Inotersen for treating hereditary transthyretin-related amyloidosis

Produced by Aberdeen HTA Group

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No competing interests to declare.

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Rider on responsibility for report

The view 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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Contribution of authors

Dwayne Boyers and Graham Scotland acted as health economists: critiqued and reviewed the cost-effectiveness evidence, checked and re-analysed the economic model, and carried out further sensitivity analyses. Moira Cruickshank and Mari Imamura acted as the systematic reviewers: critiqued the company's definition of the decision problem and the clinical effectiveness evidence. Shona Fielding acted as statistician: critiqued the statistical methods presented in the submission, checked the

numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Cynthia Fraser acted as information scientist: critiqued the methods used for identifying relevant studies. Jane Tighe acted as clinical expert: provided clinical advice and general guidance. Graham Scotland acted as project lead for this appraisal: contributed to the critique and review of the cost effectiveness methods, checked the final report and supervised the work throughout the project.

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List of abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
ASO	Antisense oligonucleotide
ATTR	Transthyretin amyloidosis
BIA	Budget Impact Analysis
BIC	Bayesian Information Criterion
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CM-ECHO	Cardiomyopathy echocardiogram
CS	Company's submission
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
ECHO	Echocardiography
eGFR	Estimated glomerular filtration rate
EQ-5D	EuroQol-5 dimensions
ERG	Evidence review group
FAD	Final Appraisal Determination
FAP	Familial amyloid polyneuropathy
FAS	Full analysis set
GI	Gastrointestinal
GLS	Global longitudinal strain
hATTR	Hereditary transthyretin amyloidosis
hATTR-PN	Hereditary transthyretin amyloidosis with polyneuropathy
hATTR-CM	Hereditary transthyretin amyloidosis with cardiomyopathy
HRDB	Heart rate response to deep breathing
HRQoL	Health-related quality of life
HRU	Healthcare Resource Utilisation
HST	Highly specialised technology

ICER	Incremental cost-effectiveness ratio
IU	International unit
IXRS	Interactive voice/web-response system
KM	Kaplan Meier
LV	Left ventricular
LY	Life year
LYG	Life years gained
LSM	Least squares mean
mBMI	Modified body mass index
MCS	Mental component summary (of SF-36)
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
mNIS	Modified neuropathy impairment score
mRNA	Messenger ribonucleic acid
NAC	National amyloidosis centre
NHS	(UK) National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Neuropathy impairment score
Norfolk QoL- DN	Norfolk quality of life – diabetic neuropathy
NSC	Neuropathy symptoms and change
NT-proBNP	N terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OLT	Orthotopic liver transplant
PAS	Patient access scheme
PCS	Physical component summary (of SF-36)
PN	Polyneuropathy
PND	Polyneuropathy disability
PRO	Patient-reported outcome
PSA	Probability sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit

QALY	Quality adjusted life year
QoL	Quality of life
RBP4	Retinol binding protein 4
RCM	Revised company model
RCT	Randomised controlled trial
RNase H	Ribonuclease H
SAE	Serious adverse event
SC	Sub-cutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short form-36
SmPC	Summary of product characteristics
SS	Safety set
TEAE	Treatment-emergent adverse event
THAOS	Transthyretin amyloidosis outcomes survey
TQoL	Total quality of life
TTO	Time trade off
TTR	Transthyretin
UPCR	Urine protein to creatinine ratio
V30M	Valine replaced by methionine at amino acid number 30
WTP	Willingness to pay

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1 Summary

Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) is a rare and devastating autosomal dominant disease caused by a mutation in the transthyretin gene that leads to neuropathy and/or cardiomyopathy. The symptoms of this adult-onset, irreversible neurological disorder include intractable, progressive sensorimotor and autonomic neuropathy, with time between diagnosis and death reported to be around 5 to 15 years. The disease is commonly classified into three stages based mainly on ambulation (stage 1: unimpaired ambulation; stage 2: assistance with ambulation required; stage 3: wheelchair bound or bedridden). The disease has a substantial mental and psychological impact on patients and their families; patients experience significant deficits in health-related quality of life and carers report high levels of anxiety and depression.

Inotersen (Tegsedi®, Ionis USA Ltd, London, UK) is a therapy based on short synthetic oligonucleotides that bind onto transthyretin mRNA, causing its degradation by RNAase H. This prevents the synthesis of transthyretin protein in the liver, resulting in significant reductions in the levels of mutated and wild type transthyretin protein secreted by the liver into the circulation. Inotersen has been authorised in the EU as Tegsedi since 6 July 2018 for the treatment of Stage 1 or Stage 2 polyneuropathy in adults with hATTR.

1.1 Critique of the decision problem in the company submission

The decision problem considered in the company's submission was broadly consistent with the NICE final scope. The NICE scope specified the population as people with hATTR; the population considered in company's submission was people with hATTR-PN. The company's rationale for this variation was to align with the licensed indication for inotersen. The ERG agrees with the company's approach. The company did not include two outcomes specified in the NICE scope: postural hypotension and effects of amyloid deposits in other organs and tissues. The ERG's clinical expert considered the omission of postural hypotension as important, as the staging of hATTR-PN strongly relates to the ability to mobilise independently, and significant autonomic symptoms, particularly postural hypotension, will impact on this. The omission of amyloid deposits in other organs and tissues was not considered important by the ERG's clinical expert.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence submitted by the company consisted of one phase 3, double-blind, placebo-controlled, multi-centre RCT (NEURO-TTR), which was funded by the company. The NEURO-TTR study was followed by an ongoing, post-trial, Phase 3, open-label extension (NEURO-TTR Extension), in the same population. Both studies contribute to the company's clinical effectiveness evidence. The NEURO-TTR trial consisted of a baseline screen period (≤ 6 weeks), a 65-week treatment period, 1-week efficacy assessment period and then 6 month post treatment evaluation period. A total of 173 participants were randomised 2:1 to inotersen 300mg or placebo, and there was one post-randomisation exclusion.

The co-primary outcomes in NEURO-TTR were change from baseline to week 66 in:

- Modified neuropathy impairment score +7 composite score (mNIS+7)
- Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN) questionnaire total score.

During the 15 months treatment period, inotersen treated patients achieved a greater improvement in neurological progression (mNIS+7), i.e. they progressed at a slower rate. Deterioration over time was still evident but was significantly less than those on placebo. The inotersen patients showed very little change from baseline for the Norfolk QoL-DN score but scores for placebo patients increased, thus a significant difference between inotersen and placebo was observed. Progression of disease at week 66 was slowed or stopped in 36.5% of inotersen patients compared to 19.2% of placebo patients (defined by improvement or no worse in mNIS+7 score).

Nearly all participants experienced at least one treatment-emergent adverse event (TEAE), the majority of which were reported to be mild to moderate in severity. In the inotersen group, 16 TEAEs (14.3%) led to permanent discontinuation of study treatment, of which four were associated with thrombocytopenia and two with glomerulonephritis. Serious TEAEs were experienced by 32.1% of participants who received inotersen compared with 21.7% in the placebo group, of which 7.1% and 1.7%, respectively, were considered related to study treatment. There were five deaths in the inotersen group, and none in the placebo group. Of these, one death was considered related to study treatment by the NEURO-TTR investigator.

[redacted] of those completing treatment in NEURO-TTR enrolled in the NEURO-TTR extension study. Interim results showed improvement in neurological disease progression (i.e. continued slowing) and QoL were maintained [redacted] with inotersen treatment.

[redacted]

[redacted] However this slowing down was not quite as pronounced for the placebo-inotersen group as it had been for those receiving inotersen in the NEURO-TTR study. Again, most participants experienced at least one TEAE, the majority of which were be mild to moderate in severity. The inotersen-inotersen group had fewer patients experiencing TEAEs related to study treatment, but more patients experiencing TEAEs leading to permanent discontinuation of study drug, compared with the placebo-inotersen group.

[redacted]. [redacted], of which none was considered related to study treatment by the NEURO-TTR investigator.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG questioned some discrepancies between the baseline characteristics reported in the company's submission and those reported in the Benson publication. The discrepancies related to the number of participants with previous treatment with tafamidis or diflunisal; disease stage 1 and 2; and V30M TTR mutation. The ERG does not understand the company's explanation that different randomisation strategies were used in the documents. The ERG also noted discrepancies in the number of participants reported in the NEURO-TTR extension study; these are assumed to relate to the analysis of the full analysis set but the ERG was unable to confirm this assumption. On the whole, the ERG concludes that inotersen has been shown to be an effective treatment in the studied population.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a Markov cohort state transition model, with a lifetime horizon, from an NHS and PSS perspective, to assess the cost-effectiveness of inotersen (Tegsedi®, Ionis USA Ltd, London, UK) compared to best supportive care (BSC) for patients with hATTR-PN. The model describes the progression of disease according to Coutinho disease stages and once the cohort enters stage 3, it is assumed they can no longer transit back to less severe stages. The model is populated with transition probabilities derived from the NEURO-TTR randomised controlled trial. The transition probabilities observed between weeks 35 and 66 are used to progress the cohort through disease stages over the remaining time horizon of the model or until death. Total inotersen treatment costs are a function of the unit cost, time to treatment discontinuation and treatment compliance. Time to treatment discontinuation is informed by parametric survival analysis, and costs while on treatment are adjusted to reflect treatment compliance. Utilities are based on a study using disease stage specific EQ-5D response data from the THAOS registry, but valued using Brazilian general population values.

The company submitted an economic model that predicted a base case ICER for inotersen compared with BSC of £324,054 per QALY gained. In response to the clarification letter, the company revised their base case to one that incorporated: 1) the correction of an error related to the modelling of treatment discontinuation; 2) updated time to treatment discontinuation curves (based on the inclusion of data from the NEURO-TTR extension study); 3) disease stage specific mortality rates, derived using hazard ratios obtained from a Delphi consensus study; 4) a revised compliance parameter to remove compliance of treatment discontinuers; and 5) the inclusion of phlebotomist time to monitor platelets. The net impact of these changes was to increase the ICER to £369,470 per QALY gained. The amendments also increased the ICERs in all the deterministic sensitivity analyses that were presented in the company's original submission.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG consider the model structure to be a fair reflection of disease progression and appropriate for use in the assessment. However, the ERG feel that the company's original and revised modelling results under-state the uncertainty surrounding the base case ICER. In particular, the company's probabilistic sensitivity analysis (PSA) assumes a standard deviation of 5% of the mean for all sampling distributions. In addition, the ERG raise a

number of concerns regarding some of the modelling assumptions and the choice of data for use in the economic model. These assumptions add substantial uncertainty to cost-effectiveness results, and the ICERs are particularly sensitive to assumptions surrounding utility input data, modelling of treatment discontinuation and compliance, and the discount rate applied to future costs and benefits. The main concerns are as follows:

- The company make a case for using a 1.5% discount rate in their analysis. However, the ERG disagrees that the company's model meets NICE's criteria for considering a departure from the reference case (3.5% discounting of costs and QALYs per annum). Specifically, the ERG find no evidence from the outputs of the company's model that sufficiently demonstrate a) a restoration of full or near full health for people who would otherwise die, b) benefits sustained over at least 30 years, or c) that significant irrecoverable costs will not have been committed.
- In relation to costs, the ICER is sensitive to assumptions regarding time to treatment discontinuation and treatment compliance. The company's base case analysis uses an exponential function to extrapolate time to treatment discontinuation data from the NEURO-TTR and NEURO-TTR extension studies. The ERG believes the exponential curve may under-estimate the proportion of the responding cohort who remain on treatment in the long-term. The ERG believe that a log logistic survival curve, which allows for a declining rate of treatment discontinuation over time, may be more appropriate. The ERG also believe that compliance based on the whole study population from NEURO-TTR, not just those who continue treatment in the long term, may be more appropriate for adjusting treatment costs.
- The ERG raise two concerns regarding the incorporation of utilities in the economic model. First, disease stage specific utilities are sourced from a conference abstract (Stewart et al), which describes how EQ-5D data from the THAOS registry were assigned Brazilian general population values. The ERG has compared the valuation sets between Brazil and the UK, and considers that there are substantial differences that limit the transferability of utility values. It would have been preferable to obtain data directly from the THAOS registry and apply the UK valuation set.
- The ERG also question whether it is appropriate to assume all patients with hATTR-PN would have two full time carers, and to what extent disease, especially Stages 1 and 2, would impact on carer's QoL. The company argue that all patients would have two carers, but this assumption is based on a previous assessment in a paediatric

population and the ERG feel it may be more reasonable to assume an average of one full time carer per patient.

- The ERG also note that the company excluded adverse events from their base case analysis. The ERG do not consider this appropriate, and believe that the company's incorporation of adverse events in response to the clarification letter was incomplete as it assumed no utility decrement and zero days duration for three serious AEs. However, the ERG also note that the model results are not sensitive to the incorporation or exclusion of adverse events as the cost and utility implications are relatively minor in the context of the inotersen drug acquisition costs and the substantial cost and utility implications of disease progression.

The ERG have highlighted the key areas of uncertainty in the company submission and note that a judgement is required with respect to the most plausible model values and assumptions for treatment discontinuation (in disease stages 1 and 2), treatment compliance, utility data, and the number of carers per hATTR-PN patient.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The NEURO-TTR study is a well conducted, robust randomised controlled trial that provides a high quality of evidence.
- The company have submitted a simple, and well described Markov cohort model, based on high quality randomised data for a very rare condition.
- The company have made substantial effort to accurately capture the longer term cost of inotersen treatment by using survival analysis methods to estimate time to treatment discontinuation.

1.6.2 Weaknesses and areas of uncertainty

- hATTR-PN is a rare health condition, with little long term follow up data to accurately determine long-term disease progression. This means that a number of questionable assumptions were required to extrapolate long-term cost-effectiveness.
- There are substantial uncertainties generated when mapping from the Norfolk QoL-DN total quality of life (TQoL) score to Coutinho disease stages, and the ERG notes

that there is substantial variability in TQoL scores among patients within each Coutinho stage.

- Utility data in the model are based on Brazilian valuations which are unlikely to adequately represent UK general population preferences for EQ-5D health states.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG have corrected two minor errors in the company's revised model (one data input error pertaining to stage 2 transition costs) and one relating to the specification of stage 3 carer disutility in the 'PSA variables' worksheet. The ERG has conducted a range of exploratory scenario analyses, the key findings of which are outlined below:

- Varying the discount rate for costs and QALYs had a modest impact on the ICER, ranging from £354,802 (0% discount rate) to £413,548 (6% discount rate).
- Using a log-logistic rather than a parametric survival curve to model treatment discontinuation increased the ICER by 6.55%. However, when combined with alternative compliance assumptions (based on all patients in the NEURO-TTR study), and a discount rate of 3.5%, the ICER increased by 17.54% to £434,408 per QALY gained.
- The ICER is particularly sensitive to the source of disease stage utility data. Applying disease stage specific utilities from the previous AGNSS assessment of tafamidis for Transthyretin Familial Polyneuropathy, based on mapping between TQoL and EQ-5D, as an alternative to the Brazilian values used by the company, increased the ICER to £503,024 per QALY gained.
- Assumptions around the number of carers for patients with hATTR-PN had a modest impact on the ICER, ranging from £341,306 (three carers) to £402,936 (one carer).
- Combining alternative utility assumptions (one carer, and disease stage utilities from the previous assessment of tafamidis) with a 3.5% discount rate, increased the ICER by 65% to £610,509 per QALY gained.
- Overall, the ERG found that the ICER varied widely, depending on the assumptions applied, between £282,232 (optimistic case for inotersen) and £834,082 (most pessimistic case for inotersen).

The ERG's preferred base case analysis combines the following: 1) a 3.5% discount rate (NICE reference case); 2) a log logistic parametric survival curve for time to treatment

discontinuation; 3) compliance based on all participants in the NEURO-TTR study; 4) carer disutility applied to one carer per patient; and 5) incorporation of utility decrements and costs for all serious treatment related AEs. The deterministic ICER for the ERG preferred analysis ranges from £478,079 to £683,178 depending on which source of utility data is applied, compared to company's preferred base case of £369,470 per QALY gained.

2 Background

This section provides a brief overview of hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) and its management. The information in this chapter is based on relevant literature and the content of the company's submission, in which further pertinent information is available.

2.1 Critique of company's description of underlying health problems

The company's description of hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. The company describes hATTR-PN as a rare and devastating autosomal dominant disease, with extensive deposition of mutant amyloid protein resulting in problems of the peripheral nervous system and vital organs. The symptoms of this adult-onset, irreversible neurological disorder include intractable, progressive sensorimotor and autonomic neuropathy, with time between diagnosis and death reported to be around 5 to 15 years.[1-5]

Hereditary ATTR is caused by a mutation in the transthyretin gene that leads to neuropathy and/or cardiomyopathy. Transthyretin is a protein that circulates in the plasma as a tetramer and is synthesised and secreted mainly by the liver. It comprises four identical 127 amino acid monomers and acts as a transport protein for circulating plasma thyroxine and retinol binding protein.[6, 7] In hATTR-PN, the most common mutation of the gene is the replacement of valine with methionine at amino acid 30, i.e. V30M. This mutation is prevalent in Portugal, Japan and Sweden (and descendents of these countries), but also occurs worldwide.[3, 8, 9] Across countries, the symptoms at presentation and clinical progression in people with hATTR-PN differ.[10]

Staging of the disease most often uses ambulatory status, as proposed by Coutinho (1980)[1]:

- Stage 1: Does not require assistance with ambulation (unimpaired ambulation); Mostly mild sensory, motor, and autonomic neuropathy in the lower limbs (e.g., weakness of extensors in big toes)

- Stage 2: Requires assistance with ambulation; Disease progression in lower limbs; Symptoms develop in hands (weakness and wasting of muscles)
- Stage 3: Wheelchair bound or bedridden; Severe sensory, motor, and autonomic neuropathy of all limbs.

The mental and psychological impact of the disease on patients and their families is substantial, due to its burden of heredity, unpredictable age at onset and devastating evolution.[11] Patients experience marked decrements in HRQoL and the burden of the condition increases as the disease progresses.[12] High rates of anxiety and depression for carers have been reported and many caregivers face the prospect of also having hATTR-PN.[13]

The company's submission described hATTR-PN as very rare, with an estimated 10000 people having a diagnosis of the condition worldwide. Inotersen was granted 'orphan medicine' designation in March 2014. The definition of an orphan medicine is:

> *"A medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs."*[14, 15]

Hospital Episode Statistics for admitted patient care in England for the year 2017-2018[16] reported 37 finished consultant episodes and 37 admissions (mean length of stay: 9 days; mean age: 60 years) for "neuropathic heredofamilial amyloidosis" (code E85.1).

The focus of treatments for hATTR-PN is on stabilising or decreasing the amount of circulating amyloidogenic protein, and relieving symptoms is a priority.[17-19] Orthotopic liver transplant is an option for people with mild or moderate hATTR-PN and is the only available treatment which modifies the disease; it removes the majority of the production of variant transthyretin and can slow disease progression or stop it completely outside the brain and eyes. Following liver transplant, it is unusual for

nerve function to improve or any existing organ damage to reverse, but autonomic disturbances may decrease. Younger patients with disease which has not reached the advanced stage generally experience better outcomes; however, not all patients report improved quality of life, despite the reversal of their disease progression.[17]

More recent treatments involve transthyretin tetramer stabilisers, which are agents designed to stabilise the normal circulating tetramic form of transthyretin. By doing so, the protein is prevented from dissociating and experiencing conformational change, leading to its aggregation as amyloid.[18] Inotersen (Tegsedi®, Ionis USA Ltd, London, UK) is a therapy based on short synthetic oligonucleotides that bind onto transthyretin mRNA, causing its degradation by RNase H. Inotersen destroys both mutant and wild type forms of the transthyretin transcript[18, 20] and has been authorised in the EU as Tegsedi since 6 July 2018 for the treatment of Stage 1 or Stage 2 polyneuropathy in adults with hATTR.[21]

2.2 Critique of company's overview of current service provision

The company's submission states that there are currently no relevant NICE guidance or guidelines for patients with hATTR-PN. The company refers to two NHS England manuals for diagnosis and management of all forms of amyloidosis.[22, 23] The documents specify that the National Amyloidosis Centre (NAC), based in University College Hospital London, provides the only specialist services for patients with amyloidosis and related disorders in the UK. The NAC provides diagnostic imaging, histology and DNA analysis, genetic counselling, monitoring of amyloid proteins in the blood, treatment recommendations and supports the evaluation of existing and new therapies. The NAC provides a diagnostic service to around 1200 new patients/year.

The company also cites the European consensus for diagnosis, management and treatment of hATTR-PN, which was published in 2016 and presents a treatment algorithm for hATTR-PN.[4] In brief, for stage 1 patients under 50 years of age with no contraindications for liver transplantation, the first line of treatment is tafamidis, followed by liver transplantation, if the disease progresses. For stage 2 patients, the strategy is protocol clinical trial or off-label diflunisal. For stage 1 patients aged over 50 years or with contraindications for liver transplantation, the strategy is tafamidis,

protocol clinical trial or diflunisal off-label. For stage 2 patients, protocol clinical trial or diflunisal off-label are the recommended strategy.

The company does not expect any significant changes in the organisation or delivery of current services with the introduction of inotersen. The submission states:

> *"It is anticipated that inotersen will fit into the current clinical pathway of care, with a highly specialised service being established aligned in line with NHS England policy. It is expected that treatment will be initiated under the care of a specialist at the NAC with the management of patients being shared with the referring centre. Due to the subcutaneous delivery of inotersen, it can be administered by the patient or their families/carers at home, avoiding the need for patients to travel to the NAC, or their local referring centre, for repeat treatments. Monitoring for thrombocytopenia as per the inotersen SmPC (platelet count every two weeks) and glomerulonephritis (UPCR and estimated glomerular filtration rate [eGFR] every three months) is expected to be undertaken in conjunction with the referring centre and primary care services.*

[redacted]

3 Critique of company's definition of decision problem

The remit of this appraisal, as defined in the final NICE scope, is to evaluate the benefits and costs of inotersen within its marketing authorisation for treating hereditary transthyretin-related amyloidosis for national commissioning by NHS England.

The European Medicines Agency (EMA) granted marketing authorisation for inotersen on 6th July 2018 for the treatment of Stage 1 or Stage 2 polyneuropathy (PN) in adult patients with hereditary transthyretin-related amyloidosis (hATTR).[15]

Table 1 presents a summary of the decision problem as set out in the NICE final scope, the company's variations from the scope, the company's rationale for any variations and comments from the ERG.

Table 1 Comparison of NICE final scope and decision problem addressed by the company, including comments from the company and the ERG

	Final scope issued by NICE	Variation from scope in the submission	Company's rationale for variation from scope in the submission	Comments from the ERG
Population	People with hereditary transthyretin-related amyloidosis (hATTR)	People with hATTR with polyneuropathy (hATTR-PN)	To align with licensed indication for inotersen	None
Intervention	Inotersen	None	Not applicable	None
Comparator(s)	Established clinical management without inotersen	This is referred to as best supportive care	No deviation apart from naming convention	None
Outcomes	• neurological impairment • symptoms of polyneuropathy • cardiac function • autonomic function (including the effects on the gastrointestinal system and **postural hypotension**) • weight loss • **effects of amyloid deposits in other organs and tissues (including the eye)** • serum transthyretin • motor function • mortality • adverse effects of treatment	None	Not applicable	The following outcomes were not included in the company's submission: • Postural hypotension • Effects of amyloid deposits in other organs and tissues (including the eye) The company provided no explanation for these omissions. The ERG notes that the NSC score includes two autonomic domains: GI/urinary incontinence, and other than GI/urinary incontinence. It is

	Final scope issued by NICE	Variation from scope in the submission	Company's rationale for variation from scope in the submission	Comments from the ERG
	• health-related quality of life (for patients and carers).			unclear to the ERG whether the latter domain encompasses postural hypotension
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	Not applicable	None
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)	No treatment continuation rules are relevant No other variation	Not applicable	None

	Final scope issued by NICE	Variation from scope in the submission	Company's rationale for variation from scope in the submission	Comments from the ERG
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	A patient access scheme has been proposed No other variation	Not applicable	None
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	Non-health benefits summarised in Section E [of submission]. No variation from scope	Not applicable	None

3.1 Population

The NICE final scope for this appraisal specified the population as people with hereditary transthyretin-related amyloidosis (hATTR). The decision problem addressed by the company focused on people with hATTR with polyneuropathy (hATTR-PN), the rationale being to align with the licence indication. The ERG considers this variation to be appropriate.

The approved indication for inotersen is for treatment of Stage 1 (patient is ambulatory) or Stage 2 (patient is ambulatory with assistance) polyneuropathy (PN) in adult patients with hereditary transthyretin-related amyloidosis (hATTR).

Key inclusion criteria for the company's NEURO-TTR study were: adults (18 to 82 years) with Stage 1 or Stage 2 polyneuropathy with hATTR who had all of the following:

1. NIS (neuropathy impairment score) ≥10 and ≤130
2. Documented TTR mutation by genotyping
3. Documented amyloid deposit by biopsy
4. In Germany and Argentina only, Stage 1 patients were also required to meet at least one of the following criteria: a) failed tafamidis, b) intolerant to tafamidis, or c) not eligible for tafamidis.

Key exclusion criteria for the company's NEURO-TTR study were:

1. Clinically-significant abnormalities in screening laboratory values
2. Karnofsky performance status ≤50
3. Other causes of polyneuropathy
4. Prior liver transplant
5. New York Heart Association (NYHA) functional classification of ≥3.

Patients who participated in the ECHO sub-study in the company's NEURO-TTR study were also required to meet the following entry criteria to be included in this subgroup:

1. Left ventricular (LV) wall thickness of ≥13 mm on transthoracic ECHO at baseline

2. No known history of persistent hypertension ≥150 mmHg within 12 months prior to screening
3. Baseline ECHO was evaluable as ascertained by the central reader.

3.2 Intervention

The intervention included in the company's submission was inotersen, which is consistent with the NICE final scope.

Inotersen (Tegsedi®, Ionis USA Ltd, London, UK) is a 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. The selective binding of inotersen to TTR mRNA causes the degradation of both mutant and wild type (normal) TTR mRNA. This prevents the synthesis of TTR protein in the liver, resulting in significant reductions in the levels of mutated and wild type TTR protein secreted by the liver into the circulation.[21] (SmPC).

The pharmaceutical formulation is 284 mg solution for injection supplied in a 1.5 ml pre-filled syringe. Inotersen solution for injection is administered as a once-weekly, single-use subcutaneous injection. The first injection administered by the patient or carer should be performed under the guidance of an appropriately qualified health care professional. Patients and/or carers should be trained in subcutaneous administration.[21]

The recommended dose is 284 mg of inotersen. Dosing should be adjusted according to laboratory values as shown in Table 2.

Table 2 Inotersen dosing and monitoring frequency for platelet count (adapted from Table 1 of Summary of Product Characteristics)[21]

Platelet count (x109/L)	Monitoring frequency	Dosing
> 100	Every 2 weeks	Weekly dosing should be continued.
≥ 75 to < 100	Every week	Dosing frequency should be reduced to 284 mg every 2 weeks
< 75	Twice weekly until 3 successive values above 75 then weekly monitoring	Dosing should be paused until 3 successive values > 100. On reinitiation of treatment dose frequency should be reduced to 284 mg every 2 weeks
< 50	Twice weekly until 3 successive values above 75 then weekly monitoring. Consider more frequent monitoring if additional risk factors for bleeding are present.	Dosing should be paused until 3 successive values > 100. On reinitiation of treatment dose frequency should be reduced to 284 mg every 2 weeks. Consider corticosteroids if additional risk factors for bleeding are present.
< 25	Daily until 2 successive values above 25. Then monitor twice weekly until 3 successive values above 75. Then weekly monitoring until stable.	Treatment should be discontinued. Corticosteroids recommended.

A tabulated list of adverse reactions to inotersen is presented in Table 3 Adverse reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to < 1/10), and uncommon (≥1/1000 to < 1/100).

Table 3 Summary of adverse reactions considered related to inotersen in clinical trials (reproduced from Table 2 of Summary of Product Characteristics)[21]

System Organ Class	Very Common	Common
Blood and lymphatic system disorders	Thrombocytopenia Anaemia Platelet count decreased	Eosinophilia
Metabolism and nutrition disorders		Decreased appetite
Nervous system disorders	Headache	
Vascular disorders		Orthostatic hypotension Hypotension Haematoma
Gastrointestinal disorders	Vomiting Nausea	
Hepatobiliary disorders		Transaminases increased
Skin and subcutaneous disorders		Pruritus Rash
Renal and urinary disorders		Glomerulonephritis Proteinuria Renal failure Acute kidney injury Renal impairment
General disorders and administration site conditions	Pyrexia Chills Injection site reactions Peripheral oedema	Influenza like illness Peripheral swelling Injection site discolouration
Injury, poisoning and procedural complications		Contusion

According to the SmPC[21], important identified risks that need special risk management activities during treatment with inotersen include:

- thrombocytopenia
- glomerulonephritis / renal function decline
- vitamin A deficiency
- liver monitoring.

Inotersen is associated with reductions in platelet count, which may result in thrombocytopenia. Platelet count should be monitored every two weeks during

treatment with inotersen. Recommendation for adjustments to monitoring frequency and inotersen dosing are as per Table 2 Patients should also be monitored for increased urine protein to creatinine ratio (UPCR) and reduction in estimated glomerular filtration rate (eGFR) every 3 months or more frequently, as clinically indicated. Patients receiving inotersen should take oral supplementation of approximately 3,000 IU vitamin A per day in order to reduce the potential risk of ocular toxicity due to vitamin A deficiency. Hepatic enzymes should be measured 4 months after initiation of treatment with inotersen and annually thereafter or more frequently as clinically indicated, in order to detect cases of hepatic impairment.[21]

3.3 Comparators

The comparator is described in the company's submission as 'best supportive care'. The NICE final scope specified the comparator as 'established management without inotersen'. The company described this variation as mere 'naming convention' with 'no deviation' from the final scope. The comparator group received placebo. The company did not specify what was included in the best supportive care. The ERG considers the company's approach to be appropriate.

3.4 Outcomes

The outcomes specified in the NICE final scope were neurological impairment; symptoms of polyneuropathy; cardiac function; autonomic function (including the effects on the gastrointestinal system and postural hypotension); weight loss; effects of amyloid deposits in other organs and tissues (including the eye); serum transthyretin; motor function; mortality; adverse effects of treatment; and health-related quality of life (for patients and carers).

The outcomes included in the company's submission are broadly in line with the NICE final scope, with the exception of the following outcomes, which were not included:

- Effects on postural hypotension
- Effects of amyloid deposits in other organs and tissues (including the eye).

The company provided no explanation for these omissions. The ERG notes that the neuropathy and change (NSC) score, which was collected by the company in the NEURO-TTR study during the neuropathy impairment score (NIS) assessment procedure, encompasses the following domains:

- Muscle weakness
- Sensory [hypo/loss of sensation]
- Sensory [paresthesia, hypersensation]
- Autonomic [GI/urinary incontinence]
- Autonomic [other than GI/urinary incontinence].

It is unclear to the ERG whether the latter domain encompasses postural hypotension. The company's submission reports the scores for the individual domains at baseline but only the NSC total score at week 66, whereas the NEURO-TTR CSR reports the on-treatment NSC autonomic domain scores at weeks 35 and 66.

The ERG's clinical expert is of the opinion that the omission of outcome data on postural hypotension is important, as the staging of hATTR-PN strongly relates to the ability to mobilise independently, and significant autonomic symptoms, particularly postural hypotension, will impact on this. The ERG's clinical expert considers that the omission of outcome data on amyloid deposits in other organs and tissues is not important as they are not life-limiting.

In the NEURO-TTR study, the co-primary outcomes were change from baseline in:

- Modified neuropathy impairment score (mNIS) +7 composite score (mNIS+7) (week 66)
- Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN; also referred to as Total QoL [TQoL] score) (week 66).

According to the company's submission, the mNIS+7 score is a composite neurological impairment score, consisting of two composite scores: the neuropathy impairment score (NIS) (maximum of 244 points) and the modified +7 score (maximum of 102.32 points). A decrease in mNIS+7 score indicates an improvement in neurological impairment.

The NIS score was originally developed for assessment of diabetic neuropathy and is a quantitative score of motor, sensory, and reflex function, as judged by the clinician.[24] The Sum 7 Test (or +7) is an objective score of large fibre function that includes measurements of nerve conduction, vibration threshold and heart rate to deep breathing (HRDB; an assessment of autonomic function).[24] As it is known that patients in later Stage 1 and Stage 2 hATTR-PN can reach a ceiling effect on the standard Sum 7 Test score, the modified +7 assessments include a greater sensory component and involve both large and small nerve fibre sensory tests, require more anatomical sites to be tested, and include both upper limb and lower limb nerve conduction tests.[25]

The Norfolk QoL-DN questionnaire assesses disease-specific changes in the patients' perceived quality of life. This instrument is a nerve fiber-specific, 5-domain tool that was validated in subjects with hATTR-PN.[26] The Norfolk QoL-DN consists of one composite total score (Total QoL [TQoL]) and five subdomain scores (physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy). The TQoL score is the sum of 35 questions across the five domains. Scores range from -4 to 135. An increase in Norfolk QoL-DN total score indicates a worsening of QoL.

Other outcomes of the NEURO-TTR study included the following:

Secondary outcomes (change from baseline):

- Norfolk QoL-DN symptom domain score in Stage 1 patients and Norfolk QoL-DN physical functioning/large fibre score in Stage 2 patients (week 66)
- Modified body mass index (mBMI) and body mass index (BMI) (week 65)
- Neuropathy impairment score (NIS) (week 66)
- modified +7 (week 66)
- NIS+7 (week 66)
- Global longitudinal strain (GLS) by echocardiogram (ECHO) in the ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set (week 65)

Tertiary outcomes:

- SF-36 questionnaire scores (week 65)
- Individual components of NIS (week 66)
- Individual components of modified +7 (week 66)
- Individual domain scores Norfolk QoL-DN domain scores (week 66)

Exploratory outcomes:

- ECHO parameters other than GLS (week 65)
- Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (week 66)
- Polyneuropathy disability (PND) score (week 65)
- Neuropathy symptoms and change score (NSC) (week 66)

Safety assessments:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory tests
- Vital signs
- 12-lead electrocardiogram (ECG) and ECG
- Ophthalmology and electroretinography to detect early signs of vitamin A deficiency

3.5 Other relevant factors

The following subgroups were evaluated the NEURO-TTR study:

1. V30M TTR mutation (Yes, No)
2. Age (<65 years old, ≥65 years old)
3. Race (White, non-White)
4. Sex (male, female)
5. Region (North America, Europe, and South America/Australasia)
6. Previous treatment with tafamidis or diflunisal (Yes, No)
7. Disease stage (Stage 1, Stage 2)
8. CM-ECHO Set (Included, Not included)

There were no further variations to the NICE scope.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company's submission reports full details of the searches that were undertaken to identify studies for the clinical effectiveness review. The major relevant databases were searched: MEDLINE, EMBASE and the Cochrane Library. The searches were undertaken in January and February 2018. Searches were limited to literature published from 2008 onwards. The search strategies are documented in full in Appendix 1 of the company's submission and the platforms used are specified in Table 1 of the company's appendices.

In addition, the company hand-searched registries (US NIH registry & results database, WHO ICTRP registry and CEA-registry), major relevant congresses between 2015 and 2017 (European congress of hereditary ATTR amyloidosis & ATTR amyloidosis meeting for patients and doctors [2015 and 2017 only], International symposium on amyloidosis [2016 only], European Academy of Neurology, American Academy of Neurology, International Society for Pharmacoeconomics and Outcomes Research US and EUROPE, American Association of Neuromuscular & Electrodiagnostic Medicine, Peripheral Nerve Society [2015 and 2017 only], American Neurological Association, American College of Cardiology, Heart Failure Society of America, European Society of Cardiology) and websites (NICE, RePEc, EQ-5D, ScHARRHUD database of health utilities' evidence and HERC-maintained mapping algorithm database) on 5th February 2018. The respective search strategies used by the company are reported in Tables 5, 6 and 7 in the company's submission appendices.

The company's search strategies combined a number of facets (i.e. the condition, relevant interventions, cost-effectiveness, quality of life and incidence/prevalence) but, ultimately, retained only the results of the condition (i.e. hATTR-PN) facet for further screening. The relevant MESH and Emtree terms were included in the single facet search, along with a comprehensive list of text terms. At clarification, the

company stated that the additional search filters were not applied as the results of the first search were manageable and the search was, therefore, kept broad.

The company's search strategy involved global searches for the relevant condition, thus, there were no separate searches for adverse events or HRQoL data.

The ERG considered that the company's search strategies were appropriate.

4.1.2 Inclusion criteria

The inclusion criteria for the searches are presented in Table 4 below.

Three publications met all the inclusion criteria, including two abstracts and one poster, all of which relate to the NEURO-TTR study.[5, 27, 28] The company states that the primary publication for the NEURO-TTR study was not identified in the searches, as this was published after the specified search date of the systematic literature review of clinical effectiveness.[29] In addition, one unpublished report was identified, an ongoing open-label extension of NEURO-TTR (the NEURO-TTR Extension study; reference 32 of company's submission). In total, four published reports and one unpublished report, all relating to the same RCT, were included as the main source of evidence in the company's review of clinical effectiveness.

Table 4 Inclusion criteria for the company's systematic review of clinical effectiveness (reproduced from Table 8 of company's submission appendices)

Study characteristics	Inclusion criteria
Population	Adults >18 years with confirmed diagnosis of hATTR-PN Familial amyloid polyneuropathy (FAP) type I & II Cardiac amyloidosis Familial amyloid cardiomyopathy (FAC)
Interventions	Inotersen Tafamidis (Pfizer) Diflunisal Patisiran (Alnylam) Liver transplant Best supportive care
Study design/ Type of studies	Randomised controlled trials (RCT) Prospective non-RCTs Open label extension (OLE) studies Single arm studies Placebo-controlled studies Crossover studies Observational studies Retrospective studies Cost effectiveness/cost analysis/resource use studies Epidemiology Guidelines
Disease profile/Treatment Outcomes	*Disease background and management* Pathogenesis/natural history Diagnosis Treatment guidelines/current management *Epidemiology* Incidence Prevalence Aetiology Risk factors Mortality *Clinical efficacy, e.g.* *Improvement in:* Neurological disability Symptoms of polyneuropathy

	Autonomic function Motor function Mortality rate *Reduction in:* TTR protein and RBP4, NT-proBNP *Clinical safety, e.g.* Thrombocytopenia, renal dysfunction, itching, fatigue *HRQoL/symptoms, e.g.* Any relevant PRO, e.g. Quality of life (mNIS+7 and Norfolk QOL-DN endpoints SF-36 PND score NSC score NIS GLS by ECHO EQ-5D, utilities Impact on carers *Resource use and costs, e.g.* Hospital admission Length of stay Physician visits Emergency department visits Pharmacy costs Procedures (defibrillator, dialysis, stent etc) costs Organ transplant related costs Cost-effectiveness studies For inotersen and other interventions
Study period	2008 to 2018
Publication	Primary publications, secondary publications / sub group analysis, pooled data analysis, Congress abstracts corresponding to the above
Language	English

Abbreviations: GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NSC, neuropathy symptoms and change; PND, polyneuropathy disability; SF-36, short form-36.

4.1.3 Critique of data extraction

The company did not report whether the methods of the systematic review of clinical effectiveness were based on published guidance. The company did not report the number of reviewers involved in the key stages of the systematic review process (i.e.

title/abstract screening, full-text screening, and data extraction) and the level of independence of researchers at each stage. It is, therefore, unclear to the ERG whether the company's methods were appropriate.

4.1.4 Quality assessment

The risk of bias of the included study was evaluated using an adapted version of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[30] The company's assessment of NEURO-TTR is summarised in Table 5.

The ERG considers that the company used an appropriate risk of bias tool and largely agrees with the company's critical appraisal of the study. However, the process of quality assessment was not fully described, in that it was not reported how many reviewers were involved in the risk of bias assessment.

Table 5 The company's quality assessment of the included study (NEURO-TTR) (Reproduced from Table C12 of company's submission)

Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Stratified randomisation (2:1), however method of randomisation has not been mentioned
Was the concealment of treatment allocation adequate?	Yes	Interactive Voice/Web-response system used.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The two groups were stratified based on disease stage, TTR mutation and prior treatments with stabilisers and had similar characteristics
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	Interactive Voice/Web-response system used for treatment allocation. The outcome assessors were blinded. Study personnel or their designees who were involved in the conduct of the study, and patients were blinded throughout the study until all subjects completed the treatment period and the EOT efficacy assessments and the database was locked. The CRO personnel involved in the regular conduct of the study, investigators, study centre personnel, and the subjects did not have access to any post-baseline PK or PD data (e.g. TTR,) that may have resulted in unblinding of treatment assignments.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes Yes	More discontinuations, 22%, in inotersen group than 13% in the placebo group, primarily due to adverse events. MMRM analysis was used to adjust for missing data.

Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	None
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 Yes	FAS included all randomised patients who had received at least one injection of the treatment drug. Predefined sensitivity analyses included alternative methods for imputing missing data at the visit level.

Abbreviations: CRO, clinical research organisation; EOT, end of treatment; FAS, Full Analysis Set; MMRM, mixed model for repeated measure; PK, pharmacokinetic; TTR, transthyretin

4.1.5 Evidence synthesis

The company submission includes a phase 3, multi-centre, stratified, placebo-controlled randomised controlled trial (RCT), the NEURO-TTR study. The NEURO-TTR study was the only available trial comparing inotersen to placebo in patients with Stage 1 and Stage 2 hATTR-PN and was administered by the company. NEURO-TTR was followed by an ongoing, post-trial, Phase 3, open-label extension, the NEURO-TTR Extension study in the same population. Both studies contribute to the company's clinical effectiveness evidence.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Summary of NEURO-TTR

The NEURO-TTR trial was carried out in 24 centres in 10 counties (Argentina, Brazil, France, Germany, Italy, New Zealand, Portugal, Spain, UK and USA). There was one centre in the UK (NAC), which recruited 6 participants to the study. The trial consisted of a baseline screening period (≤ 6 weeks), a 65-week treatment period, 1-week efficacy assessment period and then 6 month post-treatment evaluation period. A total of 173 participants were randomised 2:1 inotersen 300mg or placebo, and

there were one post-randomisation exclusion. All further trial information presented is for 172 participants. Table 6 shows the details of the trial characteristics.

The NEURO-TTR Safety Set (SS) consists of all 172 participants that were randomised and received at least one dose of the allocated treatment. The full analysis set (FAS) was defined as all randomised participants who received at least one injection of study drug and who had a baseline and at least one post-baseline measurement of mNIS+7 or Norfolk QoL-DN total score. Seven participants were excluded from the FAS as they did not have post-baseline assessment of mNIS+7 or Norfolk QoL-DN.

Table 6 Characteristics of the RCT (NEURO-TTR) included in the company's review of clinical effectiveness (Adapted from Table C3 of company's submission)

Characteristics	NEURO-TTR study details
Number of centres/ Countries	A total of 24 study centres in 10 countries: Argentina, Brazil, France, Germany, Italy, New Zealand, Portugal, Spain, UK (1 centre [n=6]; NAC, University College London), and USA
Key inclusion criteria	Adults (18 to 82 years) with Stage 1 or Stage 2 hATTR-PN who had all of the following: • NIS ≥10 and ≤130 • Documented TTR mutation by genotyping • Documented amyloid deposit by biopsy Stage 1 patients in Germany and Argentina must have met at least one of the following: failed tafamidis, intolerant to tafamidis, not eligible for tafamidis. Additional inclusion criteria for the ECHO sub-study: • Left ventricular (LV) wall thickness of ≥13 mm on transthoracic ECHO at baseline • No known history of persistent hypertension ≥150 mmHg within 12 months prior to screening • Baseline ECHO was evaluable as ascertained by the central reader
Key exclusion criteria	• Clinically-significant abnormalities in screening laboratory values • Karnofsky performance status ≤50 • Other causes of polyneuropathy • Prior liver transplant • NYHA functional classification of ≥3

Characteristics	NEURO-TTR study details
Intervention	Inotersen (n=113) Received study treatment: Inotersen (n=112) Patients received three subcutaneous (SC) doses of study drug (300 mg inotersen or placebo) during week 1 on alternate days (days 1, 3 and 5), followed by once-weekly SC administration during weeks 2 to 65 (for a total of 67 doses).
Comparator	Placebo (n=60) Received study treatment: placebo (n=60)
Co-intervention (all patients)	• Supplemental doses of the recommended daily allowance of vitamin A • Treatment with either tafamidis or diflunisal was not allowed at any time during the treatment period.
Co-primary efficacy endpoints	Change from baseline in • the modified NIS + 7 (mNIS+7) composite score (week 66) • the Norfolk QoL-DN questionnaire total score (week 66)
Secondary outcomes	Change from baseline in: • Norfolk QoL-DN symptom domain score in Stage 1 patients and Norfolk QoL-DN physical functioning/large fibre score in Stage 2 patients (week 66) • Modified BMI (mBMI) (week 65) • BMI (week 65) • NIS (week 66) • Modified +7 (week 66) • NIS+7 (week 66) • GLS by ECHO in the ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set (week 65)
Other outcomes	Tertiary outcomes (change from baseline): • SF-36 questionnaire scores (week 65) • Individual components of NIS (week 66) • Individual components of modified +7 (week 66) • Individual domain scores Norfolk QoL-DN domain scores (week 66)

Characteristics	NEURO-TTR study details
	Exploratory outcomes (change from baseline): • ECHO parameters other than GLS (week 65) • NT-proBNP (week 66) • PND (week 65) • NSC (week 66)
Safety assessment outcomes	• Treatment emergent adverse events (TEAEs) • Clinical laboratory tests • Vital signs • 12-lead ECG and ECG • Ophthalmology and electroretinography to detect early signs of vitamin A deficiency
Subgroups	Within each randomisation, patients were stratified for: • Previous treatment with tafamidis or diflunisal (Yes, No) • Disease stage (Stage 1, Stage 2) • V30M TTR mutation (Yes, No) Other pre-specified subgroups • Age (<65 years old, ≥65 years old) • Race (White, non-White) • Sex (male, female) • Region (North America, Europe, and South America/Australasia) • CM-ECHO Set (Included, Not included)
Duration of study	66 weeks (15 months)
Duration of post-treatment evaluation	6 months
Source of funding	Ionis Pharmaceuticals

Abbreviations: BMI, body mass index; CM, cardiomyopathy; ECHO, echocardiogram; ECG, electrocardiogram; GLS, Global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; kg/m^2, kilograms per square metre; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NIS, neuropathy impairment score; NT-proBNP, N terminal prohormone of brain natriuretic peptide; NSC, neuropathy impairment score; NYHA, New York Heart Association; pmol/L, picomole per litre; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin.

Baseline characteristics: NEURO-TTR

Table 7 shows the baseline demographic characteristics of the 172 patients in the safety set (SS). There were 112 in the inotersen arm and 60 in placebo. Groups were balanced with an average age of 59 years, 69% males, 92% white, 43% aged 65 and over, weight of about 70kg with nearly half from North America, and 35% from Europe. Randomisation was stratified by previous treatment with tafamidis or diflunisal (yes/no), disease stage (Stage 1 or 2) and V30M TT mutation (yes/no).
In general, balance between randomised groups was noted for the baseline disease characteristics, but there were some observed differences in means for some of the efficacy parameters. Inotersen participants had a longer duration from onset of hATTR-CM symptoms (10 months) and slightly higher (i.e. worse) mNIS+7 composite score (and some sub-scores) at baseline. An absolute difference of about 5 was observed and 2 points is considered clinically meaningful.

Table 7 Baseline characteristics of participants in the RCT (NEURO-TTR) and the post-trial extension (NEURO-TTR Extension) included in the company's review of clinical effectiveness

	NEURO-TTR (SS)		NEURO-TTR Extension (SS)	
	Placebo (N=60)	**Inotersen (N=112)**	[redacted]	[redacted]
Demographic characteristics				
Age (years) Mean (SD)	59.5 (14.05)	59.0 (12.53)		
Sex, n (%)				
Male	41 (68.3)	77 (68.8)		
Female	19 (31.7)	35 (31.3)		
Ethnicity, n (%)				
Hispanic or Latino	7 (11.7)	17 (15.2)		
Not Hispanic or Latino	53 (88.3)	95 (84.8)		
Race, n (%)				
Asian	3 (5.0)	1 (0.9)		
Black	1 (1.7)	3 (2.7)		
White	53 (88.3)	105 (93.8)		
White and Greyish-Brown	1 (1.7)	0		
Other	2 (3.3)	3 (2.7)		
Weight (kg) Mean (SD)	71.07 (18.135)	70.59 (17.032)		
Region, n (%)				
Europe	23 (38.3)	37 (33.0)		
North America	26 (43.3)	56 (50.0)		
South America/Australasia	11 (18.3)	19 (17.0)		
Randomisation stratum by IXRS at NEURO-TTR pre-treatment, n (%)				
Previous treatment with tafamidis or diflunisal				
Yes	33 (55.0)	61 (54.5)		
No	27 (45.0)	51 (45.5)		
Disease stage				
Stage 1	39 (65.0)	74 (66.1)		
Stage 2	21 (35.0)	38 (33.9)		
V30M TTR mutation				

	NEURO-TTR (SS)		NEURO-TTR Extension (SS)	
	Placebo (N=60)	**Inotersen (N=112)**	[redacted]	[redacted]
Yes	32 (53.3)	58 (51.8)	[redacted]	[redacted]
No	28 (46.7)	54 (48.2)		
Disease characteristics				
TTR genotype observed in >1 patient, n (%)				
Type VAL30MET	33 (55.0)	56 (50.0)	[redacted]	[redacted]
Type THR60ALA	8 (13.3)	14 (12.5)		
Type LEU58HIS	3 (5.0)	7 (6.3)		
Type SER77TYR	5 (8.3)	4 (3.6)		
Type PHE64LEU	3 (5.0)	5 (4.5)		
Type SER50ARG	1 (1.7)	5 (4.5)		
Type GLU89GLN	0	5 (4.5)		
Type VAL122ILE	1 (1.7)	2 (1.8)	Not reported	Not reported
Type THR49ALA	0	2 (1.8)	Not reported	Not reported
Duration of disease from hATTR-PN diagnosis (months) Mean (SD)	39.3 (40.30)	42.4 (51.19)	[redacted]	[redacted]
Duration from onset of hATTR-PN symptoms (months) Mean (SD)	64.0 (52.34)	63.9 (53.16)	[redacted]	[redacted]
Patients diagnosed with hATTR-CM, n (%)				
Yes	22 (36.7)	45 (40.2)	[redacted]	[redacted]
No	38 (63.3)	67 (59.8)		
Duration of disease from hATTR-CM diagnosis (months) Mean (SD)	21.0 (22.52), n=22	25.1 (28.62), n=44	[redacted]	[redacted]
Duration from onset of hATTR-CM symptoms (months) Mean (SD)	34.1 (29.33), n=18	44.7 (58.00), n=36	[redacted]	[redacted]
mNIS+7 composite scores Mean (SD)	74.75 (39.003)	79.16 (36.958)	[redacted]	[redacted]
Norfolk QoL-DN total scores Mean (SD)	48.68 (26.746), n=59	48.22 (27.503), n=111	[redacted]	[redacted]
PND score, n (%)				
I	23 (38.3)	32 (28.6)	[redacted]	[redacted]
II	19 (31.7)	42 (37.5)		
III	15 (25.0)	30 (26.8)		
IV	3 (5.0)	8 (7.1)		

	NEURO-TTR (SS)		NEURO-TTR Extension (SS)	
	Placebo (N=60)	**Inotersen (N=112)**	[redacted]	[redacted]
V	0	0		
BMI (kg/m^2) Mean (SD)	24.21 (4.858)	23.99 (4.896)		
NT-proBNP (pmol/L) Mean (SD)	81.98 (159.151)	121.55 (255.420)		
NYHA score, n (%)			(NEURO-TTR baseline)	(NEURO-TTR baseline)
I	40 (66.7)	71 (63.4)		
II	20 (33.3)	41 (36.6)		
III	0	0		
IV	0	0		
Karnofsky score			(NEURO-TTR baseline)	(NEURO-TTR baseline)
Karnofsky performance status ≤50	0	0	0	0
Mean (SD)	76.8 (10.81)	76.2 (11.20)		
TTR concentration (g/L) Mean (SD)	0.2186 (0.04696)	0.2134 (0.06108)		

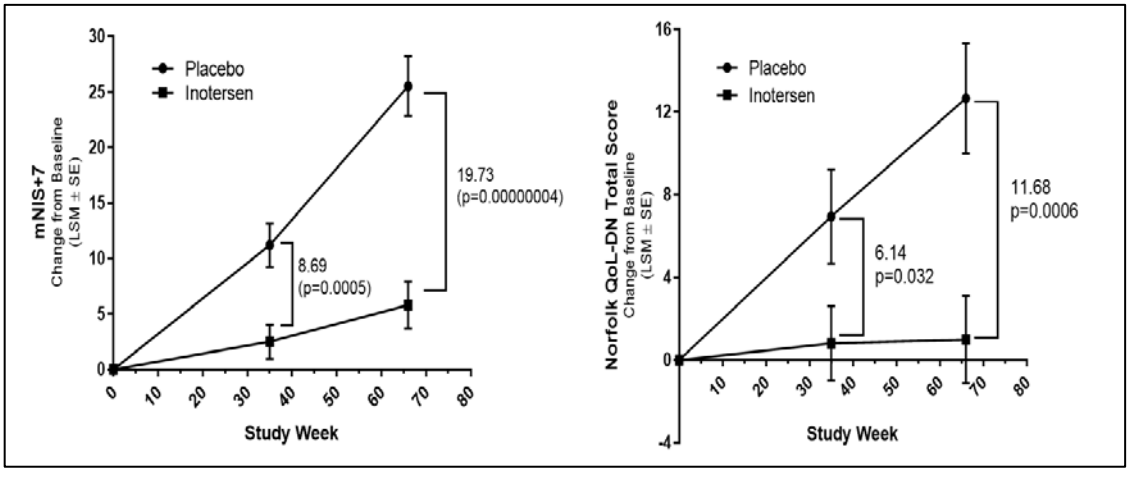
Abbreviations: BMI, body mass index; CM, cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; kg/m^2, kilograms per square metre; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NT-proBNP, N terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; pmol/L, picomole per litre; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin.

Efficacy results: NEURO-TTR

The primary and secondary efficacy outcome data were analysed using a mixed model for repeat measures (MMRM). The co-primary outcomes were change from baseline to week 66 in the mNIS+7 composite score and in the Norfolk QoL-DN questionnaire total score. Table 8 details the results for all of the primary and secondary outcomes.

During the 15 months treatment period, inotersen-treated patients achieved a greater improvement in neurological progression (mNIS+7), i.e. they progressed at a slower rate. While there was still a worsening with time, the magnitude displayed was significantly less than those on placebo (Figure 1). At week 66, placebo showed mean (SD) mNIS+7 composite score of 24.9 (24.1) compared to 4.2 (15.7) for inotersen, resulting in a reduction of -19.7 (-26.4, -13.0) for inotersen compared to placebo. The inotersen patients showed very little change from baseline for the Norfolk QoL-DN score (-0.08, SD = 19.0) but placebo patients showed an increase of 10.8 (21.1), thus a significant difference between inotersen and placebo was observed. For the co-primary outcome progression of disease at week 66, disease was slowed or stopped in 36.5% of inotersen patients compared to 19.2% placebo (defined by improvement or no worse mNIS+7 score).

Figure 1 NEURO-TTR least squares mean (LSM) change from baseline in mNIS+7 composite score and Norfolk QoL-DN total score, week 66 (FAS) (Reproduced from Figure 6 of company's submission)



Abbreviations: FAS, full analysis set; LSM, least squares mean; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; SE, standard error.

Significant differences were found for a number of secondary and tertiary outcomes, as shown in Table 8. A borderline difference was shown for BMI, but no difference for modified BMI. Standard BMI has some limitations in patients with hATTR-PN that are affected by significant wasting, because high BMI values can be observed in oedematous malnourished subjects due to low serum albumin. Therefore, modified BMI, which adjusts for low serum albumin (BMI x albumin g/L), is often used.

Table 8 NEURO-TTR summary of results (FAS)

	Placebo (N=59) Change from baseline, Mean (SD)	**Inotersen (N=106)** Change from baseline, Mean (SD)	**Difference LSM (95% CI) p-value**
Primary outcome			
mNIS+7composite score (week 66)	23.89 (24.190), n=52	4.16 (15.672), n=85	-19.7 (-26.4, 13.0) p<0.001
Norfolk QoL-DN (week 66)	10.77 (21.134), n=52	-0.08 (18.967), n=84	-11.7 (-18.3, -5.1) p<0.001
Secondary outcomes			
Norfolk QoL-DN symptoms domain score Stage 1 (week 66)	1.18 (5.270), n=33	-1.40 (4.763), n=55	-2.5 (-4.5, -0.6) p = 0.012
Norfolk QoL-DN PF/LF domain score Stage 2 (week 66)	8.74 (9.689), n=19	1.05 (11.924), n=29	-8.3 (-14.7, -1.8) p=0.013
mBMI (week 65)	-8.57 (9.159), n=49	-7.08 (9.386), n=82	2.82 (-32.1, 37.8) p=0.873

	Placebo (N=59) Change from baseline, Mean (SD)	**Inotersen (N=106)** Change from baseline, Mean (SD)	**Difference LSM (95% CI) p-value**
BMI (week 65)	-0.87 (1.202), n=49	-0.24 (1.521), n=82	0.50 (0.00, 1.01) p = 0.051
NIS composite score (week 66)	17.29 (16.986), n=52	4.47 (10.329), n=85	-13.2 (-17.7, -8.9) p<0.001
Modified +7 composite score (week 66)	6.60 (12.770), n=52	-0.31 (11.134), n=85	-6.5 (-10.3, -2.7) <0.001
NIS+7 composite score (week 66)	19.00 (16.824), n=52	5.10 (10.709), n=85	-14.5 (-19.0, -10.0) p<0.001
GLS (week 65)			
CM-ECHO Set (%)	0.46 (2.70), n=25	0.69 (3.13), n=50	0.20 (-1.2, 1.6) p = 0.771
ECHO subgroup (%)	1.05 (2.75), n=16	0.25 (3.16), n=30	-0.89 (-2.7, 0.9) p = 0.322
Tertiary outcomes			
SF-36 PCS score† (week 65)	-3.71 (8.509), n=51	0.30 (6.627), n=84	3.6 (1.07, 6.12) p = 0.006
SF-36 MCS score† (week 65)	-0.97 (9.24), n=51	1.02 (7.72), n=84	2.42 (-0.37, 5.22) p = 0.088

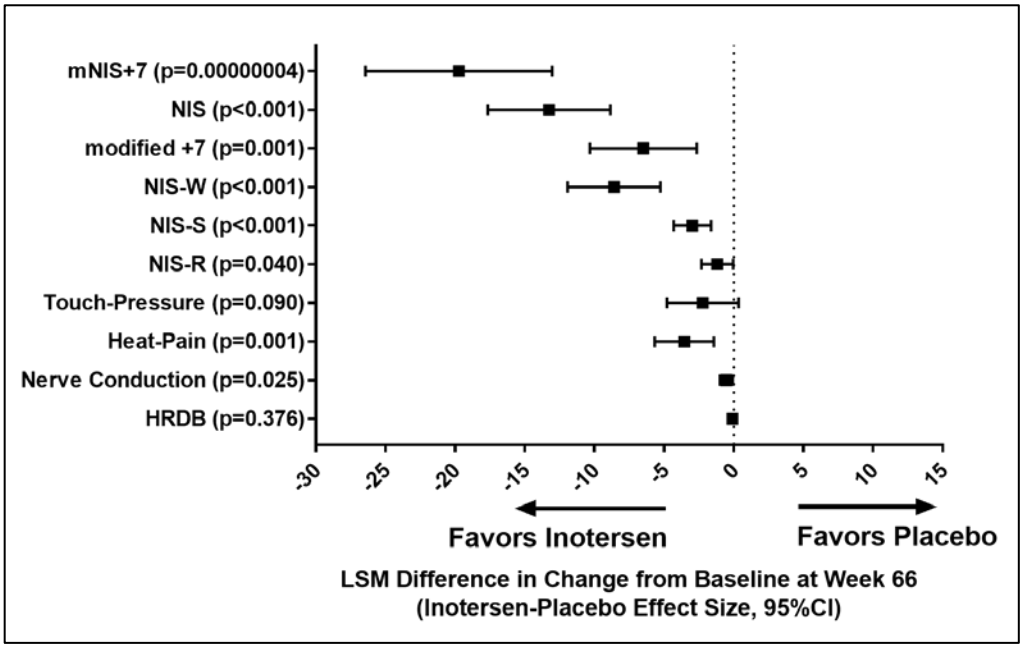
	Placebo (N=59) Change from baseline, Mean (SD)	**Inotersen (N=106)** Change from baseline, Mean (SD)	**Difference LSM (95% CI) p-value**
SF-36 mental health domain score† (week 65)	-1.67 (17.795), n=51	2.32 (14.405), n=84	5.07 (-0.11, 10.3) p = 0.055
Exploratory outcomes			
NSC total score† (week 66)	7.75 (9.138), n=52	1.20 (7.624), n=85	-6.33 (-9.12, -3.55) p<0.001
PND score (week 65)			
N	52	86	n/a
Improved, n (%)	2 (3.8)	9 (10.5)	
Not changed, n (%)	37 (71.2)	56 (65.1)	
Worsened, n (%)	13 (25.0)	21 (24.4)	
ECHO parameters in the CM-ECHO set	[redacted]		
ECHO parameters in patients with most severe CM,			

	Placebo (N=59) Change from baseline, Mean (SD)	**Inotersen (N=106)** Change from baseline, Mean (SD)	**Difference LSM (95% CI) p-value**
indicated by an IVS thickness ≥1.5 cm at baseline**			
LV Mass (g)	[redacted]	[redacted]	[redacted]
Not changed, n (%)	[redacted]	[redacted]	[redacted]
Worsened, n (%)	[redacted]	[redacted]	[redacted]
NT-proBNP (week 65)*	[redacted]*		[redacted]

† Analysis based on data collected up to 52 days after last dose of study drug; *Reported on page 72 of company's submission; **Reported in Table C16 of company's submission
Abbreviations: BMI, body mass index; CM, cardiomyopathy; CS, company submission; ECHO, echocardiogram; FAS, full analysis set; GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; IVS, interventricular septum; mBMI, modified body mass index; LSM, least squares mean; LV, left ventricular; MCS, mental component summary; mNIS+7, modified neuropathy impairment score; NIS, neuropathy impairment score; NSC, neuropathy and symptoms change score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NT-proBNP, N-terminal prohormone of Brain Natriuretic Peptide; PCS, physical component summary; PND, polyneuropathy disability; SF-36, short form-36; SD, standard deviation; SE, standard error; TTR, transthyretin.

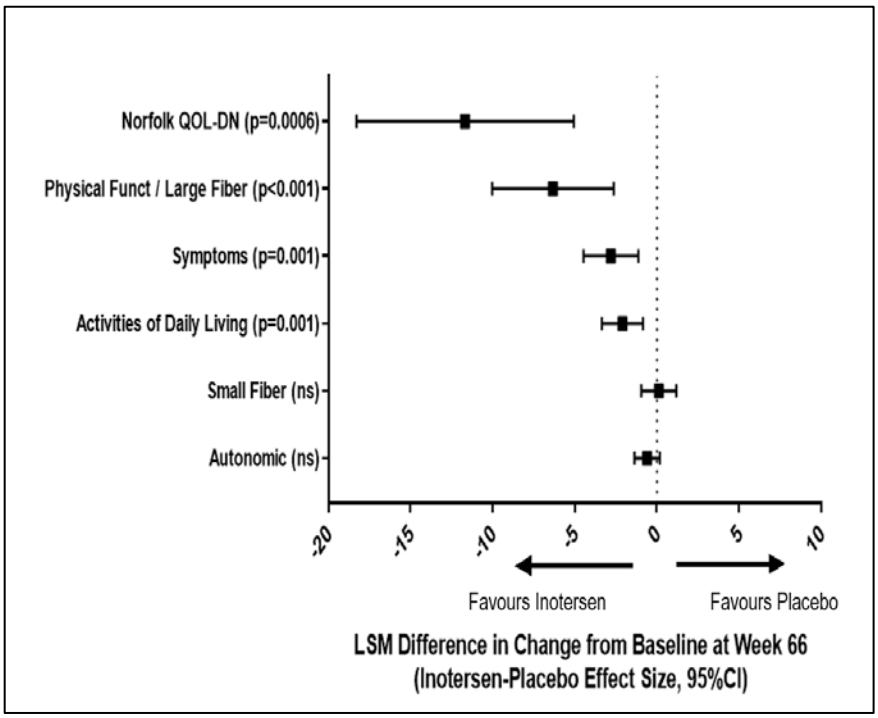
The primary outcome evaluated the overall mNIS+7 and Norfolk QoL-DN total scores. In addition, the company presented two figures (included in the clarification response) illustrating the effect of inotersen treatment on the individual components of these scores (Figure 2 and 3, respectively). There were significant differences for the sub components of mNIS+7 except for heart rate response to deep breathing (HRDB) and touch pressure, although the latter showed a trend towards inotersen. For the domain scores of Norfolk QoL-DN, significant differences were found in favour of inotersen for physical functioning/large fibre symptoms, and activities of daily living.

Figure 2 NEURO-TTR LSM difference in change from baseline for mNIS+7, and modified +7 composite scores and individual components, week 66 (Reproduced from Figure 1 of company's response to clarification)



Abbreviations: CI, confidence interval; HRDB, heart rate response to deep breathing; LSM, least squares mean; mNIS+7, modified neuropathy impairment score; NIS, neuropathy impairment score; NIS-R, Neuropathy impairment score – reflexes; NIS-S, Neuropathy impairment score – sensation; NIS-W, Neuropathy impairment score – weakness.

Figure 3 NEURO-TTR LSM difference in change from baseline for Norfolk QoL-DN domain scores, week 66 (Reproduced from Figure 8 of company's submission)



LSM least squares mean; CI confidence interval; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy.

The company reported a number of subgroup analyses (Table C15, company's submission). Inotersen was shown to be beneficial for all subgroups for the mNIS+7 outcome, but not for all subgroups in relation to Norfolk QoL-DN (Table 9).

Table 9 NEURO-TTR summary of efficacy results by subgroup, week 66 (FAS) (Reproduced from Table C15 of company's submission)

Subgroup	n, placebo, inotersen	mNIS+7		Norfolk QoL-DN	
		Difference	p-value	Difference	p-value
All patients	52, 85	-19.73	<0.001	-11.68	<0.001
V30M mutation					
V30M	29, 39	-18.86	<0.001	-12.25	0.010
Non-V30M	23, 46	-21.27	<0.001	-11.12	0.025
Disease stage					
Stage 1	33, 56	-14.20	<0.001	-9.93	0.019
Stage 2	19, 29	-29.12	<0.001	-15.04	0.008
Previous treatment tafamidis/diflunisal					
Previous treatment	25, 51	-20.02	<0.001	-9.05	0.052
No-previous treatment	27, 34	-20.84	<0.001	-14.70	0.003
CM-ECHO Set					
CM-Echo Set	31, 59	-17.17	<0.001	-9.05	0.036
Non CM-Echo Set	21, 26	-25.18	<0.001	-16.35	0.004
Age					
Age <65	30, 50	-17.76	<0.001	-16.77	<0.001
Age ≥65	22, 35	-22.27	<0.001	-4.49	0.382
Sex					
Male	37, 59	-19.49	<0.001	-12.17	0.003
Female	15, 26	-20.29	0.002	-10.59	0.087
Race					
White	47, 82	-18.62	<0.001	-12.24	<0.001
Non-white	5, 3	-29.84	0.034	-9.01	0.509
Region					
North America	23, 45	-22.24	<0.001	-8.97	0.066
Europe	18, 27	-17.99	0.002	-7.66	0.176
S. America /Australasia	11, 13	-18.25	0.024	-26.64	<0.001

Abbreviations: CM, cardiomyopathy; FAS, full analysis set; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; V30M, valine replaced by methionine at amino acid position number 30.

Adverse events: NEURO-TTR

Table 10 shows the number of treatment-emergent adverse events (TEAEs) in the NEURO-TTR study. Nearly all participants experienced at least one TEAE, the majority of which were reported to be mild to moderate in severity. In the inotersen group, 16 TEAEs (14.3%) led to permanent discontinuation of study treatment, of which four were associated with thrombocytopenia and two with glomerulonephritis, which are identified risks of inotersen. Serious TEAEs were experienced by 32.1% of participants who received inotersen compared with 21.7% in the placebo group, of which 7.1% and 1.7%, respectively, were considered related to study treatment. There were five deaths in the inotersen group, and none in the placebo group. Of these, one death was associated with intracranial haemorrhage, in association with Grade 4 thrombocytopenia with a platelet count ~10 x109/L which was considered related to study treatment by the NEURO-TTR investigator.

Table 10 NEURO-TTR incidence of TEAEs (SS) (Reproduced from Table C24 of company's submission)

	Placebo (N=60) n (%)	Inotersen (N=112) n (%)
Any TEAEs	60 (100)	111 (99.1)
TEAEs related to study treatment	23 (38.3)	87 (77.7)
TEAEs leading to permanent discontinuation of study drug	2 (3.3)	16 (14.3)
TEAEs leading to withdrawal from study	1 (1.7)	8 (7.1)
Any serious TEAEs	13 (21.7)	36 (32.1)
Serious TEAEs related to study treatment	1 (1.7)	8 (7.1)
Fatal TEAEs	0	5 (4.5)
Fatal TEAEs related to study treatment	0	1 (0.9)

Abbreviations: SS, safety set; TEAEs, treatment-emergent adverse events.

Table 11 shows frequently reported TEAEs (≥10% of patients) in the NEURO-TTR study. In the inotersen group, the most frequently reported TEAEs related to study treatment were injection site erythema (31.3% patients, 166 events), nausea (31.3% patients 44 events), fatigue (25.0%), diarrhoea (24.1%), headache (23.2%), and injection site pain (20.5%).

Table 12 shows serious TEAEs considered related to study treatment in the NEURO-TTR study. The principal safety concerns for inotersen treatment are identified as glomerulonephritis and thrombocytopenia, which were managed by enhanced monitoring. The company's submission states that

"*After the implementation of enhanced monitoring, no additional severe thrombocytopenia events occurred in the NEURO-TTR study, and a single case of glomerulonephritis was identified early without loss of renal function*" (page 83).

The company indicated that the principal safety risks associated with inotersen can be effectively monitored with routine testing in clinical practice, allowing early detection and management of the adverse events. The SmPC recommends platelet counts to be monitored every two weeks, urine protein to creatinine ratio (UPCR) and eGFR at least every three months during inotersen treatment, and hepatic enzymes after four months of treatment and annually thereafter.[21] The ERG's clinical expert agrees with this conclusion.

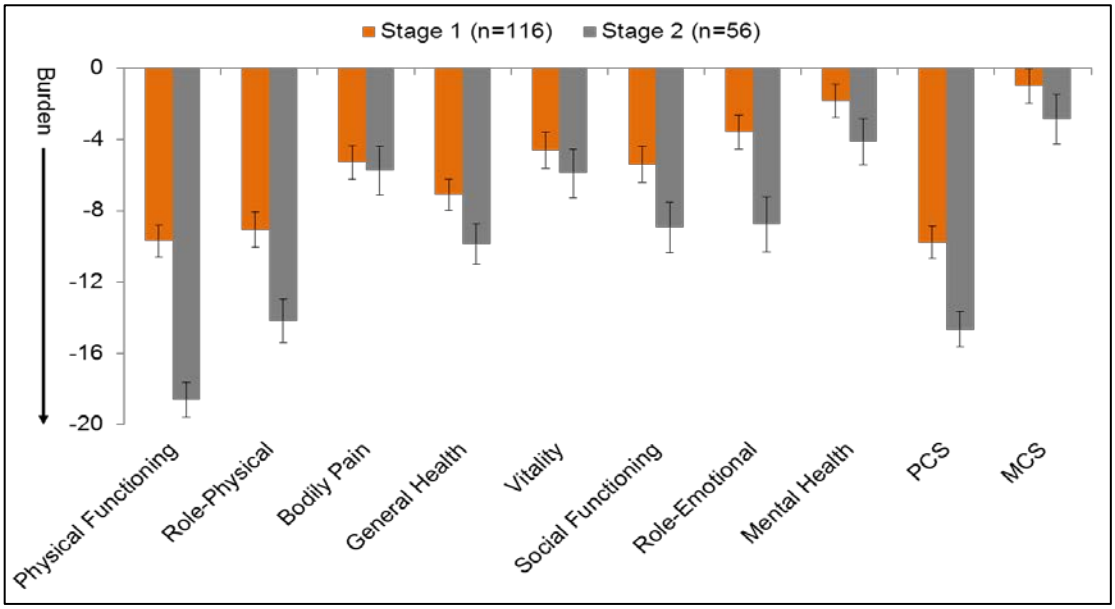
Patient experience

Loss of motor function for patients with hATTR has the highest impact on health related quality of life (HRQoL). The patient eventually loses the ability to walk and potentially becomes bedridden in the latter stages of disease. However, numerous other symptoms are experienced by patients with the disease and can vary between patients. These are described in full in section 7 of the company's submission but include: sensory and motor neuropathies; Autonomic neuropathy (dizziness or fainting, vomiting, severe diarrhoea and or constipation and neurogenic bladder); Loss of body weight in early disease, life-threatening cachexia is common; Erectile dysfunction (males); Cardiac involvement; Ocular manifestations; renal manifestations.

[redacted] To estimate burden of hATTR on patients the company presented post hoc analyses of baseline SF36v2 scores from NEURO-TTR patients. These were compared to population-based benchmark samples.

Figure 4 shows the difference in burden of hATTR patients relative to US general population norms for stage 1 and stage 2 disease. Patients with hATTR showed greater burden on all the SF36v2 domains and the burden was increased as they progressed to stage 2. Note US norms were used but only 82/172 (47.7%) were from North America.

Figure 4 Baseline burden of disease for hATTR patients relative to US general population norms, Stage 1 versus Stage 2 disease (Reproduced from Figure 10 of company's submission)



Abbreviations: MCS, mental component summary; PCS, physical component summary.
Error bars represent standard errors of means.

Table 11 NEURO-TTR frequently reported TEAEs (≥10% incidence) (safety set) (Reproduced from Table C25 of company's submission and Table 4 of company's response to clarification)

Preferred Term	Placebo (N=60)				Inotersen (N=112)			
	Number of patients, n (%)			Number of events	Number of patients, n (%)			Number of events
	Mild	Moderate	Severe		Mild	Moderate	Severe	
Injection site erythema	0	0	0	0	35 (31.3)	0	0	116
Nausea	3 (5.0)	4 (6.7)	0	9	22 (19.6)	12 (10.7)	1 (0.9)	44
Fatigue	9 (15.0)	3 (5.0)	0	14	18 (16.1)	10 (8.9)	0	43
Diarrhoea	7 (11.7)	5 (8.3)	0	16	18 (16.1)	7 (6.3)	2 (1.8)	29
Headache	4 (6.7)	3 (5.0)	0	10	24 (21.4)	2 (1.8)	0	34
Injection site pain	4 (6.7)	0	0	7	21 (18.8)	2 (1.8)	0	47
Pyrexia	5 (8.3)	0	0	6	17 (15.2)	5 (4.5)	0	32
Oedema peripheral	4 (6.7)	2 (3.3)	0	14	16 (14.3)	5 (4.5)	0	47
Urinary tract infection	6 (10.0)	6 (10.0)	0	6	12 (10.7)	9 (8.0)	0	23
Chills	1 (1.7)	1 (1.7)	0	3	15 (13.4)	5 (4.5)	0	40
Fall	8 (13.3)	4 (6.7)	1 (1.7)	16	15 (13.4)	4 (3.6)	0	26
Myalgia	5 (8.3)	1 (1.7)	0	7	14 (12.5)	3 (2.7)	0	25
Vomiting	0	3 (5.0)	0	3	11 (9.8)	5 (4.5)	1 (0.9)	22
Anaemia	1 (1.7)	1 (1.7)	0	2	9 (8.0)	6 (5.4)	0	21
Constipation	4 (6.7)	2 (3.3)	0	7	9 (8.0)	5 (4.5)	1 (0.9)	17
Thrombocytopenia	1 (1.7)	0	0	2	8 (7.1)	5 (4.5)	2 (1.8)	16
Asthenia	4 (6.7)	4 (6.7)	0	11	9 (8.0)	5 (4.5)	0	17
Arthralgia	2 (3.3)	3 (5.0)	0	8	9 (8.0)	3 (2.7)	1 (0.9)	20
Injection site pruritus	0	0	0	0	13 (11.6)	0	0	16
Dizziness	5 (8.3)	2 (3.3)	0	7	8 (7.1)	3 (2.7)	1 (0.9)	14
Platelet count decreased	0	0	0	0	8 (7.1)	4 (3.6)	0	14
Muscular weakness	1 (1.7)	5 (8.3)	0	7	7 (6.3)	4 (3.6)	0	11
Cough	7 (11.7)	1 (1.7)	0	11	8 (7.1)	2 (1.8)	0	12
Hypoaesthesia	4 (6.7)	2 (3.3)	0	8	6 (5.4)	4 (3.6)	0	11
Pain in extremity	3 (5.0)	5 (8.3)	0	7	5 (4.5)	5 (4.5)	0	11

Nasopharyngitis	6 (10.0)	0	0	7	9 (8.0)	0	0	9
Thermal burn	4 (6.7)	2 (3.3)	0	6	4 (3.6)	2 (1.8)	0	6
Neuralgia	5 (8.3)	3 (5.0)	1 (1.7)	9	2 (1.8)	1 (0.9)	0	3

Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event.

Table 12 NEURO-TTR serious TEAEs considered related to study drug (safety set) (Reproduced from Table C26 of company's submission and Table 5 of company's response to clarification)

Preferred Term	Placebo (N=60)				Inotersen (N=112)			
	Number of patients, n (%)			Number of events	Number of patients, n (%)			Number of events
	Mild	Moderate	Severe		Mild	Moderate	Severe	
Nervous System Disorders	0	0	0	0	0	0	3 (2.7)	3
Embolic stroke	0	0	0	0	0	0	1 (0.9)	1
Haemorrhage intracranial	0	0	0	0	0	0	1 (0.9)	1
Myelopathy	0	0	0	0	0	0	1 (0.9)	1
Renal and Urinary Disorders	0	0	0	0	0	1 (0.9)	2 (1.8)	4
Glomerulonephritis	0	0	0	0	0	1 (0.9)	1 (0.9)	2
Acute kidney injury	0	0	0	0	0	0	1 (0.9)	1
Tubulointerstitial nephritis	0	0	0	0	0	0	1 (0.9)	1
Blood and Lymphatic System Disorders	0	0	0	0	0	0	2 (1.8)	2
Thrombocytopenia	0	0	0	0	0	0	2 (1.8)	2
Vascular Disorders	0	1 (1.7)	0	1	0	0	1 (0.9)	1
Deep vein thrombosis	0	1 (1.7)	0	1	0	0	1 (0.9)	1
Respiratory, Thoracic and Mediastinal Disorders	0	0	0	0	0	0	1 (0.9)	1
Pulmonary embolism	0	0	0	0	0	0	1 (0.9)	1

† Patient was subsequently diagnosed with glomerulonephritis upon renal biopsy.
Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event.

4.2.2 Summary of NEURO-TTR extension

Table 13 details the characteristics of the NEURO-TTR extension study. Ninety six percent of those completing treatment in NEURO-TTR enrolled in the extension study. Table C10 of the company's submission indicated that there were 49 placebo and 84 inotersen patients entered into the extension study. The efficacy data cut for this submission was [redacted] and at that time there were 40 participants in the placebo-inotersen group and 74 in the inotersen-inotersen group. The discrepancy between patient numbers here is not clear to the ERG and is discussed in section 4.2.3.

Table 13 Characteristics of the post-trial follow-up study (NEURO-TTR Extension) included in the company's review of clinical effectiveness (Adapted from Table C4 of company's submission)

Characteristics	NEURO-TTR Extension study details
Countries	[redacted]
Inclusion criteria	Patients who had satisfactorily completed NEURO-TTR with the following as judged by the investigator or Sponsor: • Satisfactory completion of dosing and EOT efficacy assessments • No significant tolerability issues • Satisfactory compliance to the NEURO-TTR protocol
Key exclusion criteria	Have any new condition or worsening of existing condition that, in the opinion of the investigator or Sponsor, would make the patient unsuitable for enrolment or could interfere with the patient participating in or completing the study.
Intervention	[redacted]
Comparator	[redacted]
Co-intervention (all patients)	• [redacted]

Characteristics	NEURO-TTR Extension study details
Efficacy outcomes	• [redacted]
Pharmacodynamic outcomes	• [redacted]
Other exploratory outcomes	• [redacted]
Duration of study	[redacted]

Abbreviations: BMI, body mass index; ECHO, echocardiomyogram; ECG, electrocardiogram; EOT , end of treatment; GLS, Global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; kg/m^2, kilograms per square metre; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NIS, neuropathy impairment score; NT-proBNP, N terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; pmol/L, picomole per litre; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin.

[redacted]

Interim results: NEURO-TTR extension

Table 14 presents some descriptive results from the extension study at [redacted]. The final analysis will not be undertaken until the completion of the extension study (due to be [redacted]). Improvement in neurological disease progression (i.e. continued slowing) and QoL were maintained [redacted] (from NEURO-TTR baseline) with inotersen treatment. [redacted] However this slowing down was not quite as quick for the placebo-inotersen group as it had been for those receiving inotersen in the NEURO-TTR study.

Table 14 NEURO-TTR Extension summary of results (FAS)

	Placebo-inotersen (N=31) Change from baseline to Week 78, Mean (SD)	**Inotersen-inotersen (N=55)** Change from baseline, Mean (SD)
Efficacy outcome		
mNIS+7composite score		
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
NIS total score	Not reported	Not reported
Norfolk QoL-DN		
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
Norfolk QoL-DN symptoms domain score Stage 1 patients	[redacted]	[redacted]
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
Norfolk QoL-DN PF/LF domain score Stage 2 patients	[redacted]	[redacted]
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
mBMI	Not reported	Not reported
BMI	**(N=31)**	**(N=55)**
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
NIS composite score		
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
PND score		
From NEURO-TTR baseline		
N	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]
Not changed, n (%)	[redacted]	[redacted]

	Placebo-inotersen (N=31) Change from baseline to Week 78, Mean (SD)	**Inotersen-inotersen (N=55)** Change from baseline, Mean (SD)
Worsened, n (%)	[redacted]	[redacted]
From NEURO-TTR Extension baseline		
N	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]
Not changed, n (%)	[redacted]	[redacted]
Worsened, n (%)	[redacted]	[redacted]
GLS by ECHO	Not reported	Not reported
Exploratory outcomes		
SF-36 PCS score		
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
SF-36 MCS score		
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
SF-36 mental health domain score		
From NEURO-TTR baseline	[redacted]	[redacted]
From NEURO-TTR Extension baseline	[redacted]	[redacted]
NT-proBNP (change from NEURO-TTR Extension baseline)	[redacted]	
ECHO parameters	Not reported	Not reported
Pharmacodynamic (PD) outcomes		
Transthyretin (TTR) level	[redacted]	
RBP4 (retinol binding protein 4) level	Not reported	Not reported
Proportion of patients with at least 60% reduction in TTR	Not reported	Not reported

† Analysis based on data collected up to 52 days after last dose of study drug.

Abbreviations: BMI, body mass index; CM, cardiomyopathy; ECHO, echocardiogram; FAS, full analysis set; GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; mBMI, modified body mass index; LV, left ventricular; MCS, mental component summary; mNIS+7, modified neuropathy impairment score; NIS, neuropathy impairment score; NSC, neuropathy and symptoms change score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NT-proBNP, N-terminal prohormone of Brain Natriuretic Peptide; PCS, physical component summary; PND, polyneuropathy disability; SF-36, short form-36; SD, standard deviation; SE, standard error; TTR, transthyretin. Not reported: specified in methods section, but no data or comment provided in results section.

Adverse events: NEURO-TTR extension

Safety data for the NEURO-TTR extensions study is reported based on the 15th September 2017 data cut, which included [redacted] dosed patients, [redacted] originally randomised to placebo and [redacted] originally randomised to inotersen in the NEURO-TTR study. Table 15 shows the number of treatment-emergent adverse events (TEAEs) in the NEURO-TTR Extension study. Most study participants experienced at least one TEAE, the majority of which were reported to be mild to moderate in severity. The inotersen-inotersen group had fewer patients experiencing TEAEs related to study treatment, but more patients experiencing TEAEs leading to permanent discontinuation of study drug, compared with the placebo-inotersen group ([redacted]).

[redacted]. [redacted], of which none was considered related to study treatment by the NEURO-TTR investigator. According to the company submission,

"[redacted] (no numerical data provided). The company submission also states that, in relation to the NEURO-TTR study,

[redacted]" (page 84).[redacted]

Table 15 NEURO-TTR Extension incidence of TEAEs (SS) (Reproduced from Table C27 of company's submission)

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

† Includes two patients who had fatal TEAEs
Abbreviations: SS, safety set; TEAEs, treatment-emergent adverse events.

4.2.3 Critique of the clinical effectiveness evidence

In the submission, the company reported the number of participants (and %) with previous treatment with tafamidis or diflunisal; disease stage 1 and 2; V30M TTR mutation (see Table C5, company's submission, Table 7 ERG report). The numbers reported by the company differ to those presented in the main trial. publication[29] The discrepancies are noted in Table 16. At clarification, the company stated:

> "*The difference in number reported is to do with different randomisation strategies used in both documents. This is true for all three differences identified. The safety set of 172 patients was used in both documents but patients in Benson et al were randomised by CRF whereas patients in the submission were randomised by IXRS. This is due to IXRS being the most-appropriate randomisation stratification when modelling primary efficacy, which is the purpose of the cost-effectiveness model developed for the NICE submission"*.

The ERG does not understand this explanation, as the data presented are from the NEURO-TTR trial which was reported by Benson et al (2018)[29]. It is not clear to the ERG how it is possible that randomisation of patients differed, given that they are reporting the same study. All other baseline characteristics presented match between the company submission and the Benson et al.[29] publication.

Table 16 Discrepancies in NEURO-TTR baseline characteristics

	Company submission (Table C5)		Reported in Benson et al (2018)[29]	
	Placebo (N=60)	**Inotersen (N=112)**	**Placebo (N=60)**	**Inotersen (N=112)**
Randomisation stratum by IXRS at NEURO-TTR pre-treatment, n (%)				
Previous treatment with tafamidis or diflunisal				
Yes	33 (55.0)	61 (54.5)	36 (60)	63 (56)
No	27 (45.0)	51 (45.5)	Not presented	Not presented
Disease stage				
Stage 1	39 (65.0)	74 (66.1)	42 (70)	74 (66)
Stage 2	21 (35.0)	38 (33.9)	18 (30)	38 (34)
V30M TTR mutation				
Yes	32 (53.3)	58 (51.8)	33 (55)	56 (50)
No	28 (46.7)	54 (48.2)	Not presented	Not presented

IXRS, Interactive voice/web-response system

In reporting the NEURO-TTR extension study, concluding statements were made about NT-proBNP and TTR levels (Table 14) but no data were provided as evidence. The ERG cannot comment on the accuracy of the conclusion. Modified BMI was included on the list of outcomes for the extension study, but no data have been reported. General information about number of adverse events in the extension study was given, but no specific data on types of events was provided by the company.

The patient flow through the NEURO-TTR extension was not clear to the ERG.
Table C10 of the company's submission indicated that there were 49 placebo and 84 inotersen patients entered into the extension study. However, Table C11 of the company's submission, which describes the patient disposition of the NEURO-TTR extension study, indicates 40 patients for placebo and 74 for inotersen. The ERG was not able to ascertain from the information presented why there were differences between these two tables. The descriptive results were then presented for 31 placebo patients and 55 inotersen patients included in the FAS. It is assumed that the reduction in patient numbers relates to the definition of the FAS, but, again, this was not clear to the ERG.

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

Only one trial was identified by the company to compare inotersen to placebo thus no indirect or multiple treatment comparison was undertaken.

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

None.

4.6 Conclusions of the clinical effectiveness section

The presented clinical evidence comes from a single phase 3, double-blind, placebo-controlled, multi-centre RCT (NEURO-TTR), which was funded by the company. The NEURO-TTR study was followed by an ongoing, post-trial, Phase 3, open-label extension (NEURO-TTR Extension), in the same population. The NEURO-TTR trial consisted of a baseline screen period (≤ 6 weeks), a 65-week treatment period, 1-week efficacy assessment period and then 6 month post treatment evaluation period. A total of 173 participants were randomised 2:1 inotersen 300mg or placebo, and there were one post-randomisation exclusion. The co-primary outcomes in NEURO-TTR were change from baseline to week 66 in: Modified neuropathy impairment score +7 composite score (mNIS+7) and Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN).

During the 15 months treatment period, inotersen treated patients achieved a greater improvement in neurological progression (mNIS+7), i.e. they progressed at a slower rate. Deterioration over time was still evident but was significantly less than those on placebo. The inotersen patients showed very little change from baseline for the Norfolk QoL-DN score but scores for placebo patients increased, thus a significant difference between inotersen and placebo was observed. Progression of disease at week 66 was slowed or stopped in 36.5% of inotersen patients compared to 19.2% placebo (defined by improvement or no worse in mNIS+7 score).

Nearly all participants experienced at least one treatment-emergent adverse event (TEAE), the majority of which were reported to be mild to moderate in severity. In the inotersen group, 16 TEAEs (14.3%) led to permanent discontinuation of study treatment, of which four were associated with thrombocytopenia and two with glomerulonephritis. Serious TEAEs were experienced by 32.1% of participants who received inotersen compared with 21.7% in the placebo group, of which 7.1% and 1.7%, respectively, were considered related to study treatment. There were five deaths in the inotersen group, and none in the placebo group. Of these, one death was considered related to study treatment by the NEURO-TTR investigator.

The company reported that [redacted] of those completing treatment in NEURO-TTR enrolled in the NEURO-TTR extension study. Interim results showed improvement in neurological disease progression (i.e. continued slowing) and QoL were maintained [redacted] with inotersen treatment.

[redacted] However this slowing down was not quite as quick for the placebo-inotersen group as it had been for those receiving inotersen in the NEURO-TTR study. Again, most participants experienced at least one TEAE, the majority of which were be mild to moderate in severity. The inotersen-inotersen group had fewer patients experiencing TEAEs related to study treatment, but more patients experiencing TEAEs leading to permanent discontinuation of study drug, compared with the placebo-inotersen group.

[redacted], of which none was considered related to study treatment by the NEURO-TTR investigator.

On the whole, the ERG was happy with the evidence submitted, however it should be noted that the evidence is from a single study only. A few discrepancies were found between the company's submission and the publication for the trial[29] and are discussed above. In addition, the ERG was unclear of the flow of patients through the extension study. The ERG is happy to conclude that this treatment is shown to be effective in the studied population.

5 Cost effectiveness

Chapter 5 describes, summarises and critiques the cost-effectiveness evidence in the Company Submission (CS) and the company's response to NICE and ERG questions at the clarification stage. Due to a lack of published cost-effectiveness evidence, the company's economic case is primarily based on a *de novo* Markov cohort cost-effectiveness model developed using Microsoft Excel ®. The model assessed the cost-effectiveness of inotersen compared to best supportive care (BSC) in a cohort of adult patients with hATTR with polyneuropathy (hATTR-PN).

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company's search strategies to identify relevant cost-effectiveness evidence and quality of life data were performed as part of the global search to identify relevant studies for all sections of the submission (described in Section 4.1.1). Full details of the company's search strategy are provided in Appendix 18 of the CS. The ERG considers that the searches for cost-effectiveness and quality of life studies were appropriate and fit for purpose.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate.

Inclusion and exclusion criteria for the global systematic review are discussed in Section 4.1.1.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

No cost-effectiveness studies were identified. The ERG considers this is an accurate reflection of the lack of cost-effectiveness literature relating to inotersen.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The company have not identified any studies from their review that address the cost-effectiveness of inotersen compared to best supportive care. Having assessed the company's search strategy, the ERG agree with the company's conclusions that none of the identified studies from the review are relevant or appropriate to assess the economic value of inotersen. It is therefore appropriate that the company have developed a *de novo* decision analysis model to address the question of cost-effectiveness.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

This section summarises the company submitted decision analysis model, assessing the cost-effectiveness of inotersen vs. BSC, and the ERG critique of the company's model and analyses. The ERG refer to two different sources of company submitted economic evidence. The first is the original company submission (**here-after CS**) and the second is a revised company model provided alongside the company's response to the clarification letter (**here-after RCM**). Given that the RCM addresses errors identified at the response to clarification stage, the ERG refer to the RCM throughout the report unless otherwise stated. Model results are reported for the RCM only and the reader is referred to the original CS for further details of the results of the originally submitted model.

The ERG find that the scope of the economic model (hATTR-PN) is narrower than that defined by NICE (hATTR), but is in line with the licenced indication for inotersen. Further commentary on the scope is provided in Chapter 3.

5.2.1 NICE reference case checklist (Table only)

The ERG have assessed the adherence of the original CS and RCM against the NICE reference case in Table 17 below. It should be noted that the reference case criteria outlined below are adapted where necessary to account for considerations raised in NICE's interim process and methods guide for the HST programme.[31, 32] Major issues are briefly flagged in the table and discussed in more detail in the subsequent sections of the report.

Table 17 Adherence to the NICE reference case (with adaption to NICE interim methods guide on HSTs where appropriate)

Attribute	**Reference case *(and HST interim methods guidance)***	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes. Best supportive care is the comparator used in the model (and is the only comparator considered). Other potential treatments include diflunisal, patisiran, & tafamidis. However, these are not currently recommended by NICE for routine use on the NHS in England.
Patient group	As per NICE scope: "People with hereditary transthyretin-related amyloidosis (hATTR) "	The patient group modelled varies slightly from the final NICE scope (hATTR), and includes hATTR patients with polyneuropathy (hATTR-PN). This variation is appropriate and consistent with the licensed indication for inotersen.
Perspective costs	NHS & Personal Social Services	Partly, the CS includes costs to the NHS. From a PSS perspective, the costs of homecare are also included. It is however questionable whether all relevant PSS costs are included. For example, costs of residential care have not been explicitly considered in the cost-effectiveness model.
Perspective benefits	All health effects on individuals	Partly, adverse events associated with inotersen and BSC were not included in the original CS. In response to the clarification letter, some serious adverse events were included as a scenario analysis, but it was assumed that the disutility and duration of some of these were 0 due to missing data. Modelling of adverse events is therefore incomplete. The measure of health effects (QALYs) is appropriate and consistent with the NICE reference case.

Form of economic evaluation	Cost-effectiveness analysis	Yes, incremental cost per QALY gained, i.e. cost-utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, a life-time horizon, up to age 100 is modelled.
Synthesis of evidence on outcomes	Systematic review	Yes, a systematic review was conducted, that included searches for HRQOL studies. The results specific to that search are provided in Section 9.2.2 and 10.1.6 of the CS.
Outcome measure	Life years and Quality adjusted life years	Yes, benefits are measured in terms of both life years and QALYs. Mortality benefits (specific to Coutinho disease stage) were incorporated after response to the clarification letter.
Health states for QALY	Described using a standardised and validated instrument	Partly. Modelled health states (i.e. three Coutinho disease stage health states) were inferred from the NEURO-TTR study based on defined TQoL score cut-offs on the Norfolk QoL-DN measure. However, the thresholds for disease stage definition have not been formally validated, and are based on a previous ERG report[33] for an Advisory Group for National Specialised Services (AGNSS) assessment of tafamidis. The mapped disease states were matched with EQ-5D responses from the THAOS registry of patients with hATTR, which were valued using a Brazilian population tariff.[34]
Benefit valuation	Time-trade off or standard gamble	Yes, the CS references a conference abstract[35] for a study in which Brazilian values[34] were applied to EQ-5D response data from the THAOS registry.[36] The Brazilian EQ-5D valuation set was based on Time trade-off interviews.
Source of preference data for valuation of	Representative sample of the public	No. Whilst the sample used to obtain the Brazilian value set[34] for the EQ-5D appear to be a good representation of the Brazilian general population, it is unlikely that their preferences

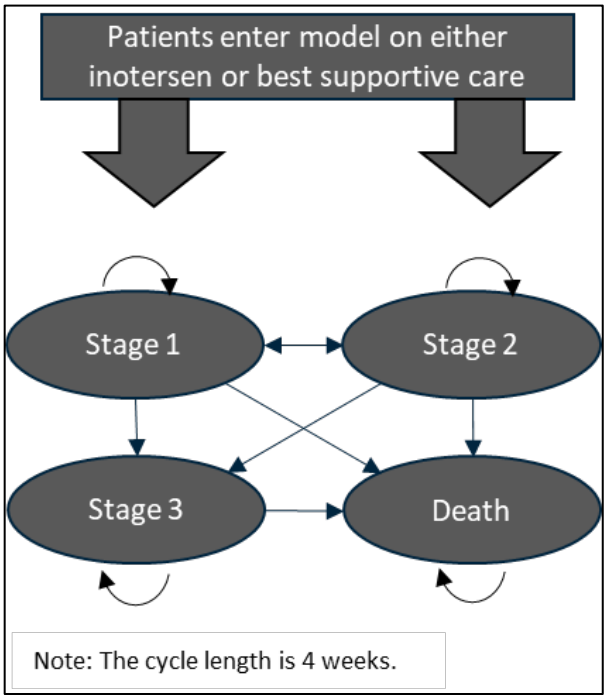
changes in HRQL		accurately reflect those of the UK general population.[32] The Brazilian value set generates substantially different utility scores to the UK value set, particularly for poorer health states (such as those experienced by people with hATTR).
Discount rate	An annual rate of 3.5% on both costs and health effects *NICE HSTs: A discount rate of 1.5% may be considered…."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)" & "the technology does not commit the NHS to significant irrecoverable costs".*	No, the company have chosen to discount costs and outcomes at a rate of 1.5% per annum in their base case analysis. The ERG are concerned that the chosen rate may not adequately meet the criteria for a 1.5% discount rate as stipulated by NICE in their interim methods guide for HSTs.[31]
Equity	Ref case: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit *NICE HSTs: QALYs may receive additional weighting if the*	Yes. All additional QALYs have been given equal weighting in the CS. The CS does not make a case for additional QALY weighting (that may be possible for HSTs). The ERG note that this is probably because the magnitude of QALYs gained in the economic model is well below the additional 10 QALYs stipulated in the NICE HST methods guide[31] before QALY weighting can be considered.

	incremental QALYs gained (per patient over a life time horizon are >10	
Probabilistic modelling	Probabilistic modelling	Partly, probabilistic sensitivity analysis has been undertaken, but the PSA does not capture uncertainty in all the important model parameters. In most cases the standard deviations of sampling distributions are assumed equal to 5% of the mean parameter value. The ERG note that this substantially underestimates the true uncertainty surrounding certain parameter values. Time to discontinuation of inotersen treatment (an important driver of cost-effectiveness), is not included in the PSA.
Sensitivity analysis		Partly, a range of univariate deterministic sensitivity analyses have been completed and reported as tornado diagrams in the CS (as ± 5% of the mean parameter value). Limited multi-parameter scenario analyses are also explored but are not conducted around the most uncertain model parameters. A more extensive exploration of multi-parameter scenario analyses would have given a better overview of the joint uncertainty in the model.

5.2.2 Models structure

The economic model is a Markov cohort state transition model, with three disease health states based on disease staging described by Coutinho et al[1] and death. The model structure is reproduced from the CS in Figure 5 below.

Figure 5 Schematic of the model structure (Re-produced from Figure 11, page 100 of the CS)



Coutinho disease staging is used to capture the increasing healthcare costs and decreased health state utility associated with progression of disease, with each stage reflecting an increased level of disability. Coutinho health states are defined according to cut-offs on the Total Norfolk QoL-DN (TQoL) score, at which point the cohort are assumed to transition between Coutinho stages. The approach to classification of disease stage is sourced from and consistent with the tafamidis assessment (manufacturer preferred approach)[33] that referred to the THAOS registry data for hATTR.[37]

TQoL scores can range from 0 (best) to 135 (worst). The model cohort is initially distributed across the three Coutinho disease stages according to the inferred distribution of disease stage among NEURO-TTR trial participants with a baseline TQoL score. Table 18 describes the assumed TQoL cut-off definitions for disease

stage used in the model, the mean and distribution of TQoL score by disease stage (taken from Faria et al, based on the THAOS registry data) for comparison, and the initial distribution of the cohort across the Coutinho disease stages.

Table 18 Distribution of model starting cohort between Coutinho disease stage states

Disease stage	Mean (P10 to P90) TQoL *(Sourced from Faria et al)*	TQoL cut-off used in the model (for entry to stage)	Initial model cohort distribution
Stage 1	48.97 (21 to 87)	2.6	[redacted]
Stage 2	72.68 (21 to 103)	54	[redacted]
Stage 3	94.83 (79 to 107)	91	0% (NEURO-TTR exclusion criteria)

P10 to P90 refers to the 10th and 90th percentile of the distribution

The ERG note that the approach, whilst consistent with the tafamidis assessment, is also subject to the same limitations outlined in Faria et al. First, the substantial heterogeneity in TQoL for each disease stage means that it is questionable whether TQoL is an accurate method to define disease stage. Secondly, the cut-offs used to define disease progression appear to be somewhat arbitrary and unjustified. The CS does not provide a clear justification for the use of the data from the tafamidis assessment or limitations of the approach taken. Further information regarding the approach would have been useful in determining the approaches validity. The ERG also note that the CS provides no discussion on the appropriateness of Coutinho disease staging, described by TQoL measures for different splits of V30M mutation. However, the ERG's clinical expert noted that whilst different mutations will be associated with varying severity of neurological disease, this will be accounted for in the disease staging and the approach taken by the company is unlikely to introduce any significant bias. Bias would only be introduced if inotersen's effectiveness was different across the mutation subgroups. There is no evidence from the NEURO-TTR study to suggest that this is the case.

Over subsequent four-week model cycles, each cohort (inotersen and BSC) are at risk of transitioning between disease stage states. In the economic model, the cohort transitions are modelled independently for each arm, instead of applying relative risks for inotersen compared to BSC. From stage 1, the cohort can transition to stages 2 or 3 in any cycle. From stage 2, the cohort may revert back to stage 1, or progress to stage 3. However, once the cohort enters stage 3 it is assumed that they cannot revert back to any of the previous, less severe disease stages. In each cycle a proportion of the cohort in each disease states also die.

Costs, life years and QALYs are accrued in each 4-weekly cycle according to state distribution in each arm of the model. The model was run over a life time horizon, from a starting age of 59 up until age 100. Cost and QALY streams were discounted at a rate of 1.5% per annum applied continuously in each model cycle. For example, costs occurring in cycle 4 are discounted at a rate of (1+discount rate)^0.31, with 0.31 reflecting the proportion of a year past in each cycle (i.e. week 16/52).

The ERG notes two differences in the model structure between the current assessment and a previous assessment of tafamidis by the Advisory Group for National Specialised Services (AGNSS), as reported in the evidence review group critique of that company's submission.[33] The previous tafamidis assessment was informed by a patient level simulation model[33] (as opposed to a Markov cohort state transition model) and included the costs and effects of liver transplantation (which have been excluded in the CS). The ERG generally agrees that both of these choices are appropriate. Use of a cohort state transition model is subject to less simulation uncertainty and is adequate for representing the key drivers of cost-effectiveness in the given population. The exclusion of liver transplantation from the model structure is also appropriate. The ERGs clinical advisor notes that liver transplantation is very rare and few patients would be treated in this way in the UK. The approach taken in the CS is also consistent with the critique of the tafamidis submission to AGNSS, provided by Faria et al.[33]

A list of modelling assumptions is provided in Table D1 of the original CS. A summary of the ERG's main concerns with the company's assumptions are listed below, with a more detailed critique in the following sections:

- Modelling of treatment discontinuation – the original CS contained an error in the calculation of the proportion of the model cohort discontinuing treatment in each model cycle. The implication was under-estimation of the treatment costs and QALY gains, with the ICER biased in favour of inotersen. The error was corrected in the RCM, in the company's response to the clarification letter.
- The cohort are assumed to discontinue treatment on entry to stage 3 disease. It is unclear whether this assumption is externally valid and transferable to real-world practice. Additionally, it is unclear how congruent a decision to withdraw treatment would be with the definition of Coutinho staging (i.e. TQoL score) used in the model. However, the ERG's clinical expert notes that, because patients are bedridden or have severe autonomic neuropathy, it is reasonable to assume they would be withdrawn from treatment soon after entry to stage 3 disease. At this stage, it is unlikely that inotersen would have a significant effect on delaying progression of symptoms. The only case in which continuation of treatment may be beneficial in the face of worsening neuropathy would be if treatment lead to cardiac improvement, and the ERG are unaware of any robust evidence to support this.
- Treatment compliance with inotersen impacts on drug costs but not on effectiveness (QALYs). The original CS assumed a compliance rate of [redacted] that included all participants in the NEURO-TTR study (treatment continuers and discontinuers). However, the RCM was based on an amended compliance parameter of [redacted], reflecting compliance only of those who continued treatment for the duration of the NEURO-TTR study.
- Once the cohort enters stage 3 disease, they cannot improve or revert back to less severe disease stages (i.e. stages 1 or 2). The company's justification for this structural assumption is that inotersen is not given in stage 3. The ERG agree that true stage 3 disease is likely to be irreversible and that the structural assumption in the model is appropriate. However, the ERG question the appropriateness of the mapping approach used to define Coutinho disease

stages (using TQoL scores) and the cut-offs in these scores that are used to define disease progression. As the TQoL score is a subjective measure, it is always possible that some improvements (even temporary, for a minority of patients) may be plausible, particularly for patients with scores close to the cut-off thresholds. The ERG note that there are some inconsistencies between the assumptions in the model and the data observed in the NEURO-TTR study, where some patients transition from stage 3 to 2. The ERG note however, that this is likely due to random variation in the TQoL score, further emphasising the limitation of using TQoL cut-offs to define disease stage.

- The cost and QALY implications of treatment related adverse events were excluded from the original CS, and only partly included (for a proportion of serious adverse events) in the RCM.
- Mortality in the original CS was dependent only on time since diagnosis of hATTR and was independent of disease severity. In response to the clarification letter, this assumption was revised, using data from a Delphi panel to gain consensus on the likely disease stage specific hazard ratios of mortality compared to the general population.

5.2.3 Population

The characteristics of the modelled cohort reflect the baseline demographic characteristics of all patients included in the NEUTO-TTR study (safety-set population, see Table C5 of the CS). The cohort were, on average age 59. [redacted] and [redacted] of the cohort had Stage 1 and 2 disease respectively upon entering the model.

The ERG note that economic model is based on a combined population with V30M and non V30M mutations. Whilst the original CS modelled mortality as the weighted average of V30M and non-V30M mutations, this was the only parameter incorporated by V30M status. Furthermore, mortality in the RCM is not dichotomised by V30M status. The company have not provided any justification for the approach taken, or discussed if subgroup modelling was feasible given the limited data available. The ERG note that, if sufficient data were available, a superior approach would have been to model each subgroup separately and generate cost-effectiveness results based on the average of the subgroups, weighted by the proportional split of V30M / Non

V30M in hATTR-PN patients in the UK. However, the ERG also acknowledge that there is limited data for the hATTR population as a whole, and splitting model parameter estimates according to subgroups would substantially increase uncertainty around parameters that are already uncertain. Furthermore, there is no evidence to suggest that treatment would be inappropriate for one mutation compared to another. A judgement call is required as to whether the benefits of a subgroup analysis are outweighed by the additional uncertainty it would create (if possible at all).

5.2.4 Interventions and comparators

The intervention (as reported in the CS) is inotersen, 284mg solution, provided in a pre-filled syringe to be self-administered as a sub-cutaneous (SC) injection, once per week, ideally on the same day each week to maintain dose consistency. The first dose should be monitored and supervised by a qualified health professional. Thereafter, the drug can be self-administered following appropriate training. Patients are assumed to remain on treatment until treatment discontinuation or death and drug costs are adjusted for treatment compliance (See Section 5.2.8).

The following dose adjustments are recommended for inotersen and are described in Section 2.3 (Table A2; Page 17) of the CS: A) For patients with a confirmed platelet count ≥75 to <100 x109/L, dose frequency should be reduced to 284 mg every 2 weeks; B) For patients with a confirmed platelet count <75 x109/L, dosing should be paused until 3 successive values > 100 x109/L are obtained. On re-initiation of treatment, dose frequency should be reduced to 284 mg every 2 weeks; C) For patients with a confirmed platelet count <25 x109/L, treatment should be permanently discontinued, and corticosteroids administered. The ERG's understanding is that dose adjustments for adverse reactions would be accounted for in the compliance parameter used in the model, and therefore the costs in the model are likely adjusted to reflect this.

The economic model did not explicitly consider other treatments that may be given to patients with hATTR-PN in either the intervention or comparator arms. Other treatments (e.g. tafamidis, diflunisal, patisiran) have previously been suggested as treatments for hATTR, but are either unlicensed for this indication, or do not have reimbursement approval for provision on the NHS. The ERG therefore agree that the

chosen comparator for the model (BSC) is in line with the NICE scope, and note that treatment of hATTR-PN symptoms is captured in the disease stage specific healthcare costs.

As there are no head-to-head comparisons of inotersen with alternative interventions, the ERG agree that the choice of intervention and comparator are appropriate.

5.2.5 Perspective, time horizon and discounting

Perspective

The economic model adopts an NHS and PSS perspective in line with NICE guidance. NHS costs include inotersen drug therapy, and Coutinho disease stage specific healthcare costs. Additionally, social care costs of homecare are also included by disease stage. The company's perspective is in line with the NICE reference case[38]

The ERG note that if an analysis were undertaken where wider personal and societal perspective costs, such as productivity losses and disability support (social welfare) costs associated with progressive disease were included, these would reduce the overall incremental cost (to society) of inotersen treatment.

Time horizon

The company have modelled a 41-year time horizon, from the model start age (59 years) to age 100. The ERG believes the chosen time horizon is appropriate and sufficient to capture important differences in long term costs and QALYs. Whilst acknowledging that it may be theoretically possible to live past age 100, this is highly unlikely in the modelled population.

Discount rates

The company have chosen to use a discount rate of 1.5% per annum for both costs and QALYs in their base case analysis. This departs from the NICE reference case for technology appraisal.[38] The NICE interim methods and process guide for HSTs outlines scenarios in which it may be appropriate to depart from the NICE reference case. The CS and response to clarification document provide the company's rationale

for using a 1.5% discount rate for costs and QALYs. This justification, together with ERG commentary on each criterion from the NICE HST interim methods guide[31] are provided in Table 19 below.

Table 19 Comparison of company's case for 1.5% discount rate against the NICE HST interim process and methods guide

NICE HST criterion for using a 1.5% discount rate	Company justification	ERG comment
"In cases where treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and…."	*"Inotersen prevents transitions into worse health states. The worst of these (Stage 3) has negative QALYs when carer disutility is included. This therefore meets any reasonable definition of 'severely impaired health'.*	The ERG agree that patients with hATTR-PN have, or are likely to, develop severely impaired health. However, the HST criteria specifically state that the intervention should **"restore"** people to **"full or near full health"**. Based on the CS, the primary mechanism of effect, and the method by which most QALYs are generated in the model, is prevention of progression to subsequently more debilitating disease stages (not restoration of full or near full health).
"When this is sustained over a very long period (normally at least 30 years) and……..it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved"	*"There is no evidence that the benefit is sustained for anything other than a lifetime time horizon; clinical consensus is that hATTR is degenerative, meaning that if inotersen delays or reverses a transition to a lower disease state this benefit is not lost provided patients remain on treatment (which the vast majority of patients do)."*	The company have provided no evidence that inotersen completely halts hATTR-PN disease, and ultimately all patients suffer early mortality, whether or not they have treatment. The RCM predicts undiscounted life years of 8.559 (inotersen) and 7.541 (BSC), an incremental LYG of 1.018[A]. These data confirm that the benefits are not sustained over a 30 year time horizon.
"….the introduction of the technology does not commit the NHS to significant irrecoverable costs."	*"As inotersen is taken weekly and can be safely discontinued, this would not commit the NHS to significant irrecoverable costs."*	It is unclear to the ERG how this criterion should be interpreted. The ERG agrees that, if inotersen is provided to patients in small batches (or there is no wastage) then the costs of treatment once a patient has discontinued are unlikely to be significant. However, the ERG also note that inotersen is a [redacted], and in cases where it does not provide substantial benefits, the NHS would have committed significant irrecoverable costs.

[A] Company's revised base case analysis following response to the clarification letter

The ERG do not believe that inotersen meets the criteria set out by NICE to justify the use of a 1.5% discount rate for the reasons outlined in Table 19 above. In response to the clarification letter, the company provided scenario analyses using a rate of 3.5%. Additional exploratory work conducted by the ERG combines the 3.5% analysis with other relevant scenario analyses in Section 5.3.2.

5.2.6 Treatment effectiveness and ***extrapolation***

Transition probabilities

Transitions between different Coutinho disease stage health states were modelled independently for each model arm, and converted to 4-weekly probabilities (model cycle length) using the data observed in the trial. Two sets of transition probabilities, sourced from the NEURO-TTR study, are used in the model: A) baseline to week 35 and B) week 35 to 66. It is unclear from the CS why these time period cut-offs were chosen, or what impact this decision has on the ICER. The transition probabilities used in the model are reported in Table 20 below.

Table 20 Model transition probabilities (Re-produced from Tables D4 to D7 of the CS)

	4-weekly probability			
	Inotersen (weeks 0-35)	**Inotersen (weeks 35-66)**	**BSC (weeks 0-35)**	**BSC (weeks 35-66)**
Stage 1 to Stage 1	[redacted]	[redacted]	[redacted]	[redacted]
Stage 1 to Stage 2	[redacted]	[redacted]	[redacted]	[redacted]
Stage 1 to Stage 3	[redacted]	[redacted]	[redacted]	[redacted]
Stage 2 to Stage 1	[redacted]	[redacted]	[redacted]	[redacted]
Stage 2 to Stage 2	[redacted]	[redacted]	[redacted]	[redacted]
Stage 2 to Stage 3	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = Best Supportive Care

Transition probabilities from the NEURO -TTR study between weeks 35 and 66 were also used to extrapolate transitions over the full life time horizon of the model for both the inotersen and BSC cohorts. The ERG note that the extrapolation of transition probabilities over a life time horizon based on short term data (weeks 35-66) raises considerable uncertainty about the accuracy of the long run disease trajectory in the

model. The company could potentially have explored the use of survival analysis to determine time to disease progression between the stages. However, the ERG acknowledge that whilst such an analysis may have been possible with the data available from the trial, it would have been based on small numbers and also subject to considerable uncertainty. Therefore, on balance, the ERG agree that, in the absence of better long-term follow up data, the approach taken by the company is justified.

Mortality

hATTR mortality in the original CS (not correlated with disease stage)

There is little data on long-term mortality for patients with hATTR and no information from the NEURO-TTR study to populate mortality by disease stage. Therefore, the original CS used mortality data from time of disease onset by V30M mutation status, obtained from digitised KM data published by Sattianayagam 2012.[3] Mortality was not age adjusted for general population norms in the original CS because the start age in Sattianayagam (age = 63) was similar to the modelled population (age = 59).

The original CS used parametric survival analysis of the digitised Kaplan Maier data to extrapolate long term mortality. Following NICE DSU recommendations,[39] a range of different parametric survival distributions were explored. These are summarised in Figure 6 below and AIC / BIC statistics for each curve are provided in Table 21. According to AIC / BIC statistics, the preferred functions were Weibull (V30M mutations) and log-logistic (Non-V30M mutations). However, based on face validity, it was determined that all extrapolation curves for non V30M survival (except Gompertz and Weibull) were clinically implausible with estimated survival times higher than the V30M population. As the Weibull curve provided a better statistical fit compared to the Gompertz, it was chosen for the modelling of mortality in the non V30M population.

Table 21 Goodness of fit statistics for V30M and non-V30M survival from diagnosis parametric distributions curve (Re-produced from Table D8 of the CS)

Distribution	V30M population		Non-V30M population	
	AIC	BIC	AIC	BIC
Exponential	166.01	167.27	231.40	233.36
Weibull	**144.24**	**146.76**	**226.93**	**230.83**
Gompertz	146.21	148.73	232.50	236.40
Log-logistic	147.49	150.01	219.38	223.28
Lognormal	147.39	149.91	220.59	224.49
Generalised Gamma	146.24*	150.01*	223.33	228.19

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion. Lower AIC/BIC indicates better fit. *The Generalised Gamma curve did not converge.

Figure 6 Kaplan Meier and parametric distributions for the V30M population (Re-produced from Figure 12 of the CS)

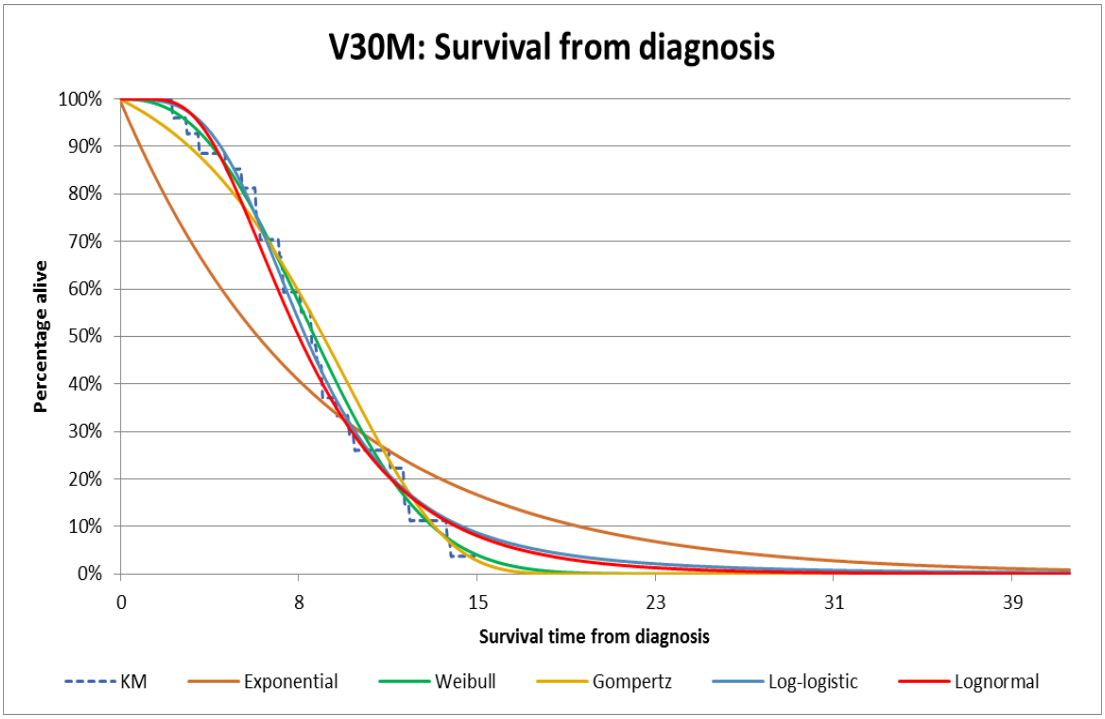
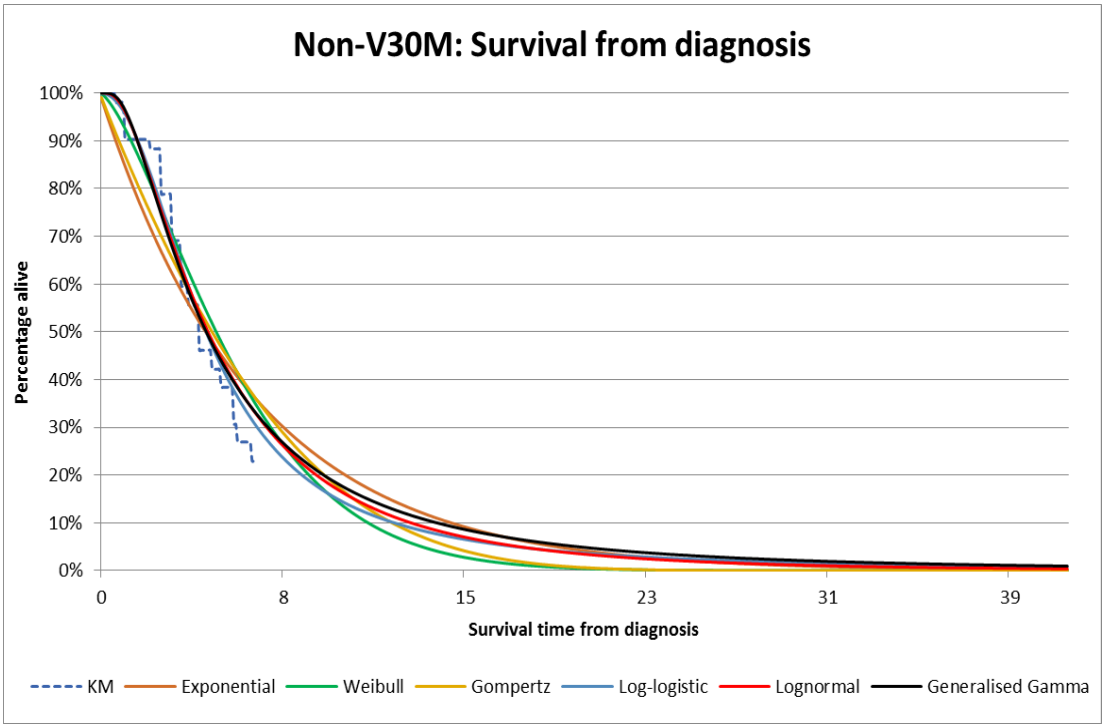


Figure 7 Kaplan Meier and parametric distributions for the non-V30M population (Re-produced from Figure 13 of the CS)



The ERG's main concern is that the company's approach has limited face validity, as it assumes equal mortality regardless of disease progression stage. This is a conservative assumption that may under-estimate expected life year, and hence QALY gains for inotersen versus BSC. Conversely, if patients in the inotersen group also live longer, it is likely that they will incur additional treatment costs during the extended survival period.

Disease stage specific mortality (revised company model)

The ERG acknowledges that there are no published data available to link Coutinho disease stage with mortality. However, the ERG's clinical expert felt that such an association was plausible, and it would therefore be appropriate to explore the impact of correlating mortality with disease stage in the model. However, it is also noted that the exact relationship is highly uncertain and likely to be based on assumption. The ERG is uncertain whether mortality hazard ratios could be estimated for each disease stage using data available from the THAOS registry. If such data were available to the company, they could have provided a useful source of data for the economic model.

In response to a clarification question on this issue, the company revised their base case analysis to incorporate disease stage specific mortality. To do this, they assembled a Delphi panel of N=4 clinical experts to gain consensus on the most likely hazard ratio of mortality by disease stage relative to general population all-cause mortality.[40] The Hazard ratios obtained from the Delphi study were as follows: Stage 1: HR = [redacted]; Stage 2: HR = [redacted]; Stage 3: HR = [redacted]. These ratios were applied to age specific UK general population mortality rates and converted to cycle specific probabilities in the model.

The ERG agree that incorporating disease specific mortality appears more plausible that the original approach of assuming no association between disease progression and death. The ERG also agree that the hazard ratios obtained from the Delphi study have been correctly implemented. As a cross validation check, the ERG compare the proportion of the cohort entering the death state over the model duration in the original CS, with the RCM in Table 22. It appears that the overall mortality in the RCM is slightly lower compared to the original CS (based on survival modelling).

Table 22 Comparison of different approaches to incorporate mortality in the economic model

Proportion of cohort dead by year:	**Original CS (no correlation between disease stage and mortality)**	**RCM (hazard ratios of disease stage specific mortality, compared to general population rates, obtained from Delphi consensus study)**
5	32.51% (both cohorts)	Inotersen: 27.01% BSC: 33.97%
10	74.64% (both cohorts)	Inotersen: 62.37% BSC: 70.89%
15	95.69% (both cohorts)	Inotersen: 88.65% BSC: 92.61%

Abbreviations: BSC = Best Supportive Care

However, it is unfortunate that the company have not provided further detail on the recruitment to the Delphi study or any other details regarding how consensus was

achieved. This limits the ERGs ability to critique the results. The ERGs clinical expert felt that the hazard ratios included in the model from the Delphi study appeared plausible. It is however likely that there is considerable uncertainty around the disease stage specific hazard ratios, and this has not been explored by the company in sensitivity analysis.

5.2.7 Health related quality of life

HRQoL data are incorporated in the economic model for both patients and carers (by Coutinho disease stage).

Patient HRQoL (Utilities)

The CS included a systematic review of HRQoL studies (as part of their global review), with the aim of identifying utility data by Coutinho disease state for application in the economic model. N=16 potentially relevant studies were assessed and summarised by the company, but only 1 was deemed relevant for inclusion in the model.[35] The remaining 15 studies were deemed inappropriate because they did not report QoL by Coutinho disease stage health state. The ERG note that the evidence base is limited, and agree that the company's search for utility data in published studies has been robust.

Patient health state utilities by Coutinho disease stage were obtained from data reported in a conference abstract.[13] Stewart et al reported EQ-5D-3L utility values by Coutinho disease stage based on data from the THAOS registry of patients with hATTR. These EQ-5D-3L values were based on the Brazilian population tariff.[34] The THAOS registry includes data for N=1,205 patients (N=970 V30M mutation and N=235 non-V30M mutation).[37] EQ-5D data were available for n=803 (V30M) and n=235 (non V30M) patients.

The ERG caution against the use of EQ-5D values based on Brazilian general population preferences as these may not be appropriate to populate a model from a UK NHS perspective. The company have provided little discussion around the limitations of their approach, other than to acknowledge that the transferability to a UK setting is unclear. No work has been carried out to determine the comparability of the valuation sets and the company have failed to conduct adequate sensitivity

analyses around these uncertain values. In light of this concern, the ERG have conducted additional work to determine the comparability of the valuation sets between Brazil and the UK. Table 23 below outlines the preferred tariffs for generating EQ-5D-3L utility weights according to Santos et al[34] (Brazil) and Dolan et al[32] (UK). Additionally, utility values obtained from a range of EQ-5D health states are compared for illustration.

Table 23 Comparison of EQ-5D valuation sets between the UK and Brazil

Parameter	**UK**	**Brazil**
Valuation set regression models		
a	0.081	(1-0.851) = 0.149
MO	0.069	0.120
SC	0.104	0.112
UA	0.036	0.097
PD	0.123	0.064
AD	0.017	0.050
M2	0.176	0.363
S2	0.006	0.218
U2	0.022	0.184
P2	0.140	0.168
A2	0.094	0.095
N2	--	--
N3	0.269	--
Model R (sq)	0.46	0.28
Utility values obtained for a range of EQ-5D health states		
EQ-5D health state	**Utility (UK)**	**Utility (Brazil)**
11121	0.796	0.787
11312	0.485	0.626
23313	0.037	0.235
33323	-0.331	-0.037
33333	-0.594	-0.176

The table highlights that there are important differences in the preference patterns between the valuation models, noting in particular that a standard decrement for any level 3 response is not applied in the Brazilian value set, meaning that poorer health states are valued substantially lower in the UK tariffs compared to the Brazilian tariffs. It is not possible to determine the magnitude and direction of any bias on the ICER caused by using the Brazilian tariff rather than UK one. This will depend on

the differences between the mean utility score by Coutinho stage with the alternative value sets. However, the ERG believe that the concerns over transferability of the value set mean it would have been appropriate for the company to consider alternative sources of utility data for use in the model. The ERG consider that there are three plausible alternative sources of data that the company could have explored.

First, the company could have attempted to obtain raw EQ-5D response data sourced directly from the THAOS study.[36] It appears, from the CS and Stewart et al, that EQ-5D data exist for 77.5% of the THAOS study cohort by Coutinho health state. The ERG note that this is a rich source of EQ-5D data among patients with a very rare condition. If the data had been obtained, it would have been possible to generate disease stage specific EQ-5D values using the UK tariff.[32] This approach would have provided a more robust estimate of UK relevant, disease stage specific utilities for use in the economic model, in line with the NICE reference case.[38]

Secondly, the ERG note that patients enrolled in the NEURO-TTR study completed SF-36 questionnaires. The ERG believe the company could have explored the option of mapping SF-36 response data to EQ-5D values using published algorithms.[41, 42]. This approach could have provided mapped EQ-5D values for Coutinho stages 1 and 2, and potential to explore the use a repeated measures model to estimate the utility impact of progression to stage 3 disease. The ERG suggested this approach at the clarification stage. However, the company responded that there were no Stage 3 patients in the NEURO-TTR study. The ERG agree that this statement accurately reflects the inclusion criteria for enrolment in the NEURO-TTR, which restricted the recruited sample to stage 1 and 2 disease. However, as reported in Tables D4 to D7 of the CS,

[redacted] The ERG agree that there may have been insufficient numbers available to conduct a robust repeated measures analysis. However, the mapped values could have been used for stages 1 and 2, with an exploration of the utility impact for those who progress. The ERGs view is that, if these data were available, they could have been used to provide an alternative source

of UK relevant utility estimates for use in the model, and could have been used to validate the company's preferred approach.

Finally, the company could have drawn upon alternative utility values reported by disease stage in Faria et al, for the AGNSS appraisal of tafamidis. Faria et al report different possible functions describing the relationship between TQoL (obtained from the Norfolk Quality of Life – Diabetic Neuropathy questionnaire) and the EQ-5D for patients with TTR-FAP.[33] All functions were obtained from a cross-sectional analysis of baseline data from the THAOS study.[36] The ERG acknowledges that the mapping approach is based on correlations between a disease specific measure (TQoL) and a generic measure (EQ-5D) of QoL and that TQoL may not fully capture all impacts of hATTR-PN on generic HRQoL. Whilst TTR-FAP and TTR-PN may not be identical conditions, the ERG's clinical expert agrees that the conditions are sufficiently similar in terms of impact on QoL to enable the use of utilities from Faria et al as a plausible alternative scenario analysis in the economic model. The ERG assumes that the utilities included in Faria et al are based on UK valuations. The ERG have therefore compared Coutinho disease stage specific utilities obtained from different mapping functions reported in Faria et al[33] to those used in the CS in Table 24 below.

Table 24 Summary of Coutinho disease stage specific utilities from different sources

Coutinho disease stage	Inotersen, company preferred approach using Stewart et al data	Faria et al (1): Linear mapping function[A]	Faria et al (2): Quadratic mapping function[B]	Faria et al (3): Cubic mapping function[C]	Faria et al (4): Disease stage specific linear mapping function[D]
Stage 1 (TQoL: 48.97)	0.697	0.636	0.646	0.662	0.705
Stage 2 (TQoL: 72.68)	0.429	0.501	0.494	0.539	0.551
Stage 3 (TQoL: 94.83)	0.084	0.375	0.331	0.366	0.170

[A] EQ5D = 0.913991 – 0.005682xTQoL;
[B] EQ5D = 0.89 – 0.004*TQoL - 0.00002*TQoL^2

[C] EQ5D = 0.90979 – 0.00712*TQoL + 0.00007123*TQoL^2 -0.000000596927*TQoL^3
[D] Linear by stage: Stage 1: EQ-5D=0.930807-0.004613*TQoL; Stage 2: EQ-5D=0.861597-0.004278*TQoL; Stage 3: EQ-5D=0.822396-0.006884*TQoL.

The ERG note that different mapping functions generate a range of different plausible health state utility values that could have been used in the model. The ERG note that, in general, the greater the difference between Stage 1 and 3 utilities, the greater the incremental QALY gains (and hence lower ICERs) for inotersen. In this regard, utilities sourced from Faria et al provide a comparatively pessimistic scenario for inotersen. In light of the uncertainty around the most appropriate utility values for use in the model, the ERG have conducted additional exploratory analyses, investigating the impact of different Coutinho disease stage utilities on the ICER in Section 5.3.2.

Carer HRQoL (Utilities)

The company's systematic review did not identify any studies that reported the utility impact on informal carers of caring for individuals with hATTR-PN in the different Coutinho disease states. The CS states that a systematic review of carer's disutility in other, similar disease areas was conducted. However, no further information is provided in the CS regarding the search strategy, inclusion / exclusion criteria, or study selection / data extraction methods for that review. It is therefore not possible to determine the robustness or completeness of the systematic review of carer disutility.

For the economic model, the company consider the impact of multiple sclerosis (MS) on carers to be an appropriate approximation for carer burden in hATTR-PN. Data from an algorithm developed by Gani et al,[43] estimating carer disutility from patient's Expanded Disability Status Scale (EDSS) score have been used in previous NICE guidance (TA533) for MS.[44] It is assumed that as hATTR-PN patients progress through disease stages, the burden on carers also increases, as it would with progression of MS disability.

The model further assumes that all patients have two full time carers, and cites the HST evaluation of ataluren for Duchenne muscular dystrophy in the justification.[45] However, that evaluation considered a pediatric population. Therefore, the ERG requested further justification at the clarification stage as to why disutility was applied

to multiple carers, taking into account the level of home care accounted for in the health state costs. In response, the company clarified that:

> *"An alternate method of calculation would be to assume hATTR patients require 'full time' care, less a 37.5 hour workweek (from homecare) and 56 hours sleep per week. This equates to 74.5 hours care delivered by one person per week; this is almost exactly half of the 144 hours care reported in the submission, and therefore two full-time carers is the minimum one could assume necessary to support a person with hATTR".*

The company provided two further analyses in response to the clarification letter, varying the number of carers between one and three. The company's base case approach to incorporation of carer disutility is reported in Table 25 below.

Table 25 Summary of carer QoL values for cost-effectiveness analysis (Re-produced from CS, Table C30)

Health state	EQ-5D-3L disutility per carer	Total disutility applied in model (for two carers)	Note
Stage 1	-0.0025	-0.0050	Average of EDSS 0-3.0 (no impairment to walking)
Stage 2	-0.0275	-0.0550	Average of EDSS 3.5-7.0 (requires walking assistance, not restricted to wheelchair)
Stage 3	-0.125	-0.2500	Average of EDSS 7.5-9.5 (restricted to wheelchair or bedridden)

Abbreviations: EDSS: Expanded Disability Status Scale

The ERG agree hATTR-PN is highly likely to place a significant burden on carers, and therefore agree that it is appropriate to consider carer disutility in the model. For the tafamidis assessment a QALY loss of 0.01 was applied for stage 3 disease only to account for utility decrements of carers, based on the NICE Final Appraisal Determination (FAD) for treatment of Alzheimer's patients. However, the ERG also note that only one carer was assumed in the tafamidis assessment and remain unclear as to whether all patients with hATTR-PN would realistically have two full time

informal carers, particularly for patients with stage 1 or even stage 2 disease. Additional scenario analyses explore the impact of carer disutility on the ICER.

Treatment related adverse event utilities

The original CS excluded the cost and utility impact of treatment related adverse events observed in the NEURO-TTR study. In response to the clarification letter, the company provide two justifications for excluding AEs. The first is that difference in the number of AE between the treatment arms of NEURO-TTR was not statistically significant. The second is that because most adverse events were deemed to be mild, and because there was a low absolute rate of serious adverse events (<5%), the impact of including AE on the ICER is minimal. The ERG disagree with both of these reasons as justification for excluding AEs from the model. Excluding AEs creates a bias, of admittedly low magnitude, in favour of inotersen and should be included in the base case analysis.

Despite the ERGs clarification request, AEs continue to be excluded from the company's preferred base case analysis. Instead, the company provide a partially complete scenario analysis where utility decrements (of some serious AEs) and costs of all but one serious AE are included in the model. Furthermore, the ERG note that the scenario analyses reported by the company are poorly referenced, particularly with respect to adverse event duration, though some data can be traced from within the company's revised economic model.

In addition to these issues, the ERG also note that the company exclude any disutility associated with myelopathy, glomerulonephritis, tubulointerstitial nephritis and thrombocytopenia from their AE scenario analysis, despite these being reported as serious AEs in the NEURO-TTR study. The approach effectively assumes that these events incur no utility loss. The justification for the exclusion is that there are insufficient data to inform these parameters. The ERG accept that data are scarce, but argue that informed assumptions regarding the utility decrement would have been superior to assuming these serious adverse events have no utility decrement.

Table 26 below describes the 4-weekly cycle specific serious adverse event rates calculated from the NEURO-TTR study, assumed durations of serious AEs, and

associated utility decrements applied. Where the company have failed to include any duration or disutility data, the ERG have attempted to source utility data, or made alternative assumptions, verified by clinical expert opinion, where possible.

Table 26 RCM vs. ERG adverse event disutility

Adverse event rates per cycle	Inotersen	BSC	Assumed duration (days)		Disutility applied		Total disutility (duration x disutility)		Utility source / ERG notes
			RCM	ERG	RCM	ERG	RCM	ERG	
Glomerulonephritis	0.18%	0.00%	0	30 (assumption)	0	-0.31 (de Wit 2001)	0	-0.025	Co source: None ERG source: de Wit, 2001[46] + assumed duration
Thrombocytonpenia	0.12%	0.00%	30		-0.108		-0.009		Co source: TTO utility value; Tolley, 2013[47]
Deep vein thrombosis	0.06%	0.11%	30		-0.110		-0.009		Co source: NICE TA341, 2015[48]
Intracranial hemorrhage	0.06%	0.00%	91		-0.309		-0.077		Co source: NICE TA341, 2015[48B]
Tubulointersitial nephritis	0.06%	0.00%	0	30 (assumption)	0	-0.31	0	-0.025	Co source: None ERG source: de Wit, 2001[46] + assumed duration
Pulmonary embolism	0.06%	0.00%	30		-0.320		-0.026		Co source: NICE TA341, 2015[48]
Embolic stroke	0.06%	0.00%	91		-0.224		-0.056		Co source: Unclear[A]
Myelopathy	0.06%	0.00%	0	91 (assumption)	0	0.639 – (average 0.575+0.55) = -0.076	0	-0.019	Co source: None ERG source: Nayak, 2016[49] + assumed duration

[A] No details of source provided, simply stated as rivaroxaban spaf in the electronic model [B] The Company have not provided details on this calculation, but it appears to be based on the average utility across Coutinho disease stages, less the average utility (0.33) of patients with intracranial haemorrhage in the NICE FAD for Apixaban. Abbreviations: BSC = Best Supportive Care; ERG = Evidence Review Group; RCM = Revised Company Model; TA = Technology Appraisal; TTO = Time trade off.

Other HRQoL issues

In addition to the issues raised above, the ERG note that the CS does not include any age adjustment of the utility weights used in the model. Given that the average age of participants in the THAOS study (reported in Stewart et al) is somewhat lower (mean age V30M: 45, mean age non-V30M: 52) than the modelled cohort (mean age = 59), it would have been desirable to age adjusted included utilities to correspond with best practice methodology. However, the ERG note that the decision not to age-adjust utility data is unlikely to have a meaningful impact on the ICER given A) the relative closeness of the ages in the THAOS study to the modelled cohort and B) the short duration of life expectancy in the model.

5.2.8 Resources and costs

This section summarises and critiques the company's costing approach, focusing on A) drug costs, B) healthcare resource use costs for treating patients in different disease stages and C) adverse event costs.

Drug costs - inotersen

Inotersen drug costs are based on a self-administered weekly sub-cutaneous injection using a pre-filled vial of inotersen, 284mg solution. The listed drug price (per weekly dose) is £5,925. A patient access scheme price is proposed in the CS, in the form of a [redacted] discount on the list price. Thus a price of [redacted] per weekly dose is applied in the economic model. The total cost of inotersen is driven by two key model parameters: a) time to treatment discontinuation and b) treatment compliance. Following the correction of an error in the estimation of treatment discontinuation rates in response to the clarification letter, total drug costs per patient (discounted at 1.5% per annum) equate to [redacted] over the lifetime of the modelled cohort in the company base case.

<u>Treatment Discontinuation</u>

The modelled cohort receiving inotersen treatment were sub-divided into those 'on treatment' and those 'not on treatment', based on a parametric survival analysis of the treatment discontinuation data observed in the NEURO-TTR study. It is further assumed that all patients entering stage 3 disease are discontinued from treatment.

In response to the clarification letter, the company made the following revisions to the modelled time to discontinuation:

1. The survival curves used to estimate time to discontinuation in the original CS were based solely on the NEURO-TTR study, but these were updated to include the longer term data available from the NEURO-TTR extension study. The ERG agrees that the revised approach is appropriate and more accurately captures the best available long term data on time to discontinuation.
2. The company corrected an error in their model, whereby the discontinuation curve suggested 80.67% of the surviving cohort would remain on treatment by the end of year 1, but only 23% were incurring the appropriate treatment costs in the model at the same time point. This error related to the survival function (indicating the probability of remaining on treatment up to any given time point) not being first converted to cycle dependent probabilities of remaining on treatment *(= S(t) / (S(t-1)))* before being applied in the cohort trace calculations. The impact of this error was that the costs of inotersen treatment were substantially under-estimated in the original model. The ERG are satisfied that it has been appropriately corrected in the revised model.

The different extrapolation curves (fitted to NEURO-TTR and NEURO-TTR extension data) and corresponding AIC / BIC scores from the RCM are reported in Figure 8 and Table 27 respectively.

[redacted]

Table 27 Goodness-of-fit statistics for two modelled parametric survival curves (Reproduced from Table 11 of the Company response to the clarification letter)

	Original data		**With extension data**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	259.471	262.189	419.268	421.986
Weibull	260.779	266.216	419.663	425.100
Gompertz	260.548	265.985	419.001	424.438
Log-logistic	260.625	266.062	419.266	424.703
Lognormal	260.221	265.658	421.059	426.496
Generalised Gamma	262.220	270.376	421.498	429.654

In the original CS, an exponential survival model provided the best statistical fit to the NEURO-TTR data based on both the AIC and BIC. However, there was little difference in AIC and BIC between most of the curves, and the company opted for the Gompertz model in their original base case. This was because they believed it was

more plausible that the likelihood of discontinuing inotersen would decrease over time as those who cannot tolerate it discontinue early due to side effects. The ERG believe that the approach taken by the company, to use a combination of AIC / BIC and clinical plausibility, is in line with NICE DSU guidance for selection of appropriate parametric survival curves.[39]

In response to the clarification letter, the company incorporated the NEURO-TTR extension study data re-ran their survival analyses. In their revised model they chose an exponential survival function (compared to gompertz in the original CS), noting that the tapering off of the KM curve was not observed within NEURO-TTR extension study as initially expected. Furthermore, the company argue that the exponential is a better fit to the longer term data based on the BIC (Table 27).

The company's preferred base case assumption, using an exponential extrapolation curve, generates the lowest estimates of treatment continuation at any one time, but also leads to the lowest projected inotersen drug costs. Within the company's model, the curves that predict lower rates of treatment continuation in the long-term generate the lowest ICERs. In this respect, the company's preferred base case analysis using the exponential curve generates the most optimistic estimate of the ICER for inotersen with respect to the alternative parametric discontinuation curves. By contrast, the Gompertz model, initially preferred in the original CS, generates the most pessimistic estimate of the ICER.

Overall, the ERG note that there is little to choose between the alternative extrapolation curves based on the AIC and BIC, and any curve could feasibly fit with the observed data. The ERG believe that the most reasonable extrapolation curve may be one which allows for a decreasing rate of discontinuation over time, as those who remain on treatment in the longer-term are likely to be those who tolerate the drug and continue to derive clinical benefit. This view is supported by the ERG's clinical expert advisor. The impact of alternative parametric curves on the ICER is explored further in Tables 34 and 40.

Discontinuation on entry to Stage 3 disease

In addition to the approach used to modelling time to treatment discontinuation, the ERG also have some concerns regarding the company's assumption that all patients will discontinue treatment immediately upon on entry to stage 3 disease. Whilst the assumption is in line with the licence for inotersen, it is unclear whether patients with hATTR-PN would be immediately denied inotersen treatment on entry to Stage 3. A further complication relates to the fact that transitions between the Coutinho stages in the company model are based on an imperfect mapping from TQoL scores, and not an objective clinical assessment of disease stage. Therefore, progression to stage 3 disease does not appear to have been an explicit criteria for discontinuation in the NEURO-TTR and NEURO -TTR–Extension studies. Therefore applying a time to discontinuation curve in combination with the assumption of stopping treatment upon to progression to stage 3, may overestimate discontinuation compared with the rate observed in the trial. This can be checked by comparing the observed Kaplan Meier data with the proportion of the surviving cohort remaining on treatment in the model, which is ~ 2.5% lower at 1 year, suggesting a modest overestimation of discontinuation in the model. Whilst this is somewhat problematic, the ERG believe it is likely that correlation does exist between disease progression and the probability of discontinuing inotersen treatment. It would therefore be inappropriate to use the single time to discontinuation curve to infer an equal rate of discontinuation across all disease states in the model.

Treatment compliance

Treatment compliance is another important driver of inotersen treatment costs and hence cost-effectiveness in the model. Treatment non-compliance was defined in the original CS as *"those who miss a dose for any reason - other than discontinuation - which is not later made up"* The original CS used a treatment compliance rate for all patients in the NEURO -TTR study of [redacted] and multiplied inotersen costs by this value in each model cycle to reflect the costs of the actual inotersen dose consumed to ensure that the benefits observed were based on actual rather scheduled dosage costs. At the clarification stage, the ERG raised a concern that changing the compliance parameter in the economic model generated potentially counter-intuitive results, because increasing compliance increased costs, but had no impact on benefits, thus making inotersen less cost-effective. In response to the clarification letter, the

company acknowledged this issue but were unable to link compliance to treatment effectiveness and argued that compliance should be considered as a fixed parameter in the model. The ERG agree with this aspect of the company's response.

However, in response to the clarification letter, the company amended the compliance parameter from [redacted] to [redacted]. The justification for reducing the compliance parameter was that the original CS *"…incorrectly counted the compliance of discontinuers"*. The company felt this was incorrect because continuers and discontinuers are likely to have different compliance profiles. The ERG make two observations on this decision. First, it is unclear as to why the compliance rate among discontinuers should be higher than in continuers. It may in fact just be a chance finding, and the company did not provide an explanation for this. Secondly, the ERG believe that it is inappropriate to exclude the compliance of discontinuers in the model (at least in the short term) because this fails to cost all doses observed up to the end of the NEURO-TTR trial. Whilst longer-term compliance may be lower, the evidence and justification for this is not strong in the RCM.

Furthermore, costing the drug based on compliance <100% makes the additional assumption that the amount of drug prescribed can be adjusted to match patient compliance. If patients were to be prescribed the recommended dose for set periods of time (e.g. a four week supply as proposed by the company) without adjustment for compliance, then there may be drug wastage that has not been captured in the economic model. Therefore, the impact of increasing the compliance parameter is explored in further sensitivity analysis conducted by the ERG (Section 5.3.2).

Drug costs - BSC

The ERG note that the CS assumes there are no additional treatment related costs specific to BSC, and that all the relevant costs are captured in the disease stage costs used in the model. This assumes that all other treatment costs are independent of allocated treatment within each stage of disease. It is difficult to determine the validity of this approach because neither the CS nor the referenced source (Faria et al), provide a detailed breakdown of the healthcare resources (including specific drug treatments) underpinning the calculation of disease stage costs. Given the lack of available evidence to suggest otherwise, the company approach appears reasonable.

Treatment related adverse event costs

As described in Section 5.2.7 above, the ERG requested an analysis including both the cost and utility implications of adverse events. The company's response to the clarification letter provided a scenario analysis incorporating the costs of all serious adverse events with the exception of myelopathy. The ERG have updated the company's model to include an assumed cost of myelopathy equivalent to the NHS reference costs of an elective inpatient stay for low back pain with interventions (HRG code: HC32G). As with utilities, these costs are added to reflect the fact that there is likely a resource use associated with treating myelopathy. The ERG note that the company have provided no information on their sources of unit costs, other than to state that they are NHS reference costs 2016/17. There is no information, for example on which HRG codes were used and thus it is impossible for the ERG to validate the costs included in the model as a result. The ERG note, however, that including NHS reference costs only (assuming one elective procedure per AE) may be a conservative estimate of the true NHS costs of treating serious adverse events. The adverse event costs included in the model (under company and ERG assumptions) are reported in Table 28 below.

Table 28 RCM vs. ERG adverse event costs

Adverse event rates per cycle	Inotersen	BSC	Assumed duration (days)		Adverse event costs (per cycle)		Utility source / ERG notes
			RCM	ERG	RCM	ERG	
Glomerulonephritis	0.18%	0.00%	0	30[A]	£1,731		Co source: Legacy screening[50]
Thrombocytonpenia	0.12%	0.00%	30		£621		Co source: NHS reference costs 16/17[51] (HRG code not specified)
Deep vein thrombosis	0.06%	0.11%	30		£614		Co source: NHS reference costs 16/17[51] (HRG code not specified)
Intracranial hemorrhage	0.06%	0.00%	91		£2,725		Co source: NICE TA341, 2015[48]
Tubulointersitial nephritis	0.06%	0.00%	0	30 [A]	£1,485		Co source: NHS reference costs 16/17[51] (HRG code not specified)
Pulmonary embolism	0.06%	0.00%	30		£1,432		Co source: NHS reference costs 16/17[51] (HRG code not specified)
Embolic stroke	0.06%	0.00%	91		£3,185		Co source: None
Myelopathy	0.06%	0.00%	0	91 [A]	0	£2,148	Co source: None ERG source: NHS ref costs 2016/17[51] (elective inpatient admission, HRG code: HC32G)

[A]: Assumption

Abbreviations: BSC: Best Supportive Care; ERG: Evidence Review Group; HRG: Healthcare Resource Group; RCM: Revised Company Model; TA: Technology Appraisal

Disease stage specific costs

Costs attributable to each health state are sourced from the tafamidis assessment[33]

Data from Faria et al include six-monthly costs of treating Polyneuropathy, Gastrointestinal disorders, Cardiac arrhythmias, Bladder dysfunction, Ocular

problems, Other issues, primary care, aids and homecare as well as one-off costs of entry to stages 2 and 3 disease.

Resource use underpinning the data used in Faria et al were based on clinical expert opinion of a group of Swedish based clinicians consulted by the manufacturer of tafamidis, and validated by the ERG's clinical expert for the tafamidis assessment. Resource use data were costed using UK national average unit cost sources (PSSRU & NHS reference costs).[52]

For the current assessment, the six-monthly costs from Faria et al are converted to 4-weekly cycle specific costs, with an additional cost applied on transition to stage 2 and stage 3 (also sourced from Faria et al.). All costs in the CS for inotersen are inflated to 2016/2017 values using PSSRU inflation indices.[52] The ERG have cross checked the data from Faria et al with the CS and are in agreement that the costs are correctly applied with one exception. The one-off costs sourced from Faria et al for entry to stage 2 should be £1,803 and not £1,083 as applied in the model. The ERG have made this correction and note that it has little impact on the ICER. The ERG note that it would have been preferable to conduct a new costing exercise, with resource use informed by a panel of UK clinicians. However, the ERG's clinical expert for this assessment considers that the cost data sourced from Faria et al. appear reasonable for use in the current assessment given the lack of alternative UK-specific resource use data.

Costs per Coutinho disease stage applied in the company's model are reproduced in Table 29 below, with the ERG's minor correction to the cost of progression to stage 2 noted in the table.

Table 29 Disease stage specific healthcare costs, per 4-weekly cycle (Reproduced from the RCM)

Stage	Primary Care	Aids	Homecare[A]	Symptom Treatment Costs	Subtotal: Total HRU Costs	Additional one off costs on transition to stage
Stage 1	£24.17	£0.56	£138.66	£229.94	£393.33	£0
Stage 2	£104.38	£1.63	£818.08	£382.77	£1,306.86	£1,218.88 **ERG correction: £2,029**
Stage 3	£49.43	£0.00	£953.06	£742.14	£1,744.63	£4,525.50
Death	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00

Abbreviations: ERG: Evidence Review Group; HRU: Healthcare Resource Utilization

[A] Homecare costs are based on the following: "Patients in stage 1 are assumed to require 6 hours of home care worker service per month. Patients in stage 2 are assumed to require 36 hours of home care worker service per month. Patients in stage 3 are assumed to require 36 hours of home care service per month and 1 day of special housing (in a residential or nursing care home unit for adults with physical disabilities) per month"[33]

The ERG note that productivity costs accrued by patients and carers are also reported in Faria et al by disease stage in 2010 values [Stage 1: £2,514; Stage 2: £8,238; Stage 3: £8,238]. These productivity costs have not been explicitly considered in the CS and this is in line with the NHS and PSS perspective taken.

5.2.9 Cost effectiveness results

This section outlines the results (including deterministic and probabilistic sensitivity analyses) of the company's preferred base case. In their response to the clarification letter, the company provided a revised electronic model addressing queries and correcting an error identified in the clarification letter. The following changes were made to the company's preferred base case analysis at this stage:

- The Markov cohort calculations were amended to correctly reference cycle specific treatment discontinuation probabilities. This change substantially increased the drug treatment cost of inotersen and increased the QALY gain versus BSC. The net impact was to increase the ICER for inotersen.
- In response to ERG clarification request B3, the company updated their analysis of time to inotersen discontinuation to include data available from NEURO-TTR extension study. The company also amended their preferred

survival curve from Gompertz to Exponential. These revisions reduced the proportion of the inotersen cohort remaining on treatment over time in the model, thereby reducing treatment costs and reducing the ICER.

- The compliance parameter in the model was updated from [redacted]% to [redacted]% in the company's preferred base case, to account for compliance only among those who continued on treatment in the NEURO-TTR study. This change was not requested by the ERG and effectively reduces the drug cost of inotersen. The impact of this change is a reduction in the ICER.
- In response to an ERG query relating to safety monitoring costs, the model was amended to include the cost of Phlebotomist time, slightly increasing the monitoring costs associated with inotersen. The impact of this change is a negligible increase in the ICER.
- In response to a request by the ERG to explore the impact of correlating mortality with disease stage, the company incorporated Coutinho disease stage specific mortality rates based on a Delphi consensus study. The amendment allows for a mortality benefit associated with inotersen to be modelled, and increases the associated life year and QALY gains. Conversely, as more patients survive on treatment, the change also increases inotersen costs. The net impact of this change is a modest reduction in the ICER.

The ERG also raised several queries at the clarification stage which the company addressed by conducting further scenario analyses, but did not incorporate these changes in their revised base case. These include:

- Incorporating cost and utility implications of serious adverse events in the model. This slightly increases the ICER.
- The company continue to argue in favour of a 1.5% discount rate for costs and QALYs in their base case model. Incorporating the higher rate of 3.5% increases the ICER for inotersen.

The ERG has checked the company's revised economic model and is satisfied that the changes outlined have been implemented correctly.

Table 30 shows the cumulative net impact on the cost-effectiveness results of the changes made to the company's preferred base case analysis in response to the clarification letter.

Table 30 Company preferred cost-effectiveness analyses in the original and revised company model (Reproduced from Table D19 of the CS and Table 6 of the response to the clarification letter)

Intervention	Total costs	Total QALYs	Total LYG	Δ Costs	Δ QALY	Δ LYG	ICER
Cost-effectiveness results (CS)							
BSC	[redacted]	[redacted]	6.806				
Inotersen	[redacted]	[redacted]	6.806	[redacted]	[redacted]	0.000	**£324,054**
Cost-effectiveness results (RCM)							
BSC	[redacted]	[redacted]	7.541				
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.018	**£369,470**

BSC: Best supportive care; CS: Company submission; ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALY: Quality adjusted life year; RCM: Revised company model

The company's revised base case analysis estimated that patients treated with inotersen gained an additional [redacted] compared to best supportive care, at an extra cost of [redacted] leading to an additional cost per QALY gained of £369,470.

Model traces

The Markov cohort traces for each health state (and death) obtained from the RCM are presented in Figures 9 and 10 for inotersen and BSC respectively.

[redacted]

[redacted]

Treatment effectiveness

The Markov cohort traces for the inotersen and BSC groups indicate a high rate of mortality in all patients with hATTR-PN, regardless of treatment arm, with more than [redacted]% of the cohort having died by cycle 100 (8.23 years) in the inotersen arm and cycle 84 (6.92 years) in the BSC arm of the model.

By year 5, [redacted]% of the inotersen cohort are in disease stage 3, compared to [redacted]% in the BSC group, illustrating the slower disease progression for people treated with inotersen. The proportion of the cohort in each state over the first 10 years of the cohort is provided in Table A2 of the company's response to the clarification letter, but the ERG noticed that, for inotersen, the proportion in Stage 3 = proportion dead. Having checked against the electronic model, the ERG can confirm that this is a typo, and the correct cohort trace is included in the revised company model.

The impact of these data on undiscounted LYGs and QALYs can be found in the Markov QALY trace (by stage), reproduced in Table 31 below. The greatest proportion of LYGs and QALYs are realised at the early stages of the model (within the first 5 to 10 years) and it is in the shorter term that the majority of the gains with inotersen are accrued. These data suggest that the life years are accrued across all the health states for survivors, but over [redacted]% of total QALYs in the inotersen arm and [redacted]% of total QALYs in the BSC arm are accrued in the Stage 1 (least severe) disease health state.

Table 31 Markov trace of undiscounted LYG and QALYs by modelled disease stage (Re-produced from the RCM)

	Undiscounted LYG benefit by health state								Undiscounted QALY benefit by health state							
	Inotersen				BSC				Inotersen				BSC			
Yr.	Stage 1	Stage 2	Stage 3	Death	Stage 1	Stage 2	Stage 3	Death	Stage 1	Stage 2	Stage 3	Death	Stage 1	Stage 2	Stage 3	Death
0	[redacted]															
1	[redacted]															
2	[redacted]															
3	[redacted]															
4	[redacted]															
5	[redacted]															
6	[redacted]															
7	[redacted]															
8	[redacted]															
9	[redacted]															
10	[redacted]															
15	[redacted]															
20	[redacted]															
25	[redacted]															
30	[redacted]															
40	[redacted]															
Cumulative (Yr 5)	[redacted]															
Cumulative (Yr 10)	[redacted]															
Cumulative (Yr 15)	[redacted]															
Cumulative (Yr 20)	[redacted]															
Cumulative (Yr 30)	[redacted]															
Cumulative (Yr 40)	[redacted]															

Abbreviations: BSC = Best Supportive Care; QALY = Quality Adjusted Life Years; LYG = Life Years Gained

Costs

The disaggregated component and total costs for each arm of the model are reported in Table 32. Aggregated total costs, for each disease stage by model arm are reported in Table 33.

Table 32 Summary of costs by category per patient (Reproduced from Table A6, response to the clarification letter)

Item	Cost intervention Inotersen[A]	Cost comparator BSC[A]	Increment
Technology cost	[redacted][B]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]
Vitamin A cost	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Transition costs	[redacted]	[redacted]	[redacted]
HRU costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

[A] Table assumes £0 costs associated with adverse events in the company's preferred base case analysis.

[B] CS contained a typo in the technology cost of inotersen: Value in table corrected from [redacted] to [redacted] to reflect the data in the RCM.

Table 33 Summary of costs by health state per patient (Reproduced from Table A7 of the company's response to the clarification letter)

Health state	Treatment costs	Admin costs	Vitamin A costs	Monitoring costs	HRU costs	Transition costs	All costs[A]
Inotersen – Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen – Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen – Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen - Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC – Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC – Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC – Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC - Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = Best Supportive Care; HRU = Healthcare Resource Utilisation.

[A] Table assumes £0 costs associated with adverse events in the company's preferred base case analysis.

Overall, inotersen generated an incremental cost of [redacted] versus BSC over the duration of the model. The cost difference is driven primarily by inotersen drug acquisition costs, accounting for [redacted]% of total costs in the inotersen arm. By contrast, in the BSC arm of the model, the majority of total costs ([redacted]%) relate to healthcare resource utilisation.

For inotersen, the greatest proportion of costs ([redacted]%) are incurred in disease stage 1, reflecting the comparably larger proportion of patients in the NEURO-TTR study in stage 1 disease still receiving the drug and thereby incurring the inotersen drug cost. Furthermore, as drug costs are only assumed to be incurred in Stages 1 and 2 disease, it is in these stages that the greatest proportion of total modelled costs occur for the inotersen arm of the model.

By contrast, only [redacted]% of BSC costs are incurred in disease stage 1, with [redacted] and [redacted] of the total cost incurred in disease stages 2 and 3 respectively. The low proportion of total costs incurred in disease stage 1 is due to the lack of active treatments and low

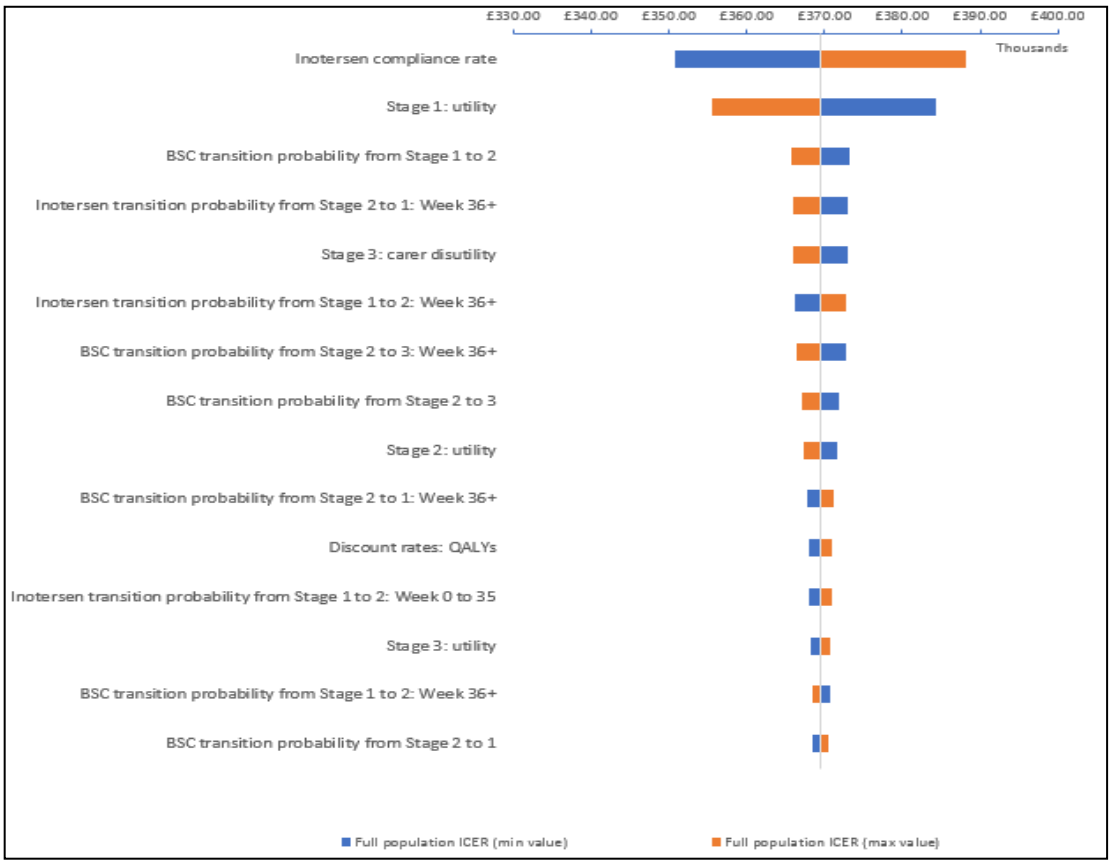
healthcare resource utilisation costs in the BSC arm. The greatest proportion of BSC costs are incurred in Stage 3, reflecting the higher progression rate and higher health state costs incurred with progressively more debilitating disease.

Deterministic Sensitivity Analyses (DSAs)

This section reports DSA and scenario analyses conducted by the company in response to the clarification letter. Further exploratory analyses conducted by the ERG are described in Section 5.3.2.

The company's sensitivity analyses were mainly uni-variate, exploring the impact on the ICER of ±5% changes single parameter values, one at a time. The parameters included in the DSA are reported in tables D9 and D10 of the original CS. The results of DSAs for the 15 most sensitive model parameters in the company's revised base case analysis (in response to clarification letter) are reported in Figure 11.

Figure 11 Company reported one-way deterministic sensitivity analyses (Re-produced from Figure A5 of the company's response to the clarification letter)



The ERG has checked each deterministic sensitivity and scenario analysis conducted in the CS and in response to the clarification letter, and are satisfied that the company's chosen DSAs have been implemented in the model as described in the CS.

However, the ERG notes that, in general, the DSAs provided by the company have minimal impact on the ICER, and none of the analyses reduce the ICER below £350,000 per QALY gained. The company also provided 12 different multi-way sensitivity analyses using ± 5% variation in transition probabilities, carer utility and patient utility (See Table A9 of the company response to the clarification letter). It is inevitable that substantial uncertainty exists surrounding transition probabilities, cost and utility parameters informed by relatively small sample sizes. The ERG believe that the company's sensitivity and scenario analyses do not adequately characterise the degree of uncertainty in the ICER. It would have been more informative to consider a wider range of single and multi-parameter sensitivity analyses to explore the impact of varying important model parameters across their estimated confidence limits (rather than ± 5% of the mean values).

Table 34 below provides details regarding 11 further scenario analyses provided by the company in their response to the clarification letter. The analyses show that the ICER for inotersen is particularly sensitive to assumptions surrounding: A) treatment discontinuation rates; B) treatment compliance; C) discount rates; and D) patient utilities applied in the model, particularly for stage 1 disease; and E) the number of assumed carers who incur disutility. The ICER is less sensitive to the inclusion or exclusion of AEs from the model.

Table 34 Scenario analyses provided in the RCM in response to the clarification letter

Intervention	Total costs	Total QALYs	Total LYG	Δ costs	Δ QALY	Δ LYG	ICER	% Change in ICER vs. base case
1. Cost-effectiveness results (RCM)[A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.018	**£369,470**	**0%**
2. 3.5% discount rate for costs and QALYs[A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.01	£389,105	+5.31%
3. Exclusion of monitoring costs (to be borne by the company)[A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.018	£369,131	-0.09%
4. Treatment discontinuation curve - Weibull [A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.660	[redacted]	[redacted]	1.120	£379,151	+2.62%
5. Treatment discontinuation curve - Gompertz [A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.993	[redacted]	[redacted]	1.453	£408,802	+10.65%
6. Treatment discontinuation curve - Log-Logistic [A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£393,684	+6.55%
7. Treatment discontinuation curve - Log-Normal [A]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.914	[redacted]	[redacted]	1.373	£400,199	+8.32%
8. Treatment discontinuation curve – Generalised Gamma [B]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.722	[redacted]	[redacted]	1.182	£384,826	+4.16%
9. Including cost and QALY implications of Adverse events (company version)[C]								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.018	£370,731	+0.34%
10. Assume one carer								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.018	£402,828	+9.03%
11. Assume three carers								
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.559	[redacted]	[redacted]	1.018	£341,214	-7.65%

[A] Analysis contained in company response to the clarification letter

[B] The ERG believes the results of this scenario were incorrectly reported, based on incorrect parameterisation of the company model for the generalised gamma distribution. Results reported in the table above incorporate a correction applied by the ERG.

[C] Note that the ERG consider the incorporation of adverse events to be inappropriate and have conducted a revised exploratory analysis in Section 5.3.2

Abbreviations: BSC: Best supportive care; ERG: Evidence review group; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: Quality adjusted life years

Probabilistic Sensitivity Analyses (PSA)

The company submission provides little information regarding how the PSA was conducted, why certain distributions were chosen, or how distribution parameters were obtained for sampling. The following is the ERGs understanding of the PSA based on reviewing the company's Excel model.

The company's PSA is based on 10,000 Monte Carlo simulations for the included model parameters. The ERG attempted to re-run the company's PSA results but were unable to do so due to an error that incorrectly assigned positive, rather than negative utility to carers of patients with stage 3 disease. The ERG have corrected the error and re-ran the PSA on the company's preferred base case analysis using the Excel model provided in response to the clarification letter. Table 35 compares the company's preferred base case deterministic and probabilistic analyses and the ERGs replicated PSA. Figure 12 reports the corresponding cost-effectiveness plane for the ERG corrected PSA.

Table 35 PSA results for company's preferred base case analysis (with ERG correction for sampling of carer disutility in Stage 3 patients)

	Base case (deterministic)	**Base case PSA[A]**	**ERG corrected base case PSA[B]**
Incremental cost	[redacted]	[redacted]	[redacted]
Incremental LYG	1.018	Simulation results not provided	Simulation results not provided
Incremental QALY	[redacted]	[redacted]	[redacted]
ICER	£369,470	£368,592	£392,667

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALY, quality adjusted life year; RCM: Revised Company Model

[A] As reported in the company's response to the clarification letter.

[B] ERG attempt to replicate company's PSA, with correction of error for sampling of carer disutility.

Figure 12 Cost-effectiveness plane (ERG replicated PSA, using company's preferred base case from the RCM)

The company have provided no justification for their chosen distributions in the PSA. However, the ERG note that the chosen types of distribution applied to model parameters appear appropriate (Costs: gamma, Utilities: beta, Transition probabilities: beta) and in line with standard practice.

The ERG have reviewed the company's submitted PSA and conclude that it does not adequately characterise the joint uncertainty in incremental costs and effects. The ERG have three main concerns regarding the company's reporting of uncertainty and the results of the submitted PSA:

1. Determining the probability of cost-effectiveness

The company have not illustrated the probability that inotersen is cost-effective at different possible thresholds of WTP for a QALY gained. This information may be helpful to the committee when making their judgment of cost-effectiveness. For the company's submitted PSA, with ERG correction of the stage 3 carer disutility parameter, the probability that inotersen is cost effectiveness at increasing thresholds of WTP per QALY gained is as follows: £200k ( ), £300k ( ), £400k ( ), £500k ( ).

2. Under-estimation of uncertainty surrounding key model parameters

Uncertainty surrounding model parameters is likely to have been substantially underestimated and this is reflected in the lack of variability in the cloud of simulations on the cost-effectiveness plane. The PSA assumes that for all parameters the SD of sampling distribution is 5% of the mean value. This decision has not been justified anywhere in the company's submission and the ERG notes that SDs of the sampling distribution could have been calculated for at least some of the model parameters (e.g. utility data sourced from Stewart et al).

The ERG note that the company would have been able to incorporate better estimates of variability around transition probabilities using the method of the moments to calculate alpha and beta parameters to sample from a beta distribution, where alpha = count of events and beta = total N – count of events.

The ERG have attempted to source standard error inputs (where possible) that could be used in the model to represent sampling variation. The ERG re-ran the PSA using estimated standard errors for patient utility inputs (Stewart et al) and calculated standard errors for reference costs (using upper and lower quartile data available from the reference costs source). Where it has not been possible to obtain such data (e.g. Faria et al healthcare utilisation costs), the ERG assume that the SD of the sampling distribution is the same fraction of the mean applied to other similarly categorized parameters. For example, the ERG assume that the SD of the sampling distribution around costs is equal to 0.406 (average of the SE divided by the mean for other cost parameters). Similarly, for stage specific carer disutility, the standard error is assumed to be the same fraction of the mean as for stage specific patient utility. The ERG note that this approach is based on an unverifiable assumption. However, in the absence of more robust data, it provides a better characterisation of uncertainty in the model.

3. Exclusion of relevant (uncertain) parameters from the PSA

The ERG are further concerned that the company's PSA does not incorporate all the important parameters that drive cost-effectiveness results. Specifically, the ERG are concerned that the company's PSA excludes variation in time to treatment discontinuation estimated using parametric survival analysis of the NEURO-TTR and NEURO-TTR (extension) discontinuation Kaplan Maier data. The ERG believe that

this is an important source of uncertainty in the company's model that should ideally be included in the PSA.

5.2.10 Budget impact

The CS includes a budget impact analysis (BIA) over a 5 year time horizon. The BIA assumes that the eligible population will grow from N= patients (Year 1) to N= (Year 5). The BIA estimates that the net impact of introducing inotersen on the NHS will be in year 1 increasing to in year 5.

Details of the BIA results are provided in Table 36 below.

Table 36 Estimated budget impact (re-produced from Table D27 of the CS)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population					
Inotersen market share (estimate)					
Population receiving inotersen (estimate)					
Annual budget (inotersen not introduced)					
Annual budget (inotersen introduced)					
Net budget impact					

The ERG note that the original CS contained no further details about the methods or assumptions informing all calculations used to inform the budget impact analysis. The ERG asked for full details regarding the BIA calculations at clarification stage, at which point the company provided the following information:

- The company stated that their BIA was informed by the same "engine" that under-pins the cost-effectiveness modelling. However, the ERG note that the approach to estimating inotersen costs is not fully consistent with the cost-effectiveness model. Instead of using survival analysis to estimate the time to discontinuation (as in the cost-effectiveness model), the company use a fixed annual rate of treatment discontinuation in their BIA [redacted], based on a linear extrapolation of discontinuation from the NEURO-TTR study.
- The eligible population for inotersen treatment is based on prevalence and incidence in England, as reported by Pinney et al,[53] and further stratified by disease stage. The BIA assumes that the distribution by stage is: Stage 1: [redacted], stage 2: [redacted], stage 3: [redacted]). Stage 3 are excluded because it is assumed patients with stage 3 disease are excluded as inotersen is not licensed for the treatment of stage 3 disease. This approach and methodology appear reasonable. However, the company have provided insufficient information to re-produce the eligible population numbers used for the BIA from Pinney et al.
- The assumed market share for inotersen for is stated to be [redacted] from years 1 through 5, based on internal company sales projections. No further details have been provided. The ERG note that the market shares appear low for the eligible population, particularly given that there are currently no other approved and funded treatment alternatives available.
- The BIA accounts for mortality. Mortality is also incorporated as a static annual risk parameter (0.55%), taken from the THAOS study.[54] Again, the ERG note that the approach departs from that used in the cost-effectiveness modelling.

The ERG have been unable to re-produce, critique, or verify the validity of the company's BIA assumptions due to a lack of information provided. The ERG find that the calculations under-pinning the reported BIA results lack transparency, because the analysis is not incorporated directly within the company's electronic model.

5.2.11 Model validation and face validity check

Section 12.6.6 of the CS states that two health economists checked each input and formula and that the model was validated by an external modelling agency. The company have included a number of summation formulae in the Markov cohort traces to help identify any issues of face validity and report that they conducted extreme value testing.

In addition to the validation exercises undertaken by the company, the ERG have checked input parameters and calculations, and conducted a number of additional tests on the company's model to identify any errors. These tests were conducted following the check-list developed by Tappenden and Chilcott.[55] The outcomes of this exercise are presented in Table 37. The company model predicted results that were in line with the check-list verification criteria. The ERG has also checked the model for accuracy by comparing data included in the report with the corresponding data entered in the economic model. All checks were applied to the company's revised economic model submitted in response to the clarification letter.

Table 37 ERG conducted 'black-box' verification tests applied to the company submitted model

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model time point (state transition models)	Total probability equals 1.0	None
	Sum expected probability of terminal nodes (decision-tree models)	Total probability equals 1.0	Not applicable
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	Minor issue: Discounting is only applied to streams of QALYs and not LYG. Therefore the QALY discount rate must be set to 0% to pass this quality check. This issue does not impact on the model results, as the assessment does not focus on LYG.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None

Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range [0-1] etc.)	None, though the ERG notes this is highly unlikely given the assumed SD of the sampling distribution for parameters included in the PSA is equal to mean parameter value x 5%.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	Minor issue: Setting drug acquisition, monitoring and admin costs of BSC = Inotersen generates drug treatment costs (see cost-effectiveness model tab) significantly greater than the inotersen arm. This is because drug costs in the BSC arm are not multiplied by discontinuation rates. There are no implications for cost-effectiveness as BSC costs are set to £0 in the model and are not varied by the company or the ERG.
	Amend value of each individual model parameter*	ICER is changed	Minor issues: A) Inputting transition probabilities to allow the cohort transit from stage 3 to 1 and 2 disease impact on the ICER when entered for BSC but not for inotersen. As these transitions are set to 0 in the model, and not varied by the company or ERG, there are no implications for the ICER. B) Increasing the rate of Myelopathy adverse events in either the BSC or inotersen arms has no impact on the ICER. This is because the company assumed the value was =0 given that no data were available on costs and QALYs. There is no impact on the company's preferred base case but the ERG have corrected this to enable scenario analyses.
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	None (except those already identified above)
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

The ERG do not have any major concerns at this stage. One minor issue was identified. The company submission (Tables D4 to D7 and Table D9) suggests that no transitions from stage 3 to less severe disease stage are possible, and this is the case in the economic model. However, the raw data from the NEURO-TTR study included in the economic model show that a small number of participants did transition out of the inferred stage 3 state. This likely reflects the fact that the Coutinho state classification applied to the NUERO-TTR cohort was based on an imperfect relationship between the Norfolk QoL-DN total score (TQoL) and Coutinho states rather than an objective clinical assessment. The ERG accept that it is implausible to allow transitions out of Countiho stage 3.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

This section details the additional work completed by the ERG, and the associated impact on the ICER. For all cases the ERG have considered their revisions according to the revised, corrected version of the economic model submitted by the company in response to the clarification letter (dated: September 20th, 2018). The impact on the ICER of correcting two minor technical and data entry errors, as well as consideration of plausible alternative assumptions regarding parameter inputs and structural assumptions is described. The section concludes with a discussion of the ERG's preferred base case ICER and a revised PSA that addresses some of the concerns already raised.

5.3.1 Correction of ERG identified minor data entry and technical errors

In addition to the errors addressed by the company in response to the clarification letter, the ERG have identified two further (minor) errors and discrepancies in the model. First, the model includes a data entry error in relation to the onetime costs applied from Fria et al for transition to stage 2 disease in the model. As noted in Section 5.2.8, the correct cost is £1,803 rather than the £1,083 applied in the model. Second, as noted previously, the company's revised model contained an error in the 'PSA variables' spreadsheet, where the disutility for a stage 3 carer was incorrectly incorporated as a positive utility. This prohibited the ERG from replicating the company's reported probabilistic results, which did not appear to have been run using the saved version of the model supplied to the ERG. Table 38 compares the company

base case deterministic ICER with the ERG corrected company base case ICER. The ERG note that the difference is negligible.

Table 38 Errors identified in the company submission and ERG corrections applied

Model parameter	Model reference	Error identified	Correction applied by ERG	Revised deterministic ICER	Change in ICER
Company preferred base case ICER				£369,470	N/A
Uninflated one off costs on progression to stage 2 disease	Tab: 'Data Store' Cell: Q14	Data entry error. Costs reported from Faria = £1,803 (entered in model as £1,083)	Data entry error corrected	£369,569	+0.03%
PSA: carer disutility at stage 3	Tab: 'PSA variables' Cells: F24, J24 & K24	Formula error: incorrectly simulated as positive rather than negative	Formulae corrected.	N/A	N/A

Abbreviations: ERG: Evidence review group; ICER: incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis

5.3.2 ERG exploratory scenario analyses

The ERG have conducted further exploratory analyses around important model parameters and aim to identify assumptions to which the ICER is most sensitive. We focus on questionable assumptions, where a judgement is required. In particular, a multi-variate sensitivity analyses are conducted to more fully explore uncertainty in the ICER. Exploratory analyses are applied to the company's preferred base case analysis with correction of the typo noted in Table 38 above. Multi-way scenario analyses are also conducted that combine plausible sets of scenarios using both the company's scenarios provided in response to the clarification letter (Table 34) and the ERGs exploratory analyses from this section. Table 39 outlines the analyses carried out together with a justification for each and Table 40 presents the results.

Table 39 Additional scenario analyses, including justifications, performed by the ERG

	Parameter / Analysis	Base case Assumption	Scenario explored	Justification	Table / section reference in ERG report
BC1	Company preferred base case analysis with correction of minor data entry error. ***(All ERG exploratory analyses are conducted using BC1)***				Table 35
Methodological choices					
1	Time horizon	Life time horizon	10 years	Alternative exploratory time horizon to minimise the uncertainties with the longer term extrapolation curves	Section 5.2.5
2	Time horizon	60 years	20 years	Alternative exploratory time horizon	Section 5.2.5
3	Discounting of costs and QALYs	1.5%	0%	To reflect lower range of NICE reference case	Section 5.2.5
4	Discounting of costs and QALYs	1.5%	3.5%	To reflect NICE reference case	Section 5.2.5
5	Discounting of costs and QALYs	1.5%	6%	To reflect upper range of NICE reference case	Section 5.2.5
Costs					
6	Inotersen treatment discontinuation curves	Exponential survival curve	Log logistic (as per company scenario analysis)	Scenario analysis reported in RCM (response to clarification letter). Log logistic curve assumes a reducing rate of discontinuation to reflect the hypothesis that the longer an individual remains on treatment in stage 1 or 2, the less likely they may be to stop treatment. In contrast the exponential curve equates to a constant rate of discontinuation.	Section 5.2.8 (Figure 8)

	Parameter / Analysis	Base case Assumption	Scenario explored	Justification	Table / section reference in ERG report
7	Treatment compliance	[redacted] (treatment continuers only)	[redacted] (treatment continuers and discontinuers)	This explores the impact of multiplying drug costs by the compliance rate for all patients in NEURO-TTR study, not just treatment continuers.	Section 5.2.8
8	Treatment compliance	[redacted] (treatment continuers only)	[redacted] (treatment continuers and discontinuers)	A more pessimistic scenario analysis, assuming that prescribing is not adjusted the patient's compliance, so costs are in line with the recommended dose rather than consumed dose.	Section 5.2.8
9	Combined scenarios 6 & 7	See above	See above	Explores the joint impact of the alternative treatment discontinuation and compliance assumptions described in 6 and 7 above.	Section 5.2.8
10	Combined scenarios 4,6&7	See above	See above	As per scenario 9, with addition of the 3.5% discount rate to reflect NICE's reference case.	Section 5.2.5 & 5.2.8
Utilities					
11	Disease stage utilities	Company preferred utility	Faria et al (linear function)	Alternative utility data as published in Faria et al.	Section 5.2.7 (Table 24)
12	Disease stage utilities	Company preferred utility	Faria et al (quadratic function)	Alternative utility data as published in Faria et al.	Section 5.2.7 (Table 24)
13	Disease stage utilities	Company preferred utility	Faria et al (cubic function)	Alternative utility data as published in Faria et al.	Section 5.2.7 (Table 24)
14	Disease stage utilities	Company preferred utility	Faria et al (linear function, by stage)	Alternative utility data as published in Faria et al.	Section 5.2.7 (Table 24)
15	Number of carers	2	1	Replication of company's scenario analysis provided in Table 34 above.	Section 5.2.7

	Parameter / Analysis	Base case Assumption	Scenario explored	Justification	Table / section reference in ERG report
16	Number of carers	2	3	Replication of company's scenario analysis provided in Table 34 above	Section 5.2.7
17	Combined scenarios 4+11+15	See above	See above	Less favourable patient utility data for inotersen, assuming one carer and discounted by 3.5% in line with NICEs reference case	Section 5.2.7
Adverse events					
18	Adverse event costs and disutility	Excluded	Company's incorporation of AE costs and disutility	RCM assumes that there was no disutility associated with glomerulonephritis, tubulointersitial nephritis or myelopathy & no costs associated with myelopathy	Section 5.2.7 (Table 26) & Section 5.2.8 (Table 28)
19	Adverse event costs and disutility	Excluded	ERGs amended costs and disutility of AEs	ERG assumptions regarding possible duration, cost and utility values associated with the AEs missing from the company's analysis (the ERG note that, due to time constraints, these are assumptions only, or are based on rapid and incomplete literature searches). More appropriate data may exist.	Section 5.2.7 (Table 26) & Section 5.2.8 (Table 28)
Mortality					
20	Disease specific mortality hazard ratio	Obtained from Delphi consensus study	Increase all hazard ratios by 50%	Exploratory analysis to determine the sensitivity of the model to disease specific mortality estimates (pessimistic scenario for inotersen)	Section 5.2.6
21	Disease specific mortality hazard ratio	Obtained from Delphi consensus study	Reduce all hazard ratios by 50%	Exploratory analysis to determine the sensitivity of the model to disease specific mortality estimates (optimistic scenario for inotersen)	Section 5.2.6

	Parameter / Analysis	Base case Assumption	Scenario explored	Justification	Table / section reference in ERG report
22	Incorporation of mortality	Disease stage specific mortality hazards, obtained from Delphi consensus study	Use assumptions from company's original submission (not Coutinho stage specific)	Exploratory analysis (pessimistic for intoersen) that uses the company's original approach, assuming there is no mortality benefit associated with inotersen.	Section 5.2.6
Plausible combinations of analyses					
23	ERG preferred analysis (with Faria et al utility)	As per BC1	Combination of scenario 4+6+7+11+15+19	The ERGs preferred base case is a combination of scenarios 4 (3.5% discounting), 6 (Log logistic treatment discontinuation curve), 7 (compliance among all patients in NEURO-TTR), 11 (Faria et al, linear calculation of utility), 15 (N=1 carer) and 19 (ERG amended costs and disutility of serious adverse events)	As above & Section 5.3.2
24	ERG preferred analysis (with company's preferred utility)	As per BC1	Combination of scenario 4+6+7+15+19	As per 23 above (but using the company's preferred source of utility)	As above & Section 5.3.2
24	Pessimistic for inotersen		combination of a gompertz treatment discontinuation	Worst case scenario for inotersen: a combination of a gompertz treatment discontinuation curve with scenarios 5 (6% discounting), 8 (Compliance =100%, full drug wastage), 11 (Faria et al, linear calculation of utility), 15	As above & Section 5.3.2

	Parameter / Analysis	Base case Assumption	Scenario explored	Justification	Table / section reference in ERG report
			curve with scenarios 5, 8,11,15, 19 and 20	(N=1 carer), 19 (ERG amended costs and disutility of serious adverse events) and 20 (increase stage specific mortality HR by 50%)	
25	Optimistic for inotersen		combination of scenarios 3, 16 and 21	Best case scenario for inotersen, a combination of scenarios 3 (0% discounting), 16 (N=3 carers) and 21 (reduced stage specific mortality hazards)	As above & Section 5.3.2

Key: AE: adverse events; BC: base case; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Table 40 Impact of alternative scenario analyses on cost-effectiveness results

		Inotersen		BSC					
Analysis	**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
Company submitted model (response to clarification)									
BC1	Company preferred analysis, with ERG correction of data entry error	£621,906	2.951	£116,546	1.583	£505,360	1.367	£369,569	0%
ERG explored analyses (All applied to BC1)									
Methodological choices									
1	Time horizon (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£407,917	10.38%
2	Time horizon (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£370,242	0.18%
3	Discount 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£354,802	-4.00%
4	Discount 3.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£389,189	5.31%
5	Discount 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£413,548	11.90%

		Inotersen		BSC					
Analysis	**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
Costs:									
6	Log logistic discontinuation curve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£393,769	6.55%
7	[redacted] compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£390,375	5.63%
8	[redacted] compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£411,349	11.30%
9	Combined scenarios 6 & 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£415,912	12.54%
10	Combined scenarios 4,6 & 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£434,408	17.54%
Utilities									
11	Faria et al (A)- linear function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£503,024	36.11%
12	Faria et al (B)- quadratic function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£475,799	28.74%
13	Faria et al (C) – cubic function	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£473,232	28.05%
14	Faria et al (D) – linear by stage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£377,717	2.20%
15	One carer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£402,936	9.03%
16	Three carers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£341,306	-7.65%
27	Combined scenarios 4+11+15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£610,509	65.19%
Adverse events									
18	Company's incorporation of AE costs and disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£370,831	0.34%
19	ERGs attempt to incorporate AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£371,581	0.54%
Mortality									

		Inotersen		BSC					
Analysis	**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
20	All stage specific HR + 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£407,297	10.21%
21	All stage specific HR - 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£322,847	-12.64%
22	Assume no correlation between mortality and stage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£400,533	8.38%
Combined analyses									
23	ERG preferred (with Faria utility) [A]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£683,178	84.86%
24	ERG preferred (with CS utility) [B]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£478,079	29.36%
25	Best case inotersen [C]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£282,232	-23.63%
26	Worst case inotersen [D]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£834,082	125.69%

[A] The ERGs preferred base case is a combination of scenarios 4 (3.5% discounting), 6 (Log logistic treatment discontinuation curve), 7 (compliance among all patients in NEURO-TTR), 11 (Faria et al, linear calculation of utility), 15 (N=1 carer) and 19 (ERG amended costs and disutility of serious adverse events)

[B] As per A above, but using the company preferred utility source. Analyses 23 and 24 illustrate the sensitivity of the ERGs preferred analysis to the choice of patient utility source.

[C] Best case scenario, optimistic estimate of the ICER is a combination of scenarios 3 (0% discounting), 16 (N=3 carers) and 21 (reduced stage specific mortality hazard ratios)

[D] Worst case scenario, pessimistic estimate of the ICER is a combination of a gompertz treatment discontinuation curve with scenarios 5 (6% discounting), 8 (Compliance =100%, full drug wastage), 11 (Faria et al, linear calculation of utility), 15 (N=1 carer), 19 (ERG amended costs and disutility of serious adverse events) and 20 (increase stage specific mortality hazard ratios by 50%)

Abbreviations: AE: Adverse Events; BSC: Best Supportive Care; BC1: Base case with data entry error corrected; ERG: Evidence Review Group; QALY: Quality Adjusted Life Year.

[redacted]

The ERG found that the ICER was most sensitive to the discount rate applied to costs and QALYs, the impact of different assumptions around treatment discontinuation and compliance (and combinations of these), the choice of source for patient utilities, and the number of assumed carers. The ERG note that the ICER was not sensitive to different assumptions regarding adverse events. This is most likely because the costs of treating events are small in comparison to the overall acquisition costs of inotersen treatment and disease stage resource use costs. Likewise, the utility decrements for adverse events applied over a short duration made little difference to QALYs relative to the utility implications of progressive disease.

Table 40 indicates that whilst some parameters in isolation may not have a large impact on the ICER, combinations of different assumptions can have a significant impact on projected costs and effects in the model. In relation to costs, the ERG considers that a plausible estimate of the ICER is obtained by assuming a log-logistic curve for projection of time to discontinuation of inotersen treatment in combination with the compliance rate applicable to the whole NEURO-TTR cohort. When combined with a 3.5% discount rate (in line with NICEs reference case), the ICER for this scenario increases by 17.54% to £434,408 per QALY gained.

With regards to utility data, the ERG consider it inappropriate that the company use Brazilian valuations, particularly when it could have been possible to obtain EQ-5D directly from the THAOS registry and apply the UK general population value set to obtain more relevant disease stage specific utility estimates. The ERG considers that a plausible combination of scenarios with regards utilities might include: a) patient utility (sourced from the company preferred approach in the tafamidis assessment); b) the assumption that adult hATTR-PN patients might require one full time informal carer; and c) discounting at 3.5% per annum (in line with the NICE reference case). This analysis increases the ICER by over 65%, to £610,509 per QALY gained.

Combining these pessimistic, but plausible scenarios for costs and utilities, including adverse event data and assuming a 50% increase in the hazard ratio of mortality by disease stage (compared to the general population) increases the ICER, in a worst case scenario for inotersen to £834,082 per QALY gained. Applying more optimistic values for important model parameters reduces the ICER to £282,232 per QALY. The ERG notes that it is

difficult to determine the most appropriate ICER with certainty as arguments can be made for a range of different plausible parameter input values and assumptions. However, what is clear is that there is significant uncertainty in the ICER that was not captured in the CS or RCM, and only when the most optimistic combination of parameter input values is applied does the deterministic ICER fall below £300,000 per QALY gained.

5.3.3 Discussion of the ERG's preferred base case analysis

The ERG's preferred base case is informed by the range of alternative analyses presented in the company's submission, company response to the clarification letter and additional ERG exploratory analyses undertaken.

The ERG prefers the use of a discount rate of 3.5% for costs and QALYs, as the estimated QALY gains from the model do not appear to justify the use of a 1.5% discount rate in light of NICEs interim methods guide for HSTs. The ERG also prefers scenarios that include the cost and utility implications of serious AEs (though their impact on the ICER is small). Given the uncertainties and limitations surrounding both the company preferred utilities and the alternative source reported in Faria et al., the ERG present their preferred base case analysis using both sources. With regards to costs, the ERG prefers a log-logistic discontinuation curve because it allows for continued discontinuation of treatment over time, but at a reducing rate as patients who tolerate the drug well and remain in pre-progressed states may be less likely to stop treatment. The ERG also prefers the adjustment of drug acquisition costs by compliance derived from all patients in the NEURO-TTR study, not just those who continue for the study duration. This is primarily because the lower rate will underestimate the drug costs during the observed phase of the model, when the majority of patients are on treatment.

The deterministic ICER for the ERG preferred analysis ranges from £478,079 to £683,178 depending on which source of utility data is applied (scenarios 23 and 24, Table 40). These two analyses illustrate the sensitivity of the ERGs preferred base case ICER to the source of patient utility data used in the model. Table 41 below presents ERGs PSA results for three analyses: A) The company's preferred base case, B) The ERGs preferred base case (using Faria et al utilities) and C) The ERGs preferred base case (using the CS utilities). It should be noted that the PSA results outlined below incorporate amendments to address each of the ERGs critiques of the PSA discussed in Section 5.2.9 above.

Table 41 Probabilistic results for ERGs preferred base case analysis

Analysis	Incremental Costs	Incremental QALYs	ICER (probabilistic)	P (C/E) @ £200k	P (C/E) @ £300k	P (C/E) @ £400k	P (C/E) @ £500k
Company's preferred base case	[redacted]	[redacted]	£405,755	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base case (with Faria et al patient utility)	[redacted]	[redacted]	£730,337	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred base case (with company's preferred patient utility)	[redacted]	[redacted]	506,353	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: Incremental Cost-Effectiveness Ratio; P (C/E) = probability of cost-effectiveness at different threshold values of willingness to pay for a QALY gained; QALY: Quality Adjusted Life Year

Figure 13 illustrates the ERGs amended PSA for the company's preferred base case model specification. The figure illustrates greater uncertainty in the ICER compared to the company's submitted PSA (see figure 12 for comparison).

Figure 13: Cost-effectiveness plane (ERG preferred specification of parameter uncertainty using the company's preferred base case)

[redacted]

5.4 Conclusions of the cost effectiveness section

The original company base case ICER for inotersen compared with BSC was £324,054 per QALY gained.

In response to the clarification letter, the company revised their preferred base case analysis to one that incorporated A) correction of an error in modelling treatment discontinuation, B) updating survival curves with additional Kaplan Meier data sourced from the NEURO-TTR (extension) study, C) Correlating mortality with disease stage, using hazard ratios obtained from a Delphi consensus study, D) amending the compliance parameter to remove compliance of treatment discontinuers (analysis not requested by ERG), E) Increasing monitoring costs to incorporate phlebotomist time. The net impact of these changes was to increase the ICER to £369,470 per QALY gained. The amendments also increased the ICERs for all deterministic sensitivity analyses and exploratory analyses.

Based on the company's scenario analyses and exploratory ERG analyses, the cost-effectiveness results were most sensitive to A) changes in the discount rate, B) the utility values assigned to stage 1 disease (as it is in stage 1 where most of the QALY gains for inotersen are accrued), C) the number of carers that experience carer disutility, and D) assumptions about treatment discontinuation and compliance that impact upon the overall acquisition cost of inotersen. It should also be noted that the company make a case for using 1.5% discounting throughout. The ERG disagree that this is appropriate and believe the CS does not meet NICE's criteria for considering 1.5% discounting.

When the ERG conducted an analysis combining a 3.5% discount rate (NICE reference case) with alternative assumptions regarding treatment discontinuation (i.e. a log logistic parametric survival curve with compliance for all participants in the NEURO-TTR study) and utilities (patient utilities sourced from Faria et al. and one carer assumed), with revised adverse event assumptions, the ICER increased by over 80% to £683,178 per QALY gained. However, the ICER for this scenario dropped to £478,079 when the utilities based on Stewart et al were used.

The following are the main findings from the ERG's further exploratory analyses:

- Varying the discount rate for costs and QALYs had a modest impact on the ICER, ranging from £354,802 (0% discount rate) to £413,548 (6% discount rate).

- Using a log-logistic rather than a parametric survival curve to model treatment discontinuation increased the ICER by 6.55%. However, when combined with an alternative compliance assumption (based on all patients in the NEURO-TTR study), and a discount rate of 3.5%, the ICER increased by 17.54% to £434,408 per QALY gained.
- The ICER is particularly sensitive to the source of disease stage utility data. Applying disease stage specific utilities from the previous AGNSS assessment of tafamidis for Transthyretin Familial Polyneuropathy, as an alternative to the Brazilian values used by the company, increased the ICER to £503,024 per QALY gained.
- Assumptions around the number of carers for patients with hATTR-PN has a modest impact on the ICER, ranging from £341,306 (three carers) to £402,936 (one carer).
- Combining an alternative set of utility assumptions (one carer, and patient disease stage utilities from Faria et al), with a 3.5% discount rate increased the ICER by over 65% to £610,509 per QALY gained.
- Overall, the ERG found that the ICER varied widely, depending on the assumptions applied, between £282,232 (optimistic case for inotersen) and £834,082 (most pessimistic case for inotersen).

6 Overall conclusions

6.1 Clinical effectiveness evidence

The company's submission considered inotersen within its licensed indication for people with hereditary transthyretin amyloidosis with polyneuropathy.
The NICE final scope included two outcomes not reported in the company's submission (postural hypotension and effects of amyloid deposits in other organs and tissues) one of which was considered important by the ERG's clinical expert (postural hypotension). One trial comparing inotersen with placebo was included in the company's clinical effectiveness evidence; NEURO-TTR was a phase 3, double-blind, placebo-controlled, multi-centre RCT, which was funded by the company. In addition, the company reported an ongoing, post-trial, phase 3 open-label extension study in the same population (NEURO-TTR Extension).

During the 15 months treatment period of NEURO-TTR, inotersen treated patients achieved a greater improvement in neurological progression. Deterioration over time was still evident but was significantly less than those on placebo. A significant difference between the inotersen and placebo groups was observed for the Norfolk QoL-DN score, albeit there was very little change for baseline for the inotersen group. Progression of disease at week 66 was slowed or stopped in around one-third of inotersen patients compared to around one-fifth of those in the placebo group.

Interim results showed that improvement in neurological disease progression and QoL were maintained with inotersen treatment in the NEURO-TTR extension study. [redacted] However, this slowing was not as pronounced for the placebo-inotersen group as it had been for those receiving inotersen in the NEURO-TTR study.

In both studies, the majority of participants experienced at least one treatment-emergent adverse event, most of which were mild to moderate in severity. There were five deaths in the inotersen group in the NEURO-TTR study (one considered treatment-related) and none in the placebo group.

The ERG noted discrepancies in some areas of the evidence reported by the company but concluded that inotersen was shown to be effective in the studied population.

6.2 Cost-effectiveness evidence

The company's main economic case considered the cost-effectiveness of inotersen compared with best supportive care (BSC) for adults with hATTR-PN. The company submitted a Markov cohort state transition economic model to estimate expected costs and QALYs accrued over a life-time horizon from an NHS and PSS perspective. States representing the three Coutinho stages of disease progression and death were included in the model. The cohort were allowed to transition between stages 1 and 2, but progression to stage 3 was assumed irreversible. The model was populated with transition probabilities from the NEURO-TTR study (for both inotersen and BSC), and it was assumed that long-run transition probabilities follow the same pattern as those observed between weeks 35 and 66 in the study.

The company model is built around data observed in the well conducted, high quality NEURO-TTR randomised controlled trial. However, the long term extrapolation and some important input parameters required a number of questionable assumptions. These assumptions add substantial uncertainty to cost-effectiveness results, and the ICERs are particularly sensitive to assumptions surrounding utility input data, the extrapolation of treatment discontinuation, treatment compliance, and the discount rate applied to future costs and QALYs. A judgement is required regarding the most plausible model values and assumptions.

6.3 Implications for research

Further work is required to make better use of the THAOS registry data, which is a valuable resource that could be used to generate better utility data for use in the model. Additionally, further work is required to robustly determine the healthcare resource utilisation, by Coutinho disease stage, from a UK NHS perspective, as the current analysis relies on Swedish expert opinion, generated over six years ago.

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