0.22	8.30
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-	-	[redacted]	-	-	[redacted]

LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; ERG – Evidence Review Group
** Results presented in this table do not include the correction of any errors discussed in Section 5.3.3*

5.3.2 Adherence of the company's model to the NICE Reference Case

The company's economic evaluation is partly in line with the NICE Reference Case.[51] The main exception relates to the use of differential discount rates, which are not advocated within the NICE Interim Methods Guide for HSTs.[52] In addition, the model assumes that a small proportion of patients with PND IV start treatment with patisiran; these patients would not be eligible for treatment according to the draft marketing authorisation for patisiran.[8] These issues are discussed in further detail in Section 5.3.3.

Table 28: Adherence of the company's model to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	With the exception of the use of differential discount rates, the company's economic analysis is generally in line with the NICE scope.[6] The company's economic analyses relate to the APOLLO mITT population.[7] This implies an assumption that the population of APOLLO is representative of the target population of patients with hATTR amyloidosis with polyneuropathy who would receive patisiran in England. Clinical advisors to the ERG believe that the APOLLO trial is broadly representative of the patient population seen in clinical practice in England, with the exception of patients with advanced polyneuropathy who were excluded from the trial. As the draft marketing authorisation is restricted to hATTR amyloidosis patients with Stage 1 and Stage 2 polyneuropathy,[8] these patients would not be eligible for treatment, hence their exclusion is appropriate. However, the ERG notes that one patient randomised to the placebo group in APOLLO had FAP Stage 3 disease and would not be eligible for treatment. The ERG considers this to be a minor issue. The population indicated by the license (adult patients with hATTR amyloidosis with Stage 1 or Stage 2 polyneuropathy) differs from the population defined in the NICE scope[6] (people with hereditary transthyretin-related amyloidosis). The ERG believes the company's variation to be appropriate.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[6] defines the comparator as *"established clinical management without patisiran."* The comparator considered within the company's economic analyses is BSC (symptomatic management), based on the list of interventions reported in Ando *et al*.[4] Clinical advisors to the ERG noted that whilst there is evidence that tafamidis has some efficacy in the treatment of hATTR amyloidosis, it is not currently available for use on the NHS in England due to a negative AGNSS recommendation. The clinical advisors also agreed with the company's view that liver transplantation is not commonly used for the treatment of hATTR amyloidosis in England. They also commented that diflunisal is sometimes used off-label to reduce amyloid progression, but is contraindicated in cardiac patients as it causes fluid retention and many patients have developed toxicity or progressed on this drug. None of these treatments are included in the company's BSC costs.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained. The company's model includes a small additional disutility for caregivers for patients whilst in the PND IV health state.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective.

Element	Reference case	ERG comments
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for patisiran versus BSC.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 40-year time horizon. Approximately 100% of patients have died by the end of the modelled time horizon.
Synthesis of evidence on health effects	Based on systematic review	Health state transitions, HRQoL estimates and AE rates for the patisiran and BSC groups are based on data from the APOLLO trial;[7] this was the only RCT identified within the company's systematic review of clinical evidence. The relationship between PND state, NT-proBNP score and survival was based on external data,[5, 37, 38] APOLLO[7] and assumptions.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	EQ-5D-5L data were collected in APOLLO. Patient utilities by PND state and the rate of improvement (patisiran group) and worsening (BSC group) were estimated using a regression model fitted to these data. Health utilities included in the model therefore reflect health effects measured in patients with hATTR amyloidosis which have been valued by the general population of England (using the mapping algorithm developed by Van Hout *et al*[27]). The disutility for caregivers was based on an estimate applied within the tafamidis AGNSS model[33] (which in turn, was based on the NICE FAD of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease[46]).
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	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	No additional equity weighting is applied to estimated QALY gains.
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	Resource components included in the company's models reflect those relevant to the NHS and PSS. Unit costs were valued at 2016/17 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	The company's model uses differential discount rates of 1.5% and 3.5% for health outcomes and costs, respectively. The CS[1] argues that using *"similar discount rates for cost and health benefits may not properly reflect changes in the value of health effects over time."* The ERG does not consider the company's discounting approach to be appropriate; this issue is discussed further in Section 5.3.3.

mITT - modified intention-to-treat; AGNSS - Advisory Group for National Specialised Services; FAP - familial amyloid polyneuropathy; BSC - best supportive care; QALY - quality-adjusted life year; PND - polyneuropathy disability; RCT - randomised controlled trial; HRQoL - health-related quality of life; NT-proBNP - N-terminal pro b-type natriuretic peptide; PSS - Personal Social Services; FAD - final appraisal determination; ERG – Evidence Review Group; hATTR amyloidosis – hereditary ATTR amyloidosis; NICE – National Institute for Health and Care Excellence; AE – adverse event

5.3.3 Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analysis. These issues are discussed in further detail in the subsequent sections.

Box 1: Summary of main issues identified within the company's model

(1) Identification of model errors
(2) Inappropriate use of differential discount rates for health outcomes and costs
(3) Issues surrounding rules for initiating and discontinuing patisiran treatment
(4) Issues relating to the company's model structure
(5) Concerns regarding the company's assumed mortality assumptions
(6) Concerns regarding the company's approach for estimating health state occupancy
(7) Issues relating to the company's HRQoL assumptions
(8) Issues surrounding resource use and costs
(9) Characterisation of uncertainty

(1) Identification of model errors

The ERG identified a number of errors in the company's model; these are described individually in the sections below.

(ii) Repeated application of "one-off" polyneuropathy costs

In order to calculate "one-off" costs, the model estimates the probability that a patient in any health state (except PND IV) progresses to the next worst health state. However, as the transition matrices (except the BSC extrapolation matrix) allow patients to transit to better (less advanced) health states, these "one-off" costs are therefore applied more than once in both treatment groups. In response to a request for clarification from the ERG[2] (question B25), the company confirmed that this aspect of the model does reflect an error and that it is a consequence of the use of a model structure which cannot capture patient histories. As part of their response, the company undertook additional analyses which indicate that excluding one-off costs from the model has only a minor impact upon the cost-effectiveness of patisiran (company's base case ICER [with PAS] = [redacted] per QALY gained; ICER excluding one-off costs [with PAS] = [redacted] per QALY gained. The ERG agrees that the company's current model structure cannot capture these costs appropriately and that the magnitude of the bias is likely to be minor.

(ii) Double-counting of "one-off" resource use items in Delphi panel

The ERG notes that the one-off polyneuropathy costs are subject to a further double-counting issue as a consequence of design of the Delphi panel. CS Appendix 3, Table 10 presents the panellists' responses

regarding the expected "one-off" resource use relating to mobility aids, home adjustments and other equipment, such as wheelchairs, sticks, frames, chairs and a homecare bed. However, the resource use estimates by PND score do not take account of the fact that the costs associated with these resource items may have already been incurred when patients progressed to earlier PND states. For example, the Delphi respondents stated that 100% of patients with PND IV would require a wheelchair; this cost is included in the model when patients reach the PND IV state. However, a significant proportion of patients would have already required a wheelchair when they progressed to PND III. The ERG considers it likely that such patients would keep their existing wheelchair rather than require a new one to be purchased. In response to a request for clarification (see clarification response,[2] question B24), the company provided additional analyses which attempt to correct for this issue; these analyses suggest that this error has only a minor impact on the ICER (although the ERG notes that issue [i] described above still applies within the company's analyses).

(iii) Administration and premedication costs of patisiran are not adjusted by RDI

The company's model applies the RDI observed in APOLLO to account for all temporary reductions or missed doses while patients are on treatment. Whilst the acquisition costs for patisiran are down-weighted by RDI, administration and premedication costs are not; except for those instances in which a partial dose is given, this implicitly assumes that patients attend hospital for their scheduled dose but do not receive it. The ERG considers this to reflect an error in the model logic.

(iv) The use of a time to treatment discontinuation function and an RDI multiplier is incorrect

The company's model estimates the acquisition costs of patisiran during each cycle using both the RDI multiplier and the cumulative probability of not yet having discontinued treatment (based on the time on treatment curve). The ERG considers this approach to be illogical, as the RDI already reflects the difference between the number of doses planned and the number of doses received – applying a further time on treatment curve means that cost savings associated with missed patisiran doses will be double-counted. The ERG also notes that because the structure of the model does not include separate matrices for patients who have discontinued patisiran, extrapolating a time on treatment curve beyond the trial duration means that the benefits of treatment are assumed to be constant despite the proportion of patients receiving that treatment being reduced over time. Given a sufficiently long time horizon (i.e. much longer than expected survival for the modelled cohort), this would lead to an illogical situation whereby all patients would have discontinued treatment whilst still accruing treatment benefit at the level of RDI observed in the trial. In response to a request for clarification on this matter (see clarification response,[2] question B20), the company acknowledged that their approach leads to *"possible double-counting."* The ERG considers this possibility to be definite and believes that only the RDI should be included in the model.

(v) Mathematical errors in adjustment of the cycle length

The ERG also notes that there is an error in the method used to adjust the cycle length of the company's transition matrices. This issue is discussed in further detail in critical appraisal point (6).

(vi) Errors and problems relating to the company's PSA

The ERG identified several further issues which impair the robustness of the company's probabilistic model. Despite the irrelevance of the time to treatment discontinuation function (see previous critical appraisal point 1[iv]), black-box testing of the model by the ERG indicates that the company's selected log normal function is not stable and a proportion of probabilistic samples of the curve are unreliable and/or incorrect. This issue appears to have arisen because the sampling method allows the scale parameter of the log normal distribution to become negative (most likely due to poorly defined parameter values). For example:

- A small proportion of sampled parameters to the time on treatment function suggest a very rapid rate of discontinuation (example shown in Figure 13). As the prognosis of patisiran discontinuers is not modelled separately, these patients accrue the same level of treatment benefit based on the RDI observed in the trial. Taken together, these two factors produce a situation whereby in some samples, patisiran either has a very low ICER or even dominates BSC. This explains why the CEACs generated using the company's model (previously shown in Figure 11) indicates that the probability that patisiran is optimal is not zero even at very low WTP thresholds. The ERG does not consider this finding to be plausible.
- In other probabilistic samples, the sampled time to discontinuation function suggests that the cumulative probability of not yet having discontinued patisiran increases over time (example shown in Figure 14). The ERG notes that it is neither logical nor correct for a cumulative survivor function to increase over time.

Figure 13: Example probabilistic sample from company's log normal time to treatment discontinuation function (rapid discontinuation)

[redacted]

Figure 14: Example probabilistic sample from company's log normal time to treatment discontinuation function (increasing cumulative probability of not having discontinued)

[redacted]

The ERG also notes that the PSA sub-routine frequently produces '#NUM' or '#VALUE' errors for the sampled one-off costs in PND 1; this is a consequence of a poorly specified gamma distribution describing the probability of receiving sildenafil. The ERG considers this to be a minor issue.

In addition, the ERG identified further problems relating to the sampling of HRQoL parameters within the company's model. As the parameters of the HRQoL OLS model and the maximum ceiling/minimum

floor caps are sampled using independent normal distributions (not bounded by 0 or 1), the model allows some sampled utilities to exceed 1.0. This reflects an unequivocal error; however, the general population utility constraint prevents this from impacting upon the model results.

(2) Inappropriate use of differential discount rates for health outcomes and costs

The company's base case analysis applies differential discount rates of 1.5% for health outcomes and 3.5% for costs. The CS[1] (page 144) argues that a health economic analysis which uses similar discount rates for cost and health effects "*may not properly reflect how the value in health effects changes over time."* The CS cites a number of studies[53-58] to support the company's position that the use of differential discount rates is appropriate. The company also argues that *"Patisiran has shown a high level of safety and effectiveness over the long term and has demonstrated the ability to halt or reverse disease progression and improve HRQoL in hATTR amyloidosis patients (Section 9).[11, 16] Thus, patisiran for hATTR amyloidosis treatment meets most of the criteria established by NICE for the consideration of a 1.5% discount rate on health effects."* With respect to this point, the CS argues that the requirement that health benefits must be sustained over at least 30 years would unfairly penalise patients with hATTR amyloidosis as they are often older and therefore would have had an additional life expectancy less than 30 years even in the absence of this disease. The discount rates chosen for the company's model are consistent with those implied by Gravelle and Smith's expanded framework for discounting non-monetary effects (i.e. QALYs).[55, 56]

The NICE Reference Case states that health outcomes and costs should be discounted at a rate of 3.5% per annum. For non-reference case analyses, the NICE interim Methods Guide for HSTs[52] states the following:

"In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs" (NICE Interim Methods Guide for HSTs[52]).

In response to a request for clarification on why the company believed the use of differential discount to be appropriate (see clarification response,[2] question B3), the company re-iterated their original arguments set out in the CS,[1] noting also that some other countries mandate a differential discount rate in reference case analyses and that NICE had previously adopted this position. The company also

commented that whilst the 48-month duration of the global OLE was *"not a very long period in the context in which discount rates are generally considered, it is nevertheless a relatively long timeframe for this exceedingly rare disease with reduced life expectancy."* [2]

Irrespective of the plausibility of the theoretical arguments regarding the use of differential discount rates, the ERG notes that:

(i) The NICE Reference Case does not support the use of differential discount rates

(ii) The non-reference case discounting scenario set out in the NICE Interim Methods Guide for HSTs[52] does not support the use of differential discount rates

(iii) The overall population of patients with hATTR amyloidosis represented in the model is not universally in close proximity to death (as indicated by the company's survival projections by health state, see Figure 9) and not all have severely impaired HRQoL (as indicated by the company's modelled HRQoL trajectory for BSC-treated patients, see Figure 22)

(iv) There is no evidence from RCTs to show that patisiran can improve patients' HRQoL or survival beyond 18-months

(v) The expected survival for an age- and sex-matched cohort without hATTR amyloidosis is less than 30 years

(vi) The company's arguments for applying differential discounting are not specific to this appraisal; the same argument could be made for any NICE appraisal.

On the basis of these issues, the ERG considers that the company's use of differential discount rates is inappropriate for NICE decision-making. Table 29, Table 30, Figure 15 and Figure 16 present the results of the company's model using equivalent discount rates of 3.5% for health outcomes and costs.

Table 29: Company's base-case cost-effectiveness results – patisiran versus BSC, company's model, health outcomes and costs both discounted at 3.5%, includes PAS

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY)
Probabilistic model*							
Patisiran	NR†	7.04	[redacted]	NR†	6.63	[redacted]	[redacted]
BSC	NR†	0.42	[redacted]	NR†	-	-	-
Deterministic model							
Patisiran	15.78	7.14	[redacted]	7.41	6.82	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; NR – not reported
**Probabilistic results based on a re-run of the company's model by the ERG*
† Not included in company's PSA macro
‡ Undiscounted

Figure 15: Cost-effectiveness acceptability curves – patisiran versus BSC, health outcomes and costs both discounted at 3.5%, includes PAS

Figure 16: DSA tornado diagram – patisiran versus BSC, health outcomes and costs both discounted at 3.5%, includes PAS (adapted by the ERG*)

** The tornado diagram presented in the CS was incorrect; the version presented in this figure has been adapted from the company's model*

Table 30: Company's scenario analysis results – patisiran versus BSC, health outcomes and costs both discounted at 3.5%, includes PAS (generated by the ERG)

Scenario	Inc. LYGs‡	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Scenario 1A – pessimistic imputation of missing transition data (all patients with missing data progress to next worst state)	6.19	6.06	[redacted]	[redacted]
Scenario 1B – optimistic imputation of missing transition data (all patients with missing data regress to next best state)*	7.70	6.87	[redacted]	[redacted]
Scenario 2 – no utility constraint†	7.41	8.59	[redacted]	[redacted]
Scenario 3 – exponential ToT function	7.41	6.82	[redacted]	[redacted]
Scenario 4 – no additional mortality risk associated with PND	3.61	8.96	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PND – polyneuropathy disability; ToT – time on treatment
** The results for this scenario appear to be incorrect in the CS*
† Assumes minimum utility for BSC equal to -1.0
‡ Undiscounted

(3) Issues surrounding rules for initiating and discontinuing patisiran treatment

(a) Initiation of patisiran treatment

The draft SmPC[8] states that treatment with patisiran is indicated in adult patients with hATTR amyloidosis with Stage 1 or 2 polyneuropathy. However, the company's model health states are defined according to PND score rather than FAP stage (although it is possible to map from PND score to FAP stage, as shown in Table 13). The ERG notes that according to the APOLLO CSR,[7] one patient who was randomised to the placebo group had FAP Stage 3 and none of the patients in either treatment group had Stage 0 disease, hence the APOLLO trial does broadly reflect the starting rule set out in the marketing authorisation. The ERG therefore does not consider this an important matter of concern. Despite the indication set out in the anticipated marketing authorisation, three of the ERG's four clinical advisors believed that there were no FAP patients for whom patisiran should not be given; one advisor noted that they would be cautious about initiating treatment in patients with inflammatory bowel disease (IBD).

(b) Discontinuation of patisiran treatment

The draft SmPC for patisiran[8] does not explicitly discuss when it might be appropriate to stop treatment with patisiran, although the ERG considers that one might infer from the marketing authorisation that this would be upon progression to PND IV (FAP Stage 3). The company's model does not include a discontinuation rule; rather, patients are assumed to receive patisiran indefinitely (until death, irrespective of PND score). In response to a request for clarification from the ERG[2] (question B7), the company stated that *"Because hATTR amyloidosis is a life-long disease and patisiran is not a one-time cure, patisiran treatment will need to continue indefinitely. Given that patisiran has demonstrated clinical benefit on multiple different endpoints, it is unclear that it would be appropriate to impose*

stopping rules based on apparent loss of efficacy on any one measure, since benefit may still be achieved on other measures. This conclusion is also based on clinical opinion received from experts at the NAC." However, the company also states that despite this interpretation of the clinical evidence, they did explore the potential for stopping rules based on loss of efficacy; these analyses were not presented in the CS. The company's clarification response also comments that the clinical experts they consulted agreed with the hypothesis that patients who transition to PND IV may still benefit from treatment with patisiran.

Clinical advisors to the ERG commented that currently there are no other effective treatment options for hATTR amyloidosis and that they would continue to treat patients with patisiran even if the patient's disease was progressing and/or their symptoms were worsening. The clinical advisors commented that the only scenario in which they would consider discontinuing treatment would be if no TTR knockdown was evident. The ERG notes that the company's model does not explicitly estimate TTR trajectory; hence, this potential criterion for treatment discontinuation cannot be directly incorporated into the company's model.

(4) Issues relating to the company's model structure

The clinical advisors to the ERG accepted that the company's general model structure, which is based PND score and cardiac involvement, is reasonable. They noted that although PND score is limited as it only reflects impairment of patient mobility, this measure is used in clinical practice, and is simple to assess. However, the clinical advisors commented that PND scores might not be very sensitive over short periods of time (e.g. in clinical trials) and noted that they do not capture symptoms relating to autonomic dysfunction. In this regard, the FAP staging system would perform better. The clinical advisors to the ERG also agreed with the company's assumptions that increasing PND scores are associated with lower HRQoL, particularly as a consequence of autonomic dysfunction. The advisors commented that loss of autonomic function and cardiac involvement are the main drivers of mortality in hATTR amyloidosis.

Despite the broadly positive views expressed by the ERG's clinical advisors, the ERG has several other concerns regarding the company's model structure. These relate to: (a) the assumed relationship between PND score, NT-proBNP score and HRQoL; (b) the assumed relationship between PND score, NT-proBNP and death; (c) the inclusion of a time to treatment discontinuation function and a single transition matrix for patients who are still on treatment and those who are not, and (d) issues relating to granularity of health states and the use of non-informative prior distributions in preference to plausible beliefs of a rational impartial observer.

(a) Modelled relationship between PND score, NT-proBNP score and HRQoL

Whilst it might be reasonable to assume that a relationship exists between PND and HRQoL, the company's approach may not be appropriate for the following reasons:

- Autonomic involvement is not explicitly captured in the model health states, although the ERG notes that the relationship between autonomic dysfunction and health losses may be implicitly reflected in the model's parameter values (e.g. within the HRQoL and health state cost parameters).
- Clinical advisors to the ERG stated that cardiac involvement is a major contributor to the deterioration of HRQoL. This view is also reflected in Section 7.1 of the CS.[2] However, this factor was not included as a covariate in the company's EQ-5D-5L regression model, and separate disutilities are not applied to those health states involving NT-proBNP≥3,000pg/mL in the company's economic model.
- The company's model assumes a constant rate of improvement or worsening in HRQoL over time within each PND state. These predicted values are then superseded by the maximum/minimum utility caps applied in each treatment group. The ERG does not consider this structural approach to be appropriate and notes that this breaks the link between the description of the health state and how being in that health state impacts on patient outcomes. At a minimum, the company's PND-HRQoL approach suggests an implicit view that PND score is not a good descriptor of HRQoL.

The ERG notes that the draft ICER evaluation report for inotersen and patisiran[35] and the previous AGNSS tafamidis report[33] both adopted model structures which were based on FAP stage rather than PND score. The ICER model also incorporates different utility values for patients with cardiac involvement.[35]

(b) Relationship between PND score, NT-proBNP and death

The company's clarification response[2] highlights that there is only one study which reported an association between PND score and death (Suhr *et al*).[37] The ERG believes that despite the limitations of the available evidence, the approach taken to model mortality conditional on PND score (and NT-proBNP score) is convoluted, circular and highly uncertain. Within the ICER analysis, mortality rates by FAP stage were estimated using a retrospective natural history study of 266 hATTR amyloidosis patients treated at the Mayo clinic (Swiecicki *et al*[59]), whilst the impact of NT-proBNP score on mortality was estimated using trial data reported by Slama *et al*.[60] The ERG notes that it would have been possible to use similar mortality assumptions by mapping from PND score to FAP stage.

(c) Approach used to model treatment discontinuation and health state transitions

As noted in critical appraisal point (1), the ERG has concerns regarding the company's use of both: (i) a transition matrix which is intended to reflect outcomes for patients who are currently receiving patisiran treatment and those who have discontinued patisiran, and (ii) a time to treatment discontinuation function which assumes a continued probability of discontinuation beyond the 18-month follow-up period of APOLLO. The ERG notes that the observed transition matrix for patisiran reflects outcomes for patients who received patisiran at the RDI level observed in APOLLO. However, the use of a separate parametric time to discontinuation curve results in an implicit assumption that over time, an increasing proportion of patients will discontinue, yet all patients will experience the same treatment benefits observed according to the amount of patisiran usage during the first 18-month period. This means that given a sufficiently long time horizon, all patients would still accrue the observed benefits of treatment despite all patients having previously discontinued the drug. The ERG believes that this produces a bias in favour of patisiran. If the company had intended to reflect a scenario in which the probability of discontinuing patisiran increases after the end of follow-up in APOLLO, this would require the inclusion of either: (a) separate matrices describing the trajectories of patients who are still on treatment and patients who have discontinued, or (b) a time-varying adjustment of the overall patisiran extrapolation matrix.

(d) Issues relating to model granularity and availability of data

Costs and health outcomes within the company's model are driven by four 12x12 matrices of transition probabilities between health states (excluding death). The "within-trial" patisiran matrix is populated using data from [redacted] patients, whilst the "within-trial" BSC matrix is populated using data from [redacted] patients. As a consequence, the matrices feature many blank cells whereby transitions may plausibly occur, but such transitions were not observed in APOLLO (for patisiran 29 of 144 cells have data; for BSC 19 of 144 cells have data, see Table 15 and Table 16, respectively). The ERG has concerns that the company's model structure may "stretch" the APOLLO data too far, thereby resulting in a situation in which the posterior probabilities are largely, or in some instances, entirely, reliant on the "non-informative" prior distributions. The ERG considers this to be a situation when an elicitation of experts' beliefs is appropriate[61] or when it would be prudent to consider combining health states (e.g. by FAP stage) to reduce the sparseness of the transition matrices. In response to a request for clarification[2] (question B4), the company stated: *"In order to capture the changes in the health states with the maximum possible precision, we selected the PND classification as the basis for the definition of health states in the model because with its five scores for symptomatic patients (I, II, IIIA, IIIB, IV) it provides a more granular assessment of the disease than is possible using only the three FAP stages applicable to symptomatic patients (I, II, III)."* The ERG considers that the estimation of transition probabilities at this level of granularity must reflect reasonable beliefs of a rational impartial observer and should not be based on "non-informative" prior distributions. In addition, the company's clarification response[2]

(question B5) asserts that PND score was *"the only feasible choice of clinical staging scale to characterise health states within our pharmacoeconomic model… PND score was chosen over FAP stage because of its greater granularity."* The ERG considers this statement to be contradictory as a choice of metric does exist (PND or FAP) and notes that defining states by FAP stage may have led to the generation of smaller matrices in which the priors do not dominate the observed data. Such an approach would however lead to a more "blunt" model which may be less sensitive to changes in disease severity.

(5) Concerns regarding the company's assumed mortality assumptions

The ERG has several concerns regarding the company's approach to modelling mortality risks within the model:

- A purpose of a clinical trial is to estimate relative treatment effects on a suitable scale which are assumed to be, and usually are, transportable across different patient populations. Estimates of absolute effect are generated by adding the relative treatment effect to the baseline response in the target patient population. The CS reports that a multivariable analysis using data from APOLLO[7] to model the effect of different degrees of polyneuropathy on survival was planned, but was not conducted due to the low number of deaths in APOLLO. No consideration was given to plausible underlying hazard functions or to supplementing the observed data with experts' beliefs in order to estimate parameters.

- Mortality according to PND score was estimated using information reported by Suhr *et al.*[37]
  - The ERG has some concerns with the reporting of the study and the statistical methods used to analyse the data. For example, there is ambiguity whether patients had to be under 50 years of age to be part of the study or under 50 years of age at symptomatic onset of FAP, and no information is provided about the characteristics of the patients.
  - No discussion was provided in the CS regarding the relevance of this study to the target patient population.
  - The definition of time zero when analysing survival times is not specified but is assumed to be the onset of symptoms, which is different to the definition used in APOLLO.
  - The analysis of survival data does not take into account censored observations; this is important because only 13 of 27 patients died during the investigation.
  - No information is provided by Suhr *et al*[37] about the number of deaths by PND stage.
  - The mean survival times by PND state used in the CS are treated as if they are population values with no allowance for uncertainty.
  - Mean survival for patients with PND I-II and PND III-IV is derived by weighting the means in each PND stage according to sample size, whereas the appropriate weight based on maximum likelihood estimates would be the number of events.

- Hazard rates are estimated from the mean values assuming an underlying exponential distribution for the time to death without any justification.
- HRs are adjusted for the proportion of patients by NT-proBNP group in APOLLO and the weighted average of HRs (for Stage 2 versus Stage 1 cardiac transthyretin amyloidosis) for the V-122I group and the non- V-122I group in Gillmore *et al 2017*. No discussion is provided regarding whether these weightings relate to the target patient population; this is particularly relevant as the parameters of interest principally relate to patients with low NT-proBNP scores.

(6) Concerns regarding the company's approach for estimating health state occupancy

The ERG has concerns regarding the methods used by the company to estimate health state occupancy over the course of the time horizon. These relate to: (a) the initial health state distribution; (b) the generation of 6-month transition matrices, and (c) the company's gamma function method.

(a) Initial distribution at model entry

The initial distribution across the model health states was defined by the baseline distribution of PND scores in APOLLO and the probability that a patient's NT-proBNP score is greater than 3,000pg/mL. This approach forces the relative proportions of patients in each PND state and high NT-proBNP score to be identical to those for the same patient with low NT-proBNP score. The ERG considers this approach to reflect an unnecessary approximation – the initial distribution across all model health states could have been calculated directly using the baseline data from APOLLO. As part of their clarification response[2] (question B17), the company provided the data necessary to produce this distribution (see Table 31). As shown in the table, the proportion of patients with NT-proBNP≥3,000 is similar, but not the same, across each PND state.

Table 31: Initial distribution of patients in APOLLO by PND and NT-proBNP score threshold (reproduced from clarification response, question B17)

PND score	NT-proBNP			
	<3,000pg/mL		≥3,000pg/mL	
	N	%	N	%
PND 0	[redacted]	[redacted]	[redacted]	[redacted]
PND I	[redacted]	[redacted]	[redacted]	[redacted]
PND II	[redacted]	[redacted]	[redacted]	[redacted]
PND IIIA	[redacted]	[redacted]	[redacted]	[redacted]
PND IIIB	[redacted]	[redacted]	[redacted]	[redacted]
PND IV	[redacted]	[redacted]	[redacted]	[redacted]

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre; N - number

(b) Problems in the calculation of health state transition probabilities

The transition matrices have been estimated using data relating to the interval between baseline and 18-months in APOLLO. These matrices are then converted into rates in order to adjust the cycle length to

the 6-month interval adopted by the model, assuming that each rate is constant and independent of other rates in the matrix. This transformation is based on the "traditional method", based on equation [i]:

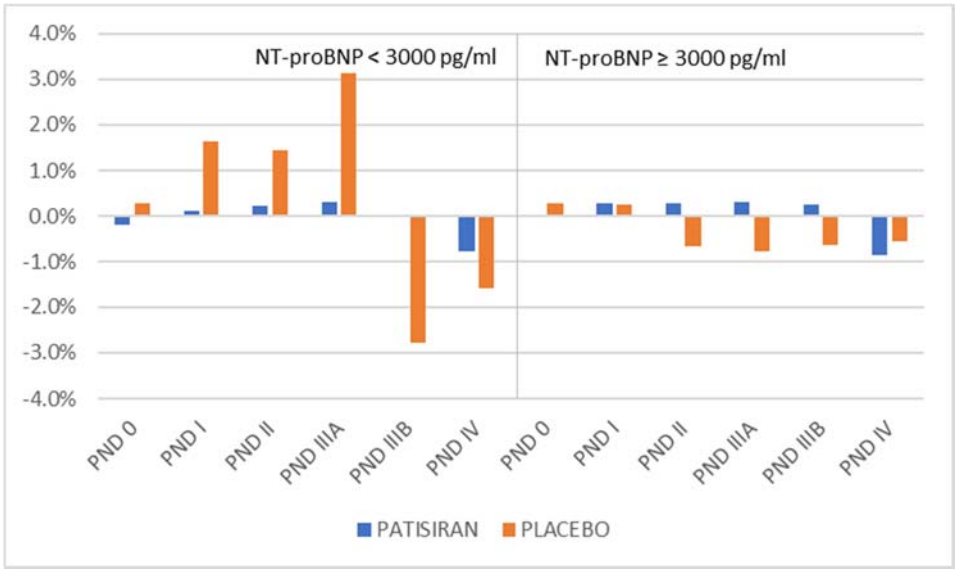
$$p = -\log (1-r)^{1/n} \quad [i]$$

where: p is the probability of the event, r is the instantaneous rate and n is the cycle duration

The ERG notes that this approach fails to reflect the multinomial nature of the data and the possibility of competing risks of different events (transitions) within the matrices. This "traditional" method has been shown to produce bias in instances whereby the underlying model contains more than two health states.[62, 63]

During the clarification process (see clarification response,[2] question B13), the ERG highlighted this issue to the company. In response, the company acknowledged that their method is imperfect and attempted to use the Eigendeconstruction method reported by Craig and Sendi[62] and Chhatwal *et al.*[63] However, the suggested transformation was unsuccessful as some of the eigenvalues are complex numbers (rather than real numbers) due to the nature of the matrix itself. As a consequence, this method did not produce robust matrices; similar attempts by the ERG produced negative transition probabilities. As part of their clarification response, the company attempted to explore the magnitude of the bias resulting from the use of the "traditional method" by comparing the distribution of patients in health states produced by the economic model after 18 months with an 18-month model (assuming no patients die in either model). The results of this exploratory analysis suggest that the traditional matrix adjustment method produces a small bias which favours the BSC group (see Figure 17). The ERG notes however that repeatedly applying an inaccurate matrix in each model cycle will compound the problem to produce a greater bias over longer time horizons. However, the ERG accepts that given the company's selected model structure and selected cycle duration, there is not an obvious means of converting the cycle length for the matrices given the observed data. It is likely that this issue would have been lessened by defining model states using FAP stage rather than PND score, although this would still have required the use of external evidence (e.g. expert elicitation) to inform transitions for patients with FAP Stage 3 disease. It is certain however, that this problem would not have arisen if an 18-month cycle duration was used; the ERG notes that there is no clear justification for adopting a 6-month cycle duration.

Figure 17: Difference in patient distribution at 18 months between the submitted model and an 18-month–cycle model (reproduced from company's clarification response, question B13)



NT-proBNP - N-terminal pro B-type natriuretic peptide; PND - polyneuropathy disability.
Note: graph shows the difference between the two models

The ERG also notes that the company's approach does not include any consideration of the observed PND patient count data at the 9-month time-point. During the clarification stage, the ERG requested that the company provide the equivalent patient count transition data for each assessment. In response, the company provided these data but stated a belief that using the 0-18 month matrix is more appropriate because it gives *"a clearer idea of treatment separation over time"* and allows the model to *"more accurately extrapolate the treatment benefits of patisiran relative to best supportive care."* The ERG does not necessarily agree with this view and believes that it may have been informative to explore whether these data indicate a different underlying distribution of health state transition rates. In a crude exploratory analysis undertaken by the ERG (not shown), the transitions for the patisiran group were extrapolated using the 9-18 month matrix (adjusted using the "traditional method"); whilst the estimated health outcomes for patisiran were different to those estimated using the 0-18 month matrix, the ICER remained broadly stable (~[redacted] per QALY gained).

(c) Concerns regarding the company's gamma function method

The company modelled the NT-proBNP data using a gamma distribution in preference to a log normal distribution on the basis that *"the long tail of the [log normal] distribution makes it a less appropriate choice."* However, according to Section 9.8.3 of the CSR, *"Based on published literature, a logarithmic transformation was applied to normalise the distribution of NT-proBNP."*

The company's model assumes that all patients' NT-proBNP increases by a fixed amount during each 6-month cycle, whilst the variance is held at the baseline level. The ERG believes that the company's

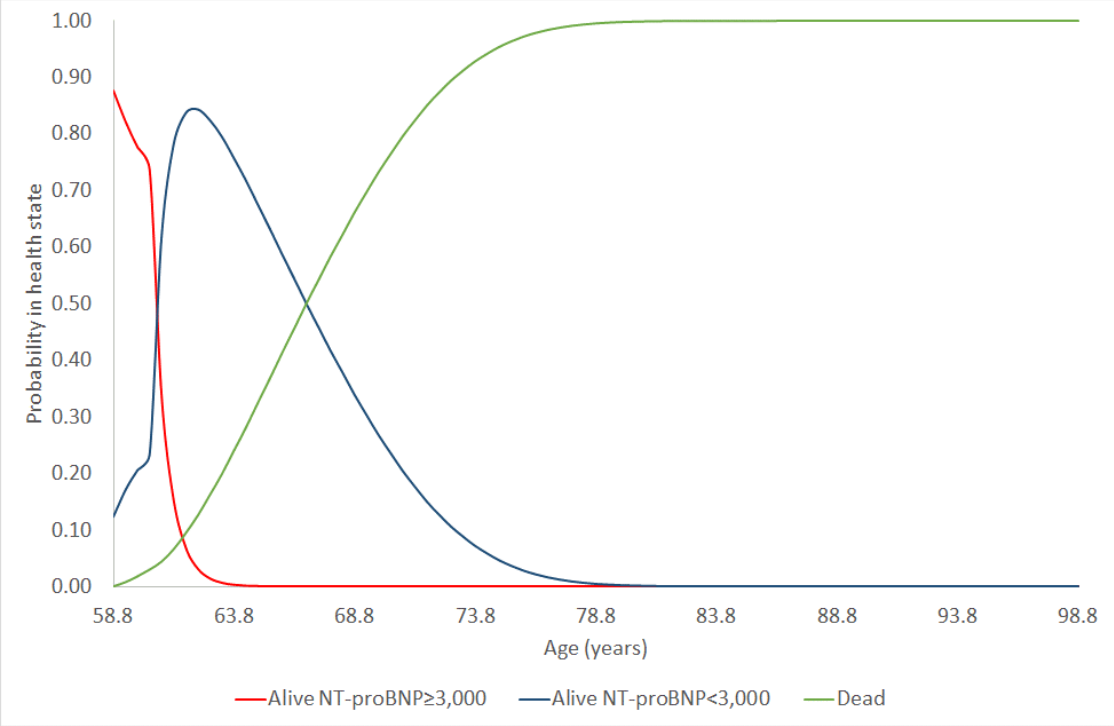
intended approach was to assume that by changing the mean but fixing the variance of the distributions at baseline and 18 months, the whole distribution would shift to the right (as shown in Figure 18). However, the parameters of the gamma distribution (alpha [shape] and beta [scale]) are a function of both the mean and the variance; consequently, the baseline and 18-month distributions appear very different to the company's hypothetical example given in the CS (see Figure 19). The ERG is unsure whether the company intended to implement this approach or how it ought to be interpreted. As a consequence of the company's gamma function method, the Markov trace for the BSC group indicates that all surviving patients develop NT-proBNP involvement after around 5 years (see Figure 20).

Figure 18: Descriptive representation of the method to estimate transition probabilities between NT-proBNP states, based on the NT-proBNP mean change (reproduced from CS, Figure 28)

The shaded area represents the percentage of patients with NT-proBNP ≥3000pg/mL

Figure 19: Modelled NT-proBNP probability density functions based on the company's gamma model parameters (generated by the ERG)

Figure 20: Modelled probability of being in NT-proBNP<3,000, ≥3,000 or dead (generated by the ERG)



(7) Issues relating to the company's HRQoL assumptions

Figure 21 and Figure 22 show the company's utility projections by PND and time for the patisiran and BSC groups, respectively. The ERG makes the following observations with respect to the company's assumed HRQoL projections:

- In general, the ERG believes that regression using a forward selection process is unreliable and that variables should be selected based on knowledge of the context. Furthermore, the CS[1] states that *"The forward selection process identified PND score and the product of treatment arm by time as significant covariates."* This model omits the main effects of treatment and time, which the ERG considers inappropriate.[64]
- The CS (page 130) refers to the use of maximum caps to avoid "ceiling effects." The ERG notes that the concept of ceiling effects relates to utility measurement, not the application of fitted utilities within a model. The ERG considers that the phenomenon described within the CS is actually the consequence of a poorly specified statistical model.
- The ERG believe that the company should have fitted a more appropriate statistical model to the APOLLO EQ-5D-5L data which properly takes into account the distribution of the underlying data and which does not permit impossible values (e.g. a Tobit model). This would have avoided the need for arbitrary maximum/minimum caps and would have avoided the possibility of sampled utility values exceeding 1.0 in the PSA.[65]

- Whilst the model includes age-specific utilities which decrease with advancing age, these are for the most part, overridden by the PND-specific caps; hence, as patients age, their utility increases or plateaus. The ERG does not consider this to be realistic.
- Over time, patisiran-treated patients with PND II are assumed to have the same HRQoL as that of a patient with asymptomatic disease. This does not appear plausible.
- BSC-treated patients with PND 0 (asymptomatic disease) are assumed to suffer considerable reductions in HRQoL. This does not appear plausible.
- Based on the mean undiscounted QALY gains and the mean undiscounted LYGs, patients in the patisiran group are assumed to have a mean utility of 0.64 whilst patients in the BSC group are assumed to have a mean utility of 0.02.

Figure 21: Modelled relationship between HRQoL, treatment and time – patisiran group (generated by the ERG)

Figure 22: Modelled relationship between HRQoL, treatment and time – BSC group (generated by the ERG)

Given the uncertainty in the EQ-5D-5L data from APOLLO, the ERG considers that the company should have further explored the impact health utility studies from the literature. Following a request for clarification[2] (question B1c), the company provided a list of 23 HRQoL studies which were identified by their searches but which were excluded from the CS because they did not meet the NICE scope.[6] Of these, four studies report health utility values.[34, 66-68] One of these studies (Stewart *et al*[34]) reports health utility values according to FAP stage (for Val30Met mutations and "other mutations" categories). In addition, other estimates of health utility by FAP stage are reported in the tafamidis AGNSS report,[33] and the ICER evaluation report[35] (see Table 32). The ERG believes that the company should have explored these alternative estimates of HRQoL within the model.

Table 32: Summary of health utility values by FAP stage from the literature

Study	State	Population / treatment/ model	FAP 1	FAP 2	FAP 3
Stewart *et al*[34]	Utilities (Brazilian tariffs)	Val30Met mutation	0.7	0.44	0.1
		other mutations	0.68	0.4	0.05
ICER report[35]	Model base case	If NT-proBNP ≤3,000	0.71	0.57	0.17
		If NT-proBNP >3,000	0.639	0.513	0.153
	Utility gains by treatment	Patisiran	0.073	0.097	0.097
		Inotersen	0.048	0.072	0.072
	Scenario analysis	using York report	0.636	0.501	0.375
		Stewart *et al* 2017 worst-case	0.57	0.41	0.05
AGNSS tafamidis report[33]	Statistical model type	By Stage	0.705	0.551	0.17
		Quadratic	0.646	0.494	0.331
		Cubic	0.662	0.539	0.366

FAP – familial amyloidotic polyneuropathy; ICER – Institute for Clinical and Economic Review; AGNSS – Advisory Group for National Specialised Services; NT-proBNP - N-terminal pro B-type natriuretic peptide;

(8) Issues relating to resource use and costs

The company's model calculates costs of SAEs according to treatment group, based on the observed rates observed in APOLLO, but also assumes that an increasing proportion of patients discontinue patisiran over time (based on the time to treatment discontinuation curve). The ERG considers this assumption to be illogical as given a sufficiently long time horizon within the company's model, all patients would have discontinued patisiran, but all patients would be experiencing SAEs based on the SAE rates for the patisiran group in APOLLO. As noted in critical appraisal point 4(c), the ERG considers that unless the transition matrix is modified to reflect different proportions of patients being on treatment, it is more appropriate to exclude the time to treatment discontinuation curve from the model altogether. In addition, the model assumes a single incidence rate for all SAEs across all health states which is constant over time. The ERG considers it likely that some AEs would be attenuated after some time, especially those related to the infusions, and their frequency is likely to be related to health state (NT-proBNP and possibly PND score).

An additional issue related to costs in the CS[1] refers to the absence of homecare costs in the model estimates. The pathway of care proposed in the CS involves an initial treatment given at the NAC, and subsequent treatment may be available to the patient, at the clinician's discretion, via a homecare service every 3 weeks, whilst being monitored by the central unit biannually. Nevertheless, the model assumes that patisiran will be administered in a day case setting at the NAC for all patients indefinitely. The CS justifies this assumption stating that *"the number of patients who would be eligible and who would choose to undergo home infusion is not known."*[1] Furthermore, the company's clarification response[2] (question B26) states that it is not yet known if the option of a homecare service will be available, and if so, it is unclear which party will pay for home infusions. Given the potential impacts on the healthcare system that such arrangements might result in, especially to local and regional authorities, the ERG

considers that an alternative analysis exploring this scenario should have been provided by the company.

(9) Characterisation of uncertainty

Transition matrices

Parameter values of transitions matrices are estimated primarily from sample data from APOLLO and "non-informative" prior distributions. The use of "non-informative" prior distributions is reasonable when there are sufficient sample data with which to estimate parameters. However, parameter estimates based on "non-informative" prior distributions are unlikely to represent reasonable beliefs when the sample data are limited.

The company's transition probabilities have been defined such the company is certain (i.e. with probability one) that no patient receiving BSC can transition to an improved state or worsen by more than one health state during the extrapolation period. This is a strong assumption and implies that even if further evidence became available of a patient treated with BSC who improved or worsened by more than one health state then it would not be believed and it could not be used to update the transition matrix.

Resource use

There are three main protocols for eliciting experts' beliefs about parameters, namely the Sheffield method, Cooke's method and the Delphi method.[69] There are advantages and disadvantages associated with each method. The company commissioned a Delphi panel report to elicit experts' beliefs about resource use (CS, Appendix 3). A particular limitation with the Delphi method as typically applied, and as applied in this submission, is that is does not yield a probability distribution representing uncertainty about parameters of interest.

In the case of PND-related resource use, experts were presented with estimates of resource use used in the AGNSS tafamidis submission[33] and *"were asked to indicate their agreement with the plausibility of the estimates of [resource use] at PND I and PND IV"* (CS,[1] Appendix 3, page 9). In the case of cardiomyopathy-related resource use, experts were asked to *"provide estimates of the use of each cardiomyopathy-related resource"* according to NT-proBNP levels above or below 3,000pg/ml (CS, Appendix 3, Appendix A). In each case, the experts were not given guidance regarding the value that their estimate represented. The ERG believes that the elicitation of moments of probability distributions such as the mean and variance is problematic; rather, it is recommended that such exercises involve the elicitation of other characteristics such as the median and quartiles. The mean and standard error of the experts' values were calculated and used to generate parameter values of beta distributions for proportions and of gamma distributions for numbers. Resource use was sampled from these probability

distributions and combined to produce overall once-only and per-cycle costs by health state. Using standard errors to represent uncertainty does not capture the true uncertainty associated with the group as a whole or what might be regarded as the opinion of a rational impartial observer. The ERG has concerns with the process that was followed when the CS concluded that *"After consulting with the ARC (a patient group) and clinical experts at the NAC, the consensus was that the Delphi panel process … did not adequately capture the [resource use] for patients in PND IV."* (CS, Appendix 3, page 12). The ERG believes that the current model is unlikely to reflect the true expected cost and uncertainty associated with resources used to treat patients with hATTR amyloidosis. Finally, it would be reasonable to assume that beliefs about the true value of resource use at a particular PND score or NT-proBNP level would affect beliefs about resource use at other PND scores or NT-proBNP level, respectively. Thus, not only should the estimates of resource use used in the CS reflect genuine uncertainty but it should also incorporate correlation between parameters.

5.4 Exploratory analysis undertaken by the ERG

5.4.1 ERG's exploratory analyses - methods

The ERG undertook two broad sets of exploratory analyses. The first set involved fixing errors identified within the ERG's critical appraisal (see Section 5.3.3) and modifying model inputs and assumptions in order to form an ERG-preferred analysis. The second set of analyses involved exploring residual uncertainty using this ERG-preferred model. All exploratory analyses were undertaken including the PAS discount; the results of the analyses using the list price for patisiran are provided in Appendix 2. Methods for applying the ERG's exploratory analyses within the company's model can be found in Appendix 3.

ERG-preferred analysis

The ERG-preferred analysis includes six general amendments to the company's base case model:

(1) Correction of errors

Three model errors were corrected:

(a) Patisiran administration and premedication costs were down-weighted by RDI;
(b) One-off costs were removed from the analysis for all PND scores;
(c) The cumulative probability of being on treatment was set equal to 1.0 over the entire time horizon (i.e. time to treatment discontinuation function was removed from the model)

All subsequent exploratory analyses include these error corrections

(2) Equal discount rates applied

In line with the NICE Interim Methods Guide for HSTs,[52] discount rates for health outcomes and costs were set equal to 3.5%.

(3) Recalculation of initial distribution by PND and NT-proBNP score

The initial distributions of patients across the model health states were recalculated using data on the probability of a patient having NT-proBNP≥3,000pg/mL conditional on PND score.[1] This alternative analysis also involved removing the placebo group patient with baseline FAP stage 3 from the initial distribution.

(4) Use of general population HRQoL from Ara & Brazier

The HRQoL for the general population was based on the formula reported by Ara and Brazier[70] instead of Kind *et al*[40]

(5) Adjustment of calculations to estimate mortality risk by PND stage for low NT-proBNP states

Within this analysis, the inflation of mortality risk due to NT-proBNP (using an HR from Gillmore *et al*[5]) was removed from the analysis of survival by PND stage using Suhr *et al* data[37] for the low NT-proBNP model health states.

(6) ERG-preferred analysis (analyses [1] to [5] combined)

The ERG's preferred analysis involved all changes listed in analyses 1-5. The probabilistic version of this analysis (6b) addresses some of the ERG's concerns regarding the company's PSA by fixing the cost of sildenafil and constraining maximum utility (see Appendix 2). It should be noted that whilst the ERG prefers this analysis to the company's base case, there remains considerable uncertainty surrounding the cost-effectiveness of patisiran (see Section 5.7).

The results of these the ERG's preferred analyses are presented Table 33.

Table 33: Results of ERG-preferred analysis

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(1) Correction of errors†							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(2) Equal discount rates applied							
Patisiran	15.78	7.14	[redacted]	7.41	6.82	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(3) Recalculation of initial distribution by PND and NT-proBNP score							
Patisiran	15.79	8.53	[redacted]	7.42	8.31	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(4) Use of general population HRQoL from Ara & Brazier							
Patisiran	15.78	8.54	[redacted]	7.41	8.32	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(5) Adjustment of calculations to estimate mortality risk by PND stage for low NT-proBNP states							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(6a) ERG-preferred analysis (deterministic, analyses 1-5 combined)							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(6b) ERG-preferred analysis (probabilistic, analyses 1-5 combined)							
Patisiran	NR§	7.09	[redacted]	NR	6.68	[redacted]	[redacted]
BSC	NR§	0.42	[redacted]				

BSC - best supportive care; Inc - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

** Undiscounted; † Analyses 2-6 each include error corrections from analysis 1; §Not included in company's PSA macro*

As shown in Table 33, amending the discount rate to be in line with the NICE Reference Case has the most substantial impact on the ICER for patisiran versus BSC. Based on the ERG-preferred analysis using the probabilistic version of the model, patisiran is expected to generate an additional 6.68 QALYs at an additional cost of [redacted]; the corresponding ICER for patisiran versus BSC is [redacted] per QALY gained. The deterministic version of the model yields a lower ICER of [redacted] per QALY gained. The deterministic analysis suggests that patisiran generates approximately 9.76 additional undiscounted QALYs compared with BSC.

Additional exploratory analyses using the ERG's preferred analysis

The ERG undertook eight further additional analyses using the ERG's preferred version of the model. The following analyses were undertaken:

(7) Time by treatment interaction term removed from model

Within this analysis, the parameters relating to the change in health utilities over time (0.003 increase for patisiran and -0.005 decrease for BSC, per month) were set equal to zero, hence both treatment groups accrue the same HRQoL within each PND state.

(8) Utility values from Stewart et al[34]

Health utilities by PND score were based on those reported by Stewart *et al*.[34] In this analysis, utilities for each PND state were applied by mapping from FAP state to PND score. HRQoL for PND 0 was assumed to be equivalent to general population health utility. In addition, the maximum/minimum utility caps were set equal to 1.0 and -1.0, respectively. The rate of change for health utility was set equal to zero. Separate analyses were undertaken using utilities based on utility estimates reported for:

(a) The Val30Met mutation group
(b) The "other mutations" group

(9) Lower HRQoL assumed for NT-proBNP ≥3,000pg/mL

A utility decrement of 10% was applied for patients with NT-proBNP ≥3,000. This decrement was applied relative to the utility for each PND state and was applied after the utility caps. A similar assumption was made within the ICER evaluation report.[35]

(10) Relative reduction in resource use for patisiran-treated patients

The estimated relative reduction in health care resource use for patisiran-treated patients were:

(a) Halved
(b) Removed

(11) Removal of PND-related mortality

The additional mortality risk associated to PND was removed (HRs set to 1.0)

(12) Zero change in NT-proBNP

The expected change in the mean NT-proBNP level was set to zero.

Table 34 presents the central estimates of health outcomes, costs and cost-effectiveness from the additional exploratory analysis.

Table 34: Results of ERG exploratory analysis using the ERG-preferred model

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
(6) ERG-preferred analysis							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(7) Time by treatment interaction term removed from model							
Patisiran	15.79	5.58	[redacted]	7.42	3.87	[redacted]	[redacted]
BSC	8.37	1.71	[redacted]	-	-	-	-
(8a) Utility values from Stewart *et al* - Val30Met mutation							
Patisiran	15.79	5.75	[redacted]	7.42	3.51	[redacted]	[redacted]
BSC	8.37	2.25	[redacted]	-	-	-	-
(8b) Utility values from Stewart *et al* - other mutations							
Patisiran	15.79	5.36	[redacted]	7.42	3.41	[redacted]	[redacted]
BSC	8.37	1.95	[redacted]	-	-	-	-
(9) Lower HRQoL assumed for NT-proBNP ≥3,000pg/mL							
Patisiran	15.79	7.08	[redacted]	7.42	6.73	[redacted]	[redacted]
BSC	8.37	0.35	[redacted]	-	-	-	-
(10a) Relative reduction in resource use for patisiran-treated patients halved							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(10b) Relative reduction in resource use for patisiran-treated patients set to zero							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(11) Removal of PND-related mortality							
Patisiran	18.15	7.96	[redacted]	3.62	8.99	[redacted]	[redacted]
BSC	14.53	-1.03	[redacted]	-	-	-	-
(12) Zero change in NT-proBNP							
Patisiran	15.79	7.17	[redacted]	5.36	7.30	[redacted]	[redacted]
BSC	10.43	-0.12	[redacted]	-	-	-	-

BSC - best supportive care; Inc - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** Undiscounted*

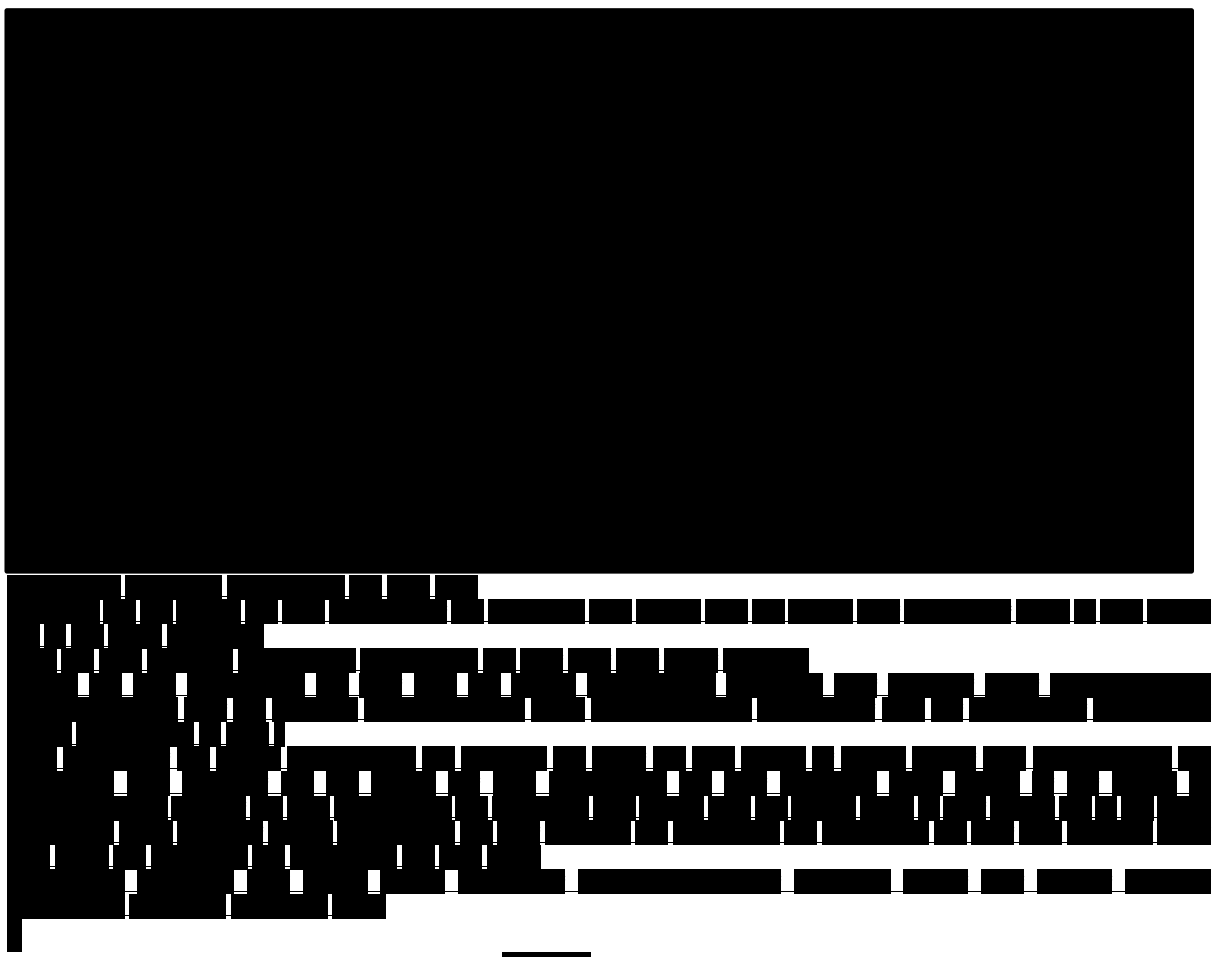
As shown in Table 34, the assumptions regarding health utilities, particularly the assumed increase for patisiran and decrease for BSC, have a significant impact upon the ICER. The inclusion of an HRQoL impact associated with NT-proBNP≥3,000pg/mL has only a minor impact on the model results. The relative reductions in resource use associated with patisiran are also not influential parameters. The exploratory analyses also indicate that the inclusion of PND-related mortality and the assumed increase in patients with NT-proBNP≥3,000pg/mL within the extrapolation period for the BSC group have a significant unfavourable impact on the ICER for patisiran. The ERG notes that the behaviour of the model is significantly impacted upon by the assumption that HRQoL is dependent on the treatment received; unless this assumption is removed, other changes to the model (e.g. the transitions matrices) have only a limited impact on the model results.

5.5 Costs to the NHS and PSS - eligible population and net budget impact

The CS[1] estimates that 100 patients will be eligible for treatment with patisiran in Year 1 based on the following assumptions:

- Based on the number of patients registered at the NAC, the company estimates that 150 patients in the UK have hATTR amyloidosis.
- Based on the FAP stage distribution in APOLLO, 99.56% of these patients are assumed to have Stage 1 or 2 FAP
- Using on data from the NAC, 75% of these patients are assumed to live in England.
- 65% of patients present with polyneuropathy
- 27 newly diagnosed patients will also be eligible for treatment.
- The CS indicates that the prevalent population eligible for treatment with patisiran in England will rise to 187 patients by Year 5.

Figure 23: Eligible population of hATTR amyloidosis patients in England (reproduced from CS, Figure 43)



The CS indicates an expected uptake of [redacted] per year, taking into consideration a proportion of patients who wish to participate in clinical trials, defer treatment or receive an alternative treatment.[2]

The net budget impact (excluding any cost savings due to reduced resource use) is estimated to be [redacted] in Year 1, rising to [redacted] in Year 5.

The CS notes that no additional costs to the NHS or PSS are expected with patisiran. The CS also argues that cost savings are expected, partly on account of the proposed homecare service which will reduce hospital costs as well as travel and accommodation costs for patients who do not live in the proximity of the NAC.

The ERG notes the following observations regarding the company's budget impact analyses:

- The stage distribution assumed may not be fully representative of the overall population of patients seen in clinical practice as APOLLO listed PND ≤3b (i.e. FAP stage 1 or 2) as an inclusion criterion.
- The ERG considers it likely that if patisiran is available, the level of uptake will be higher than the estimates predicted by the company, hence the net budget impact may be considerably higher than the estimates presented in the CS.
- As the cost estimates have been derived from the company's model, these do not take into account the scenario in which patisiran is delivered through the proposed homecare service.
- It is unclear whether the budget impact estimates include the proposed PAS.

Overall, the ERG believes it is likely that the net budget impact of patisiran has been underestimated.

5.6 Potential wider costs and benefits not included in the company's economic analysis

The CS[1] (pages 206 and 207) states that patisiran is anticipated to generate other significant economic benefits beyond the NHS and PSS sector, in terms of:

(i) Improvement in patient and caregiver productivity and ability to participate in activities, and associated decrease in the absenteeism and loss of income;

(ii) Reductions in the out-of-pocket costs, such as acquisition of mobility equipment, home equipment, adaptations or maintenance, and travelling costs for treatment (including transportation and overnight accommodation/meals);

(iii) Reductions in the financial support needed from external sources, such as continuing healthcare, disability allowance, and attendance allowance, some of them incurred by local government and county council programmes.

In response to a request for clarification from the ERG (see clarification response,[2] question B19), the company noted that such effects are to be logically expected given the clinical benefits in terms of disability experienced by patients receiving patisiran. The clinical advisors to the ERG considered this

expectation to be reasonable. However, as stated within the company's clarification response,[2] there is no direct evidence currently available to support this assertion. The ERG also notes that the extent to which the expected benefits of patisiran will influence patients, caregivers and families' productivity losses and indirect costs will be dependent on the extent to which disability is reduced, the patient's age and remaining time prior to retirement.

5.7 Discussion

The CS includes systematic reviews of existing health economic studies and HRQoL valuation studies. Even though the searches and inclusion criteria applied in the company's review were not restricted by intervention, any HRQoL or economic evaluation study that did not specifically include patisiran was excluded. As such, the company's review did not identify any published economic evaluations of patisiran in this indication, and the only study involving preference-based valuations of HRQoL discussed in the CS is APOLLO. However, there are other health economic studies of treatments for hATTR amyloidosis available from the grey literature[33, 35] and one conference abstract[34] reported EQ-5D estimates according to PND score (the metric used to define model health states). These studies could have been discussed within the company's review, particularly with respect to the structure and parameterisation of the company's model.

The company's Markov model assesses the cost-effectiveness of patisiran given alongside BSC versus BSC in patients with hATTR amyloidosis with polyneuropathy. Incremental health gains, costs and cost-effectiveness of patisiran are evaluated over a 40-year time horizon from the perspective of the NHS and PSS. The company's model structure includes 12 alive health states, based on PND and NT-proBNP scores, and an additional state for death. The model uses a 6-month cycle duration. The risk of death is assumed to increase with advancing PND score and/or an NT-proBNP score ≥3,000pg/mL. HRQoL is assumed to be principally determined by PND score, treatment group and time. Costs are assumed to increase with increasing PND score and NT-proBNP scores ≥3,000pg/mL. Transition probabilities were informed by 18-month patient count data from APOLLO[7] (including additional data and assumptions to extrapolate outcomes for BSC). Mortality risks by PND and NT-proBNP scores were based largely on external data[5, 37, 38] and assumptions. Resource use estimates and costs were based on a Delphi panel study[1] and routine sources.[41-44] The model includes a PAS for patisiran. The model does not include a stopping rule (all patients receive patisiran indefinitely irrespective of PND score). The CS includes differential discount rates of 1.5% for health outcomes and 3.5% for costs; the ERG does not consider this to be appropriate.

Based on the probabilistic version of the model (including the PAS and differential discount rates), patisiran is expected to generate an additional 8.11 QALYs at an additional cost of [redacted] compared with BSC: the corresponding ICER for patisiran versus BSC is [redacted] per QALY gained.

The deterministic version of the company's model produces a slightly higher ICER of [redacted] per QALY gained. Assuming a WTP threshold of £100,000 per QALY gained, the company's model suggests that the probability that patisiran produces more net benefit than BSC is approximately [redacted]. Assuming WTP thresholds of £200,000 and £300,000 per QALY gained, the probability that patisiran produces more net benefit than BSC is estimated to be [redacted] and [redacted], respectively. The lowest ICER presented in any of the company's DSAs and scenario analyses is in excess of [redacted] per QALY gained.

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. These include: (i) identification of model errors; (ii) the inappropriate use of differential discount rates for health outcomes and costs; (iii) issues surrounding rules for initiating and discontinuing patisiran treatment; (iv) issues relating to the company's model structure; (v) concerns regarding the company's assumed mortality assumptions; (vi) concerns regarding the company's approach for estimating health state occupancy; (vii) issues relating to the company's HRQoL assumptions; (viii) issues surrounding resource use and costs; and (ix) characterisation of uncertainty.

The ERG undertook two broad sets of exploratory analyses using the company's model. The ERG's preferred model includes the correction of three model errors regarding the inclusion of RDI for patisiran administration and pre-medications, the removal of one-off costs and the exclusion of the time to treatment discontinuation function. In addition, four amendments were also included in this ERG-preferred analysis: (i) discount rates for health outcomes and costs were set equal to 3.5%; (ii) the initial distribution of patients was recalculated; (iii) an alternative general population HRQoL model was applied;[70] and (iv) mortality risks by PND stage were modified to remove excess cardiac risk for patients without this characteristic. The ERG-preferred model produces a probabilistic ICER for patisiran versus BSC of [redacted] per QALY gained.

Additional exploratory analyses were also undertaken using the ERG's preferred version of the model to explore the impact of alternative parameter values on the model results. These analyses involved using alternative assumptions and sources for HRQoL parameters, altering assumptions regarding the relative reduction in resource use for patisiran-treated patients, removing PND-related mortality and assuming no change in mean NT-proBNP level for BSC-treated patients. These analyses produced ICERs for patisiran versus BSC ranging from [redacted] per QALY gained (removal of PND-related mortality) to [redacted] per QALY gained (utilities from Stewart *et al* – "other mutations"). Most of these additional exploratory analyses led to increases in the ICER; however, removing PND-related mortality and assuming no change in NT-proBNP score for BSC-treated patients each improved the

cost-effectiveness of patisiran (ICERs for these scenarios were [redacted] and [redacted] per QALY gained, respectively).

The ERG considers the following to represent the key uncertainties within the company's health economic analysis:

- The long-term comparative benefits of patisiran versus BSC in terms of PND and NT-proBNP
- The survival benefit associated with patisiran
- The level of HRQoL experienced by patients who receive patisiran or BSC over time
- The potential impact of introducing a stopping rule for patisiran.

6 OVERALL CONCLUSIONS

6.1 Clinical effectiveness

Compared with placebo, patisiran has demonstrated efficacy on change from baseline mNIS+7 score, TTR knockdown, HRQoL and key cardiac outcomes, including NT-proBNP. Mean TTR knockdown was 87.8% in the patisiran arm of APOLLO, and 82% in the Phase 2 OLE study. Most patients across studies experienced AEs, and similar proportions of patients in the patisiran and placebo arms of APOLLO experienced severe and serious AEs, and fewer patisiran group patients discontinued or withdrew due to an AE compared with the placebo group. Thirteen deaths were reported in APOLLO (7 [4.7%] in the patisiran group and 6 [7.8%] in the placebo group), none of which were considered related to patisiran. One death was reported in the Phase 2 OLE study, and 11 deaths were reported in the interim data-cut of the Global OLE. The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to APOLLO: (1) a greater proportion of patients in the patisiran group than the placebo group met the criteria for cardiac involvement, and may thus have had a worse prognosis; (2) a greater proportion of placebo than patisiran patients discontinued treatment and withdrew from the study. The other three studies adopted a single-arm design, and the Phase 2 OLE study and the Global OLE study are open-label and are thus susceptible to bias.

6.2 Cost-effectiveness

The ERG's preferred assumptions increase the probabilistic ICER for patisiran versus BSC from [redacted] (the company's base case) to [redacted] per QALY gained. Within the ERG's preferred analysis, the most significant contributor to this higher ICER is the use of equal discount rates for health outcomes and costs. The ERG's additional exploratory analyses using this preferred analysis produce ICERs which are in the range [redacted] to [redacted] per QALY gained. These additional analyses indicate that some of the company's assumptions are unfavourable to patisiran, for example, the assumed relationship between PND score and mortality and the assumed increase in NT-proBNP score for BSC. These exploratory analyses also highlight the significant influence of the company's assumptions regarding HRQoL being dependent on the treatment received. The ERG considers the following to represent key areas of uncertainty:

- The long-term comparative benefits of patisiran versus BSC in terms of PND and NT-proBNP
- The survival benefit associated with patisiran
- The level of HRQoL experienced by patients who receive patisiran or BSC over time
- The potential impact of introducing a stopping rule for patisiran.

6.3 Implications for research

The ERG believes that the following future research priorities may help to reduce decision uncertainty:

- Further long-term comparative studies of patisiran versus current treatments. The ERG recognises that whilst ideal, such studies may not be ethically feasible
- Natural history studies to estimate long-term disability and survival trajectories for patients not receiving patisiran
- More appropriate statistical analysis of the EQ-5D-5L data from APOLLO, taking into account the nature of the data. This analysis could be undertaken without further data collection.

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8 APPENDICES

Appendix 1: Patient count data from APOLLO

Table 35: Patient transition count data, patisiran group

From \ to state		NT-proBNP<3000pg/mL						NT-proBNP≥3000pg/mL					
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
NT-proBNP <3000pg/mL	PND 0												
	PND I												
	PND II												
	PND IIIA												
	PND IIIB												
	PND IV												
NT-proBNP ≥3000pg/mL	PND 0												
	PND I												
	PND II												
	PND IIIA												
	PND IIIB												
	PND IV												

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre

Table 36: Patient transition count data, placebo group

From \ to state		NT-proBNP<3000pg/mL						NT-proBNP≥3000pg/mL					
		PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
NT-proBNP <3000pg/mL	PND 0												
	PND I												
	PND II												
	PND IIIA												
	PND IIIB												
	PND IV												
NT-proBNP ≥3000pg/mL	PND 0												
	PND I												
	PND II												
	PND IIIA												
	PND IIIB												
	PND IV												

PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre

Appendix 2: Results of company's analyses and ERG's exploratory analyses using the list price for patisiran

(A) Company's results using patisiran list price

Table 37: Company's base-case cost-effectiveness results – patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5% respectively, list price

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Probabilistic model*							
Patisiran	NR†	8.41	[redacted]	NR†	8.08	[redacted]	[redacted]
BSC	NR†	0.33	[redacted]	-	-	-	-
Deterministic model							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life years; ICER - incremental cost-effectiveness ratio
**Probabilistic results based on a re-run of the company's model by the ERG*
† Not included in company's PSA VBA sub-routine
‡ Undiscounted

Figure 24: Cost-effectiveness acceptability curves – patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, list price

[redacted]

[redacted]

Figure 25: DSA tornado diagram – patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, list price (adapted by the ERG*)

** The tornado diagram presented in the CS was incorrect;[2] the version presented here has been generated by the ERG using the company's model*

Table 38: Company's scenario analysis results - patisiran versus BSC, health outcomes and costs discounted at 1.5% and 3.5%, respectively, list price (generated by the ERG)

Scenario	Inc. LYGs‡	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Scenario 1A – pessimistic imputation of missing transition data (all patients with missing data progress to next worst state)	6.19	7.36	[redacted]	[redacted]
Scenario 1B – optimistic imputation of missing transition data (all patients with missing data regress to next best state)*	7.70	8.46	[redacted]	[redacted]
Scenario 2 – no utility constraint†	7.41	10.61	[redacted]	[redacted]
Scenario 3 – exponential ToT function	7.41	8.30	[redacted]	[redacted]
Scenario 4 – no additional mortality risk associated with PND	3.61	11.17	[redacted]	[redacted]

LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PND – polyneuropathy disability
** The results for this scenario appear to be incorrect in the CS*
† Assumes minimum utility for BSC equal to -1.0
‡ Undiscounted

Table 39: Comparison of company's base case model and ERG's rebuilt model results, health outcomes and costs discounted at rates of 1.5% and 3.5%, respectively, list price*

Model outcome	Company's model			ERG's rebuilt model		
	Patisiran	BSC	Incremental	Patisiran	BSC	Incremental
LYGs	13.73	7.78	5.95	13.73	7.78	5.95
QALYs	8.52	0.22	8.30	8.52	0.22	8.30
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-	-	[redacted]	-	-	[redacted]

** Results presented in this table do not include the correction of any errors discussed in Section 5.3.3*

Table 40: Company's base-case cost-effectiveness results – patisiran versus BSC, company's model, health outcomes and costs both discounted at 3.5%, list price

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs ‡	QALYs	Cost	ICER (per QALY)
Probabilistic model*							
Patisiran	NR†	7.03	[redacted]	NR†	6.63	[redacted]	[redacted]
BSC	NR†	0.41	[redacted]	NR†	-	-	-
Deterministic model							
Patisiran	15.78	7.14	[redacted]	7.41	6.82	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life years; ICER - incremental cost-effectiveness ratio
**Probabilistic results based on a re-run of the company's model by the ERG*
† Not included in company's PSA macro
‡ Undiscounted
[redacted]

Figure 26: Cost-effectiveness acceptability curves – patisiran versus BSC, health outcomes and costs both discounted at 3.5%, list price

Figure 27: DSA tornado diagram – patisiran versus BSC, health outcomes and costs both discounted at 3.5%, list price (adapted by the ERG*)

** the version presented in this figure has been adapted from the company's model*

Table 41: Company's scenario analysis results – patisiran versus BSC, health outcomes and costs both discounted at 3.5%, list price (generated by the ERG)

Scenario	Inc. LYGs‡	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Scenario 1A – pessimistic imputation of missing transition data (all patients with missing data progress to next worst state)	6.19	6.06	[redacted]	[redacted]
Scenario 1B – optimistic imputation of missing transition data (all patients with missing data regress to next best state)*	7.70	6.87	[redacted]	[redacted]
Scenario 2 – no utility constraint†	7.41	8.59	[redacted]	[redacted]
Scenario 3 – exponential ToT function	7.41	6.82	[redacted]	[redacted]
Scenario 4 – no additional mortality risk associated with PND	3.61	8.96	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PND – polyneuropathy disability; ToT – time on treatment
** The results for this scenario appear to be incorrect in the CS*
† Assumes minimum utility for BSC equal to -1.0
‡ Undiscounted

(B) ERG exploratory analysis results using patisiran list price

Table 42: ERG-preferred analysis, list price

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(1) Correction of errors†							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(2) Equal discount rates applied							
Patisiran	15.78	7.14	[redacted]	7.41	6.82	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(3) Recalculation of initial distribution by PND and NT-proBNP score							
Patisiran	15.79	8.53	[redacted]	7.42	8.31	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(4) Use of general population HRQoL from Ara & Brazier							
Patisiran	15.78	8.54	[redacted]	7.41	8.32	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(5) Adjustment of calculations to estimate mortality risk by PND stage for low NT-proBNP states							
Patisiran	15.78	8.52	[redacted]	7.41	8.30	[redacted]	[redacted]
BSC	8.37	0.22	[redacted]	-	-	-	-
(6a) ERG-preferred analysis (deterministic, analyses 1-5 combined)							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(6b) ERG-preferred analysis (probabilistic, analyses 1-5 combined)							
Patisiran	NR§	7.08	[redacted]	NR	6.66	[redacted]	[redacted]
BSC	NR§	0.43	[redacted]				

** Undiscounted*
† Analyses 2-6 each include error corrections from analysis 1
§Not included in company's PSA macro
BSC - best supportive care; Inc - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

Table 43: Results of the exploratory analysis, list price

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
(6) ERG-preferred analysis							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(7) Time by treatment interaction term removed from model							
Patisiran	15.79	5.58	[redacted]	7.42	3.87	[redacted]	[redacted]
BSC	8.37	1.71	[redacted]	-	-	-	-
(8a) Utility values from Stewart *et al* - Val30Met mutation							
Patisiran	15.79	5.75	[redacted]	7.42	3.51	[redacted]	[redacted]
BSC	8.37	2.25	[redacted]	-	-	-	-
(8b) Utility values from Stewart *et al* - other mutations							
Patisiran	15.79	5.36	[redacted]	7.42	3.41	[redacted]	[redacted]
BSC	8.37	1.95	[redacted]	-	-	-	-
(9) Lower HRQoL assumed for NT-proBNP ≥3,000pg/mL							
Patisiran	15.79	7.08	[redacted]	7.42	6.73	[redacted]	[redacted]
BSC	8.37	0.35	[redacted]	-	-	-	-
(10a) Relative reduction in resource use for patisiran-treated patients halved							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(10b) Relative reduction in resource use for patisiran-treated patients set to zero							
Patisiran	15.79	7.17	[redacted]	7.42	6.85	[redacted]	[redacted]
BSC	8.37	0.32	[redacted]	-	-	-	-
(11) Removal of PND-related mortality							
Patisiran	18.15	7.96	[redacted]	3.62	8.99	[redacted]	[redacted]
BSC	14.53	-1.03	[redacted]	-	-	-	-
(12) Zero change in NT-proBNP							
Patisiran	15.79	7.17	[redacted]	5.36	7.30	[redacted]	[redacted]
BSC	10.43	-0.12	[redacted]	-	-	-	-

** Undiscounted*

BSC - best supportive care; Inc - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

Appendix 3: Methods for applying the ERG's exploratory analyses within the company's model

Exploratory analysis 1- Correction of errors

Amend the formula in worksheet "Costs" cell E43 to "=310*D10*D12".

Amend the formula in worksheet "Costs" cell E51 to "='CostData'!G26*D10*D12".

Replace the values in worksheet "Costs" cells E73:E77 with "0".

Replace the values in worksheet "Functions" cells I3:I485 with "1.0".

Exploratory analysis 2 - Equal discount rates applied

Replace the values in worksheet "Settings" cell E11 with "3.5".

Exploratory analysis 3 - Recalculation of initial distribution by PND and NT-proBNP score

Replace the values in worksheet "Markov Patisiran" cells O6:Z6 and in worksheet "Markov BSC" cells O6:Z6 with the values presented in Table 44.

Table 44: ERG analysis 3 - baseline distribution by health state groups

NT-proBNP<3,000 pg/ml (low)						NT-proBNP≥3,000 pg/ml (high)					
PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
[redacted]											

Exploratory analyses 4 - Use of general population HRQoL from Ara & Brazier

Go to worksheet "Markov Patisiran" cell DJ6. Replace the value with the formula "=0.9508566 + 0.0212126*'Clinical'!$E$12 - 0.0002587 * $D6 - 0.0000332 * $D6^2". Drag the formula down to row 86.

Go to worksheet "Markov BSC" cells DJ. Replace the value with the formula "=0.9508566 + 0.0212126*Clinical!$E$12 - 0.0002587*$D6 - 0.0000332*$D6 ^2". Drag the formula down to row 86.

Exploratory analyses 5 - Adjustment of calculations to estimate mortality risk by PND stage for low NT-proBNP states

Replace the formula in worksheet "Mortality Data" cell J89 with "=1/H89".

Replace the formula in worksheet "Mortality Data" cell J90 with "=1/H90".

Replace the formula in worksheet "Mortality Data" cell J91 with "=1/H91".

Replace the formula in worksheet "Mortality Data" cell J92 with "=1/H92".

Exploratory analyses 6a - ERG-preferred analysis (deterministic)

Apply all changes from ERG exploratory analyses 1-5, as described above. Analyses 7-12 should start from this version of the model.

Exploratory analyses 6b - ERG-preferred analysis (probabilistic)

Apply all changes from ERG exploratory analyses 1-5, as described above.
Go to worksheet "HCRU Data" cell L62. Replace the value with the formula "=H62".
Go to worksheet "HRQoL" cell K11. Replace the formula with "=MIN(NORM.INV(RAND(),E11,F11),1)".
Drag the formula down to row 18. Then copy the formula to cells K22:K27 and K31:K36.
Go to worksheet "PSA" in the area around cells K9 to M9. Click the button "Run PSA".

Exploratory analysis 7 - Time by treatment interaction term removed from model
Replace the values in worksheet "HRQoL" cells E17 and E18 with "0".

Exploratory analysis 8 - Utility values from Stewart et al

For exploratory analysis 8a and 8b, replace the values in worksheet "HRQoL" cells with the values presented in Table 45 and Table 46, respectively.

For both analyses, also replace the values in cells E17:E18 with "0", E22:E27 for "1.0" and E31:E36 for "-1.0".

Go to worksheet "Markov Patisiran", cell DK6 and replace the value to "=DJ6". Drag the formula down to row 86.

Go to worksheet "Markov BSC", cell DK6 and replace the value to "=DJ6". Drag the formula down to row 86.

Table 45: Health utilities for ERG exploratory analysis 8a – Val30Met mutation

PND score	utility
PND I	0.7
PND II	0.44
PND IIIa	0.44
PND IIIb	0.44
PND IV	0.1

Table 46: Health utilities for ERG exploratory analysis 8b – other mutations

PND score	utility
PND I	0.68
PND II	0.4
PND IIIa	0.4
PND IIIb	0.4
PND IV	0.05

Exploratory analysis 9 - Lower HRQoL assumed for NT-proBNP ≥3,000pg/mL

Go to worksheet "Markov Patisiran", cell DQ6 and replace the formula with "=DK6*0.9" Drag the formula across and down to cell DV86.

Go to worksheet "Markov BSC", cell DQ6 and replace the formula with "=DK6*0.9" Drag the formula across and down to cell DV86.

Exploratory analysis 10 - Relative reduction in resource use for patisiran-treated patients

For exploratory analysis 10a, replace the formula in worksheet "Costs" cell E81 with "='HCRU Data'!B147/2".

Replace the formula in worksheet "Costs" cell E82 for "='HCRU Data'!B148/2".

For exploratory analysis 10b, replace the formulas in worksheet "Costs" cells E81 and E82 with "0".

Exploratory analysis 11 - Removal of PND-related mortality

Replace the values in worksheet "Clinical" cells E47 and E48 with "1.0".

Exploratory analysis 12 - Zero change in NT-proBNP

Go to worksheet "TransMx", cell B10 and replace its content to "0".

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

You are asked to check the ERG report from School of Health and Related Research (ScHARR), The University of Sheffield to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Monday 29 October** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Preamble

We wish to express our sincere appreciation for the time and effort invested by the ERG in its review of our evidence submission and follow-up clarifications. Overall, we are in agreement with the majority of the ERG report; we are grateful that the ERG recognised the strengths of our submission, and we acknowledge most of its limitations as identified in the report. In the following tables we are proposing a limited number of specific amendments that we believe will further improve the report.

Please note that in the following tables the page numbers refer to the numbers appearing in the page footers of the ERG report, which are all +1 higher than the actual page number in the Word document because the title page starts at 2.

Response to ERG Report

Issue 1 Characterisation of systematic literature review (SLR) for best supportive care (BSC)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 12 The ERG report states that, "The company did not present a systematic review of the comparator, BSC." Section 4.6.1, page 68 The ERG report states that, "A systematic review of studies relating to BSC, listed as the comparator in the NICE scope,[6] was not presented in the CS.[1]" Section 4.6.2, page 68 The ERG report states that, "The company did not	Alnylam requests that all three sentences be amended to read, "The company did not identify any studies of the comparator, BSC, in its systematic reviews."	Alnylam requests that these three sentences be corrected. BSC was not excluded from the SLRs conducted for the CS, either as an intervention or as a comparator. Nevertheless, the SLRs did not identify any studies that explicitly compared a treatment to BSC. Although not explicitly described as such by the studies we reviewed, it is likely that some studies provided BSC in conjunction with a pharmacological intervention or with a placebo; however, we were not able to determine if this was the case from the information provided in the published reports that were reviewed. The requested amendments will make the report more internally consistent, given the ERG's	This is not a factual inaccuracy. Irrespective of whether the searches did or did not include restrictions on interventions, the CS does not present a systematic review of studies of BSC.

present a systematic review of the comparator, BSC." These sentences imply that BSC was not considered in the company's evidence review, but in fact the SLRs were run without restriction as to treatment, and it was simply the case that no studies of BSC were identified.		evaluation in the following sentence on page 27: "The ERG agrees with the broad structuring of the company's search strategies to retrieve all clinical, economic, and HRQoL studies without restrictions made to interventions, comparators or outcomes according to the PICOS criteria (population, intervention, comparator, outcomes and study design). The population terms for polyneuropathy and the sources used were considered to be comprehensive and the ERG believes it is unlikely that studies relevant to the decision problem have been missed."	

Issue 2 Characterisation of discontinuations and withdrawals in APOLLO

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 13 Section 4.6.2, page 69 In both locations, the ERG report states, "Data from APOLLO demonstrated that almost all patients who received patisiran and placebo experienced adverse events (AEs), similar proportions of patisiran and placebo patients experienced severe and serious AEs, and slightly fewer patisiran group	Alnylam requests deletion of the word "slightly" in all three locations.	The requested amendments will avoid misrepresenting the nearly three-fold difference in AE-related discontinuations and almost five-fold difference in AE-related withdrawals between the two treatment arms.	We agree. The text has been amended.

patients discontinued or withdrew due to an AE compared with the placebo group." Section 6.1, page 134 The ERG report states, "Most patients across studies experienced AEs, and similar proportions of patients in the patisiran and placebo arms of APOLLO experienced severe and serious AEs, and slightly fewer patisiran group patients discontinued or withdrew due to an AE compared with the placebo group." The use of the word "slightly" in all three instances does not accurately describe the large between-group differences in discontinuation and withdrawal rates. As reported on page 100 of the CS, 5% (7/148) of patients discontinued due to an AE in the patisiran arm vs. 14% (11/77) in the placebo arm. As reported on page 80 of the CS, 2% (3/148) of patients withdrew due to an			

AE in the patisiran arm vs. 9% (7/77) in the placebo arm.			

Issue 3 Characterisation of deaths in the patisiran vs placebo groups of the APOLLO trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 13 Section 4.6.2, page 69 Section 6.1, page 134 In all three locations, the ERG report states, "Thirteen deaths were reported in APOLLO (7 in the patisiran group and 6 in the placebo group), none of which were considered to be related to patisiran." Given the 2:1 randomisation for patisiran vs placebo in APOLLO, reporting only the absolute numbers of deaths without the percentages is misleading.	Alnylam requests that in all three locations the percentages be added to this sentence as follows: "Thirteen deaths were reported in APOLLO (7 [4.7%] in the patisiran group and 6 [7.8%] in the placebo group), none of which were considered to be related to patisiran."	The requested amendment will avoid misinterpretation of the mortality data from APOLLO, given the 2:1 randomisation for patisiran vs placebo in the APOLLO study.	This is not a factual inaccuracy. For clarity, we have amended the text in line with the company's suggestion.

Issue 4 Characterisation of the Global OLE study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 13 Section 4.6.2, page 69 As currently worded, the following text in both locations could be misinterpreted to mean that the Global OLE has been completed: "In the Global OLE, 89.6% patients experienced at least one AE, 18% patients experienced at least one severe AE and 26.1% experienced at least one serious AE. In the Phase 2 OLE, there was one death (myocardial infarction) after the patient had completed 24 months of treatment, and 11 deaths were reported in the Global OLE." Section 6.1, page 134 The same issue applies to the sentence: "One death was reported in the Phase 2 OLE study, and 11 deaths were reported in the Global OLE."	Alnylam requests that the text on pages 13 and 69 be revised as follows: "In the ongoing Global OLE, 89.6% patients have experienced at least one AE, 18% patients have experienced at least one severe AE and 26.1% have experienced at least one serious AE. In the Phase 2 OLE, there was one death (myocardial infarction) after the patient had completed 24 months of treatment, and 11 deaths ~~were~~have been reported in the Global OLE." Alnylam also requests that on page 134 the text be revised as follows: "One death was reported in the Phase 2 OLE study, and 11 deaths ~~were~~have been reported in the ongoing Global OLE."	The amendment will clarify that the Global OLE study has not been completed, so the mortality data are interim.	We have clarified that this is an interim data-cut. The report states several times that the Global OLE is ongoing.

Issue 5 Characterisation of hATTR disease concepts

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1, page 23 The last sentence of this section states, "The CS does not contain any evidence relating to the use of patisiran for the treatment of patients with predominantly cardiac forms of hATTR in the absence of polyneuropathy." This wording could lead to a false impression that cardiac forms of hATTR amyloidosis are mutually exclusive with polyneuropathy.	Alnylam requests that this sentence be simplified as follows: "The CS does not contain any evidence relating to the use of patisiran for the treatment of patients with ~~predominantly cardiac forms of~~ hATTR amyloidosis in the absence of polyneuropathy."	The current understanding of hATTR amyloidosis recognises that these disease concepts are not mutually exclusive, so this sentence should more accurately reflect any patients without polyneuropathy, without using qualifiers such as "predominantly" when referring to other disease manifestations.	The existing wording does not imply that the concepts are mutually exclusive. The text has not been amended.

Issue 6 Characterisation of the duration of the Global OLE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, page 39 The last sentence in the *Intervention* subsection before the *Ongoing studies* subsection states, "Patients received patisiran for an additional 52 weeks,	Alnylam requests deletion of this sentence.	In addition to being misleading, this sentence is unneeded since the following paragraph under *Ongoing studies* clarifies the duration of the Global OLE (up to 5 years) and specifies that 52 weeks refers to an interim data cut that has been reported in the CS and the Suhr et al. 2018 abstract. Deletion of the sentence will avoid	We have amended the text in line with the company's suggested revision.

following completion of another patisiran study." This misrepresents the duration of the ongoing Global OLE and implies that all patients enrolled in it have stayed on treatment for 52 weeks.		misinterpretation. The paragraph from which it is deleted will then comprise one sentence: "Patients in the Global OLE received 0.3mg/kg patisiran every 3 weeks (CS,[1] Appendix 1, Table S6)." This is sufficient for the *Intervention* subsection.	

Issue 7 NT-proBNP assessment time point in APOLLO

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4, page 50 The last sentence on this page states, "In the mITT population of APOLLO, NT-proBNP levels were also reduced significantly in the patisiran group relative to placebo (ratio fold change 0.47, 95% CI 0.39, 0.56), although the timepoint of this change was not reported.[10]" Although it is true that the Solomon et al. 2018 publication omits explicitly mentioning the timepoint, this was at 18 months, as reported in Table 38 of the APOLLO CSR. As such, it does not seem meaningful to highlight the omission from the publication.	Alnylam requests that the sentence be revised and a citation to the APOLLO CSR added, so that the sentence reads as follows: "In the mITT population of APOLLO, NT-proBNP levels were also reduced significantly <u>from baseline to 18 months</u> in the patisiran group relative to placebo (ratio fold change 0.47, 95% CI 0.39, 0.56)~~, although the timepoint of this change was not reported~~.<u>,7</u>[10]"	The requested amendment would avoid leaving the mistaken impression that it is impossible to determine the timepoint for this result.	We agree and have amended the text in line with the company's suggestion

Issue 8 Missing measure for small-fibre function

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4, Table 8, page 54 Section 4.2.4, Table 11, page 66 The *Measure* for *Small fibre function* is missing.	Alnylam requests the insertion of the following text in the blank table cell in question (this appears on page 134 of the APOLLO CSR): "QST-BSA$_{HP}$ + HRdB + postural BP" To reflect this revision, the following abbreviation definitions should be inserted (in alphabetical order) in the footnotes to Table 8 and 11: "HRdB - heart rate variability with deep breathing;" "QST-BSA$_{HP}$ - quantitative sensory testing heat pain by body surface area;"	Without this amendment, readers will incorrectly assume that the measure for small-fibre function is the same as for large-fibre function, which is reported above the small-fibre function cell in Tables 8 and 11.	We agree – the tables have been amended.

Issue 9 Characterisation of half-cycle correction in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, page 103 The text for point (1)(i) in the *Identification of model errors* section states, "The	Alnylam requests that the entire point (1)(i) be removed from the ERG report.	Point (1)(i) is incorrect because a half-cycle correction is applied not only when calculating costs but also LYs and QALYs. Additionally, it is untrue that patients who	The ERG has revisited this issue and agrees with the company. This point has been removed from the ERG report.

company's model calculates total acquisition, administration and premedication costs for patisiran using half-cycle correction. The ERG notes that this will slightly underestimate the costs of patisiran as some patients who receive the drug and die in a given cycle will not incur the drug costs. The ERG notes however that due to the different lengths of the interval between patisiran doses (3 weeks) and the between the model cycles (6 months), using the uncorrected trace to calculate patisiran costs would produce a greater degree of bias. As such, the ERG believes that this is a minor issue which will slightly favour patisiran." This interpretation is incorrect, and this should not be characterised as a model error.		receive the drug and die in a given cycle will not incur the cost of the drug; they will incur the drug cost for half the cycle length—i.e., 3 months. In the same manner they will obtain a survival of 3 months. The use of half-cycle correction is recommended in methodological guidelines such as the ISPOR-SMDM best practices for state-transition modelling [Siebert et al., 2012]. Also, as noted by the ERG itself, its exclusion would have produced a greater degree of bias. Taking all of these points into consideration, we do not believe that our implementation of half-cycle correction can be characterised as a model error.	

Issue 10 Characterisation of the time to treatment discontinuation function in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
Section 5.3.3, page 105 The text for point (1)(v) in the *Identification of model errors* section states, "Given a sufficiently long time horizon, this leads to an illogical situation whereby all patients have discontinued treatment whilst still accruing treatment benefit at the level of RDI observed in the trial." This scenario is implausible, and should not be characterised as a model error.	Alnylam requests deletion of the sentence "Given a sufficiently long time horizon, this leads to an illogical situation whereby all patients have discontinued treatment whilst still accruing treatment benefit at the level of RDI observed in the trial."	The situation described in the ERG sentence is purely paradoxical. The log-normal function chosen to simulate the time on treatment in the simulation is almost flat. At the end of the simulation (40 years) it reaches the value 0.92 (meaning that a cumulative 8% of the total cohort discontinued). Even if the curve is prolonged to an entirely unrealistic time horizon of 200 years, the value will still be 0.89 (11% of the total cohort discontinued). As such, the sort of illogical situation described by the ERG is practically impossible to occur, and thus we do not believe this sentence should be included as a model error.	This text was provided to illustrate the point – we agree that the necessary time horizon is longer than expected survival for the cohort. However, the point is that it is illogical to apply a time on treatment curve without separately modelling what happens to patients when they discontinue treatment. For clarity, we have amended the text to clarify that this is an illustrative point.

Issue 11 Characterisation of the impact of utility caps in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, pages 106-107 The last paragraph in point (1)(vii), in the *Identification of model errors* section states, "In addition, the ERG identified further problems	Alnylam requests that the sentence "This reflects an unequivocal error which biases in favour of patisiran." be changed to: "However, this has no practical	The requested amendment will make this paragraph consistent with the previous description of the UK population constraint in the ERG report at page 75: 'The model includes two different types of utility "caps" which are used to constrain a possible infinite growth or decrease in the	The ERG agrees. The text has been amended.

relating to the sampling of HRQoL parameters within the company's model. As the parameters of the HRQoL OLS model and the maximum ceiling/minimum floor caps are sampled using independent normal distributions (not bounded by 0 or 1), the model allows some sampled utilities to exceed 1.0. This reflects an unequivocal error which biases in favour of patisiran." While the error exists, the conclusion about its outcome is wrong because utilities are constrained not to exceed population norms.	impact on the results of the analysis because utilities are always constrained to be lower than the utility of the general UK population."	utilities for patisiran and BSC patients, respectively; these were based on the maximum and minimum observed EQ-5D estimates in any group at any timepoint in APOLLO. A second constraint is also applied to ensure that the projected utility never exceeds the estimated HRQoL of the corresponding age- and sex-matched general population in England.' Consequently, even if the first cap assumes a value exceeding 1 due to the error described in the PSA routine, the second cap (utility of the general population) still holds, ensuring that utilities in the model never assume impossible values. Thus, from a practical point of view the error reported does not have any consequences and therefore is not biasing the results of the analysis.	

Issue 12 Characterisation of the FAP vs PND staging systems

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Section 5.3.3, page 111

In the first paragraph under item (4), the text states, “However, the clinical advisors commented that PND scores might not be very sensitive over short periods of time (e.g. in clinical trials) and noted that they do not capture symptoms relating to autonomic dysfunction. <u>In this regard, the FAP staging system would perform better.</u>” Although the first sentence is indisputable, we disagree that the second (underlined) sentence is a valid conclusion, given that FAP staging does not capture autonomic symptoms independently of mobility impairment.</td>
<td>Alnylam requests deletion of the sentence, “In this regard, the FAP staging system would perform better.”</td>
<td>Although the FAP staging system does mention autonomic involvement, it does not separate autonomic function from the other criteria in each stage, and thus cannot be considered to provide additional discrimination in comparison with the PND classification system. This can be readily seen in the following table [Adams, 2013, Ando et al., 2013]:
<table>
<tr><td>PND classification</td><td></td><td>FAP stage classification</td><td></td></tr>
<tr><td>Score</td><td>Symptoms</td><td>Stage</td><td>Symptoms</td></tr>
<tr><td>0</td><td>No impairment</td><td>0</td><td>No symptoms</td></tr>
<tr><td>I</td><td>Sensory disturbances but preserved walking capability</td><td>1</td><td>Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs</td></tr>
<tr><td>II</td><td>Impaired walking capability but ability to walk without a stick or crutches</td><td rowspan="3">2</td><td rowspan="3">Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk</td></tr>
<tr><td>IIIA</td><td>Walking only with the help of one stick or crutch</td></tr>
<tr><td>IIIB</td><td>Walking with the help of two sticks or crutches</td></tr>
<tr><td>IV</td><td>Confined to a wheelchair or bedridden</td><td>3</td><td>Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs</td></tr>
</table>
</td>
<td>We agree that FAP staging has limitations. However, as noted in the ERG report, we consider that there are numerous issues in the use of PND scores to define health states, and that granularity may not be valuable in instances in which observed data are severely lacking.</td>
</tr>
</table>

		Notably, although autonomic dysfunction is mentioned in the FAP classification, this system provides no way for a clinician to sub-classify patients on the basis of autonomic involvement independently of their mobility status. Indeed, with reference to the table above, it is unclear how the FAP staging system could reliably be applied to cases such as a patient who is wheelchair-bound yet does not present with *severe* sensory, motor, *and* autonomic involvement of *all* limbs. In order to capture the changes in the health states with the maximum possible precision, we selected the PND classification as the basis for the definition of health states in the model. As shown in the table above, with its five scores for symptomatic patients (I, II, IIIA, IIIB, IV) the PND classification provides a more granular assessment of the disease than is possible using only the three FAP stages applicable to symptomatic patients (1, 2, 3). The table above presents the mapping from PND score to FAP stage reported by Adams 2013. From this mapping, it is evident that the three PND scores II, IIIA and IIIB have far greater resolution than the single FAP stage 2 within which they are subsumed. Given these important advantages of the PND scoring system and the afore-mentioned inability of the FAP staging system to capture autonomic dysfunction separately from mobility limitation, we do not	

		believe that the ERG report should conclude that the FAP staging system would perform better than the PND score classification.	

Issue 13 Characterisation of assumptions about mortality by FAP stage in the Institute for Clinical and Economic Review (ICER) report on inotersen and patisiran for hATTR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, page 112 The third sentence in point (4)(b) states, "Within the ICER analysis, mortality rates by FAP stage were estimated using a retrospective natural history study of 266 hATTR amyloidosis patients treated at the Mayo clinic (Swiecicki *et al*[60]), whilst the impact of NT-proBNP score on mortality was estimated using trial data reported by Slama *et al*.[61]" The first part of the sentence mistakenly suggests that mortality rates by FAP stage are reported in the study from Swiecicki *et al*.[60] In fact, mortality by FAP used in the ICER analysis is simply based on assumptions	Alnylam requests that the first part of the sentence: "Within the ICER analysis, mortality rates by FAP stage were estimated using a retrospective natural history study of 266 hATTR amyloidosis patients treated at the Mayo clinic (Swiecicki *et al*[60])" be changed to: "Within the ICER analysis, mortality rates by FAP stages 1, 2, and 3 were approximated by the "without neuropathy" curve, the "with neuropathy" curve, and the "with weight loss" curve, respectively, from a retrospective natural history study of 266 hATTR amyloidosis patients treated at the Mayo Clinic (Swiecicki *et al*[60])"	The requested amendment will more accurately characterise how mortality rates were assigned to FAP stages as described on page 46 of the ICER report [ICER, 2018]: 'Mortality for FAP stages 1, 2 and 3 are approximated by the "without neuropathy" curve, the "with neuropathy" curve, and the "with weight loss" curve, respectively, from a natural history study published by Swiecicki et al.[31]' We would like to take this opportunity to strongly dispute the validity of ICER's extrapolation from these symptoms/signs to FAP stage. As can be seen by referring to the table presented above in Issue 12, patients in FAP stage 1 would be expected to have mild sensory, motor, and autonomic neuropathy in the lower limbs, whereas the ICER analysis defines FAP stage 1 as the *absence* of neuropathy. "With neuropathy" could justifiably be applied to FAP stages 1, 2, and 3, not only FAP stage 2 as done by ICER. Rather than being restricted to FAP stage 3 as assumed by ICER, weight loss	The additional detail reflects a point of clarification rather than a factual inaccuracy. We have not amended the text. We note that the company's approach to modelling mortality was also hindered by available data and the need to make multiple chains of assumptions. We did not state that this approach reflects an improvement over the company's model; rather, we were highlighting that there are alternative choices regarding how to model mortality. Irrespective of which approach is preferred, it is important to note that the relationship between PND score and mortality is highly uncertain.

regarding how symptoms/signs will map onto FAP stage, rather than on actual observed data categorised by FAP stage.		can be observed even in FAP stage 1 [Araki and Ando, 2010]. Taken together, these considerations demonstrate that the relationship between FAP stage and death used by ICER is unjustifiable, and should not be considered by the ERG to represent an improvement over our decision to model mortality conditional on PND score.	

Issue 14 Characterisation of the assessment of APOLLO mortality data for the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, page 114 The first bullet under point (5) states, "No attempt was made to use the observed data on mortality from APOLLO[7] to estimate treatment effects." This is incorrect—as explained on page 143 of the CS, the company did in fact intend to use data from APOLLO to model the relationship between polyneuropathy and mortality, but found that this could not be done due to the low number of deaths in the trial.	Alnylam requests that this bullet be replaced with the following text: "The CS (Section 12.1.6)[1] reports that "*A multivariate analysis using data from APOLLO to model the effect of different degrees of polyneuropathy on survival was planned, but was not conducted due to the low number of deaths in APOLLO.*"	As written, the bullet does not accurately report the company's efforts to follow best practices for modelling. The requested amendment will fairly present the attempts to use the APOLLO data to model mortality by PND score. Confirming the impact of data limitations rather than any oversight or unwillingness to use observed data to estimate treatment effects, the CS also reports (page 139) that we were unable to perform a regression analysis for mortality by mNIS+7 score using APOLLO data due to the limited number of deaths observed in the trial.	The text has been modified to include the company's point, with additional comments from the ERG.

Issue 15 Characterisation of health-state transition probability calculations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, page 116 The last paragraph on this page states, "However, the ERG accepts that given the company's selected model structure and selected cycle duration, there is not an obvious means of converting the cycle length for the matrices given the observed data. It is likely that this issue would have been lessened by defining model states using FAP stage rather than PND score, although this would still have required the use of external evidence (e.g. expert elicitation) to inform transitions for patients with FAP Stage 3 disease. It is certain however, that this problem would not have arisen if an 18-month cycle duration was used; the ERG notes that there is no clear justification for adopting a	Alnylam requests that the underlined text be deleted from the ERG report.	As described above in Issues 12 and 13, the FAP staging system would have introduced more limitations rather than advantages had we used this instead of PND scores. Thus, it is not justifiable to include the first underlined sentence which implies that we should have used FAP stage. In our response to clarification questions, we explained that we had a strong clinical rationale for adopting a 6-month cycle duration, namely to match routine clinical practice in the UK, in which patients visit a physician one to two times a year for a clinical examination. During the course of routine clinical practice during these 6-month intervals, the physician could be expected to examine patients to determine if they have experienced substantial disease progression. Had we used 18-month cycle durations, our model would potentially have up to a 1-year delay in detecting progression compared with our use of 6-month cycles, and this would have been unrealistic in the context of UK clinical practice. Given this justification, we request deletion of the second underlined section of text.	This is not a factual inaccuracy. If FAP stage been used to characterise the disease states, the data would have been spread across fewer health states. The issues relating to cycle length as discussed in the ERG report are also not factually incorrect. Given that the company elected to use the data relating to the interval from baseline to 18-months, using an 18-month cycle duration would have avoided the need to use an incorrect method to adjust the cycle duration. If this interval was considered too long, the company should have instead used the observed data relating to the intervals 0-9 months and 9-18 months.

6-month cycle duration." The underlined text does not accurately characterise the validity of the decisions we took.			

Issue 16 Removal of time-by-treatment interaction term in the ERG's exploratory analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.4.1, page 127 and Table 34, page 128 In the additional exploratory analyses for the ERG's preferred analysis described in point (7), the ERG set to zero a portion of the regression equation to estimate health utilities.	Alnylam requests that the entire point (7) on page 127 be removed from the set of exploratory investigations to assess residual uncertainty around the ERG-preferred model, and that the corresponding rows for exploratory analysis (7) be deleted from Table 34.	The requested amendment will avoid arbitrary modification of a portion of a regression equation, which cannot be considered an estimate of residual uncertainty. All parameters in the original regression equation were derived from APOLLO data and the terms that the ERG removed were statistically significant.	The ERG disagrees with the company's suggested amendment. We disagreed with the company's modelling approach that identified relevant variables based solely on their statistical significance and omitted main effect terms but included their interactions. The point of this exploratory analysis is to demonstrate that the underlying assumption of increasing utility for patisiran and decreasing utility for BSC has a substantial impact of the cost-effectiveness of patisiran. The analysis has not been amended.

Issue 17 Use of Brazilian utility valuations in the ERG's exploratory analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, page 121 The ERG report states, "One of these studies (Stewart et al[35]) reports	Alnylam requests that the identified sentence on page 121 be deleted, and the entire point (8) on page 127 be removed from the set of exploratory	The requested amendments will avoid introduction of inapplicable utility scores, because the use of utilities determined with a Brazilian tariff is not acceptable in the NICE reference case. The NICE *Guide to*	The ERG disagrees with the company's suggested amendment. hATTR amyloidosis is a disease area in which there is very limited evidence on health-related quality of life, particularly when estimated using a

health utility values according to FAP stage (for Val30Met mutations and "other mutations" categories)." Section 5.4.1, page 127 and Table 34, page 128 The additional exploratory analyses for the ERG's preferred analysis described in point (8) used health utilities by PND score based on those reported by Stewart *et al*.[35] We believe it is inappropriate to advocate use of these utilities because the source study calculated utility scores using the Brazilian valuation set for the EQ-5D-3L [Stewart et al., 2017].	investigations to assess residual uncertainty around the ERG-preferred model, along with the corresponding rows for exploratory analyses (8a) and (8b) in Table 34.	*the methods of technology appraisal* states that the UK population valuation set should be applied to EQ-5D measurements to generate health-related utility values [National Institute for Health and Care Excellence, 2013]. For this reason, the company did not use this source even though it emerged from its SLR. The ERG undertook this set of additional exploratory analyses to explore "residual uncertainty using this ERG-preferred model." We believe that utilities which would not be acceptable to use in the reference case should not be considered in the context of residual uncertainty. Additionally, this analysis explicitly excludes mutations associated with a cardiac disease ATTR phenotype (e.g., Thr60Ala, Val122Ile), which comprise the majority of mutations found in the UK. As a result, this analysis may not be an appropriate representation of the prevalent genotypic and phenotypic characteristics in the UK. Finally, this is a cross-sectional analysis of patients that assumes patients have a given EQ-5D value solely based on disease stage. In contrast, the EQ-5D data from APOLLO show that patients' HRQoL changes longitudinally through time, even in a given PND Score/FAP Stage. We believe that this dataset is inappropriate and insufficient for modelling changes in HRQoL over time.	preference-based measure. We agree that using the Brazilian EQ-5D tariff is not ideal; however, it would be unhelpful to ignore such evidence on this basis alone. The point of this exploratory analysis is to demonstrate the impact of using alternative utility values on the cost-effectiveness of patisiran. As shown in the analysis, the use of alternative values which are constant over time has a substantial impact of the cost-effectiveness of patisiran. The analysis has not been amended.

Issue 18 Correction to referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.3, page 89 The source reference is incorrect in the sentences, "The company's model applies a disutility score for caregivers of 0.01 of patients with PND IV. This estimate was taken from a previous model of treatments for Alzheimer's disease.[47]"	Alnylam requests that the text be changed to: "The company's model applies a disutility score for caregivers of 0.01 of patients with PND IV. This estimate was ~~taken from a previous model of treatments for Alzheimer's disease .~~[47]based on an estimate used in the tafamidis AGNSS evaluation.[34]"	The requested amendment will make this text consistent with the correct reference as described in the second-to-last bullet on page 76 of the ERG report.	This is not a factual inaccuracy. Both statements are true - the caregiver disutility value was taken from the AGNSS report, which in turn was taken from the Alzheimer's appraisal.

Issue 19 Copyedits to correct transcription errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.3, Table 16, page 81 The table title currently is "Per-cycle transition probabilities, BSC group, observed period (cycles 1-3), N contributing data = 52 patients". The number of patients contributing to the matrix is incorrect.	Alnylam requests that the title be changed to "Per-cycle transition probabilities, BSC group, observed period (cycles 1-3), N contributing data = 51 patients"	The correct number of patients contributing to the transition matrix for the placebo arm in the APOLLO study is reported in the model. The requested amendment will make the Table 16 title consistent with the correct number as reported in the following text on page 113 of the ERG report: 'The "within-trial" patisiran matrix is populated using data from 134 patients, whilst the "within-trial" BSC matrix is populated using data from 51 patients.'	We agree – the table heading has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.3, Table 22, page 90 The cost for "Drug acquisition (without PAS) – patisiran" is mistakenly reported as [redacted]. Also, the row-2 heading, "Costs due to neuromyopathy (per-cycle)", uses different terminology from the rest of the ERG report and the CS.	Alnylam requests that the number for "Drug acquisition (without PAS) – patisiran" be changed to "[redacted]". Alnylam also requests that the row-2 heading in question be revised to read "Costs due to polyneuropathy (per-cycle)"	The requested amendments will make Table 22 consistent with the correct drug cost as reported in cell D23 in the *Costs* worksheet of the submitted model, and with the "polyneuropathy" terminology used throughout the ERG report and the CS.	Apologies – this is a typographical error. The cost without PAS has been corrected. We have also amended the title as suggested.
Section 5.2.6, page 96 The text preceding Table 25 incorrectly states: "The deterministic model suggests that patisiran generates approximately 9.86 additional undiscounted QALYs compared with BSC". In fact, 9.86 is the number of QALYs accrued with patisiran, rather than the difference between patisiran and BSC which is 9.73 QALYs.	Alnylam requests that the text be changed to "The deterministic model suggests that patisiran generates approximately 9.73 additional undiscounted QALYs compared with BSC".	The requested amendment will make the table consistent with the correct value, as reported in Table D20 on page 173 of the CS.	We agree. The wording has been amended in line with the company's suggested revision.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.2, Table 28, page 102 In the "Discount rate" row, a word is missing in the sentence, 'The CS[1] argues that using *"similar discount rates for cost and health benefits may not properly changes in the value of health effects over time."'*	Alnylam requests insertion of the missing word (underlined below) and deletion of the internal quotation marks and italics such that the sentence reads: "The CS[1] argues that using similar discount rates for cost and health benefits may not properly <u>reflect</u> changes in the value of health effects over time."	This copyedit should be implemented to clarify the meaning of the sentence in question in Table 28. Notably, "properly <u>reflect</u>" appears on page 107 of the ERG report, where the relevant sentence from page 144 of the CS is quoted verbatim. Also, we recommend removal of the internal quotation marks in this cell of Table 28 since the corresponding text in the table is a paraphrase rather than a verbatim quote from the CS.	We agree. The wording has been amended in line with the company's suggested revision.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3, page 111 There is a grammatical issue with the last sentence on this page: "These relate to: (a) the assumed relationship between PND score, NT-proBNP score and HRQoL; (b) the assumed relationship between PND score, NT-proBNP and death; (c) the inclusion of a time to treatment discontinuation function and a single transition matrix for patients who still on treatment and those are not, and (d) issues relating to granularity of health states and the use of non-informative prior distributions in preference to plausible beliefs of a rational impartial observer."	Alnylam suggests revision of part (c) of this sentence to read: "the inclusion of a time to treatment discontinuation function and a single transition matrix for patients who are still on treatment and those who are not,"	Minor correction.	We agree. The wording has been amended in line with the company's suggested revision.

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