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
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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.

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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

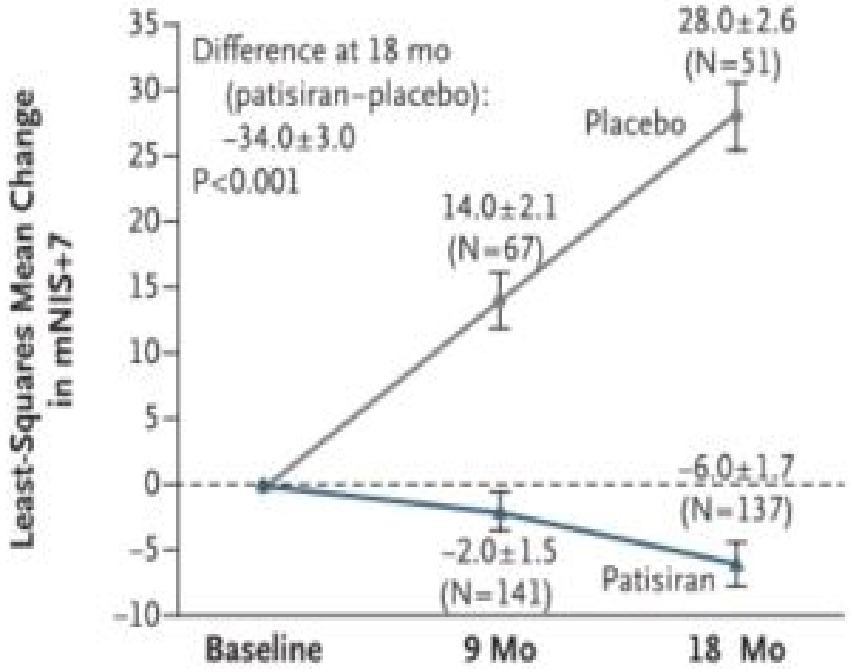
The mNIS+7 is a 304-point composite measure of neurological impairment, which includes: lower limb, upper limb and cranial nerve function; small and large nerve fibre function; touch pressure and heat pain; and autonomic function (postural hypotension).[1] Within their clarification response[2] (question 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]

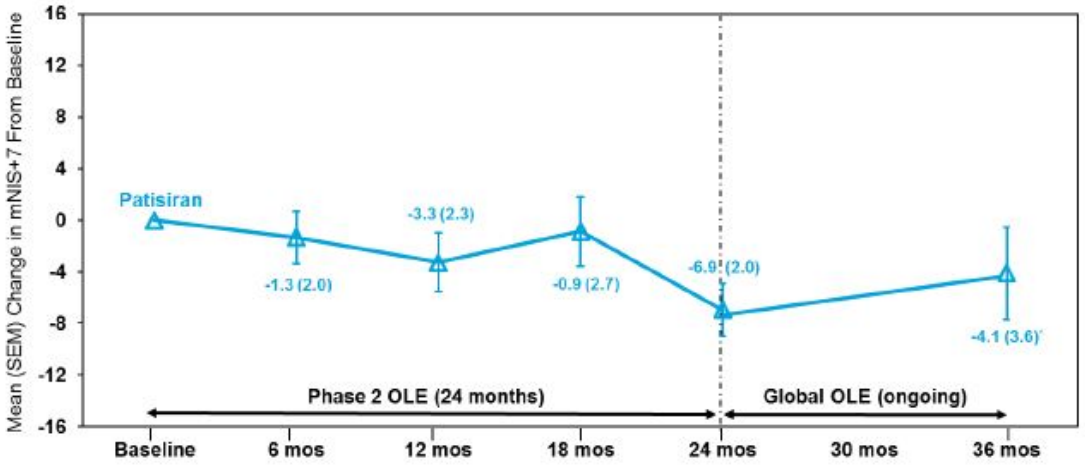
Phase 2 OLE

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)



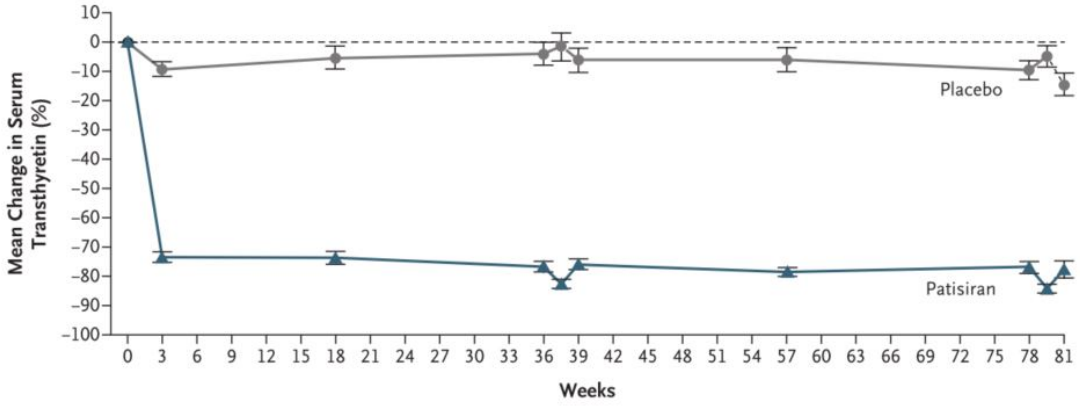
TTR knockdown

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]

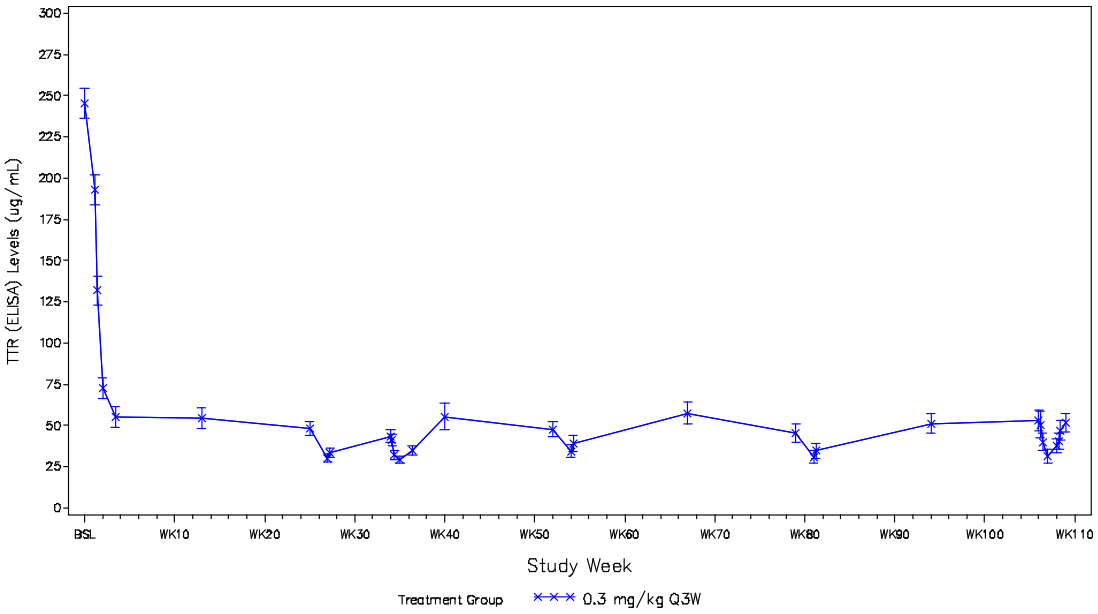
Phase 2 dose escalation study

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.

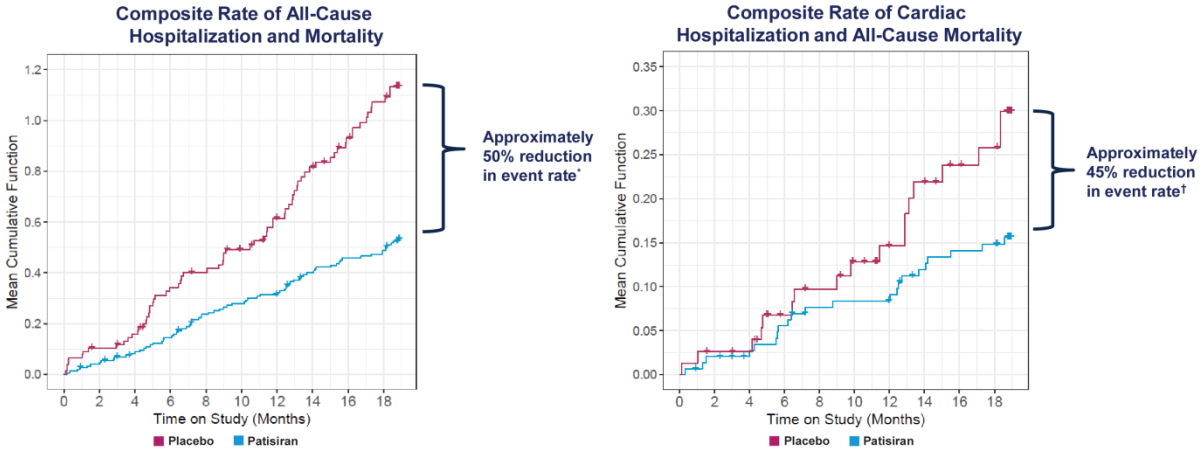
Table 9: Exploratory endpoint results in APOLLO (reproduced from company's clarification response, question A31)

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]	[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				
Cardiac failure	3 (2.0)	2 (2.6)	NR	NR
Cardiac failure congestive	3 (2.0)	2 (2.6)	NR	NR

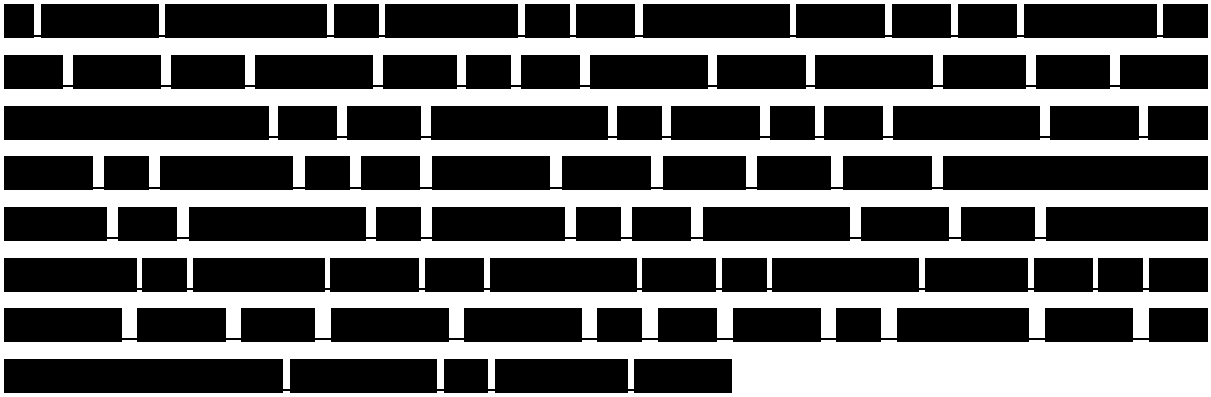
AE	APOLLO		Phase 2 OLE (n=25) n (%)[e]	Global OLE[22] n (%)
	Patisiran (n=148) n (%)	Placebo (n=77) n (%)		
Orthostatic hypertension	3 (2.0)	1 (1.3)	NR	NR
Atrioventricular block complete	3 (2.0)	0	NR	NR
Gastrointestinal				
Diarrhoea	8 (5.4)	1 (1.3)	NR	NR
Dehydration	1 (0.7)	3 (3.9)	NR	NR
Vomiting	1 (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.



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]

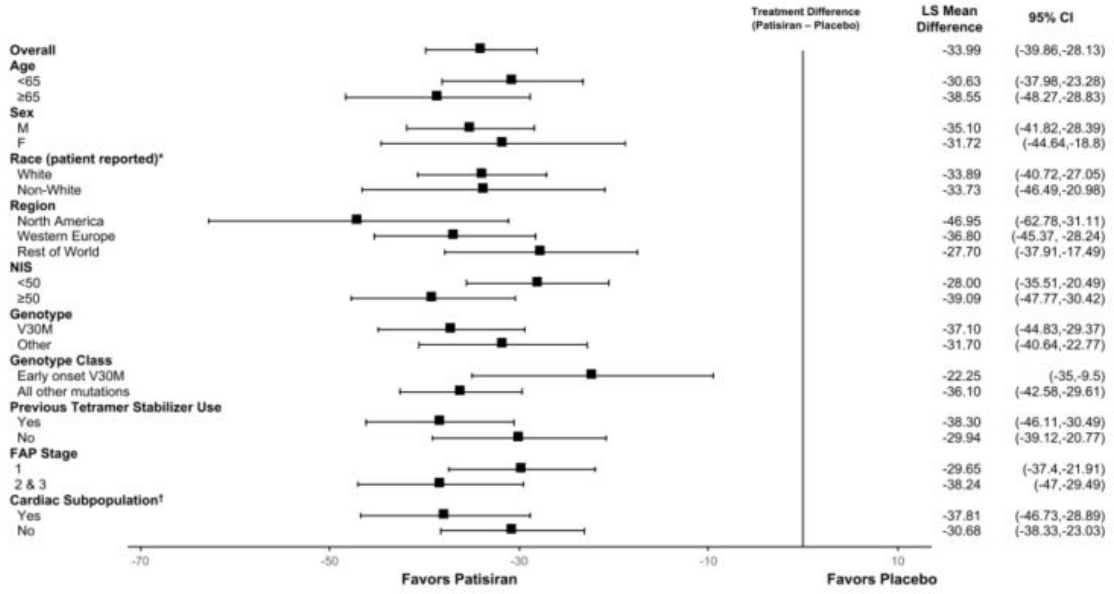
In APOLLO, compared with the population of patients outside the cardiac subtype, a higher proportion of patients in the cardiac subpopulation were NYHA Class II (60.3% vs. 38.1%), had a non-Val30Met genotype (73.0% vs. 37.4%), and had greater signs of cardiac dysfunction at baseline.[10] Genotypes that 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

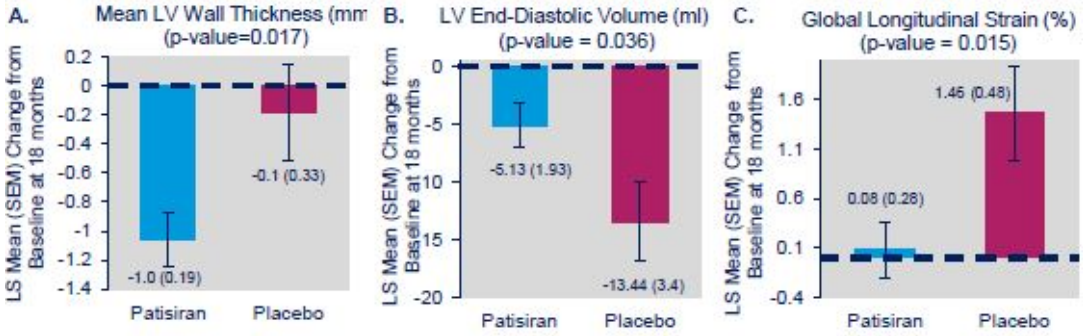
TTR knockdown was not reported in the cardiac subpopulation for either APOLLO or the Phase 2 OLE.

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.

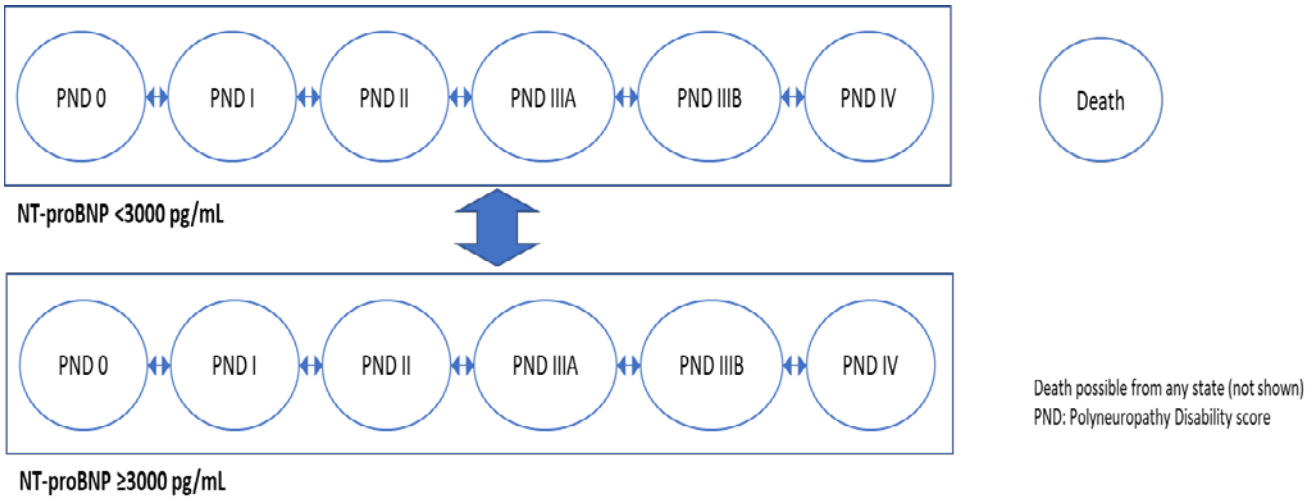
Intervention

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	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	0.00	0.00	0.00	0.00
	PND II	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	0.00	0.00	0.00
	PND IIIA	0.00	[redacted]	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	0.00	0.00	0.00	[redacted]
	PND IIIB	0.00	0.00	[redacted]	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]	[redacted]
	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	[redacted]	0.00	[redacted]	0.00	0.00	[redacted]	[redacted]	0.00	0.00	0.00
	PND II	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	[redacted]	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	[redacted]	0.01	[redacted]
	PND IIIB	0.01	0.01	0.01	0.01	[redacted]	0.01	0.01	0.01	0.01	0.01	0.62	[redacted]
	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

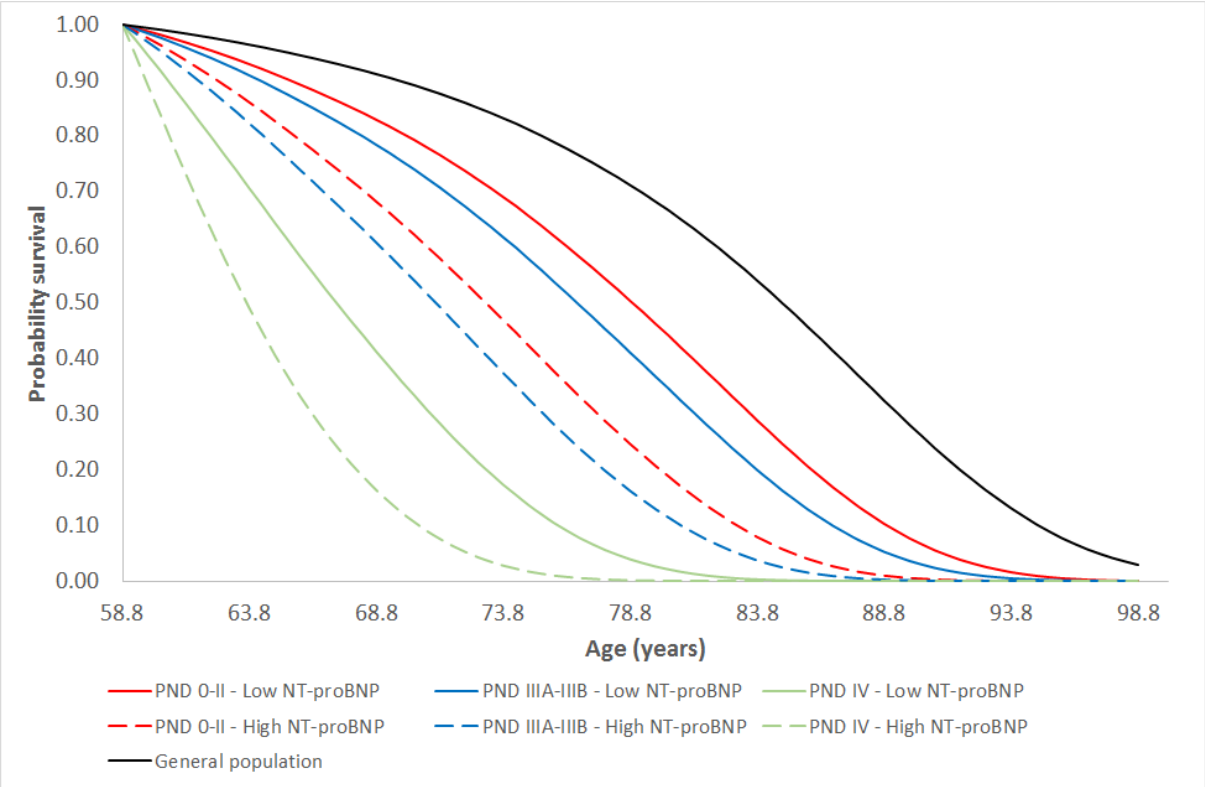
The model does not use mortality data from APOLLO. Instead, mortality risk is modelled using a series of HRs applied to general population life tables for England.[38] As the patient's PND score increases, or if their NT-proBNP score exceeds 3,000pg/mL, more HRs are combined to estimate the overall HR 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

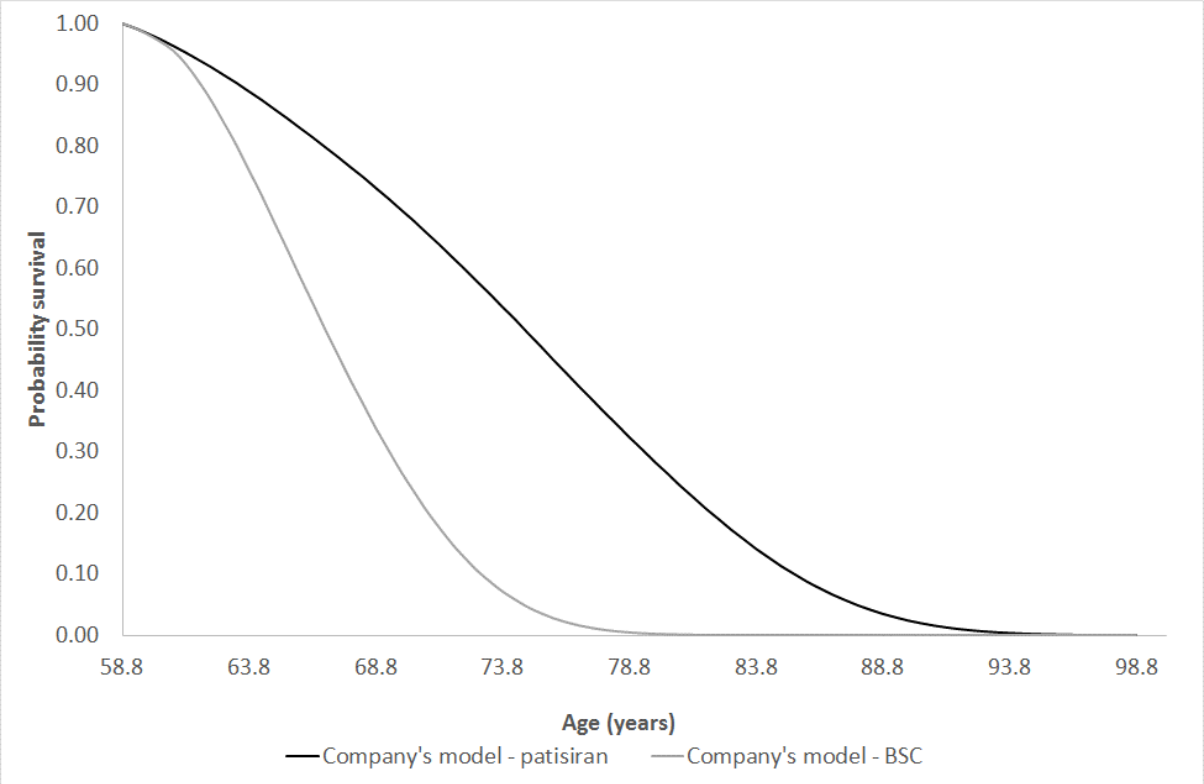
PND – polyneuropathy disability; NT-proBNP- N-terminal pro b-type natriuretic peptide; pg/mL – nanogram/millilitre; HR – hazard ratio

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						
PND II						
PND IIIA						
PND IIIB						
PND IV						

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	[redacted]	[redacted]
	PND II	[redacted]	[redacted]
	PND IIIA	[redacted]	[redacted]
	PND IIIA	[redacted]	[redacted]
	PND IV	[redacted]	[redacted]
Costs due to cardiomyopathy (per cycle)	NT-proBNP <3,000pg/mL	[redacted]	[redacted]
	NT-proBNP ≥3,000pg/mL	[redacted]	[redacted]
One-off polyneuropathy costs	PND I	[redacted]	[redacted]
	PND II	[redacted]	[redacted]
	PND IIIA	[redacted]	[redacted]
	PND IIIA	[redacted]	[redacted]
	PND IV	[redacted]	[redacted]
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).

.

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*)

[redacted]

** 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]:

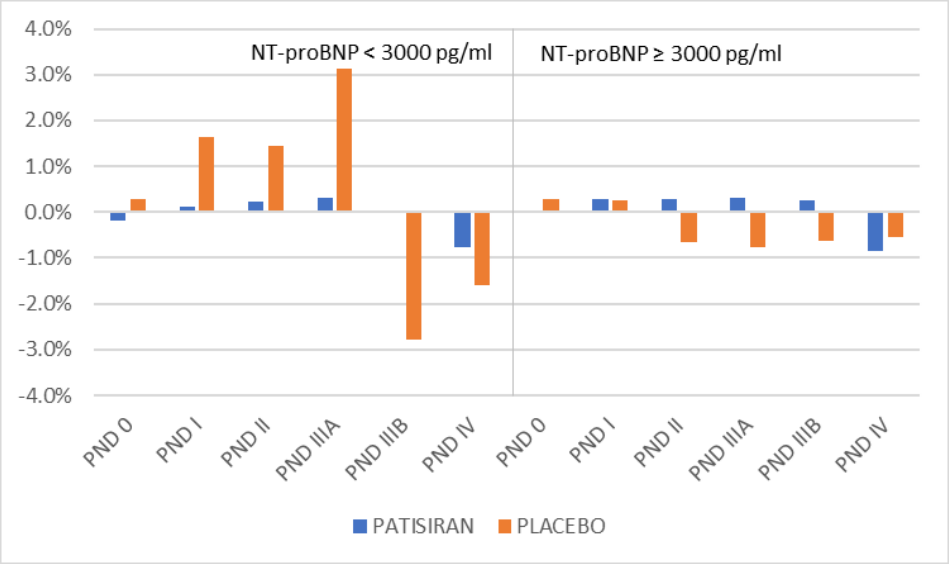
$$p = -\log (1-r)^{1/n} \quad \text{[i]}$$

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

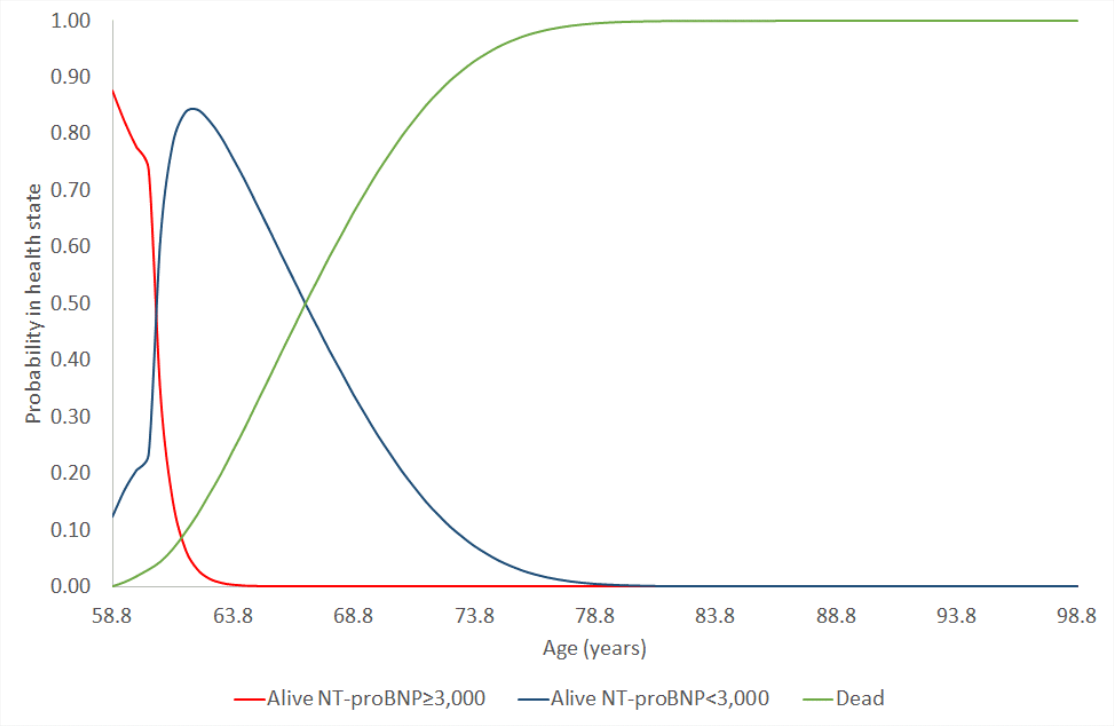
intended approach was to assume that by changing the mean but fixing the variance of the distributions at baseline and 18 months, the whole distribution would shift to the right (as shown in Figure 18). However, the parameters of the gamma distribution (alpha [shape] and beta [scale]) are a function 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*

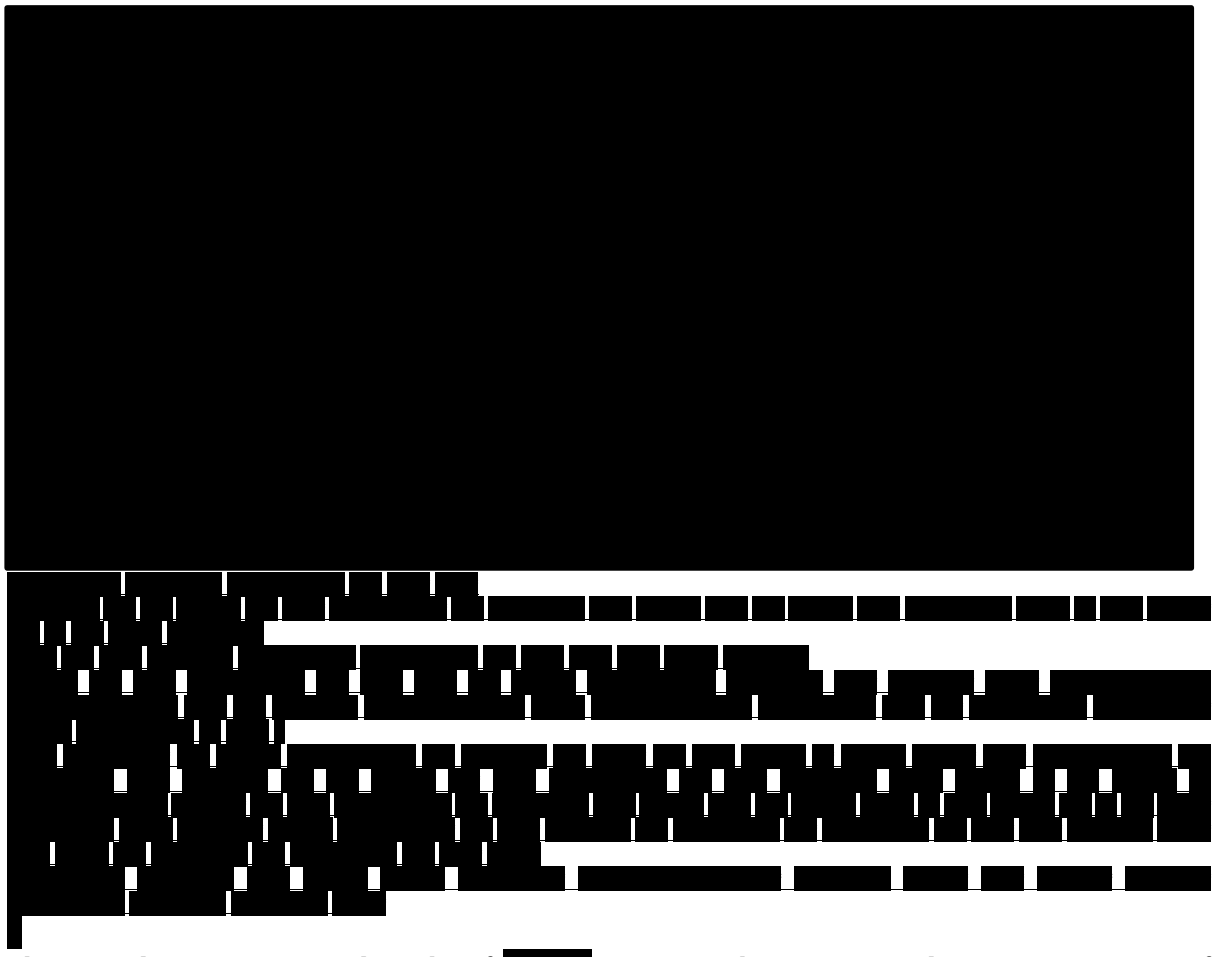
As shown in Table 34, the assumptions regarding health utilities, particularly the assumed increase for patisiran and decrease for BSC, have a significant impact upon the ICER. The inclusion of an HRQoL impact associated with NT-proBNP≥3,000pg/mL has only a minor impact on the model results. The relative 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”.