NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin-related amyloidosis [ID1242]

Evaluation Report

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

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

NICE National Institute for Health and Care Excellence

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Pre-meeting briefing

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

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

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

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

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

[redacted]

Key abbreviations

AE	Adverse event	LSM	Least squares mean
AGNSS	Advisory Group for National Specialised Services	LYG	Life years gained
BSC	Best supportive care	mNIS+7	Modified Neuropathy Impairment Score +7
CEAC	Cost-effectiveness acceptability curve	NAC	National Amyloidosis Centre
CHMP	Committee for Medicinal Products for Human Use	NIS+7	Neuropathy Impairment Score +7
CM	Cardiomyopathy	Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
CS	Company submission	PAS	Patient Access Scheme
DSA	Deterministic sensitivity analysis	PND	Polyneuropathy disability
ECHO	Echocardiography	PSA	Probabilistic sensitivity analysis
EQ-5D-5L	EuroQol 5-Dimensions, Five Level Questionnaire	PCS	Physical component summary
FAP stage	familial amyloidotic polyneuropathy	QALY	Quality-adjusted life year
GI	gastro intestinal	SAE	Serious adverse event
hATTR	Hereditary transthyretin-related	SD	Standard deviation
hATTR-CM	Hereditary transthyretin amyloidosis with cardiomyopathy	TEAE	Treatment-emergent adverse event
hATTR-PN	Hereditary transthyretin amyloidosis with polyneuropathy	THAOS	Transthyretin amyloidosis outcomes survey
HR	Hazard ratio	TQoL	Total QoL
HRU	Healthcare Resource Utilisation	TTR	transthyretin
HRQoL	Health-related quality of life	UCLH	University College London Hospital
ICER	Incremental cost-effectiveness ratio	V30M	Valine replaced by methionine at amino acid position number 30
KM	Kaplan Maier	WTP	Willingness-to-pay

Key issues for consideration

Clinical evidence

- Are NEURO-TTR and NEURO-TTR Extension generalisable to clinical practice in the UK?

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

- Does the committee consider inotersen clinically effective?

- How does the committee view the safety profile of inotersen?

[redacted]

Disease background I.

Hereditary transthyretin-related (hATTR) amyloidosis

- Autosomal dominant inherited disorder caused by mutations in the transthyretin (TTR) gene
- Leads to production of abnormal TTR protein by the liver, which accumulates as deposits in the tissues of the body (amyloidosis) mostly in the peripheral nervous system or in the tissues of the heart
- There are approximately XX* patients with Stage 1 or Stage 2 hATTR-PN diagnosed in England that will be eligible for inotersen treatment
- A spectrum of clinical manifestations of hATTR amyloidosis:
  - polyneuropathy (hATTR-PN) – ***presents with most disabling symptoms***
  - cardiomyopathy (hATTR-CM) – ***reported in 80% of patients with hATTR-PN***
  - polyneuropathy and cardiomyopathy (most people have mixed phenotype)
- Common genetic mutations include Val122Ile (39%), Thr60Ala (25%) and V30M (17%)
  - V30M mutation is associated with higher survival rate
- Life expectancy from onset of symptoms is 3 to 15 years
  - People die from heart failure or complications of autonomic neuropathy resulting in wasting

[redacted]

* Estimated by Akcea Therapeutics

Disease background II.

hATTR amyloidosis

- hATTR amyloidosis is a systemic disorder with diverse clinical presentations and varying degrees of rapidly progressive disease:

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

Classification of hATTR amyloidosis

- Diagnostic workup involves a comprehensive clinical assessment
  - Including neurological, cardiological, renal and ophthalmological assessments, complete family history
- Symptoms of hATTR-PN are frequently attributed to more common disorders
  - Average diagnostic delay of 4 years
- Age at symptom onset ranges from the 2nd to 9th decade of life, with great variations across different populations and mutations
- hATTR-PN most often can be staged using ambulatory status

Coutinho* Stage	Ambulatory Status
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

Source: Table B1 Company submission

[redacted]

* Staging first published by Coutinho et al., (also known as FAP stages)

Current treatment options

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

- 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 → diagnostic imaging, histology and DNA analysis, genetic counselling, monitoring of amyloid proteins in the blood, treatment recommendations and evaluation of existing and new therapies

[redacted] AGNSS: Advisory Group for National Specialised Services

Inotersen (Tegsedi)

Akcea Therapeutics

Marketing authorisation	Indicated for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis
Mechanism of action	Inotersen is a novel, first-in-class 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide (ASO) that inhibits production of transthyretin protein in adult patients with hATTR amyloidosis
Administration & dose	• Subcutenous injection • Recommended dose is 284 mg once every week (injection should be given on the same day every week) – additionally 3000 IU vitamin A given per day • Dose adjustments in case of reduction in platelet count: ○ For patients with a confirmed platelet count ≥75 to <100 x109/L, dose frequency should be reduced to 284 mg every 2 weeks ○ 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 ○ For patients with a confirmed platelet count <25 x109/L, treatment should be permanently discontinued, and corticosteroids administered
List price and PAS discount	• The list price for inotersen is £5,925 per weekly dose • Simple discount patient access scheme (PAS) approved*

**All results will incorporate PAS discount*

Decision problem

	NICE final scope	Company submission	ERG comments
Population	People with hATTR amyloidosis	People with hATTR-PN	Population aligned with CHMP opinion
Intervention	Inotersen	As per scope	NA
Comparator	Established clinical management without inotersen	As per scope	NA
Outcomes	• Neurological impairment • Symptoms of polyneuropathy • Cardiac function • Autonomic function (including the effects on the GI system and postural hypotension) • Weight loss • Effects of amyloid deposits in other organs and tissues (including eye) • Serum transthyretin • Motor function • Mortality • Adverse effect of treatment • HRQoL (for patients and carers)		• Postural hypotension and effects of amyloid deposits in other organs and tissues (including the eye) not included in submission • No explanation provided • Not clear whether GI/urinary incontinence, and other than GI/urinary incontinence encompasses postural hypotension

[redacted]

CHMP: Committee for Medicinal Products for Human Use

Impact of hATTR amyloidosis on patients I.

Amyloidosis Research Consortium (ARC) UK survey 2018

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

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

Impact of hATTR amyloidosis on patients II.

Amyloidosis Research Consortium (ARC) UK survey 2018

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

<u>Significant unmet need</u>

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

<u>Experience with inotersen treatment</u>

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

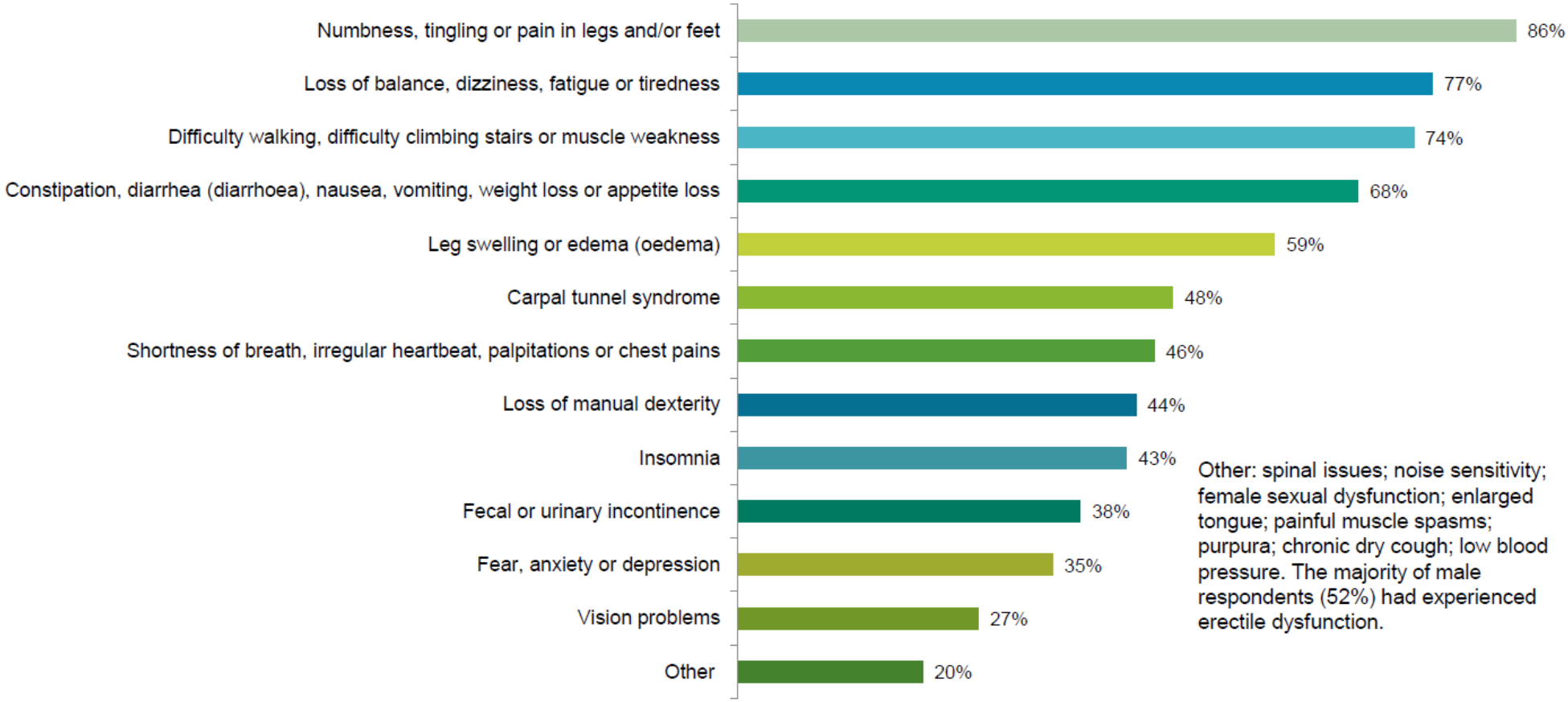
[redacted]

Impact of hATTR amyloidosis on patients III.

Amyloidosis Research Consortium (ARC) UK survey 2018

Patients experience a high, multi-systemic symptom burden

Amyloidosis Research Consortium UK



Q. In the last 12 months which symptoms have you experienced? (n=98)

[redacted]

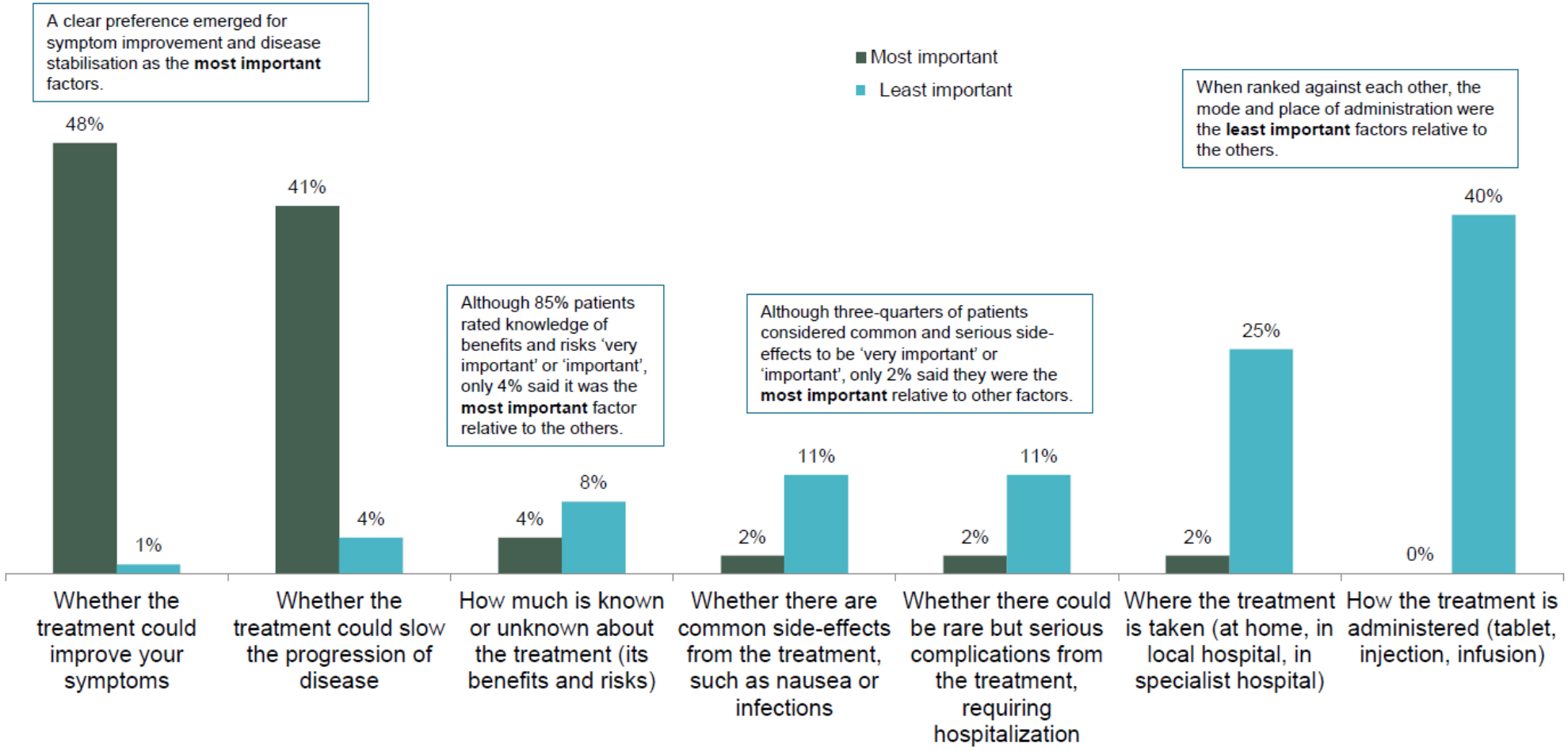
Source: Slide 7 – ARC summary report

Impact of hATTR amyloidosis on patients IV.

Amyloidosis Research Consortium (ARC) UK survey 2018

Forced ranking shows patients give greatest weight to efficacy and least to convenience

Amyloidosis Research Consortium UK



Q. Which of these is the single most important and the single least important factor to you? (n=92)

[redacted]

Source: Slide 14 – ARC summary report

Impact of hATTR amyloidosis on carers I.

Amyloidosis Research Consortium (ARC) UK survey 2018

The disease has a substantial lifelong impact on entire families

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

Impact of hATTR amyloidosis on carers II.

Amyloidosis Research Consortium (ARC) UK survey 2018

Carers experience a significant practical and emotional everyday burden

Amyloidosis Research Consortium UK

"Supporting him with his disappointment and frustration regarding the increased symptoms."

Providing emotional support to deal with patient's disappointment

"Accompanying my husband to London for each infusion, which takes a whole day including travel. It's a very long and tiring day."

I've gone part-time to fully support him during the various hospital appointments he attends."

Dealing with own worries, concerns and disappointment

Accompanying to appointments

"Had to give him the injection, which was so painful, it made me cry causing him so much pain."

Taking time off work

Administering treatment

"It's very hard to see when medicine does not work and you don't have any hope. Some days I feel very low."

Managing treatment regimen

"Ongoing changes in medications keep me on my toes, as I am the one who arranges meds daily."

[redacted]

Source: Slide 20 – ARC summary report

Clinical experts and professional organisations comments I.

Condition

- hATTR is a rare, progressive, devastating and dignity-removing disease that leads to death within 7-10 years
- Patients presenting with cardiac involvement have a worse prognosis (survival is around 4-5 years) than those presenting with a peripheral neuropathy

New technologies

- First technologies inhibiting the production of amyloid precursor proteins, transthyretin (TTR); it is seen as a “giant leap”
- Aim to slow or (ideally) stop progression, enable gradual improvement and recovery, and thereby improve mobility and prevent disability; both would be given in addition to current supportive care

Outcome

- mNIS+7 is a sophisticated outcome to assess motor strength, reflexes, sensation, nerve conduction and postural blood pressure
- Clinically significant outcome is maintenance of ability to walk, and without greater walking aids

Clinical experts and professional organisations comments II.

Epidemiology

- About 30 new cases each year. Most patients are based in England but around 5-10 patients are from Scotland, Northern Ireland or Ireland
- Mid estimated prevalence of hATTR (Schmidt et al., 2018) is 97. More than 50% are expected to receive treatment

- Patients are most likely to benefit from the new technologies if they are diagnosed early (Stage 1); patients in Stage 3 disease (unable to walk) may benefit from treatment (although not possible to assess in trials)

Current treatment options are limited

- Tafamidis is not available in the UK
- Diflunisal is often used off-license but has little impact on the progression of the disease and can cause side effects
- Liver transplantation is used in very few patients (high costs, limited by the availability of donor organs)

- No guidelines exist to support clinical practice; there is no defined pathway of care

[redacted]

Clinical experts and professional organisations comments III.

Administration of inotersen

- UK patients with hATTR amyloidosis are assessed (for overall clinical status, neuropathy progression and cardiac involvement) and followed up for 6 months at NAC; additional neurological measurements are assessed at the National Hospital for Neurology, UCLH
- Inotersen can be self-administered at home (bi-weekly blood tests are required)
- Patients with hand weakness from neuropathy require a carer or district nurse to administer the medication

Implementation

- The proposed treatment will require patient or carer training to administer the subcutaneous injections and also regular blood monitoring
- A specialist nurse would be required to undertake training of patients and carers in the administration of the medication and to undertake blood monitoring
- New systems to facilitate delivery and monitoring of the medication result in little change to current models of care

Safety profile

- Patients with a known bleeding disorder may be at risk if thrombocytopenia is severe
  - ➢ Patients were happy to have weekly blood tests in order to receive inotersen in the open label study

[redacted]

NAC: National Amyloidosis Centre; UCLH: University College London Hospital

NHSE comments

- Not published guideline for this condition
- NAC is the recognised centre for diagnostic evaluation of patients suspected of amyloid-forming conditions
- Pathway for ongoing care and treatment of patients with an established diagnosis is less well defined
- Some patients may be under the care of local neurologists or other specialists
- The availability of disease modifying treatment is likely to improve the definition and clarity of pathways for ongoing care
- If recommended, extra resource use will be in monitoring the effects of treatments
  - Increased outpatient attendance and costs of investigations or imaging
- There will a small requirement for staff training

[redacted]

Clinical effectiveness evidence

Clinical trial evidence

	NEURO-TTR – completed	NEURO-TTR Extension – ongoing
Design	Phase 2/3 multicentre, double-blind, randomised, stratified, placebo-controlled study	Phase 3 multicentre, open-label extension of NEURO-TTR
Intervention +	Inotersen (n=113‡) + Vitamin A	[redacted]
Comparator	Placebo (n=60) + Vitamin A	[redacted]
Location	24 centres in 10 countries: UK (1 centre [n=6]; NAC)	9 countries: [redacted]
Duration	15 months (66 weeks)	Ongoing (260 weeks)
Inclusion	Adults (18 to 82 years) with Stage 1 or Stage 2 hATTR-PN	Adults with Stage 1 and Stage 2 hATTR-PN (satisfactorily completed NEURO-TTR)
Primary outcomes	Change from baseline in modified Neuropathy Impairment Score (mNIS+7) composite score and Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire total score at week 66	Changes from NEURO-TTR baseline and NEURO-TTR Extension baseline [redacted] mNIS+7 total score; NIS total score, Norfolk QoL-DN questionnaire total score, symptoms domain score (Stage 1 patients only) and physical functioning/large fibre neuropathy domain score (Stage 2 patients only)

‡n=112 patients received study treatment; NIS: Neuropathy impairment score

[redacted]

Co-primary endpoint definition: mNIS+7 and Norfolk QoL-DN

mNIS+7

- A composite neurological impairment score consisting of two composite scores
  - The neuropathy impairment score
  - And the modified +7 score - involve both large and small fibre sensory tests
- A decrease in mNIS+7 score indicates an improvement in neurological impairment
- mNIS+7 was specifically modified from NIS+7 to better characterise and quantify sensation anywhere on the body, autonomic function, and nerve conduction changes that are typical in hATTR with Stage 1 and Stage 2 polyneuropathy
- Modifications aimed at ensuring the tests remain sensitive to change with disease progression

Norfolk QoL-DN

- It is a patient-reported measure which has been validated in patients with hATTR-PN
- Designed to capture the impact of neuropathy on quality of life, consisting of:
  - One composite total score (Total QoL [TQoL]) - sum of 35 questions across five domains, scores range from -4 to 135
  - 5 subdomains (physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy)
- A decrease in Norfolk QoL-DN total score indicates an improvement of quality of life

[redacted]

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

Baseline characteristics in main clinical studies

Patients in the inotersen arm of the NEURO-TTR study and patients on the placebo-inotersen arm in the NEURO-TTR and Extension tudies had greater disease severity at baseline

(numbers in Table are rounded)	NEURO-TTR*		NEURO-TTR Extension‡	
	Placebo (N=60)	Inotersen (N=112)	[redacted]	[redacted]
Age (years) Mean	60	59	[redacted]	[redacted]
Male (%)	68	69	[redacted]	[redacted]
Disease Stage 1 (%)	65	66	[redacted]	[redacted]
Disease Stage 2 (%)	35	34	[redacted]	[redacted]
V30M TTR mutation (%)	53	52	[redacted]	[redacted]
PND score I, n (%)	38	29	[redacted]	[redacted]
PND score II, n (%)	32	38	[redacted]	[redacted]
PND score III, n (%)	25	27	[redacted]	[redacted]
PND score IV, n (%)	5	7	[redacted]	[redacted]
PND score V, n (%)	0	0	[redacted]	[redacted]
Duration from onset hATTR-PN (months) Mean	64	64	[redacted]	[redacted]
Patients diagnosed with hATTR-CM (%)	37	40	[redacted]	[redacted]
Duration from onset hATTR-CM (months) Mean	***34***	***45***	[redacted]	[redacted]
mNIS+7 composite scores Mean	***75***	***79***	[redacted]	[redacted]
Norfolk QoL-DN total scores Mean	49	48	[redacted]	[redacted]

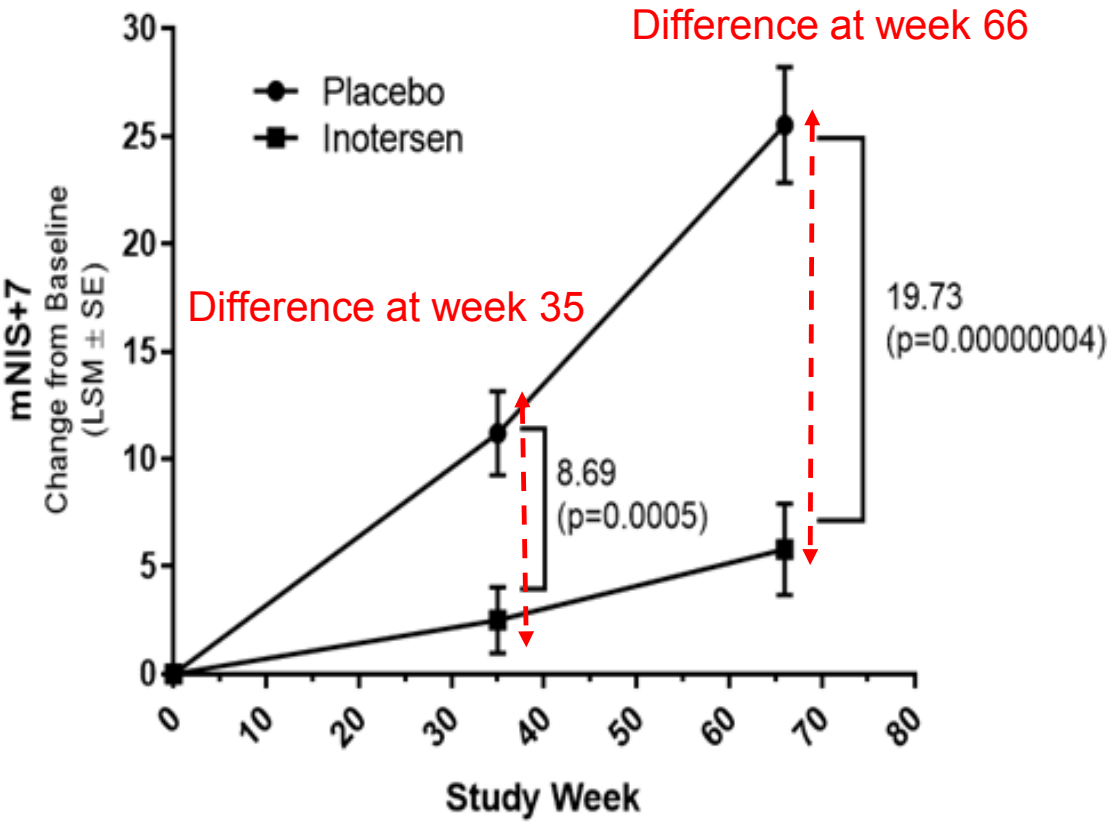
[redacted]

*NEURO-TTR Safety Set (SS) and Full Analysis Set (FAS) differed by seven patients; ‡NEURO-TTR [redacted] PND: polyneuropathy disability

Source: Tables C5, C6, C7 and C9 of company submission

Clinical results: NEURO-TTR least squares mean (LSM) change from baseline in mNIS+7 composite score

Full Analysis Set, week 66



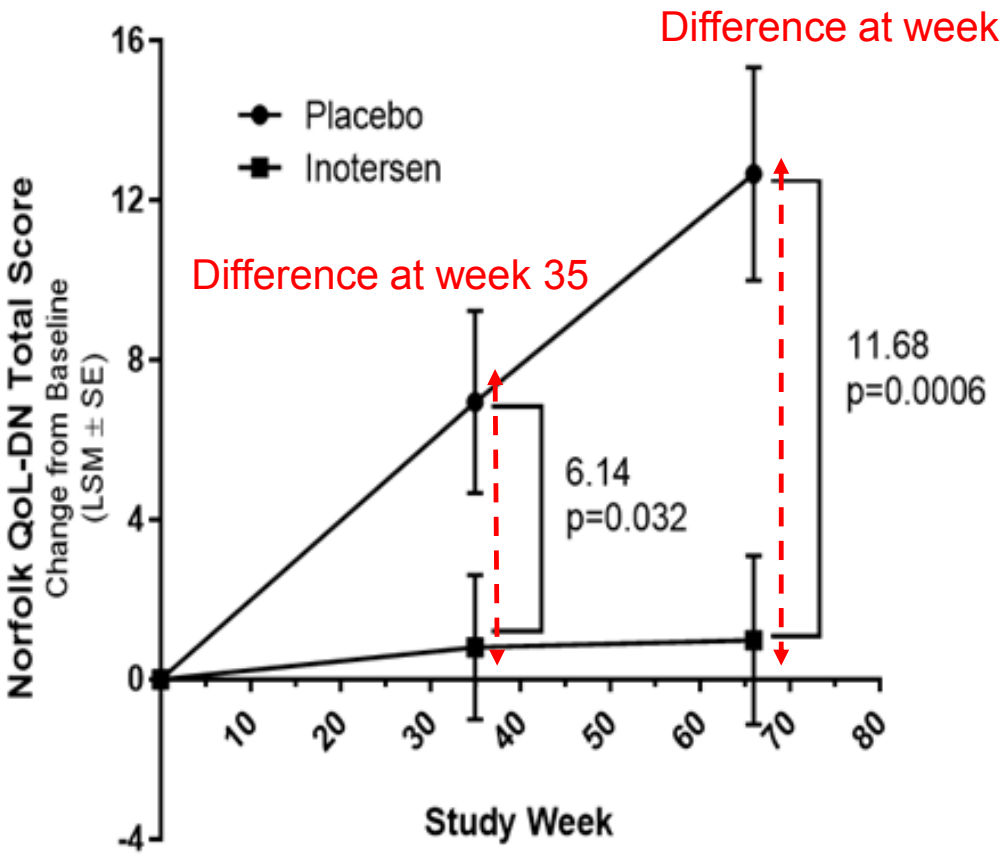
Source: Figure 6 of company submission

- Statistically significant improvement observed in neurological disease progression with inotersen
- **mNIS+7:** mean mNIS+7 composite score on placebo arm was ***24.9*** compared to ***4.2*** on inotersen arm (week 66)
- Inotersen patients had a greater disease severity at baseline → magnitude may be bigger
- ***ERG comment***: inotersen treated patients achieved a greater improvement in neurological progression (progressed at a slower rate)
    - Deterioration over time was still evident but was significantly less than on placebo treatment

[redacted]

Clinical results: NEURO-TTR least squares mean (LSM) change from baseline in Norfolk QoL-DN total score

Full Analysis Set, week 66



Source: Figure 6 of company submission

- Statistically significant improvement observed in QoL with inotersen
- **Norfolk QoL-DN**: very little change from baseline score in the inotersen arm at week 66 ***-0.08***; ⟺ increase of ***10.8*** observed on placebo arm (week 66)
- Inotersen patients had a greater disease severity at baseline → magnitude may be bigger

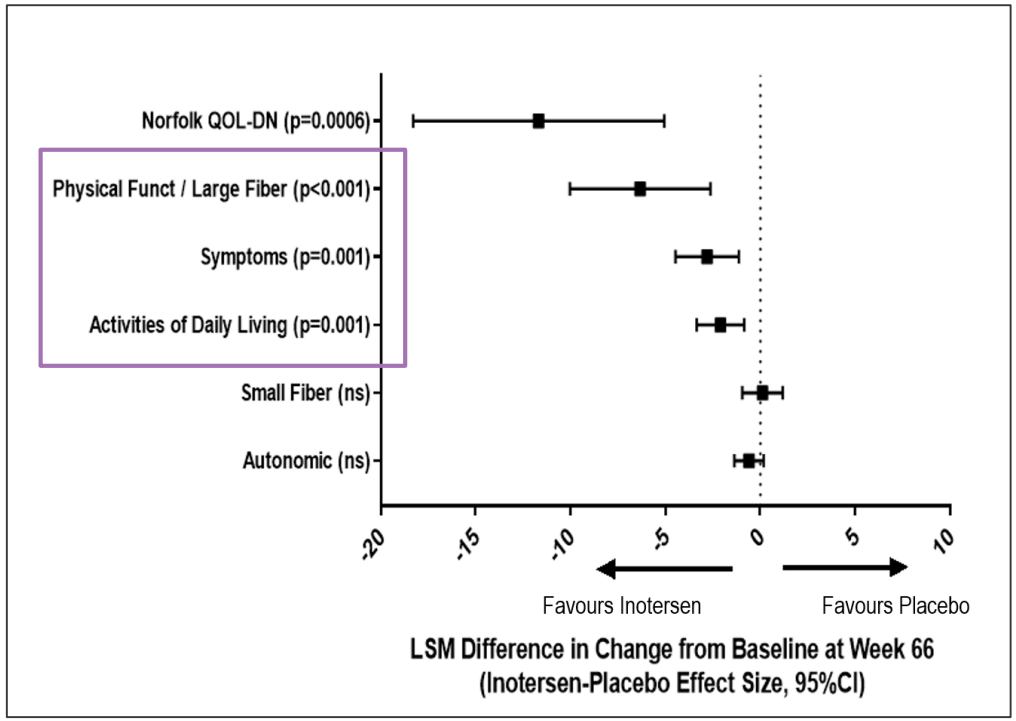
[redacted]

Clinical results: Effect of inotersen treatment on the individual components of mNIS+7 and Norfolk-DN

NEURO-TTR LSM difference in change from baseline for mNIS+7, and modified +7 composite scores and individual components, week 66

[redacted]

NEURO-TTR LSM difference in change from baseline for Norfolk QoL-DN domain scores, week 66



- Significant difference for the sub components of mNIS+7 except for **heart rate response to deep breathing (HRDB)** and **touch pressure**
- Significant difference found in favour of inotersen for **physical functioning/large fibre, symptoms, and activities of daily living**

[redacted]

Source: Figure 1 of Clarification response and Figure 8 of company submission

Clinical results: post hoc analysis of subset of patients with severe cardiomyopathy (CM) at baseline

Decrease in cardiac thickness and mass suggest regression of cardiac amyloidosis

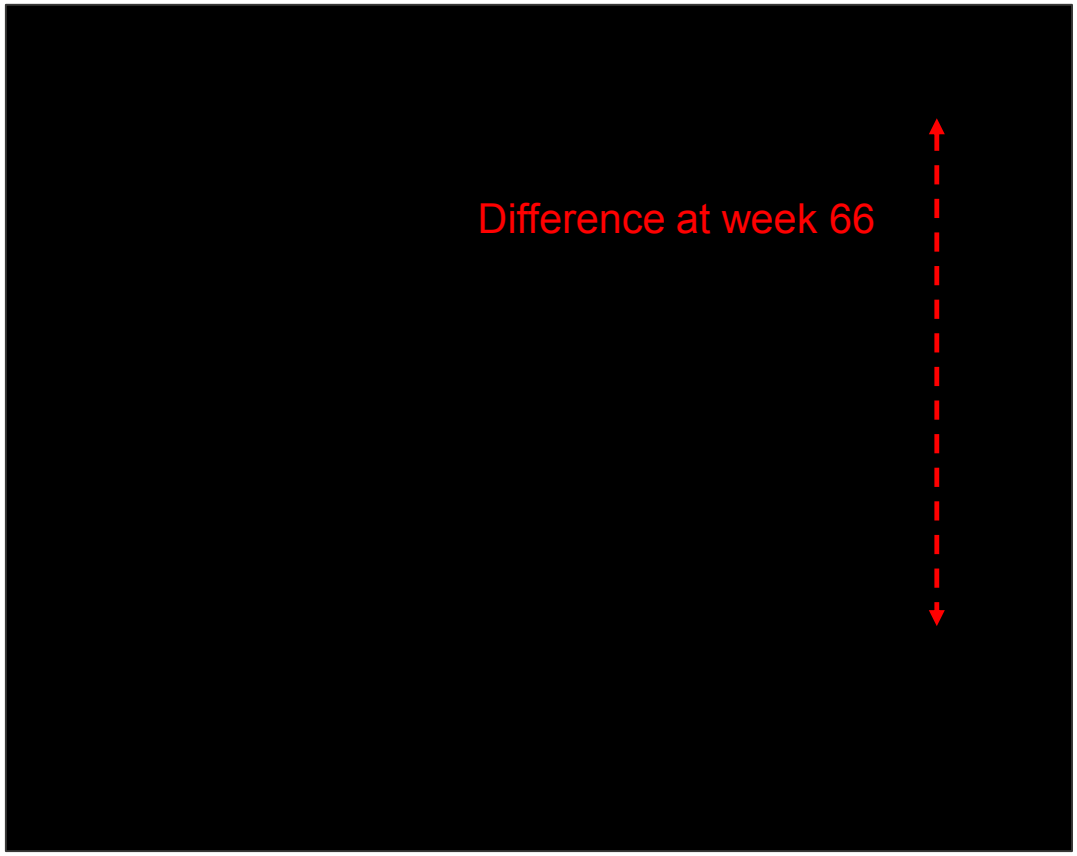
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
	n LSM; 95% CI	n LSM; 95% CI	LSM; 95% CI p-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Table C16 of company submission

Clinical results: Proportion of patients with ≥60% decrease in TTR levels (week 66)



Source: Figure 9 of company submission

- Over 80% of patients in the inotersen study arm showed a ≥ 60% decrease in TTR plasma levels by week 13 through to week 66
- The differences in LSMs for change from baseline in TTR were statistically significant in favour of inotersen (p<0.001) at all time points
- Placebo group mean serum TTR concentration decreased by 8.50% at week 3 and then remained constant throughout the study period

[redacted] TTR: transthyretin; LSM: least squares mean

Clinical results: SF-36 component scores

- Statistically significant difference in favour of inotersen treatment (LSM difference 3.59, p=0.006) was observed in the physical component summary (PCS) score of the SF-36 health survey at week 65
  - Clinically meaningful for patients in terms of physical functioning
- Clinically significant worsening in the mean change from baseline in PCS score, defined as a change of at least 3, was noted in the placebo group at week 65
- Improvements in the mental component summary score and the mental health domain score were observed at week 65 in the inotersen group compared to a worsening in the placebo group (LSM difference: 2.42, p=0.088; 5.07, p=0.055)

[redacted]

Clinical results: Additional analysis on disease progression, week 66

- Progression of disease at week 66 was slowed or arrested in 36.5% of patients in the inotersen arm
  - Improvement (negative change) or no worsening seen in mNIS+7 (p=0.032)
- In 50% of patients in the inotersen arm improvement (negative change) or no worsening seen in Norfolk QoL-DN (p=0.008)

Treatment group	mNIS+7		Norfolk QoL-DN	
	Placebo N=52	Inotersen N=85	Placebo N=52	Inotersen N=84
No disease progression (week 66 change from baseline), n (%) p-value	10 (19.2)	31 (***36.5***) p=0.032	14 (26.9)	42 (***50***) p=0.008

Source: Table C14 of company submission

[redacted]

Clinical results: Subgroup analysis

Inotersen showed to be beneficial for all subgroups for the mNIS+7 and Norfolk QoL-DN outcome; except for previous treatment in relation to Norfolk QoL-DN

Subgroup	n, placebo, inotersen	mNIS+7		Norfolk QoL-DN	
		Difference	p-value	Difference	p-value
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

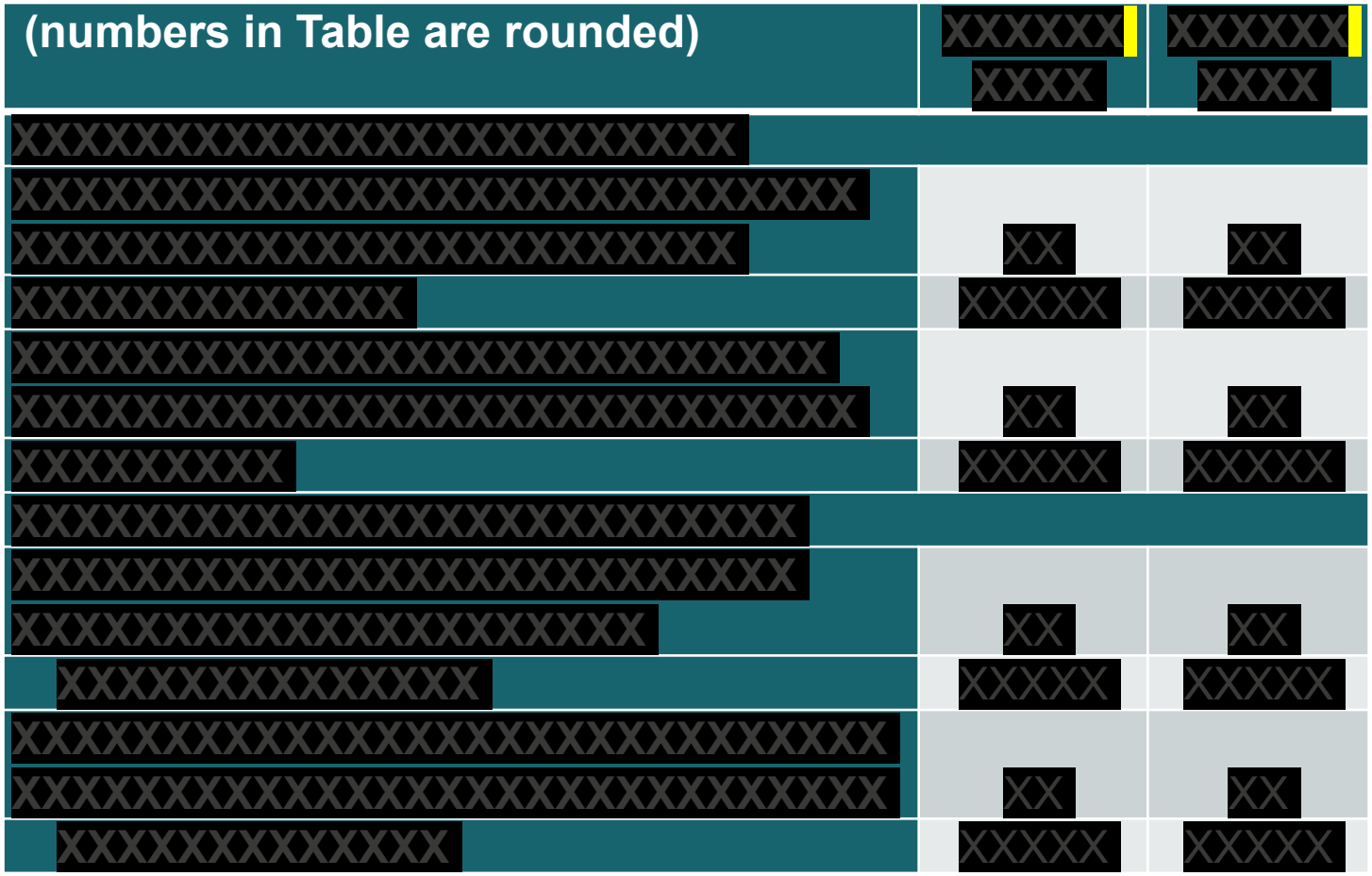
Source: Table C15 of company submission

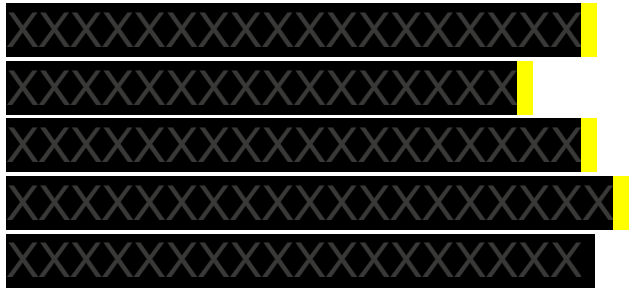
[redacted]

V30M: Valine replaced by methionine at amino acid position number 30;
CM: Cardiomyopathy; ECHO: Echocardiography

Interim clinical results: NEURO-TTR extension study FAS

Change from baseline in the mNIS+7 composite score and Norfolk QoL-DN total score



- Patients continued to receive benefit with extended dosing
- 
- → increased benefit with earlier treatment persisted over time

Source: Table C17 of company submission *Full Analysis Set:

ERG comment: in placebo-inotersen group changes in both scores observed from baseline in Extension study
→ rate of disease progression following inotersen treatment slower in the Extension study compared to rate of progression in NEURO-TTR

Interim clinical results: SF-36 health survey

- Patients in the [redacted] continued benefit with inotersen extended dosing [redacted] from NEURO-TTR Extension baseline to [redacted]
  - Changes observed [redacted] than those observed over 65 weeks in NEURO-TTR
- Patients in the placebo-inotersen group [redacted]
  - Mean change from NEURO-TTR Extension baseline to [redacted]: -0.987
- [redacted]
- [redacted]
  - [redacted]

[redacted]

Adverse events – NEURO-TTR study

	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)

Source: Table C24 of company submission

- Most frequently reported study related TEAEs: injection site erythema (31.3%), nausea (31.3%), fatigue (25.0%), diarrhoea (24.1%), headache (23.2%), injection site pain (20.5%)
  - No adverse events at the injection site resulted permanent discontinuation of inotersen

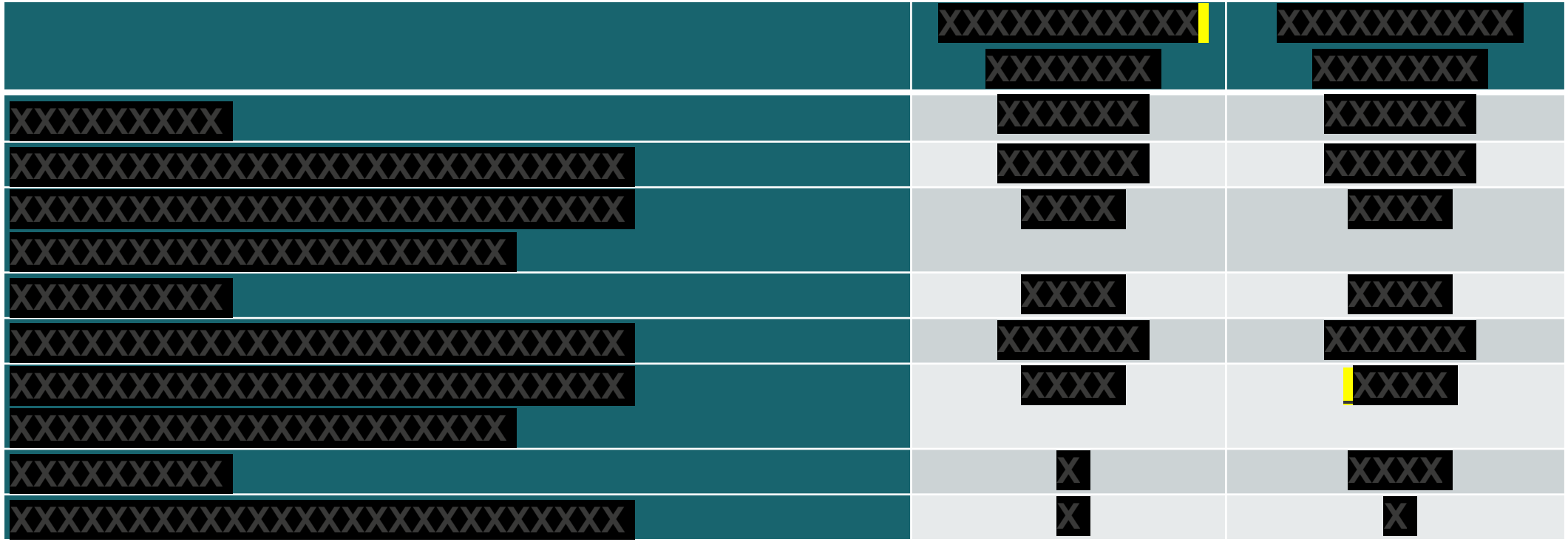
- There were 5 deaths in the inotersen group, and none in the placebo group
  - 1 death associated with intracranial haemorrhage → *considered related to study treatment*
  - 4 out of the 5 deaths were consistent with progression or complication of the underlying disease

[redacted]

TEAE: Treatment-emergent adverse event

Adverse events – NEURO-TTR Extension study

Safety data cut



Source: Table C27 of company submission

- Most frequently reported study drug-related TEAEs
  - Majority of TEAEs
-
-
  -

ERG critique on clinical evidence I.

Literature review, data extraction

- ERG considered that the company's search strategies were appropriate
- Unclear whether data extraction method was appropriate:
  - Company did not report whether the methods of the systematic review were based on published guidance
  - The company did not report the number of reviewers of the systematic review process, level of independence of researchers at each stage

Quality of trials

- Company used an appropriate risk of bias tool → the ERG largely agrees with the company's critical appraisal of the studies
- Process of quality assessment was not fully described → not reported how many reviewers were involved in the risk of bias assessment
- Generally well conducted trials
- ERG found the evidence submitted reasonable, however it should be noted that the evidence is coming from a single study only

[redacted]

ERG critique on clinical evidence II.

Adverse events

- ***NEURO-TTR***:
  - Principal safety concerns for inotersen treatment are identified as glomerulonephritis and thrombocytopenia
  - 1 death associated with intracranial haemorrhage → led to implementation of more frequent platelet monitoring
  - Safety risks associated with inotersen can be effectively monitored with routine testing in clinical practice
    - ➢ Allowing early detection and management of the adverse events
  - ERG clinical expert agrees with the above conclusion
- ***NEURO-TTR Extension***:
  - 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
  - In the inotersen-inotersen group [redacted], compared with the placebo-inotersen group ([redacted]

[redacted]

ERG critique on clinical evidence III.

Discrepancy between number of participants with reported in submission and Benson et al.

- Numbers reported in the submission differ to those presented in the main trial (*previous treatment with tafamidis or diflunisal; disease stage 1 and 2; V30M TTR mutation*)→ explanation provided during clarification → it is not clear how randomisation of patients can differ, given that both documents report results from the same study

Discrepancy between number of patients entering the studies

- Patient flow through the NEURO-TTR extension study is not clear
- [redacted] placebo and [redacted] inotersen patients entered the NEURO-TTR Extension study ⟷ but patient disposition indicates [redacted]
- [redacted] ERG was not able to ascertain from the information presented why there were differences between the numbers
- Results were for [redacted]

[redacted] It is assumed that the [redacted] in patient numbers relates to the definition of the FAS → not clearly presented

[redacted]

V30M TTR: Valine replaced by methionine at amino acid position number 30

Key issues for consideration

Clinical evidence

- Are NEURO-TTR and NEURO-TTR Extension generalisable to clinical practice in the UK?

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

- Does the committee consider inotersen clinically effective?

- How does the committee view the safety profile of inotersen?

[redacted]

Cost-effectiveness evidence

Key issues for consideration I.

Cost-effectiveness evidence

- What is the committee's view of the structure and assumptions in the economic model?
  - Patients were assumed to discontinue treatment on entering Stage 3
  - Two sets of transition probabilities sourced from NEURO-TTR study: A) baseline to week 35 and B) week 35 to 66 to extrapolate transitions over the full life time horizon for both arms
  - Mortality data: hazard ratios obtained from Delphi panel
  - Modelled health states were inferred from the NEURO-TTR study based on defined TQoL score cut-offs on the Norfolk QoL-DN measure
  - Each patient has two full-time carers
  - Adverse events partially included in economic model
  - Time to discontinuation in NEURO-TTR and NEURO-TTR Extension studies used to calculate survival curves
  - Model used XXX treatment compliance rate

[redacted]

Key issues for consideration II.

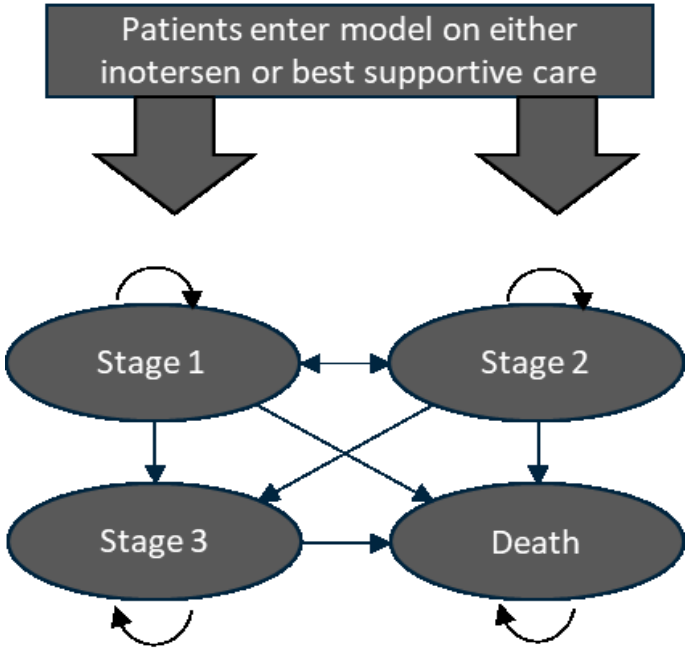
Cost-effectiveness evidence

- What is the most appropriate source of utility for each health state?
- Should a 1.5% or 3.5% discount rate be used?
- What are the most plausible ICERs?
- What factors affecting the guidance need to be taken into account?
- Should QALY weighting be used in decision-making?
- Equality issues raised: any additional considerations required?

[redacted]

Model structure

Cohort-based Markov state-transition model



Note: The cycle length is 4 weeks.

Source: Figure 11 of company submission

- Markov model compares inotersen vs. established clinical management without inotersen (BSC)
- 4 health states based on 3 Coutinho staging + death
- Lifetime duration (from age of 59 to until age of 100); 1.5% discount rate; 4 weeks cycle - reflect the approximate length of time between healthcare system contacts in UK clinical practice; NHS/PSS perspective
- Cohort of hATTR amyloidosis patients (NEURO-TTR trial population)

ERG comment:

- Model structure is a fair reflection of disease progression and appropriate for use in the assessment

[redacted]

BSC: best supportive care

Model – distribution of starting cohort

- Health states defined according to cut-offs on the Total Norfolk QoL-DN (TQoL) score range from 0 (best) to 135 (worst), at which point the cohort are assumed to transition between Coutinho stages

- Approach sourced from tafamidis evaluation (Vyndaqel for the treatment of transthyretin familial amyloid polyneuropathy)
  - Refers to the THAOS registry data funded by tafamidis manufacturer, with aim of studying the natural history of patients with transthyretin amyloidosis

- Model cohort is distributed across 3 Coutinho stages according to the inferred distribution of disease stage among NEURO-TTR trial participants with a baseline TQoL score

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

[redacted]

Source: Table 18 of ERG report

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

ERG critique on distribution of model starting cohort

Approach consistent with the tafamidis assessment, but has the same limitations

- TQoL score is a subjective measure, always possible that some improvements (even temporary) may be plausible, particularly for patients with scores close to the cut-off thresholds
- Substantial heterogeneity in TQoL for each disease stage →questionable whether TQoL is an accurate method to define disease stage
- Cut-offs used to define disease progression appear arbitrary and unjustified
- No clear justification for use of data from tafamidis assessment or limitations of approach
- Different mutations will be associated with varying severity of neurological disease, however, this will be accounted for in the disease staging and the approach taken by the company is unlikely to introduce any significant bias

[redacted]

Model structure – discontinuation rule in the model

- Patients were assumed to discontinue treatment on entering Stage 3
  - Company explained this is in line with license
- Discontinuation also based on discontinuation of treatment for other reasons which has been modelled using survival curves (see in later slide)

- ***ERG comment***:
- Unclear how consistent a decision to withdraw treatment would be with Coutinho staging (i.e. TQoL score) used in the model
- ERG's clinical expert notes: patients are bedridden or have severe autonomic neuropathy, 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 if treatment lead to cardiac improvement → ERG are unaware of any robust evidence to support this

[redacted]

Transition in the model

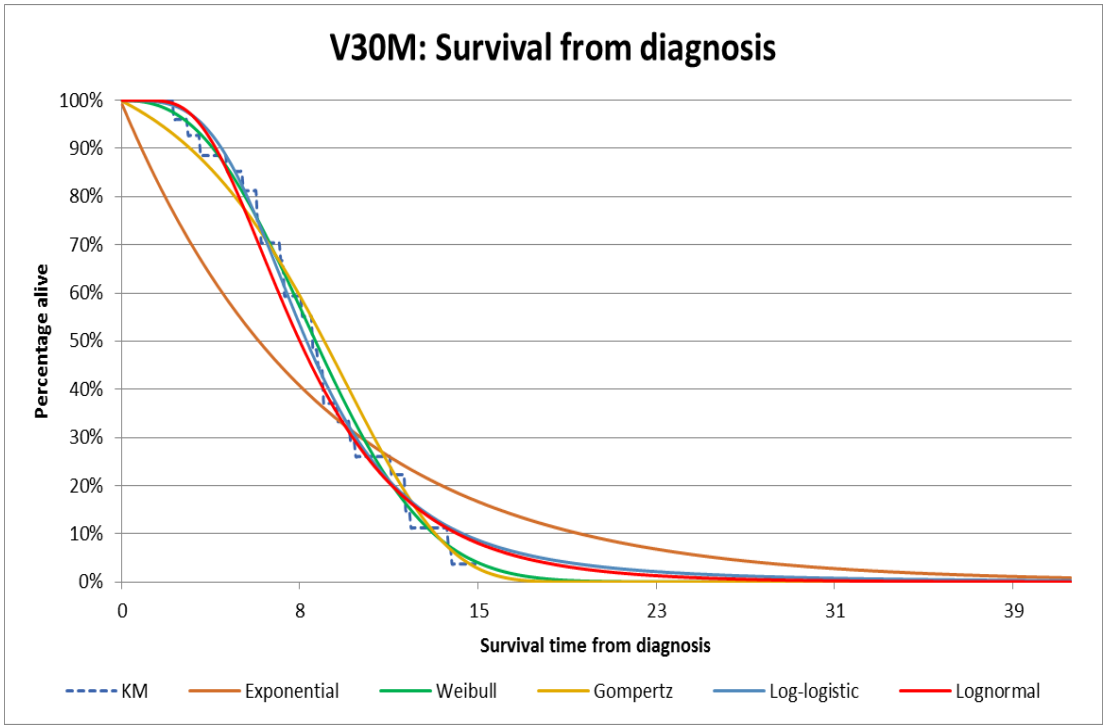
- Transitions between Coutinho disease stages modelled independently for each model arm
  - Patients cannot move back from Stage 3 to Stage 2 or Stage 1
  - Inotersen is not given in Stage 3
- Transitions converted to 4-weekly probabilities using the data observed in NEURO-TTR study
- Two sets of transition probabilities sourced from NEURO-TTR study: ***A) baseline to week 35*** and ***B) week 35 to 66*** (relate to time points of data collection in trial)

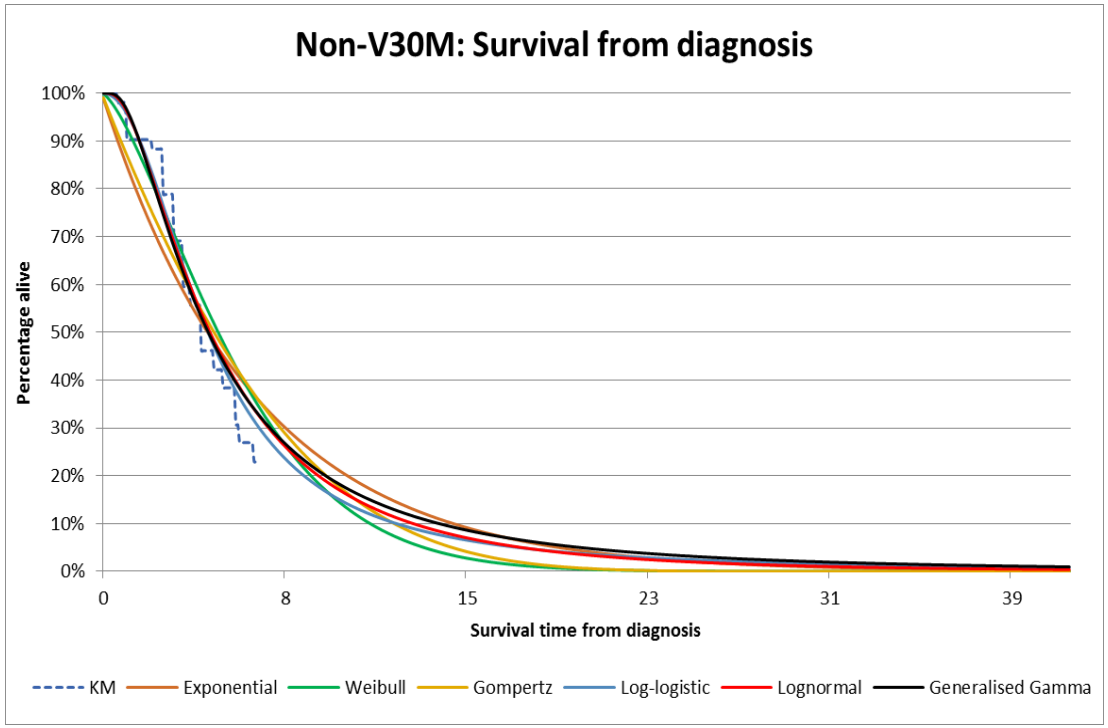
- ***ERG comment:*** unclear what impact this decision has on the ICER
- Transition probabilities from the NEURO -TTR study between weeks 35 and 66 were used to extrapolate transitions over the full life time horizon for both arms
- Extrapolation raises uncertainty about accuracy of the long run disease trajectory in model
  - In absence of better method → ***approach is justified***

[redacted]

Modelling mortality I.

- There are no published data available to link Coutinho disease stage with mortality
  - Original submission used mortality data from time of disease onset by V30M mutation status, obtained from Kaplan Maier data published by Sattianayagam et. al, 2012
  - Used parametric survival analysis of the digitised Kaplan Maier data to extrapolate long term mortality; did not incorporate disease stage specific mortality
- ***ERG comment:*** approach has limited face validity, as it assumes equal mortality regardless of disease progression stage





Source: Figure 12 and 13 of company submission

V30M: Valine replaced by methionine at amino acid position number 30

Modelling mortality II.

- During clarification, a Delphi panel of N=4 clinical experts was assembled to source likely hazard ratios (HR) of mortality by disease stage relative to general population mortality
- Hazard ratios obtained were as follows: Stage 1: HR = [redacted]; Stage 2: HR = [redacted]; Stage 3: HR = [redacted] → ratios were applied to age-specific UK general population mortality rates and converted to cycle-specific probabilities in the model

- ***ERG comments***: agrees that HRs obtained from Delphi study have been correctly implemented
- ERG's clinical expert felt that HRs included in the model appeared plausible → there is considerable uncertainty around the disease stage specific HRs → has not been explored by the company in sensitivity analyses

Proportion of cohort dead by year:	Original model	Revised company model
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%

[redacted]

Source: Table 22 in ERG report

Health state utilities used in the model

- There are no published mapping algorithms to map Norfolk QoL-DN to EuroQoL-5 Dimensions (EQ-5D)
  - Published literature used to inform health state utilities in the model

- Stewart et al. reported health-related quality of life (HRQoL) according to clinical stage for 1,205 patients with hATTR-PN included in the THAOS registry
  - Cohort consisted of 970 patients with the V30M mutation and 235 patients with a non-V30M mutation - median age of 40 and 54 years, respectively
  - The publication reports data for 93 Brazilian patients by Coutinho Stage (Stage 1: n=55; Stages 2: n=15; and Stage 3: n=8)

- Brazilian value set for weighting patient scores was used to calculate utilities

Health state	Patient EQ-5D-3L utility
Stage 1	0.697
Stage 2	0.429
Stage 3	0.084

Source: Table C29 of company submission

[redacted]

V30M TTR: Valine replaced by methionine at amino acid position number 30, THAOS: Transthyretin amyloidosis outcomes survey

ERG critique of health state utilities I.

Alternative sources of utility data for use in the model should have been considered

- Transferability to a UK setting is unclear
- Use of EQ-5D values based on Brazilian general population preferences is questionable
  - May not be appropriate from a UK NHS perspective
- No work has been carried out to determine the comparability of the valuation sets
  - Company did not conduct adequate sensitivity analyses around these uncertain values
- Utility values obtained from a range of EQ-5D health states are compared for illustration

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

Source: Table 23 of ERG report

- Important differences in the preference patterns between the valuation models
  - Standard decrement for any level 3 response is not applied in the Brazilian value set
    - ➢ Poorer health states are valued substantially lower in the UK tariffs

[redacted]

EQ-5D: EuroQoL-5 Dimensions

ERG critique of health state utilities II.

Alternative sources to obtain utility values

The ERG consider that there are three plausible alternative sources of data that could have been explored

1) Obtain raw EQ-5D response data sourced directly from THAOS study
   - EQ-5D data exist for 77.5% of the THAOS study cohort by Coutinho health state → generate disease stage specific EQ-5D values using UK tariff → more robust disease stage specific utilities for use in the economic model
2) Mapping SF-36 response data to EQ-5D values using published algorithms
   - Mapped values could be used for Stages 1 and 2, with an exploration of the utility impact for those who progress → provide an alternative source of UK relevant utility estimates
3) Alternative utility values reported by disease stage in Faria et al, for tafamidis appraisal
   - Different possible functions (e.g. linear mapping function) describing relationship between TQoL and EQ-5D → plausible alternative scenario analysis in the economic model
   - Different mapping functions generate a range of different plausible health state utility values → the greater the difference between Stage 1 and 3 utilities, the greater the incremental QALY gains (and hence lower ICERs) for inotersen

Additional ERG scenario analysis conducted to explore impact of different Coutinho disease stage utilities on the ICER

[redacted]

EQ-5D: EuroQoL-5 Dimensions; THAOS: Transthyretin amyloidosis outcomes survey

Carer disutility

- Quality of life impact on carers in hATTR is significant and substantial
- No studies assessed the impact on carer quality of life by health states described in model
  - Systematic literature review → disutility can be 0.14 (e.g. multiple sclerosis, stroke patients)
    - Gani et al. developed an algorithm which calculated carer disutility → attributed a rising disutility for carers as severity worsened
- As hATTR-PN patients progress through disease stages, the burden on carers also increases

Health state	EQ-5D-3L disutility per carer	Total disutility applied in model (2 x 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 (walking assistance)
Stage 3	-0.125	-0.2500	Average of EDSS 7.5-9.5 (wheelchair or bedridden)

- It was assumed in the model that each patient has two full-time carers

[redacted]

Source: Table C30 of company submission

ERG critique of carer disutility

- ERG agree hATTR-PN is highly likely to place a significant burden on carers, therefore agree that it is appropriate to consider carer disutility in the model
- For tafamidis a QALY loss of 0.01 was applied for stage 3 disease based on Alzheimer appraisal
  - One carer was assumed in the tafamidis assessment
- Remain unclear whether all patients with hATTR-PN would realistically have two full time informal carers
  - Particularly patients with Stage 1 or even stage 2 disease

Additional ERG scenario analyses conducted to explore the impact of carer disutility on the ICER

[redacted]

QALY: Quality-adjusted life year

Adverse event utilities and costs

- Originally cost and utility impact of treatment related adverse events observed in the NEURO-TTR study were excluded from model
- Company provided justifications at clarification stage
  - Difference in the number of adverse events (AE) between the treatment arms of NEURO-TTR was not statistically significant
  - Most AEs were mild, low rate of serious adverse events (<5%), the impact of including AE on the ICER is minimal
- Company provided 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
- Disutility associated with myelopathy, glomerulonephritis, tubulointerstitial nephritis and thrombocytopenia were excluded from the AE scenario analysis, despite these being reported as serious AEs in the NEURO-TTR study → incur no utility loss
- Monitoring cost updated with cost of Phlebotomist time → negligible impact on the ICER
- ***ERG comment***: excluding AEs creates a bias, in favour of inotersen and should be included in the base case analysis
- Informed assumptions regarding the utility decrement would have been superior to assuming these serious adverse events have no utility decrement
  - ERG have attempted to source utility data, or made alternative assumptions, verified by clinical expert opinion, where possible

[redacted]

Company and ERG adverse event disutilities used in the model

Adverse event rates per cycle	Inotersen	BSC	Assumed duration (days)		Disutility applied		Total disutility (duration x disutility)	
			CS	ERG	CS	ERG	CS	ERG
Glomerulonephritis	0.18%	0%	0	***30***	0	***-0.31 (de Wit 2001)***	0	-0.025
Thrombocytonpenia	0.12%	0%	30		-0.108		-0.009	
Intracranial hemorrhage	0.06%	0%	91		-0.309		-0.077	
Tubulointersitial nephritis	0.06%	0%	0	***30***	0	***-0.31***	0	-0.025
Myelopathy	0.06%	0%	0	***91***	0	***0.639 – (average 0.575+0.55) = -0.077***	0	-0.019

Source: Table 26 of ERG report

Resource use

- Total cost of inotersen is driven by two key model parameters
  a) **Time to treatment discontinuation**
  b) **Treatment compliance**

Time to treatment discontinuation

- Time to discontinuation in NEURO-TTR study used to calculate survival curves
- Based on parametric survival analysis modelled cohort receiving inotersen were divided into people 'on treatment' and 'not on treatment'
  - Preferred extrapolation curve: Gompertz over exponential

- During clarification survival curves updated using data from both NEURO-TTR and NEURO-TTR Extension study → using exponential survival curves
- ***ERG comment***: the revised approach is appropriate, accurately captures the best available long term data on time to discontinuation

- Model error corrected about incurring treatment costs (before that inotersen treatment costs were underestimated)
- ***ERG comment***: error appropriately corrected in model

[redacted]

Parametric survival curves for time to discontinuation of inotersen treatment

Source: Table 3 of clarification response

- ***ERG comment***: lower rates of treatment continuation in the long-term generate the lowest ICERs

- ***Exponential curve*** generates most optimistic estimate of ICER for inotersen ←→ ***Gompertz curve*** generates the most pessimistic ICER

- Most reasonable extrapolation curve may be which allows for a ***decreasing rate of discontinuation over time***

- ERG chose ***log-logistic curve*** which is considered to be a plausible estimate

[redacted]

Resource use: model assumptions

Discontinuation on entry to Stage 3 disease

- Applying time to discontinuation curve and stopping treatment at Stage 3 may overestimate discontinuation ←→ rate observed in the trial
- ***ERG comment***: correlation might exist between disease progression and probability of discontinuing inotersen treatment → inappropriate to use single time to discontinuation curve

Treatment compliance

- Model used XXXXX treatment compliance rate for all patients in the NEURO -TTR study
- ERG raised a concern: increasing compliance increased costs without having impact on benefits → making inotersen less cost-effective
  - Company could not establish relationship between compliance and effectiveness
    - Compliance relatively high in NEURO-TTR study
- During clarification, rate amended to XXXX
- ***ERG comment***: ERG's understanding based on response to clarification letter that company's revised calculation may have excluded the compliance of discontinuers
  - Inappropriate as it would not cost all doses observed up to the end of NEURO-TTR trial

[redacted]

Additional ERG scenario analysis was conducted to explore impact of increasing compliance parameter

Resource use: Costs per treatment/patient associated with inotersen in the model

Items	Value	Source
Cost of inotersen per patient per cycle (4-week)	£23,580*	Company
Cost of vitamin A per treatment/patient cycle per cycle (4-week)	£0.65	Assumed to be equal to 'Vitamins capsules' on NHS Electronic Drug Tariff, accessed 27/07/18
Administration cost	£0.00	The administration costs were assumed to be zero
Unit cost of platelet count test per patient every 2 weeks	£1.69	NHS reference costs 2016/17
Unit cost of eGFR test per patient every 3 months	£1.69	NHS reference costs 2016/17
Unit cost of UPCR test per patient every 3 months	£1.13	NHS reference costs 2016/17
Unit cost of hepatic enzyme testing (yearly)	£1.69	NHS reference costs 2016/17

- ***ERG comment***: no additional treatment related costs specific to BSC
  - All relevant costs are captured in the disease stage costs used in the model

[redacted]

Source: Table D13 of company submission

* Using list price

Resource use: health state costs

- Resource use data underpinning the stage costs were sourced from Faria et al, based on clinical expert opinion of Swedish clinicians for the tafamidis assessment by AGNSS
  - 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
- ***ERG comment***: costs are correctly applied
  - ERG corrected 1 item in one-off costs entry to Stage 2 (£1,803, not £1,083)
- Would be preferable to conduct new costing exercise → resource use informed by UK clinicians
- Cost data sourced from Faria et al. appear reasonable given the lack of alternative UK-specific resource use data

Stage	Primary Care	Aids	Home-care	Symptom Treatment Costs	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

AGNSS: Advisory Group for National Specialised Services

Source: Table 29 of ERG report

Discount rate used for costs and benefits in model

Company argues that 1.5% discount rate appropriate and it is in line with NICE Reference Case

NICE reference case: 3.5%

- ***Company***: Inotersen prevents transitions into worse health states → Stage 3 has negative QALYs (carer disutility included) → meets reasonable definition of 'severely impaired health'
- ***ERG comment***: Patients with hATTR-PN have, or likely to develop severely impaired health

- ***Company***: no evidence that benefit is sustained for anything other than a lifetime time horizon
- ***ERG comment***: no evidence provided that inotersen completely halts hATTR-PN disease
  - Undiscounted life years XXXXX (inotersen) and XXXXX (BSC), incremental LYG of XXXX → benefits not sustained over a 30 year time horizon

- ***Company***: Inotersen is taken weekly and can be safely discontinued → not commit the NHS to significant irrecoverable costs
- ***ERG comment***: Unclear how this criterion should be interpreted
  - Inotersen is a XXXXXXXXX, if not provide substantial benefits, NHS would have committed significant irrecoverable costs

Additional ERG scenario analysis conducted to explore the impact of varying the discount rate for costs and benefits

Summary of modelling assumptions I.

Element	Company assumption	ERG response
Dosage	284mg solution, provided in a pre-filled syringe to be self-administered as a sub-cutaneous injection, once per week	In line with marketing authorisation
Population	Adults with hATTR-PN	Scope of model is narrower than defined by NICE, is in line with licenced indication for inotersen
Time horizon	Lifetime (41 years) - average age in model is 59	Chosen time horizon is appropriate
Starting population	Cohort of adult patients with hATTR-PN - XXXX Stage 1 and XXXX Stage 2, based on NEURO-TTR study	No change to starting cohort
Discontinuation of inotersen	Patients discontinue treatment on entering Stage 3 Discontinuation in Stages 1 and 2 disease modelled using survival analysis	Assumption around Stage 3 is in line with the licencing authorisation for inotersen
Transition probabilities	Trial gives data for transition probabilities between 0 and 35 weeks, and 35 and 66 weeks - points relate to time points of data collection in trial	Unclear what impact this decision has on the ICER → approach justified

[redacted]

Summary of modelling assumptions II.

Element	Company assumption	ERG response
Mortality	Mortality data from time of disease onset by V30M mutation status, obtained from digitised KM data published by Sattianayagam 2012 ***Clarification: Delphi panel provided HRs of mortality compared to general population***	HRs obtained from Delphi study correctly implemented, but there is considerable uncertainty around the method. Revised approach improves face validity
Health states for QALY	Modelled health states inferred from NEURO-TTR study based on defined TQoL score cut-offs on the Norfolk QoL-DN measure Mapped disease states matched with EQ-5D responses from THAOS registry of patients with hATTR (valued using a Brazilian population tariff)	Thresholds for disease stage definition not formally validated, based on a previous ERG report for AGNSS assessment of tafamidis ***Additional ERG scenario analysis conducted to explore impact of different Coutinho disease stage utilities on the ICER***
Source of utility data	Stewart et al. - describes how EQ-5D data from the THAOS registry were assigned Brazilian general population values	Alternative utility values reported by disease stage in Faria et al used in ***ERG base-case A***
Carer disutility	It was assumed in the model that each patient has two full-time carers	***Additional ERG scenario analyses conducted to explore the impact of carer disutility on the ICER***
Adverse events [redacted]	Adverse events assumed to have a minimal impact HRQoL – ***partly included in model in a scenario analysis after clarification***	ERG attempted to source utility data, or made alternative assumptions, verified by clinical expert opinion, where possible

Summary of modelling assumptions III.

Element	Company assumption	ERG response
Time to treatment discontinuation	Time to discontinuation in NEURO-TTR study used to calculate survival curves ***Clarification: curves updated using data from both NEURO-TTR and NEURO-TTR Extension study → using exponential survival curves***	***Additional ERG scenario analysis conducted to explore impact of using different parametric survival curve***
Perspective and costs	NHS & Personal Social Services	Questionable whether all relevant PSS costs included → costs of residential care not explicitly considered in model
Discount rate	1.5% discount rate	***Additional ERG scenario analysis conducted to explore the impact of varying the discount rate for costs and benefits***
Treatment compliance	Originally XXX that included all participants in the NEURO-TTR study → ***During clarification, rate amended to XXX - corrected an error in the way in which compliance of discontinuers was counted in NEURO-TTR study***	***Additional ERG scenario analysis conducted to explore impact of increasing compliance parameter***

[redacted]

Summary of company's model corrections during clarification stage

1) Correction of an error related to the modelling of treatment discontinuation (***not discussed here in details – implementation error in model, company substantially underestimated inotersen costs in the original submission***)

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

5) Inclusion of phlebotomist time to monitor platelets (***not discussed here in details – impact of change is negligible***)

[redacted]

Company base-cases

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	Incremental LYGs	ICER
Original base-case							
BSC	XXXXXX	XXXX	6.806				
Inotersen	XXXXXX	XXXX	6.806	XXXXXX	XXXX	0.00	£324,054
Revised base-case after clarification							
BSC	XXXXXX	XXXX	7.541				
Inotersen	XXXXXX	XXXX	8.559	XXXXXX	XXXX	1.018	£369,470

LYG: life years gained, QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio

Source: Table 30 of ERG report

+12 %

<u>Company corrections to base-case</u>

- Revised base case analysis estimated that patients treated with inotersen gained an additional XXXXXX compared to BSC, at an extra cost of XXXXXX leading to an additional cost per QALY gained of £369,470
- ***<u>ERG comment</u>***: changes outlined implemented correctly
  - Amendments increased the ICER and all deterministic sensitivity analyses

[redacted] **Results of the original company base-case won't be considered further**

Markov traces in model

Trace for inotersen

Source: Figures 9 and 10 of ERG report

Trace for BSC

- High rate of mortality in all patients with hATTR-PN regardless of treatment arm
- XXX of cohort died by cycle 100 (8.23 years) in inotersen arm and cycle 84 (6.92 years) in BSC arm
- By year 5, XXX of inotersen cohort are in disease stage 3 ←→ XXX in BSC group
  - Slower disease progression for people treated with inotersen
- Greatest proportion of LYGs and QALYs realised within first 5 to 10 years
  - Over XXX of total QALYs in the inotersen arm and XXX of total QALYs in the BSC arm are accrued in the Stage 1

[redacted]

QALY: Quality-adjusted life year; BSC: best supportive care

Costs by health state per patient

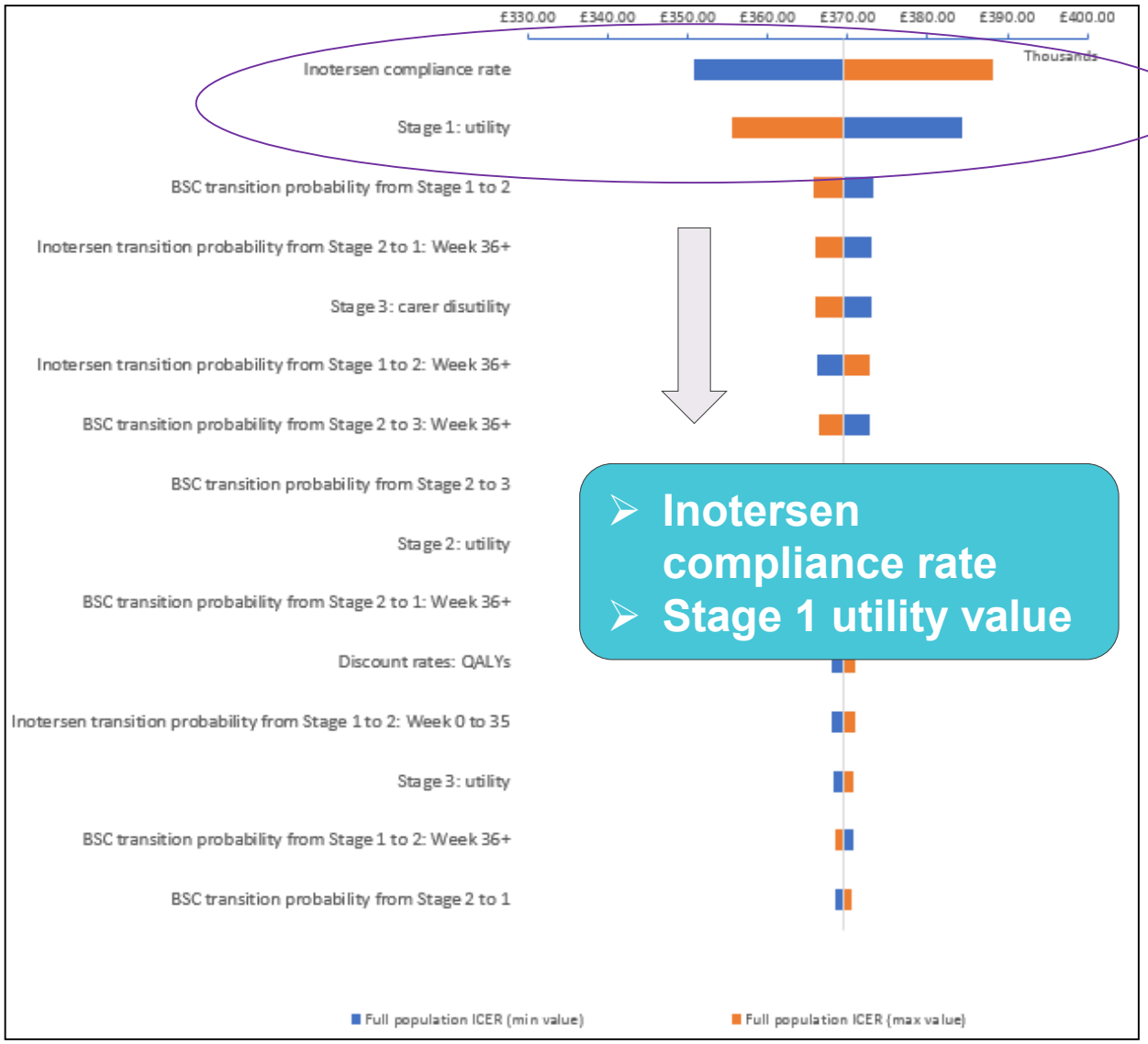
Health state	Treatment costs	Admin. costs	Vitamin A costs	Monitoring costs	HRU costs	Transition costs	All costs
INO St. 1	XXXXXX	XX	XXX	XXXX	XXXXX	XX	XXXXXX
INO St. 2	XXXXXX	XX	XX	XXXX	XXXXX	XXXXX	XXXXXX
INO St. 3	XX	XX	XX	XXXX	XXXXX	XXXXX	XXXXXX
INO Total	XXXXXX	XX	XX	XXXX	XXXXX	XXXXX	XXXXXX
BSC St. 1	XX	XX	XX	XX	XXXXX	XX	XXXXXX
BSC St. 2	XX	XX	XX	XX	XXXXX	XXXXX	XXXXXX
BSC St. 3	XX	XX	XX	XX	XXXXX	XXXXX	XXXXXX
BSC Total	XX	XX	XX	XX	XXXXX	XXXXX	XXXXXX

Source: Table A7 of clarification letter

- Difference is driven primarily by inotersen drug acquisition costs
  - Accounting for XXX of total costs in the inotersen arm
- In the BSC arm, majority of total costs (XXX) relate to healthcare resource utilisation
- Greatest proportion of costs (XXX) are incurred in disease Stage 1 in inotersen arm
- Only XX% of BSC costs are incurred in disease Stage 1
  - XXX and XXX of the total cost incurred in disease Stages 2 and 3 respectively

HRU: Healthcare Resource Utilisation

Company uni-variate deterministic sensitivity analyses



- DSAs have *minimal impact* on ICER → none of the analyses reduce the ICER below £350,000 per QALY gained

- ***ERG comment***: satisfied that the company's chosen DSAs implemented in model as described in submission

- Sensitivity and scenario analyses do not adequately characterise degree of uncertainty in ICER

- +/- 5% mean values were used rather than confidence intervals

    - Need to consider wider range of single and multi-parameter sensitivity analyses → explore the impact of varying important model parameters

[redacted] Source: Figures A5 of clarification letter (Appendix)

DSA: deterministic sensitivity analysis

Company probabilistic sensitivity analyses results

With ERG correction for sampling of carer disutility in Stage 3 patients

ERG comment: little information regarding how probabilistic sensitivity analysis (PSA) conducted

ERG corrected and error (positive, rather than negative utility assigned to carers of patients with Stage 3 disease), then re-ran the PSA on company's preferred base case analysis

	Base case (deterministic)	Base case PSA	ERG corrected base case PSA
Incremental cost	XXXXXX	XXXXXX	XXXXXX
Incremental LYG	1.018	Simulation results not provided	Simulation results not provided
Incremental QALY	XXXX	XXXX	XXXX
ICER	£369,470	£368,592	£392,667

LYG: life years gained, QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis

[redacted]

Source: Table 35 of ERG report

Company cost-effectiveness plane

WTP: Willingness to pay

Source: Figure A6 in clarification response (Appendix)

ERG comment:

- PSA not adequately characterise joint uncertainty in incremental costs and effects
- The probability that inotersen is cost-effective at increasing thresholds of WTP per QALY gained is as follows: £200k (XXX), £300k (XXX), £400k (XXX), £500k (XXX)
- Uncertainty surrounding model parameters is likely to have been substantially underestimated

ERG exploratory analyses: Impact of alternative scenario analyses on cost-effectiveness results

	Inotersen		BSC					
Description	Cost	QALY	Cost	QALY	Inc. Cost	Inc. QALY	Determin. ICER	% change in the ICER
Company preferred analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£369,569	0%
ERG preferred A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£683,178	84.86%
ERG preferred B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£478,079	29.36%

LYG: life years gained, QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio

ERG preferred base-case with Faria utility ***(ERG base-case A)***:

- Assumptions: 3.5% discounting; Log logistic treatment discontinuation curve; compliance among all patients in NEURO-TTR; Faria et al, linear calculation of utility; N=1 carer and ERG amended costs and disutility of serious adverse events

ERG preferred base-case with utility from company submission ***(ERG base-case B)***:

- Assumptions: ERG base-case A, but using company preferred utility source

[redacted]

Source: Table 40 of ERG report

Further results of ERG exploratory analyses

ERG conducted numerous additional scenario analyses

- Varying the discount rate for costs and QALYs had an impact on the ICER, ranging from £354,802 (0% discount rate) to £413,548 (6% discount rate)
- Using a log-logistic rather than an exponential parametric curve to model treatment discontinuation increased the ICER by 6.55%. Combined with alternative compliance assumptions 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 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
- ICER varied widely, depending on the assumptions applied, between £282,232 (optimistic case for inotersen) and £834,082 (most pessimistic case for inotersen)

[redacted]

ERGs amended PSA for the company's preferred base case model specification

Source: Figure 13 of ERG report

- Greater uncertainty in the ICER compared to the company's submitted PSA

PSA: probabilistic sensitivity analysis

Additional work done by the ERG

Problem in CS	ERG amendment	Level of mitigation
Discrepancies in model	1. Data entry error in relation to the onetime costs applied from Fria et al for transition to stage 2 disease in the model 2. Error in the 'PSA variables' spreadsheet of the model	**Errors corrected**
Concerns regarding some of the modelling assumptions and the choice of data for use in the economic model	**Exploratory analyses** are applied to the company's preferred base case analysis	**Problem partially mitigated** • 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
Modelling results under-state the uncertainty surrounding the base case ICER	**Multi-variate sensitivity analyses** are conducted to more fully explore uncertainty in the ICER	**Problem partially mitigated** • ERG 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

ICER does not fall below £300,000 per QALY gained in any scenario (only in most optimistic)

ERG conclusions

- ICER was ***most sensitive to***:
  - Discount rate applied to costs and QALYs
  - Impact of different assumptions around treatment discontinuation and compliance (and combinations of these)
  - Choice of source for patient utilites
  - Number of assumed carers

- 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

- Company ***makes a case for using 1.5% discounting*** → ERG disagree that this is appropriate
- Difficult to determine the most appropriate ICER with certainty
  - There is significant uncertainty in the ICER that was not captured
- ***ICER does not fall below £300,000 per QALY gained*** → only when the ***most optimistic combination*** of parameter input values is applied

[redacted]

QALY: Quality-adjusted life year

QALY weighting

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

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

QALY gain discounted and undiscounted

Deterministic analyses		QALY difference undiscounted	QALY difference discounted	ICER (per QALY gained)
Company	Base case	XXX	XXX	£369,569
ERG	Base case A	XXX	XXX	£683,178
	Base case B	XXX	XXX	£478,079

- Company submission does not make a case for additional QALY weighting
- ***ERG comment***: magnitude of QALYs gained in the economic model is well below the additional 10 QALYs stipulated in the NICE HST methods guide

[redacted]

Budget impact analysis

- BIA was informed by the same approach that under-pins the cost-effectiveness modelling
- [redacted] patients will be treated with inotersen in Year 1
- [redacted] patients will be treated with inotersen in Year 5
- Assumed market share for inotersen for is stated to be [redacted]

and [redacted] from years 1 through 5

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Annual budget (without INO)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget (with INO)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- ERG have been unable to re-produce, critique, or verify the validity of the company's assumptions due to a lack of information provided
  - Not incorporated directly within the company's electronic model

[redacted]

Source: Table D27 of company submission

Equality

- Most common genetic variants of hATTR amyloidosis in England (V122I and T60A) are more prevalent in people with African–Caribbean and Irish family origins
- hATTR amyloidosis typically affects older people
- hATTR amyloidosis is a chronic and disabling condition

Innovation

The company considers inotersen an innovative treatment because:

- First licensed medicine for the treatment of hATTR-PN to target the underlying cause of the disease
- Potential to dramatically improve patients' lives via slowing, arresting or reversing disease progression, which has not been achievable before
- Inotersen meets a high unmet medical need for patients with hATTR-PN → has the potential to radically change the way the disease is treated and may allow patients to live a full and fulfilling life for longer

[redacted]

Factors affecting the guidance

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

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

Key issues for consideration I.

Cost-effectiveness evidence

- What is the committee's view of the structure and assumptions in the economic model?
  - Patients were assumed to discontinue treatment on entering Stage 3
  - Two sets of transition probabilities sourced from NEURO-TTR study: A) baseline to week 35 and B) week 35 to 66 to extrapolate transitions over the full life time horizon for both arms
  - Mortality data: hazard ratios obtained from Delphi panel
  - Modelled health states were inferred from the NEURO-TTR study based on defined TQoL score cut-offs on the Norfolk QoL-DN measure
  - Each patient has two full-time carers
  - Adverse events partially included in economic model
  - Time to discontinuation in NEURO-TTR and NEURO-TTR Extension studies used to calculate survival curves
  - Model used XXX treatment compliance rate

[redacted]

Key issues for consideration II.

Cost-effectiveness evidence

- What is the most appropriate source of utility for each health state?
- Should a 1.5% or 3.5% discount rate be used?
- What are the most plausible ICERs?
- What factors affecting the guidance need to be taken into account?
- What QALY weighting should be used in decision-making?
- Equality issues raised: any additional considerations required?

[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

INTERIM

Specification for company submission of evidence

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

July 2018

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Abbreviations

Abbreviation	Definition
2'MOE	2'-O-2-methoxyethyl
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ASO	Antisense oligonucleotide
ARC	Amyloidosis Research Consortium
ATTR	Transthyretin amyloidosis
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
BSI-53	Brief Symptom Inventory-53
CHMP	Committee for Medicinal Products for Human Use
CD	Crohn's disease
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CHF	Chronic heart failure
CM	Cardiomyopathy
CRO	Clinical research organisation
CSR	Clinical study report
DET	Data extraction table
DN	Diabetic neuropathy
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiography
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of treatment
EQ-5D	EuroQoL-5 Dimensions
ERG	Evidence review group
FAC	Familial amyloidal cardiomyopathy
FAP	Familial amyloid polyneuropathy
FAS	Full Analysis Set
FDA	Food and Drug Administration
GI	Gastrointestinal
GLS	Global longitudinal strain
GSI	Global symptom index
HRQoL	Health related quality of life
HRDB	Heart rate response to deep breathing
hATTR	Hereditary transthyretin amyloidosis
hATTR-CM	Hereditary transthyretin amyloidosis with cardiomyopathy
hATTR-PN	Hereditary transthyretin amyloidosis with polyneuropathy

HRU	Healthcare resource use
IBS	Irritable bowel syndrome
ICER	Incremental cost-effectiveness ratio
IXRS	Interactive voice/web-response system
LSM	Least squares mean
LV	Left ventricular
LY	Life year
LSM	Least squares mean
MAA	Marketing authorisation application
mBMI	Modified body mass index
MCMC	Markov chain Monte Carlo
MCS	Mental component summary
MedDRA	Medical dictionary for regulatory activities
MID	Minimally important difference
mg	Milligrams
MMRM	Mixed model for repeated measures
mNIS	Modified neuropathy impairment score
mRNA	Messenger RNA
MS	Multiple sclerosis
NAC	National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Neuropathy impairment score
NIS-C	Neuropathy impairment score-cranial
NIS-R	Neuropathy impairment score-reflexes
NIS-S	Neuropathy impairment score-sensation component
NIS-W	Neuropathy impairment score-weakness
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
PbR	Payment by results
PCS	Physical component summary
PD	Pharmacodynamic
PK	Pharmacokinetic
PN	Polyneuropathy
PND	Polyneuropathy disability
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life

RCT	Randomised clinical trial
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short form-36
SLR	Systematic literature review
SmPC	Summary of product characteristics
SS	Safety Set
TEAE	Treatment-emergent adverse event
THAOS	Transthyretin Amyloidosis Outcomes Survey
TQoL	Total quality of life
TTR	Transthyretin
UCL	University College London
UK	United Kingdom
UPCR	Urine protein to creatinine ratio
US	United States
V30M	Valine replaced by methionine at amino acid position number 30

Executive Summary

Nature of the condition

Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) is a rare and devastating disease. It is an autosomal dominant, hereditary polyneuropathy in which widespread deposition of mutant amyloid protein leads to the disruption of the nervous system and key organs. This leads to a rapid decline in functional status, mobility, and independence, as well as premature death. Patients with hATTR-PN have a median survival of 3 to 15 years from symptom onset (1, 2).

hATTR-PN is a rapidly progressing disease and unrelenting. As the disease progress to Stages 2 and 3, accumulation of TTR amyloid in various tissues and organs continues and sensorimotor symptoms such as severe pain, tingling and weakness progresses from distal lower limbs to upper limbs symmetrically before becoming more proximal, eventually rendering patients wheelchair-bound or bedridden.

hATTR-PN has a significant impact on patients' and their carers' quality of life in many different aspects. The issue is further compounded by multiple generations of families suffering from the disease, and having to take on dual roles as patients and carers.

The physical impact of hATTR-PN is devastating for patients; disease progression is associated with the continuous decline in physical capabilities and the corresponding loss of independence. Patients with hATTR-PN exhibit a consistent pattern of clinically meaningful deficits in health-related quality of life (HRQoL), particularly in the physical domains (3, 4). Patients are increasingly reliant on family members and carers to support daily activities as the disease progresses to more advanced stages.

The psychological impact takes its toll on both patients and carers, with the knowledge of the rapid progressive nature of the disease associated with loss of independence and inevitably, premature death. Patients and their carers are often withdrawn and feel isolated, commonly suffering depression and anxiety (5, 6).

The HRQoL of carers of patients with hATTR is also significantly impacted. Carers are typically family members or friends and, as the disease progresses, patients gradually lose their independence and become increasingly reliant on the support of their carers for basic daily living activities, including dressing and washing. Patients often require multiple carers to support their needs, with studies reporting a median of 100 to 144 hours per week spent caring for patients with hATTR (1).

Current treatment options available in England only provide symptomatic relief. As such, there is a significant clinical unmet need for novel treatments which treat the underlying cause of the disease, with the potential to slow, arrest or reverse disease progression.

Impact of the new technology

Inotersen (brand name: Tegsedi™) is a novel, first-in-class 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide (ASO) that inhibits production of TTR protein in adult patients with hATTR. It is the first licenced medicine to target and address the underlying cause of the disease; marketing authorisation was granted by the European Medicines Agency (EMA) on the 6th July 2018 for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hATTR (hATTR-PN).

The selective binding of inotersen to the TTR messenger ribonucleic acid (mRNA) causes the degradation of 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 (7). This reduction in TTR production decreases the formation of TTR deposits in tissues and organs, and is associated with improved clinical outcomes by slowing, arresting or reversing disease progression.

Inotersen is a self-administered once weekly subcutaneous (SC) injection at a dose of 284 mg per week(7). The clinical effectiveness of inotersen in patients with hATTR-PN has been demonstrated, primarily through the pivotal multi-centre, placebo-controlled Phase 2/3 NEURO-TTR study (8). The NEURO-TTR study is one of the largest studies (n=172) of hATTR-PN patients to date with patients followed for 15 months.

In the NEURO-TTR study, co-primary endpoints were the modified neuropathy impairment score (mNIS) +7 composite score and the Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN) score (also referred to as Total QoL [TQoL score]). Inotersen treatment resulted in clinically meaningful, substantial, and highly statistically significant improvements in both neurological disease progression and QoL versus placebo (primary outcomes least squares mean [LSM] difference: mNIS+7, $p<0.001$; Norfolk QoL-DN, $p<0.001$) at 15 months. Statistically significant improvements for both primary outcomes were achieved despite inotersen patients having had a greater disease severity at baseline versus patients in the placebo group.

A statistically significant treatment benefit as per these primary endpoints was achieved in patients with hATTR-PN as early as 8 months after treatment initiation with inotersen. Furthermore, the magnitude of treatment benefit of inotersen, as per both primary outcome measures, increases over time on treatment, suggesting that the maximally achievable treatment effect may not have been captured during the study duration. This indicates that the magnitude of the treatment effect observed in the study may underrepresent the actual treatment benefit of inotersen.

Progression of disease was slowed or arrested in 36.5% of patients treated with inotersen, indicated by improvement (or no worsening) in the mNIS +7 composite score ($p=0.033$). Response rate was consistently higher in the inotersen group than the placebo group across all thresholds evaluated, with an approximate 2-fold difference observed between the inotersen and placebo groups at each threshold.

Fifty per cent of patients receiving inotersen treatment showed improvement or no worsening in Norfolk QoL-DN total score ($p<0.008$). Inotersen treatment demonstrated robust reductions in circulating TTR, where over 80% of patients in the inotersen study arm showed a $\geq$60% decrease in TTR plasma levels by week 13 through to week 66 (differences in LSM change from baseline between treatment arms: $p<0.001$ at all time points). Overall, the results from NEURO-TTR demonstrated that inotersen has the potential to slow, arrest or reverse disease progression in patients with Stage 1 or 2 hATTR-PN.

Safety data from the NEURO-TTR study and NEURO-TTR extension showed that inotersen has a manageable safety and tolerability profile, with the majority of drug-related treatment-emergent adverse events (TEAEs) mild to moderate in severity.

Results from the NEURO-TTR Extension study demonstrated continued slowing of disease progression and QoL benefits were maintained in the long-term (up to 144 weeks) with inotersen treatment. The results demonstrate treatment with inotersen should be initiated early, with the magnitude of treatment benefits having been shown to increase over time.

New treatments specifically targeting the underlying cause of hATTR offer significant hope to patients, their families and carers (9). hATTR-PN is a multi-system, progressively debilitating, and fatal neurodegenerative disease. Current treatment options are limited, and most patients only receive symptomatic therapies that do not address the underlying cause or change the course of disease. By inhibiting hepatic production of both mutant and wild type (normal) TTR, inotersen represents a step-change in treatment, for patients with hATTR-PN who have a short life expectancy, high morbidity, and a high unmet medical need.

Value for money

As part of this submission, a patient access scheme has been proposed, with a net price of [redacted] per weekly dose.

A cohort-based Markov state-transition model was used to estimate long-term costs and consequences for the treatment of hATTR-PN in adults patients, compared to best supportive care (BSC). The choice of model structure was based upon an existing model submitted to the Advisory Group for National Specialised Services (AGNSS) in a related disease area. To capture the differences in costs and outcomes as patients progress in hATTR-PN, health states were based on Coutinho staging (10). A lifetime horizon (41 years) was adopted to fully capture the impact of disease and mortality, and a cycle length of 4-weeks was modelled.

Clinical effectiveness for both inotersen and BSC were sourced from the pivotal NEURO-TTR study, with disease progression estimated through evaluation of the trial's TQoL score. Since mortality data from the NEURO-TTR study were immature, an AGNSS evidence review group (ERG) report in a related disease area was used to inform the transition to the death state for both treatment arms. Discontinuation on intotersen was extrapolating by fitting a Gompertz distribution to data from the NEURO-TTR study. Compliance for patients receiving inotersen was calculated based on the NEURO-TTR study.

Health state costs, patient utilities and caregiver disutilities for UK hATTR-PN patients were based upon the AGNSS ERG report, NHS reference costs and relevant published literature.

After applying a discount rate of 1.5%, patients receiving inotersen accrued [redacted] QALYs compared to BSC, at an additional cost of [redacted] per patient. This corresponded to an incremental cost-effectiveness ratio (ICER) of £324,054 per QALY gained. Deterministic, probabilistic and scenario analyses demonstrated that the economic results are robust to changes to key model parameters. The model was most sensitive to clinical transition probabilities and health state utilities.

The estimated number of hATTR-PN patients eligible is approximately [redacted] patients based on expert opinion and it is estimated that the net budget impact of inotersen in year 1 will be [redacted] rising to [redacted] in Year 5.

Impact of the technology beyond direct health benefits

Given the progressively debilitating nature of the disease, patients with hATTR-PN suffer extensively in terms of their health and emotional wellbeing; however, the impact of patients' progressive loss of independence and dignity extends into many other aspects of their lives and the lives of their carers. This includes a high financial burden, loss of patients' and carers' ability to work associated with a significantly reduced earning potential, and a detrimental impact of patient's ability to undertake everyday activities and actively participate in family life and social activities.

Patients' ability to undertake paid work is significantly reduced, given the progressively debilitating nature of the disease and poor life expectancy, resulting in around two-thirds of patients unable to work (11).

Family members are often carers for patients with hATTR-PN, providing medical support and care and assisting with activities of daily living, including household chores such as shopping and cooking. At advanced stages of the disease, carers also provide daily personal care. Consequently, carers' own ability to work and work productivity is significantly impaired.

Inotersen has the potential to slow, arrest or reverse disease progression, with patients remaining in earlier stages of the disease (Stage 1 or 2) for longer. In turn, this allows patients to stay in a better health state and retain their independence for longer via the preservation of their ambulatory ability and key health domains, providing patients the opportunity to continue with employment, as well as actively participate in family life and social activities. Inotersen also has the potential to reduce the burden falling on carers, in terms of their wellbeing, work productivity and participation in family and social activities.

It is anticipated that inotersen will fit into the current clinical pathway with a highly specialised service being established. [redacted]

Summary

Inotersen is the first licenced treatment to offer the potential to slow, arrest or reverse disease progression in patients with Stage 1 or 2 hATTR-PN by targeting the underlying cause of the disease. The reimbursement of inotersen will offer hope to patients, carers and families, and importantly will relieve the burden of the disease by allowing patients and their carers to continue paid work and maintain active participation in family and social activities.

Section A – Decision problem

1 Statement of the decision problem

Table A1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with hereditary transthyretin-related amyloidosis	People with hATTR with polyneuropathy (hATTR-PN)	To align with licensed indication for inotersen
Intervention	Inotersen	None	Not applicable
Comparator(s)	Established clinical management without inotersen	This is referred to as best supportive care	No deviation apart from naming convention
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 • health-related quality of life (for patients and carers).	None	Not applicable
Nature of the condition	• disease morbidity and patient clinical disability	None	Not applicable

	with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options		
Clinical Effectiveness	• overall magnitude if 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
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
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	Non-health benefits summarised in Section E. No variation from scope.	Not applicable

	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		

Abbreviations: hATTR-PN, hereditary transthyretin amyloidosis; HRQoL, health-related quality of life; N/A, Not applicable; NICE, National Institute for Health and Care Excellence; TTR, transthyretin

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Tegsedi™

Approved name: Inotersen

Therapeutic class: N07 – other nervous system drugs

2.2 What is the principal mechanism of action of the technology?

Inotersen is a 2'-O-2-methoxyethyl (2'MOE) phosphorothioate ASO that inhibits hepatic production of both mutant and wild type (normal) TTR, the carrier protein for thyroxine,vitamin A and the protein that is deposited as amyloid fibrils in hATTR.

The selective binding of inotersen to TTR mRNA causes the degradation of 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 (7).

Reduction in TTR production by the liver with inotersen treatment is associated with improved clinical outcomes in hATTR, likely due to decreasing the formation of TTR amyloid fibril deposits thus slowing, arresting or reversing disease progression - see Section 9.6.1.1, **Error! Reference source not found.**. Inotersen therefore represents a step-change in treatment in hATTR-PN.

2.3 Please complete the table below.

Table A2. Dosing information of technology being evaluated

Pharmaceutical formulation	284 mg solution for injection supplied in a 1.5mL pre-filled syringe
Method of administration	Self-administered SC 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 SC administration.
Doses	Each pre-filled syringe contains 284 mg inotersen (equivalent to 300 mg inotersen sodium).
Dosing frequency	The recommended dose is 284 mg by SC injection once every week. For consistency of dosing, patients should be instructed to give the injection on the same day every week.
Average length of a course of treatment	Chronic therapy, until discontinuation or death
Anticipated average interval between courses of treatments	Weekly
Anticipated number of repeat courses of treatments	Chronic therapy, until discontinuation or death
Dose adjustments	Inotersen is associated with reductions in platelet count, which may result in thrombocytopenia. Dosing should be adjusted according to laboratory values as follows: • For patients with a confirmed platelet count ≥75 to <100 x109/L, dose frequency should be reduced to 284 mg every 2 weeks • 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 • For patients with a confirmed platelet count <25 x109/L, treatment should be permanently discontinued, and corticosteroids administered Other than in accordance with the algorithm above, dosing adjustment is not required in the elderly, patients with mild or moderate renal impairment or hepatic impairment.

Abbreviations: L, litre; SC, subcutaneous.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the current regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Inotersen was granted a marketing authorisation by the EMA on the 6th July 2018 for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hATTR.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Anticipated date of UK availability: Q4 2018.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Inotersen was granted a marketing authorisation by the EMA on the 6th July 2018 and therefore is approved in all EU countries as well as the UK. The US Food and Drug Administration (FDA) granted Priority Review of inotersen in January 2018 and is under review with the FDA as well as the Canadian regulatory authority. The FDA previously granted inotersen Orphan Drug Designation and Fast Track Status.

3.4 If the technology has been launched in the UK provide information on the use in England.

Inotersen has not yet been launched in the UK.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table A3. Inotersen ongoing studies with data available in the next 12 months **20**

Study acronym and NCT number	Design	Population	Intervention and comparator(s)	Status†
NEURO-TTR Extension; NCT02175004 (unpublished)	Open label	Stage 1 and Stage 2 patients, who completed the NEURO-TTR study, with hATTR-PN with an NIS ≥10 and ≤130 at NEURO-TTR baseline	Inotersen only	Ongoing

† Exact date of data analyses not yet determined, interim results for this study ([redacted]) are presented within this submission.
Abbreviations: hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NIS, neuropathy impairment score.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

At the time of submission, inotersen is not subject to any other form of assessment in the UK. Akcea Therapeutics intends to make a submission to the Scottish Medicines Consortium in Q4 2018, with their advice anticipated to be published in 2019.

5 Equality

5.1 Please let us know if you think that this evaluation:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Akcea Therapeutics does not believe that there are any equality issues for this evaluation.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable – no equality issues have been identified.

Section B – Nature of the condition

Summary

- hATTR-PN is a rare and devastating disease. The widespread deposition of mutant TTR amyloid protein leads to disruption of the nervous system and key organs. This leads to a rapid decline in functional status, independence and mobility.
- Patients with hATTR-PN suffer premature mortality, with a median survival of 3 to 15 years from symptom onset (1, 2).
- hATTR-PN is a rapidly progressing disease and unrelenting. As the disease progresses to Stages 2 and 3, there is progressive loss of motor function and ultimately patients are confined to a wheelchair or become bedridden.
- hATTR-PN has a significant impact on patients and their carers' quality of life in many different aspects. The issue is further compounded by multiple generations of families suffering from the disease, and having to take on dual roles as patients and carers.
    - The physical impact of hATTR-PN is devastating for patients; disease progression is associated with the continuous decline in physical capabilities and the corresponding loss of independence. Patients are increasingly reliant on family members and carers to support with daily activities as the disease progresses to more advanced stages.
    - The psychological impact takes its toll on both patients and carers.
    - Patients often require multiple carers to support their needs. The HRQoL of carers of patients with hATTR is also significantly impacted, with studies reporting a median of 100 to 144 hours per week spent caring for patients with hATTR (1).
- It is estimated that there are approximately [redacted] patients with Stage 1 or Stage 2 hATTR-PN diagnosed in England that will be eligible for inotersen treatment.
- Current treatment options only provide symptomatic relief. Inotersen is the first licenced medicine to treat the underlying cause of the disease, with the potential to slow, arrest or reverse disease progression.

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

6.1.1 Disease Overview – hATTR-PN is a rare and devastating disease

Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN, historically called Familial Amyloid Polyneuropathy) is a rare, autosomal dominant, hereditary polyneuropathy in which widespread deposition of mutant amyloid protein leads to disruption of the peripheral nervous system and key organs. This leads to a rapid decline in functional status, independence and mobility, followed by premature death.

Hereditary amyloidosis is caused by mutations in genes that code for the transthyretin (TTR) protein. The TTR protein is predominantly synthesised in the liver as a tetrameric structure, before being secreted into the blood where it acts as a carrier for retinol and the thyroid hormone thyroxine. Gene mutations cause the synthesis of misfolded, structurally unstable TTR proteins which dissociate and form monomeric amyloid fibrils that accumulate in tissues, disrupting normal cellular function. Aggregations of mutant TTR are known to occur in various organs systems including peripheral, central and autonomic nerves, the heart, kidneys and eyes and rarely the central nervous system (12).

hATTR-PN is very rare, with an estimated 10,000 sufferers globally (8). Over 100 genetic mutations associated with hATTR have been identified since the disease was first described in 1952 in Portugal.

hATTR-PN presents with the most disabling symptoms. Sensorimotor symptoms such as severe pain, tingling and weakness progress from distal lower limbs to upper limbs symmetrically before becoming more proximal; eventually rendering patients wheelchair-bound or bedridden. Autonomic symptoms such as nausea, vomiting, diarrhoea, constipation and orthostatic hypotension can lead to weight loss and muscle wasting, further contributing to significant limitations to the ability to undertake everyday activities, independence and quality of life, all of which affects both patients and their carers (1).

Mortality from hATTR-PN typically occurs on average 3 to 15 years from symptom onset. Cachexia, infection and cardiac causes are the usual causes of fatality with this devastating disease (13).

6.1.2 Disease Course – hATTR-PN is rapid and unrelenting

As TTR amyloid aggregates in various tissues, symptoms can appear in multiple organ systems, at different ages and progress at different rates. Symptoms of hATTR-PN are frequently attributed to more common disorders, resulting in an average diagnostic delay of 4 years and visits to many different specialists prior to

establishment of the correct diagnosis (13). Age at symptom onset ranges from the second to ninth decade of life, with great variations across different populations and mutations (14).

hATTR is characterised by progressive sensory, motor, and autonomic neuropathy, associated with significant morbidity and disability (15). TTR amyloid deposits often accumulate in the heart, kidneys and eyes (8, 16). Most patients have a mixed phenotype and experience overlapping symptoms of PN and cardiomyopathy (CM).

Symptoms typically start with discomfort (numbness, tingling, pins and needles) in the feet, impairing sensory and pain perception (1, 14). [redacted] (9). The neurological deficit progresses to the legs and the upper limbs, resulting in a profound loss of motor function (1, 14). [redacted] .

Autonomic symptoms typically include dizziness or fainting, vomiting, severe diarrhoea and/or constipation and neurogenic bladder, which eventually become life-threatening (14). In men with hATTR, erectile dysfunction is an early feature and has been reported by 52% of patients with hATTR (14). [redacted] . The severity of symptoms increases as the disease progresses, resulting in a continuous and rapid decline in the HRQoL of patients and their families and carers.

The diagnostic workup for suspected hATTR involves a comprehensive clinical assessment (including neurological, cardiological, renal and ophthalmological assessments) and a complete family history. Biopsies are taken from sites and subjected to immunohistological staining and genetic testing is performed (13).

The impact of polyneuropathy can be monitored using a variety of disease specific and non-specific tools (e.g. Neuropathy impairment score [NIS], Neuropathy impairment score–lower limb [NIS-LL], Sum 7 test, Modified Neuropathy Impairment Score +7 [mNIS+7], Norfolk quality of life diabetic neuropathy [Norfolk QoL-DN] score).

hATTR-PN most often can be staged using ambulatory status (Coutinho Stages 1-3) (10):

Table B1. hATTR-PN disease stages

HTTR-PN Coutinho Stage	Ambulatory Status
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

Focal lesions may occur at disease onset and carpal tunnel syndrome is a common, non-specific, manifestation of hATTR-PN (14). Other manifestations include ocular abnormalities (e.g., vitreous opacities, chronic open-angle glaucoma and scalloped pupils) and renal involvement (14).

Cardiac manifestations have been reported in 80% of patients with hATTR-PN (14). Patients with cardiac involvement experience episodes of arrhythmias and severe conduction disorders, including atrioventricular block with faintness, syncopes, or even sudden death. Atrioventricular block and bundle branch blocks are common, and implantation of a pacemaker is often needed. The presence of CM is generally associated with a worse prognosis (14).

The average life expectancy from symptom onset for patients with hATTR-PN is 3 to 15 years (2). Patients typically die due to malnutrition and cachexia consequent to general physical wasting including loss of weight and muscle mass, cardiac disease, renal failure, and sudden death (presumed to be cardiac).

6.1.3 The Patient Need – Treat the underlying cause

The current management paradigm for patients with hATTR-PN has been focused upon symptom management. [redacted] (9).

Drugs which can stabilise the TTR tetramer have been tried in clinical practice. Diflunisal (off-label) and Tafamadis (licensed for hATTR but not reimbursed in England) have properties which can stabilise mutant TTR, however evidence for both is limited and usage in the NHS very low.

As such, patients with impending neurological decline leading to immobility, loss of bowel and bladder control, and the risk of early mortality have no effective treatment options to significantly impact disease progression. Clinicians have little more to offer than palliation.

Due to its unique mechanism of action, inotersen has the potential to provide significant benefit to a broader group of patients with hATTR compared with existing symptomatic treatments because it addresses the cause of the underlying disease. Inotersen is an ASO drug targeted to human TTR messenger RNA (mRNA). Hybridisation to the cognate TTR mRNA results in the RNase H1-mediated degradation of the TTR mRNA, preventing production of the TTR protein.

Inotersen was designed to avoid hybridisation to any known TTR mutation site, is highly specific for TTR and therefore does not hybridise to any other known human gene. The strategy behind treating patients with hATTR with inotersen is to reduce the levels of mutated and wild-type TTR protein secreted by the liver, the primary site of TTR production and ASO distribution after systemic delivery. Wild-type TTR can continue to deposit as amyloid.

By decreasing the amount of liver-derived TTR protein circulating in the plasma, inotersen treatment results in decreased formation of TTR amyloid fibril deposits in organ tissues, thus slowing, arresting or reversing disease progression consequent to these deposits. This strategy is similar to orthotopic liver transplant (OLT), with the exception that inotersen reduces all forms of TTR (wild-type and mutated). Given that wild-type TTR can continue to deposit as amyloid following liver transplantation (17-20), this distinction may represent a therapeutic advantage for inotersen treatment over OLT.

The main clinical benefits of inotersen treatment are that it allows patients to remain in disease Stages 1 and 2 for longer, slowing, arresting or reversing their decline. As a result, patients will retain their mobility and independence and be active and productive members of their family, community and society for longer.

The ability to routinely self-administer inotersen treatment at home or at a place of the patient's choice provides convenience and eliminates the need for patients to travel to a specialist centre to receive the treatment. This reduces absenteeism and maintains patients' independence to continue with employment as well as actively participate in family and social life which might otherwise be compromised.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

It is estimated that there are approximately [redacted] patients with Stage 1 or Stage 2 hATTR-PN diagnosed in England that will be eligible for inotersen treatment (see Section 13).

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

Patients with hATTR-PN suffer premature mortality, with a median survival of 3 to 15 years from symptom onset (1, 2).

There is a scarcity of published data reporting survival data in the UK. However, a study by Sattianayagam *et al.* (2) reported survival data for 52 UK and Canadian patients with a non-V30M (T60A) mutation and 26 Swedish patients with a V30M mutation. Median survival from time of diagnosis was 3.4 years and 6.6 years from

symptom onset for non-V30M patients versus 8.2 years and 12 years for V30M patients, respectively.

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

7.1.1 Emotional wellbeing

The psychological impact of hATTR-PN is significant. Patients live with the knowledge that their disease is progressive and incurable and will inevitably lead to profound disability and morbidity, the gradual loss of independence and, eventually, death. The hereditary nature of the condition means that patients are likely to have witnessed other family members struggling and dying from the disease. Patients may feel guilty about passing the disease onto their children, and they often mask their feelings to protect other members of the family. As the disease progresses, patients increasingly withdraw from family and social activities leading to feelings of isolation, depression and anxiety. hATTR has been found to considerably impact patients' independence and sense of normality; in particular their ability to work, participate in family and social life, be mobile, leave the house and undertake daily activities and hobbies, all of which are likely to be detrimental to their emotional wellbeing. [redacted] (9).

Lopes *et al.* reported on the psychological burden associated with hATTR-PN in both asymptomatic carriers (n=81) and patients with an established diagnosis (n=109) (5) In the study, the Brief Symptom Inventory (BSI-53) and a social demographic questionnaire were administered to patients and the results compared with those for the general population of Portugal. For all three Global Symptom Index (GSI) domains, 42% of individuals with hATTR-PN had scores above those of the general population (with higher scores representing poorer QoL), and the proportion was higher for the subgroup with a confirmed diagnosis of hATTR-PN compared with the subgroup of asymptomatic carriers. Median values for all dimensions of the BSI were higher in the group with a confirmed diagnosis than for carriers, with a statistically significant difference for somatisation, depression, anxiety, and psychoticism.

In a further study, Lopes *et al.* described the impact of hATTR-PN from a patient's perspective based on responses to two questionnaires (6). Over a third (37.6%) of patients with hATTR-PN reported that their parent's disease had resulted in adverse changes to their own life such as experiencing fear of the future, giving up school to help with family needs, and having feelings of not having had a normal childhood (6). The majority of patients (54%) had been their parent's carer, a third of patient

respondents (37%) said that genetic testing had had an impact on their lives, and a quarter (26.5%) reported having psychiatric problems, most frequently depression and anxiety.

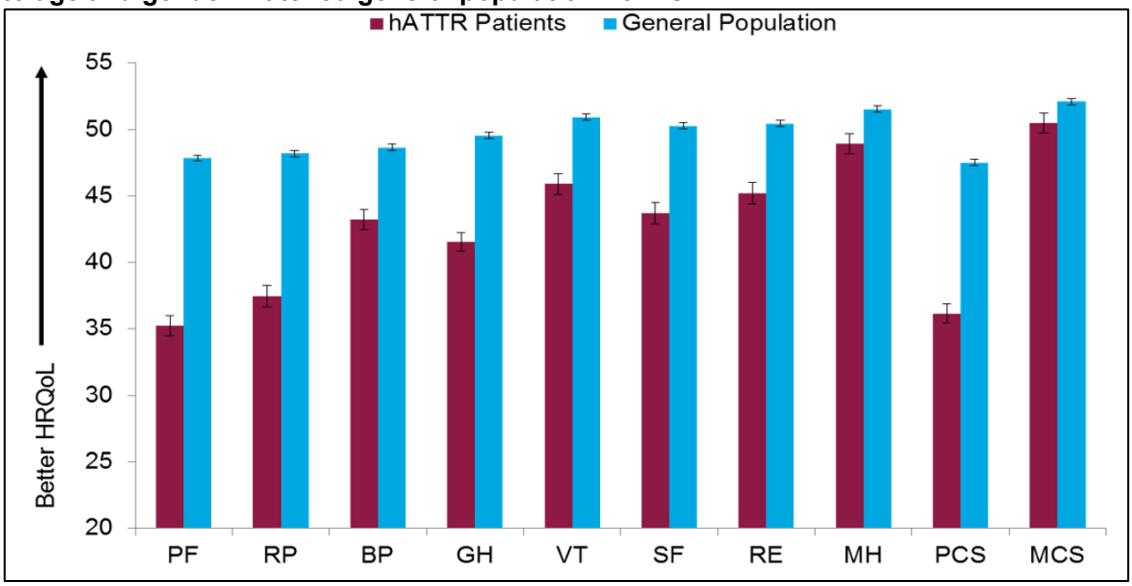
7.1.2 Physical health

The physical impact of hATTR-PN is devastating; disease progression is associated with the continuous decline in physical capabilities, and patients eventually are confined to a wheelchair or become bedridden. Patients with hATTR-PN exhibit a consistent pattern of clinically meaningful deficits in HRQoL, particularly in the physical domains.

[redacted]

When compared with age- and gender-adjusted general population norms, mean baseline scores for hATTR-PN patients show considerable HRQoL burden in all physical domains and for the physical component summary (PCS) – see Figure 1**Error! Reference source not found.**. (3)

Figure 1: Mean SF-36v2 health survey scores for the hATTR-PN patient sample relative to age and gender-matched general population norms



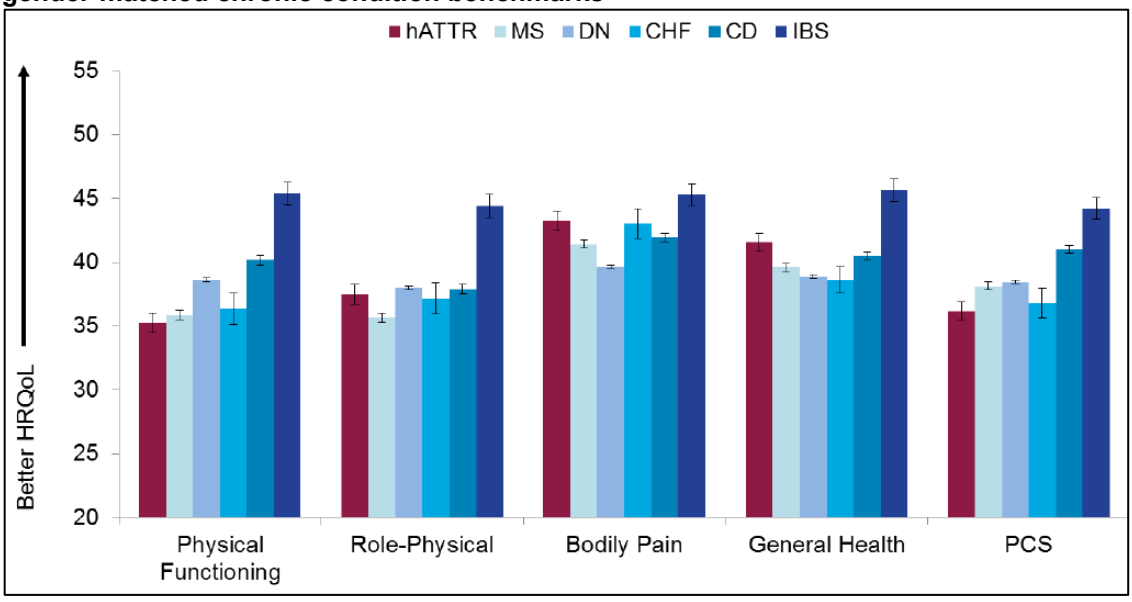
Abbreviations: BP, bodily pain; GH, general health; hATTR, hereditary ATTR amyloidosis; MCS, mental component summary; MH; mental health; PCS, physical component summary; PF, physical functioning; RE; role-emotional; RP, role-physical; SF, social functioning; SF-36, short form-36; VT, vitality.
Error bars represent standard errors of means.
Source: Lovley *et al.*(3).

Patients with hATTR-PN experience a greater impairment in HRQoL compared to patients with other chronic diseases. Comparisons between hATTR-PN patients' baseline Short Form-36 version 2 (SF-36v2) health survey scores and several of the

condition-specific benchmarks show the relative burden of hATTR-PN on patients' physical functioning – see Figure 2**Error! Reference source not found.** .

- Scores for the physical functioning domain and overall physical health (i.e. PCS) were worse for hATTR-PN patients by a greater-than minimally important difference (MID) magnitude than for Crohn's disease (CD), diabetic neuropathy (DN), and irritable bowel syndrome (IBS) benchmark samples.
    - The burden on physical functioning and PCS for hATTR-PN patients was similar to those observed for chronic heart failure (CHF) and multiple sclerosis (MS) benchmark samples.
- Scores for the role-physical and general health domains were worse for hATTR-PN patients by a greater-than-MID magnitude than for the IBS benchmark sample.
    - The burden on role-physical and general health for hATTR patients was similar to that observed for CD, CHF, DN, and MS benchmark samples.
- The score for the bodily pain domain was better for hATTR-PN patients by a greater-than-MID magnitude than that for the DN benchmark sample.
- The burden on bodily pain for hATTR-PN patients was similar to those observed for CD, CHF, IBS, and MS benchmark samples.

Figure 2: Mean SF-36v2 scores for the hATTR-PN patient sample relative to age and gender-matched chronic condition benchmarks



Abbreviations: CD, Crohn's disease; CHF, congestive heart failure; DN, diabetic neuropathy; hATTR, hereditary ATTR amyloidosis; IBS, irritable bowel syndrome; MS, multiple sclerosis; PCS, physical component summary.
Error bars represent standard errors of means.
Source: Lovley *et al.*(3).

Berk *et al.* evaluated the impact of inotersen on HRQoL on patients with hATTR-PN who were enrolled in the NEURO-TTR study relative to healthy controls(4). HRQoL was assessed using the patient-reported questionnaires Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) and the SF-36v2 Health Survey. For both

metrics, mean baseline HRQoL scores for hATTR-PN patients were significantly worse than scores reported for healthy controls. The baseline mean (standard deviation [SD]) Norfolk QoL-DN score in hATTR-PN patients was 48.4 (27.2) compared with 2.6 (5.0) for healthy controls (higher scores reflect worse HRQoL)(4). The mean (SD) SF-36v2 PCS score in hATTR patients was 36.3 (9.1) compared with 50.0 for healthy controls (lower scores reflect worse HRQoL) (4). Severity of disease, as measured by neuropathy instruments (such as mNIS+7), and patient-reported HRQoL measures were strongly correlated.

7.1.3 Everyday life

The impact of the hATTR-PN on everyday life is variable but progressively worsens as the disease progresses and disability increases. The burden of hATTR on patients and families is significant. As hATTR is a multi-systemic disease, [redacted] (9).

In the early stages of disease, patients are likely to continue with work, family life and social activities. As the disease progresses, the severity of symptoms increases and there is a progressive loss of patients' independence, and work and social activities are impacted. Patients may, for example, experience severe bouts of constipation or diarrhoea, stopping them from leaving the house. Pain may lead to lack of sleep, causing fatigue which further exacerbates the decline in physical functioning. As the impairment of motor function progresses, patients become more restricted, with less ability to stand and walk, restricting their mobility and making everyday activities such as climbing the stairs difficult.

In a study by Berk *et al.*, 27% and 30% of patients with Stage 1 and Stage 2 hATTR-PN reported some difficulty with reading a newspaper or book and eating, respectively (21). Many patients could not perform tasks requiring coordination and muscle strength; dancing (59%), running (76%), standing for long periods of time (63%). The number of tasks and activities that ≥50% of patients were unable to perform increased between disease stages (53% of patients with Stage 1 disease and 96% with Stage 2 disease were unable to run).

Many patients of working age experience major impairment of their ability to work, are forced to reduce their working hours or give up employment altogether. Denoncourt *et al.* reported that almost two-thirds of patients (64%), could not work because of hATTR-PN (11). In a further study, Stewart *et al.* reported 11.8% of patients missed work, 32.2% were impaired at work and 38.5% reported overall work impairment due to hATTR-PN.

7.1.4 Carers

The HRQoL of carers of patients with hATTR is also significantly impacted. Carers are typically family members or friends and, as the disease progresses, patients gradually lose their independence and become increasingly reliant on the support of their carers for basic daily living activities, including dressing and washing. Among carers who do not have hATTR-PN themselves, the median amount of time spent per week caring for patients with hATTR was reported at 144 hours, whilst it was estimated at a median of 100 hours weekly for carers who also had hATTR-PN (1).

The significant amount of time spent caring for patients results in carers relinquishing their own social activities and employment, and results in moderate to high levels of fatigue (1). Numerous carers may be involved in caring for a patient with hATTR, thus multiplying the impact - further details on this impact are outlined in Section **Error! Reference source not found.**.

There is a substantial mental health burden and impact to the emotional wellbeing of carers (1). [redacted] (9). Furthermore, the disease can be devastating for multiple generations of families with the burden of disease compounded by the knowledge of what lies ahead.

The impact of the disease on a carer is captured in the following excerpt from the hATTR Patient and Carer Survey:

[redacted]

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Inotersen is the first licensed treatment to target and address the cause of the underlying disease in a group of patients who have a short life expectancy, high morbidity, and a high unmet medical need. Evidence from the NEURO-TTR study clearly demonstrated a slowing, arresting or reversing of disease progression, which has not previously been achievable before (other than with liver transplantation) (8). A significant number of patients experienced *improvement* in their neuropathies and HRQoL with inotersen treatment, i.e. a reversal of prior deterioration.

By treating patients with inotersen during the earlier stages of the disease (i.e. Stages 1 or 2), treatment has the potential to slow, arrest or reverse disease progression, which will positively impact patients and their carers via maintaining patients' independence and improving patients' and carers' QoL. Study data indicates that patients receiving inotersen remain at Stage 1 and/or Stage 2 for longer periods than would otherwise be expected following a natural disease course without active intervention. Slowing, arresting or reversal of disease progression by inotersen delays

the morbid deterioration in both physical and psychological health that hATTR-PN brings for patients and their carers who shoulder much of the associated burden.

The slowing, arresting or reversing disease progression is important at both Stage 1 and Stage 2, provising significant benefits to patients and their carers. Patients 'enter' Stage 2 being mobile with relatively good neurological function: by slowing, arresting or reversing progression to Stage 3, inotersen treatment has the potential to enable patients to remain independent in many aspects of their lives, including employment with a substantially improved QoL than would otherwise be expected without treatment.

New treatments specifically targeted at the undelying cause of hATTR-PN offer significant hope to patients and their families, especially in the context of the disease being hereditary, associated with a short life expectancy, high morbidity, high impact on QoL, and lack of effective treatment alternatives (9). The inclusion of inotersen in the treatment paradigm for hATTR-PN patients addresses the high unmet medical need and provides a significant step-change in the management of the disease with the potential to dramatically improve patients' lives and their carers.

In the hATTR Patient and Carer Survey, [redacted] (9). Therefore, self-administration of inotersen is beneficial in that it negates the need for patients to take time off work and the expense (both in monetary terms and time) of travelling to the specialist centre.

The benefits of inotersen treatment may also translate to carers allowing them to continue their everyday lives, including employment for a longer period (see Section 14 for further information).

[redacted]

(9).

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are no relevant National Institute for Health and Care Excellence (NICE) guidance or guidelines specifically for patients with hATTR-PN.

There are two relevant NHS England Manuals for amyloidosis which encompass diagnosis and management for all forms of amyloidosis.

- NHS England Manual for prescribed specialised services, service 46: Diagnostic service for amyloidosis (adults), 2017/18

- NHS England standard contract for diagnostic service for amyloidosis (all ages), 2013/14 (22)

A European consensus for the diagnosis, management, and treatment of hATTR-PN was published in 2016 by Adams *et al.* (13).

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

The National Amyloidosis Centre (NAC) is part of the University College London (UCL) Centre for Amyloidosis and Acute Phase Proteins. It is the only centre in the UK specialising in hATTR. Funded by NHS England, the NAC provides a diagnostic service and regular assessment (six-month appointments) for the UK national caseload of patients with hATTR-PN.

Accurate diagnosis can take many years from the first signs and symptoms of the disease (23). Most patients present with symptoms in primary care and are then referred to secondary care after approximately 6-8 months due to unresolved symptoms. Patients are commonly referred to gastroenterology, cardiology and neurology departments; however other specialities may also be involved. Eventually they are referred to the UK National Amyloidosis Centre (NAC), which can happen up to 10 years after the first signs and symptoms of the disease first arose. Patients with a known relative with hATTR may present early and be referred directly to the NAC.

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]

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

hATTR-PN is a rapidly progressive disease with significant impact on patients' physical health, ambulatory status, independence and QoL as the disease worsens. Current clinical practice is limited to symptomatic treatment and, at the termal stage of the condition, palliation. Therapeutic interventions that can slow, arrest, and reverse the disease are vital and should be started as soon as possible after diagnosis to minimise progression to significant disability.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

It is anticipated that inotersen will fit into the current clinical pathway of care, with a highly specialised service being established 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.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Inotersen is a novel, first-in-class 2'-O-2-methoxyethyl phosphorothioate ASO developed to inhibit production of TTR protein in patients with hATTR-PN, targeting the underlying cause of the disease (formation of TTR amyloid deposits).

Inotersen has the potential to dramatically improve patients' lives. Evidence from the NEURO-TTR study demonstrated slowing, arresting or reversing of disease progression – something that has not been achieved before other than with liver transplantation. In addition, a significant number of patients experienced improvement in relation to their neuropathies and HRQoL with inotersen treatment.

The clinical trial results, based on two primary end-points (mNIS+7, a clinical assessment of motor, sensory and autonomic neuropathy, and Norfolk QoL-DN, a patient-reported measure of HRQoL) demonstrated that inotersen has a significant and substantial positive impact on disease progression and improves HRQoL.

The inclusion of inotersen in the treatment paradigm for hATTR-PN patients has the potential to radically change the way the disease is treated, and offers patients and their families significant improvements to HRQoL and daily living. Inotersen will provide patients with a treatment for hATTR-PN that slows, arrests and potentially reverses disease progression, thereby alleviating the physical and emotional effects of the disease and allowing them to remain active, independent and productive members of their family, community, and society for longer.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

No significant changes to the way current services are organised or delivered are expected with the introduction of inotersen. [redacted]

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration

requirements, associated with using this technology that are over and above usual clinical practice.

In line with the SmPC, patients receiving inotersen treatment should take oral supplementation of approximately 3000 IU vitamin A per day in order to reduce the potential risk of ocular toxicity due to vitamin A deficiency (7).

Platelet count, liver enzymes, estimated eGFR, and UPCR should be measured prior to treatment with inotersen and monitored as follows during treatment:

- Platelet count every two weeks
- eGFR and UPCR every three months

In addition, as inotersen is contraindicated in patients with severe hepatic impairment, hepatic enzymes should be measured prior to treatment and then monitored after the first four months of treatment and annually thereafter (7).

Vitamin A supplements and monitoring (as outlined above) have a low impact on costs (see Section **Error! Reference source not found.**).

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

As inotersen is administered by the patient or their carer at home at at a location of their choice after treatment initiation in a specialist centre, no additional facilities, technologies or infrastructure are required.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

There are no tests, investigations, interventions, facilities, or technologies that would no longer be needed with inotersen treatment.

Section C – Impact of the new technology

Summary

- The pivotal clinical study for inotersen was NEURO-TTR, which demonstrated that inotersen has the potential to slow, arrest or reverse disease progression with patients with Stage 1 or Stage 2 hATTR-PN.
- In patients with hATTR-PN, inotersen treatment resulted in a clinically meaningful, substantial, and highly statistically significant improvement in neurological disease progression and QoL, versus placebo (primary outcomes LSM difference: mNIS+7, $p<0.001$; Norfolk QoL-DN, $p<0.001$) at 15 months.
    - Significant improvements in disease progression were seen as early as 8 months after treatment initiation (LSM difference: $p<0.001$).
    - Progression of disease was slowed or arrested in 36.5% of inotersen-treated patients (demonstrated by improvement [negative change] or no worsening in the mNIS+7, $p=0.033$).
    - Improvement or no worsening in QoL was seen in 50% of inotersen-treated patients (demonstrated by improvement [negative change] or no worsening in Norfolk QoL-DN, $p=0.008$).
    - The magnitude of treatment benefit of inotersen, as per both primary outcome measures, increases over time on treatment, suggesting that the maximally achievable treatment effect may not have been captured during the study duration.
- Several tertiary and exploratory outcomes demonstrated a statistically significant improvement in neuropathy and QoL metrics (as measured by SF-36 and Norfolk QoL-DN domain scores) with inotersen treatment.
- Inotersen treatment resulted in robust reductions in circulating TTR.
    - Over 80% of patients in the inotersen study arm showed a $\geq$60% decrease in TTR plasma levels by week 13 through to week 66.
- Inotersen has a predictable and manageable safety profile
    - The majority of drug-related treatment-emergent adverse events (TEAEs) were mild to moderate.
    - The principal safety concerns identified for inotersen treatment were glomerulonephritis and thrombocytopenia. Both of these are effectively detected with enhanced monitoring, as observed in NEURO-TTR and reflected in the SmPC.

9 Published and unpublished clinical evidence

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A systematic literature review (SLR) was conducted to identify relevant clinical studies for inotersen. The SLR also included HRQL and economic evidence to support other parts of the submission. Full details of the search are provided in the Appendix 18 (section 18.1).

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Sources of unpublished clinical data relevant to this appraisal were identified by the manufacturer and included in this submission.

9.2 Study selection

Published studies

9.2.1 Complete table C1 below to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

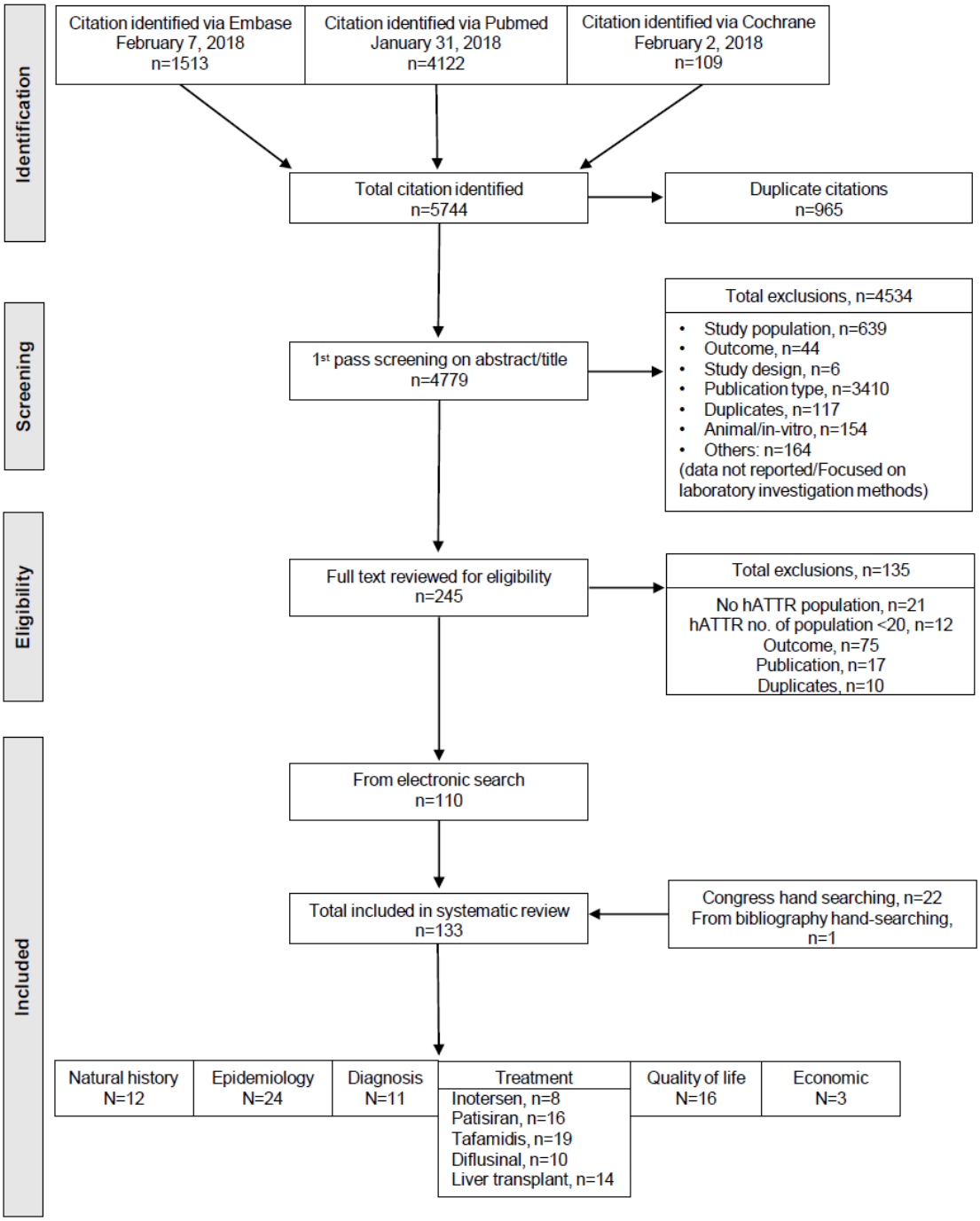
The inclusion and exclusion criteria used in the SLR are outlined in section 18.1.6, Table 8.

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Following assessment and exclusion of studies based on title, abstract and full text, eight publications were identified reporting efficacy and safety data for inotersen, which covered two studies of inotersen. Three publications covered the pivotal trial for inotersen, the NEURO-TTR study (24-26). The five remaining publications were related to an open-label study in patients with hATTR predominantly presenting with CM or wild-type ATTR (27-31). Given that the patient population for this open-label study was not relevant to the decision problem, this was not reported further in this submission.

The SLR schematic is shown in Figure 3.

Figure 3: Schematic for the SLR



Abbreviations: hATTR, hereditary transthyretin amyloidosis; SLR, systematic literature review.

Unpublished studies

9.2.3 Complete the table below to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Relevant inotersen studies were identified by the manufacturer using the same criteria with regard to study design as outlined in section 18.1.6, Table 8. The patient population of interest was hATTR-PN, as per the NICE final scope.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Only one relevant unpublished study was identified (NEURO-TTR Extension), an ongoing open-label extension of the pivotal NEURO-TTR study. The data sources for NEURO-TTR Extension are provided in **Error! Reference source not found.**.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

The primary publication for the NEURO-TTR study was not identified in the SLR as this was published after the search date used in the SLR. However, the details for this publication are provided in Table C1(8), along with the three publications (one poster and two abstracts) identified in the SLR related to the NEURO-TTR study.

Table C1. List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Benson *et al.*, 2018 (8) (primary publication)	NEURO-TTR†	Stage 1 and Stage 2 patients with hATTR-PN with an NIS ≥10 and ≤130 at baseline	Inotersen	Placebo
Benson *et al.*, 2015 (24) (abstract)				
Benson *et al.*, 2017 (25) (abstract)				
Wang *et al.*, 2017 (26) (poster)				

† Referred to throughout this submission as NEURO-TTR.
Abbreviations: hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NIS, neuropathy impairment score.

Table C2. List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Interim CSR (32)	NEURO-TTR Extension†	Stage 1 and Stage 2 patients with hATTR-PN with an NIS ≥10 and ≤130 at NEURO-TTR baseline	Inotersen	Placebo

† Referred to throughout this submission as NEURO-TTR Extension. NEURO-TTR Extension is an ongoing open-label extension study of NEURO-TTR, results are presented within this submission for the interim analysis at [redacted]
Abbreviations: CSR, clinical study report; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NIS, neuropathy impairment score.

9.3.2 State the rationale behind excluding any of the published studies listed in table C5 and C6.

None of the studies listed in Table C1 and Table C2 have been excluded.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies. A separate table should be completed for each study.

Inotersen was evaluated in a Phase 1, first-in-human-study pharmacodynamic (PD), pharmacokinetic (PK) and safety study (Study CS1). The 300 mg dose level showed a substantial PD effect after six doses (>70% mean reduction in plasma TTR levels). Given that the PD effect observed was similar between the 300 mg and 400 mg dose level, the 300 mg per week dose was selected for the Phase 2/3 study (NEURO-TTR). Preliminary PK/PD modelling (based on data from the Phase 1 study and

extrapolation to steady-state) predicted mean total (wild-type and mutant) TTR steady-state reductions of ~80% with a 300 mg/week regimen. No further data are presented herein for the Phase 1 study.

The clinical programme continued with the pivotal Phase 2/3 study, NEURO-TTR, followed by the ongoing, Phase 3, open-label extension, NEURO-TTR Extension. These studies provide the evidence for the clinical efficacy and safety of inotersen for this submission.

The study design and methodology for NEURO-TTR and NEURO-TTR extension is summarised in Table C3 and Table C4, Figure 4 and Figure 5 below.

Table C3. NEURO-TTR summary of methodology

Study name	NEURO-TTR
Objective	Primary: To evaluate the efficacy of inotersen compared with placebo when administered for 65 weeks as measured by the change from baseline in the mNIS+7 composite score and in the Norfolk QoL-DN questionnaire total score in patients with hATTR-PN
Location	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 of London), and US
Design	Phase 2/3 multicentre, double-blind, randomised, stratified, placebo-controlled study
Duration of study	66 weeks (15 months) The study consisted of the following periods (see Figure 4): • Screening and baseline assessment period (≤6 weeks) • Treatment period (65 weeks) • EOT efficacy assessment period (1 week), and • Post-treatment evaluation period (6 months)
Sample size	A total of 173 subjects were randomised 2:1 to 300 mg inotersen or placebo
Key inclusion criteria	Adults (18 to 82 years) with Stage 1 or Stage 2 hATTR-PN who had all of the following: • NIS score ≥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 Patients who participated in the ECHO substudy were also required to meet the following entry criteria to be included in this subgroup: 1. 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 To be eligible for study participation, potential patients were required to satisfy all of the eligibility criteria within 6 weeks of Study day 1 or at the time point specified in the individual inclusion or exclusion criterion.
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
Method of randomisation	There were two separate and independent randomisations: one for patients in the PK subgroup‡ and one for patients who were

	not in the PK subgroup. Within each randomisation, patients were stratified for: • Previous treatment with tafamidis or diflunisal vs. no known previous treatment • Stage 1 vs. Stage 2 disease • V30M TTR mutation vs non-V30M TTR mutation
Method of blinding	Sponsor personnel or their designees who were involved in the conduct of the study, monitors, study centre personnel, and patients were blinded throughout the study until all patients completed the treatment period and the EOT efficacy assessments and the database was locked.
Intervention(s) (n = 113) and comparator(s) (n =60)	Randomised: Inotersen (n=113) and placebo (n=60). Received study treatment: Inotersen (n=112) and placebo (n=60) Patients received three 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). Thirteen of 67 doses (19%) were required to be administered at pre-specified clinical visits. All other doses could be administered at home by the patient, trained family member or health professional. All patients received supplemental doses of the recommended daily allowance of vitamin A (approximately 3000 IU vitamin A or the closest approximate dose as available in the region in which the patient resides). Treatment with either tafamidis or diflunisal was not allowed at any time during the treatment period.
Baseline differences	Demographic characteristics were well balanced between the treatment groups. Baseline disease characteristics were generally balanced between treatment groups. However, when the disease characteristics and baseline values for efficacy parameters were examined in greater detail, it was noted that many of the parameters showed worse mean values for the inotersen group compared with the placebo group. These differences suggested that patients in the inotersen group had more advanced autonomic neuropathy, sensorimotor neuropathy, and CM at baseline.
Duration of follow-up, lost to follow-up information	6 months (post-treatment evaluation period)
Statistical tests	The primary efficacy outcome data were analysed using an MMRM. If a patient completed at least part of the mNIS+7 assessment procedure at a visit, then imputation methods were used to impute missing assessment level data. If a patient missed a visit, or the entire mNIS+7 assessment procedure was not conducted at a visit, then the mNIS+7, the composite, components, and sub-components were considered to be missing at that visit and the analysis model was used to address missing visit level data. The normality assumptions for the MMRM were formally tested using a Shapiro-Wilk test at the 0.01 significance level. If the Shapiro-Wilk test assessing normality of the MMRM residuals from week 66 was statistically significant at the 0.01 level, formal hypothesis testing for that outcome was completed at

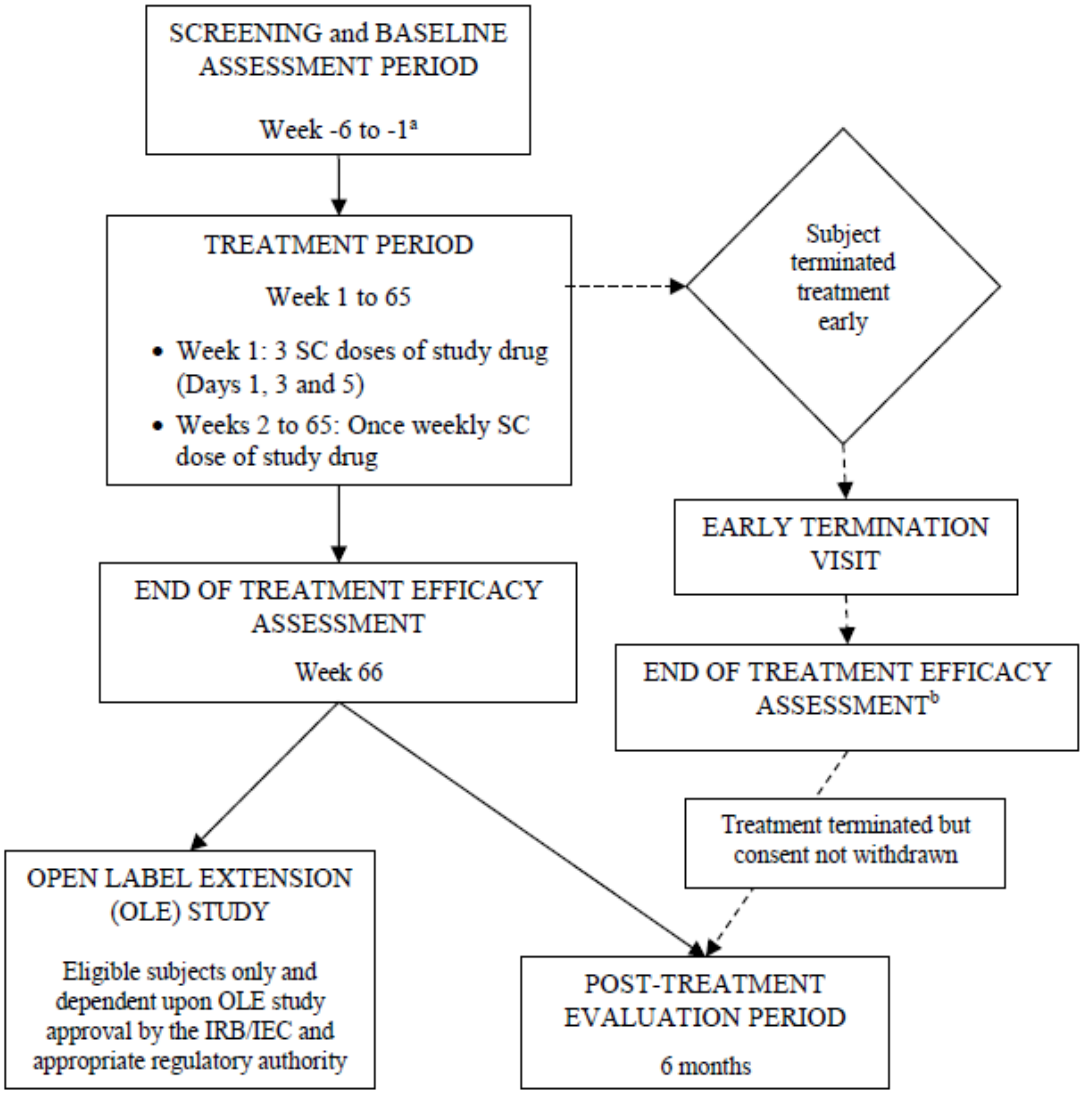
	the 0.025 1-sided significance level using a non-parametric re randomisation-test. Interpretation was made in a stepwise approach; i.e., if the null hypothesis for the mNIS+7 was rejected, then the null hypothesis for the Norfolk QoL-DN questionnaire total score was tested. However, if the null hypothesis for the mNIS+7 was not rejected, testing for the Norfolk QoL-DN questionnaire total score was considered exploratory. No adjustment was made for multiple testing (both outcomes were tested at a 2-sided alpha of 0.05) based on previously published methodology. Secondary and tertiary efficacy outcome analyses were performed using the same method as the primary efficacy outcome (i.e., MMRM). Exploratory analyses involving ECHO parameters, NSC (total and individual domains), and NT-proBNP (log-transformed) were summarised and analysed using the MMRM. Summary statistics were used to describe the other exploratory outcomes.
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline to week 66 in the mNIS+7 composite score and in the Norfolk QoL-DN questionnaire total score. <u>mNIS+7</u> Modifications to the NIS+7 (i.e., mNIS+7) are aimed at including a more quantitative measurement of the motor and sensory loss that is typical in patients with Stage 1 and Stage 2 hATTR-PN (33). The modifications are also aimed at ensuring the tests remain sensitive to change with disease progression as it is known that patients with late Stage 1 disease can reach a ceiling effect on the standard Sum 7 Test (+7). The modified +7 assessments involve both large and small fibre sensory tests, require more anatomical sites to be tested, and include both upper limb and lower limb nerve conduction tests (34). Thus, the modifications take into account the generalised, small and large fibre, length-dependent, and symmetrical nature of the polyneuropathy commonly observed in hATTR-PN patients. The mNIS+7 is a composite neurological impairment score, consisting of two composite scores: the NIS composite score (maximum of 244 points) and the modified +7 composite score (maximum of 102.32 points), each of which consist of four individual components - see **Error! Reference source not found.**. An increase in mNIS+7 score indicates a worsening of disease. The mNIS+7 assessment was conducted at baseline (two assessments), week 35 (one assessment), and week 66 (two assessments). The two assessments at baseline and week 66 were averaged at the component level. <u>Norfolk QoL-DN</u> The impact of neuropathy symptoms on QoL were measured using the Norfolk QoL-DN questionnaire, a patient-reported measure which has been validated in patients with hATTR-PN (35). Designed to capture the impact of neuropathy on patient QoL, the Norfolk QoL-DN consists of one composite total score (Total QoL [TQoL]) and 5 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 - see **Error! Reference**

	source not found.. An increase in Norfolk QoL-DN total score indicates a worsening of QoL. The scoring of the Norfolk QoL-DN was conducted according to the scoring manual developed at the Eastern Virginia Medical School (36). The Norfolk QoL-DN questionnaire was administered at baseline and at week 35 and week 66 during the Treatment Period. For patients who entered the Post-treatment Evaluation Period, the mNIS+7 assessment and Norfolk QoL-DN questionnaire were also performed at week 91. For patients who prematurely discontinued study treatment, the mNIS+7 assessment and Norfolk QoL-DN questionnaire were to be performed at the early termination visit, preferably within 14 days after the last dose of study drug.
Other outcomes (including scoring methods and timings of assessments)	Secondary: • 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) • 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 CM-ECHO Set (week 65)† Tertiary: • 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: • ECHO parameters other than GLS (week 65) • NT-proBNP (week 66) • PND (week 65) NSC (week 66) Safety assessments include: • TEAEs • Clinical laboratory tests • Vital signs • 12-lead ECG and ECG • Ophthalmology and electroretinography to detect early signs of vitamin A deficiency

† Approximately 62% of patients either had a diagnosis of hATTR-CM at NEURO-TTR study entry or were eligible to participate in the NEURO-TTR ECHO substudy in which they received additional transthoracic ECHO assessments during the treatment period and comprised the CM-ECHO Set. Presence of CM was defined by a diagnosis of TTR CM at study entry and/or by the following criteria: interventricular wall thickness of ≥13 mm on transthoracic ECHO at baseline as ascertained by a central reader, no known history of persistent hypertension ≥150 mmHg within 12 months prior to screening.
‡ A small number of patients (n=18) were included in in a PK subgroup to undergo additional sampling for PK, ECG, complement, coagulation, inflammatory, and haematology assessments.
Abbreviations: BMI, body mass index; CM, cardiomyopathy; ECG, electrocardiogram; ECHO, echocardiogram; EOT, end of treatment; GLS, global longitudinal strain; hATTR-CM, hereditary

transthyretin amyloidosis with cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; LV, left ventricular; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment score; MMRM, mixed model for repeated measures; NAC, National Amyloidosis Centre; NIS, neuropathy impairment score; NSC, neuropathy and symptoms change score; NT-proBNP; N terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamic; PK, pharmacokinetic; PND, polyneuropathy disability; QoL, quality of life; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; SC, subcutaneous; SF-36, short form-36; TEAE, treatment-emergent adverse events; TTR, transthyretin; V30M, valine replaced by methionine at amino acid position number 30.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

Figure 4: NEURO-TTR study design



[a] Exceptions to the 6-week period to perform screening evaluations and baseline assessments were allowed for the TTR genotyping and amyloid biopsy tests. These tests were allowed up to 10 weeks prior to Study Day 1 and were only conducted if appropriate documentation was not already available. In addition, ERG and ophthalmology examinations were allowed up to 1 week after Study Day 1, if needed for scheduling purposes.
[b] Patients who terminated treatment early were to complete the early termination visit and EOT efficacy assessments within 14 days from the last dose of study drug. These patients then entered the post-treatment evaluation period.
Abbreviations: EOT, end of treatment; ERG, electroretinography; IEC, Independent Ethics Committee; IRB, Institutional Review Board; OLE, open-label extension; SC, subcutaneous.

Table C4. NEURO-TTR Extension summary of methodology (ongoing study)

Study name	NEURO-TTR Extension
Objective	To evaluate the long-term efficacy and safety (up to 5 years [260 weeks]) of inotersen, in patients with Stage 1 and Stage 2 hATTR-PN
Location	Argentina, Brazil, France, Germany, Italy, Portugal, Spain, UK [redacted] and US
Design	Phase 3 multicentre, open-label extension of NEURO-TTR
Duration of study	260 weeks (5 years), ongoing The study consisted of the following periods (see Figure 5): • Screening assessment period (≤4-week) • Treatment period of up to 260 weeks (5 years) • Post-treatment evaluation period (3 months)
Sample size	No sample size calculations were performed for NEURO-TTR Extension as this was an extension study to the double-blind, placebo-controlled NEURO-TTR study. Approximately 135 patients (90 inotersen and 45 placebo) were planned to be eligible to enrol in NEURO-TTR Extension.
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 Under special circumstances, patients who participated in NEURO-TTR but did not complete the full treatment period may have been allowed to participate in this study with approval from the Sponsor.
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(s) (n =) and comparator(s) (n =)	Placebo-inotersen† (n=40), inotersen-inotersen‡ (n=74). All patients received 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.
Baseline differences	Demographic characteristics were well balanced between the treatment groups. Patients in the placebo-inotersen treatment group had more severe peripheral neuropathy at the time of NEURO-TTR Extension. This is consistent with placebo-inotersen patients having experienced a faster rate of disease progression as a consequence of receiving placebo during NEURO-TTR.

Study name	NEURO-TTR Extension
Duration of follow-up, lost to follow-up information	After completion of treatment, patients enter the 3-month post-treatment evaluation period that consists of clinic and non-clinic visits for safety monitoring
Statistical tests	The interim analysis data are presented as summary statistics only and do not include the primary statistical analysis; the MMRM analyses will be completed at the end of the study. [redacted]
Outcomes (including scoring methods and timings of assessments)	Efficacy outcomes: Changes from NEURO-TTR baseline and NEURO-TTR Extension baseline at [redacted] • mNIS+7 total score • NIS total score • Norfolk QoL-DN questionnaire total score, symptoms domain score (Stage 1 patients only) and physical functioning/large fibre neuropathy domain score (Stage 2 patients only) • mBMI and BMI • PND score • GLS by ECHO (in the ECHO and CM-ECHO Sets) PD outcomes: Changes from NEURO-TTR baseline and NEURO-TTR Extension baseline at week 78 and week 156 for: • TTR level • RBP4 level • Proportion of patients with at least 60% reduction in TTR Exploratory outcomes: Changes from NEURO-TTR baseline and NEURO-TTR Extension baseline at NEURO-TTR Extension [redacted] for: • ECHO parameters (except GLS) (in the ECHO and CM-ECHO Sets) • NT-proBNP • SF-36 questionnaire scores Scoring methods were the same as in the NEURO-TTR study.

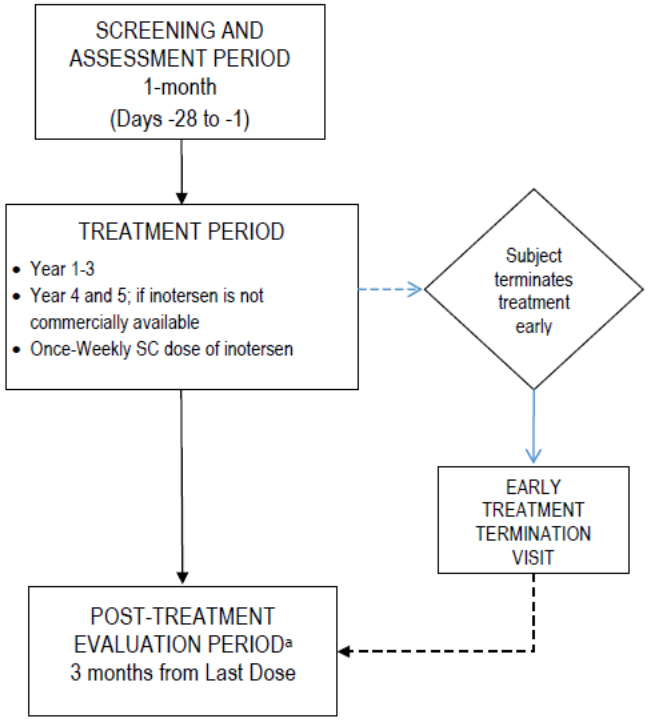
† Patients who received placebo in NEURO-TTR and received inotersen in the NEURO-TTR Extension.

‡ Patients who received inotersen in NEURO-TTR and continued to receive the same dosing regimen in NEURO-TTR.

Abbreviations: BMI, body mass index; CM, cardiomyopathy; ECHO, echocardiogram; EOT, end of treatment; GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment score; MMRM, mixed model for repeated measures; NAC, National Amyloidosis Centre; NCS, neuropathy and symptoms change score NIS, neuropathy impairment score; NT-proBNP; N terminal prohormone of brain natriuretic peptide; PD, pharmacodynamic; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; PND, polyneuropathy disability; RBP4, retinol binding protein 4; SF-36, short form-36; TTR, transthyretin; V30M, valine replaced by methionine at amino acid position number 30.

Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

Figure 5: NEURO-TTR Extension study design



a. If a subject discontinues treatment in this study, but is continuing to receive treatment with inotersen via another mechanism (i.e., commercially available or expanded access), the entry of the subject into the 3-month post-treatment evaluation period may be omitted.

Abbreviation: SC=subcutaneous

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

NEURO-TTR data were sourced from the published study (8) and unpublished Ionis Pharmaceuticals/Akcea Therapeutics data on file reports (summary of clinical efficacy, clinical overview and the clinical study report [CSR]) (32, 37, 38). Neuro-TRR Extension data were sourced from the unpublished CSR (for efficacy) and the 90-day safety update [redacted] (32, 39).

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

9.4.3.1 Baseline demographic characteristics (NEURO-TTR)

The NEURO-TTR Safety Set (SS) and Full Analysis Set (FAS) differed by seven patients. The demographics were consistent between the two data sets; therefore, the baseline demographic characteristics are presented for the SS. Baseline demographic characteristics were well balanced between treatment groups in NEURO-TTR – see Table C5.

The incidence of all stratification factors was well-balanced between treatment groups (see Table C5). Baseline demographics represent a diverse hATTR-PN population, where 65.7% of treated patients had Stage 1 hATTR-PN at baseline and 34.3% of patients had Stage 2. 54.7% of patients received prior treatment with tafamidis or diflunisal.

Table C5. NEURO-TTR baseline demographic characteristics (SS)

	Placebo (N=60)	Inotersen (N=112)	Total (N=172)
Age (years)†			
Mean (SD)	59.5 (14.05)	59.0 (12.53)	59.2 (13.04)
Median	63.0	62.0	62.5
Minimum, maximum	28, 81	27, 78	27, 81
Age group (years)			
≤18	0	0	0
19 to 64	34 (56.7)	64 (57.1)	98 (57.0)
≥65	26 (43.3)	48 (42.9)	74 (43.0)
Sex, n (%)			
Male	41 (68.3)	77 (68.8)	118 (68.6)
Female	19 (31.7)	35 (31.3)	54 (31.4)
Ethnicity, n (%)			
Hispanic or Latino	7 (11.7)	17 (15.2)	24 (14.0)
Not Hispanic or Latino	53 (88.3)	95 (84.8)	148 (86.0)
Race, n (%)			
Asian	3 (5.0)	1 (0.9)	4 (2.3)
Black	1 (1.7)	3 (2.7)	4 (2.3)
White	53 (88.3)	105 (93.8)	158 (91.9)
White and Greyish-Brown	1 (1.7)	0	1 (0.6)
Other	2 (3.3)	3 (2.7)	5 (2.9)
Weight (kg) †			
Mean (SD)	71.07 (18.135)	70.59 (17.032)	70.76 (17.373)
Median	69.93	70.10	69.95
Minimum, maximum	38.2, 126.0	37.0, 140.4	37.0, 140.4
Region, n (%)			
Europe	23 (38.3)	37 (33.0)	60 (34.9)
North America	26 (43.3)	56 (50.0)	82 (47.7)
South America/Australasia	11 (18.3)	19 (17.0)	30 (17.4)
Randomisation stratum by IXRS at NEURO-TTR pre-treatment, n (%)			
Previous treatment with tafamidis or diflunisal			
Yes	33 (55.0)	61 (54.5)	94 (54.7)
No	27 (45.0)	51 (45.5)	78 (45.3)
Disease stage			
Stage 1	39 (65.0)	74 (66.1)	113 (65.7)
Stage 2	21 (35.0)	38 (33.9)	59 (34.3)
V30M TTR mutation			
Yes	32 (53.3)	58 (51.8)	90 (52.3)
No	28 (46.7)	54 (48.2)	82 (47.7)

† Age and weight for NEURO-TTR are as reported at NEURO-TTR Screening.
Abbreviations: IXRS, interactive voice/web-response system; Kg, kilogram; SD, standard deviation; SS, safety set; TTR, transthyretin; V30M, valine replaced by methionine at amino acid position number 30.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

9.4.3.2 Baseline demographic characteristics (NEURO-TTR Extension)

For NEURO-TTR Extension, demographic characteristics for the SS are presented in

. Baseline demographic characteristics were well balanced between treatment groups in NEURO-TTR Extension - see Table C6.

In NEURO-TTR Extension, disease stage at NEURO-TTR baseline was similar for both groups and [redacted] had Stage 1 hATTR-PN.

Table C6. NEURO-TTR Extension baseline demographic characteristics (SS)

[redacted]

† Age and weight for NEURO-TTR Extension are as reported at NEURO-TTR Extension Screening.
Abbreviations: IXRS, interactive voice/web-response system; Kg, kilogram; SD, standard deviation; SS, safety set; TTR, transthyretin; V30M, valine replaced by methionine at amino acid position number 30.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

9.4.3.3 Baseline disease characteristics (NEURO-TTR)

Baseline disease characteristics in NEURO-TTR (see Table C7), were generally balanced between treatment groups. However, when the disease characteristics and baseline values for efficacy parameters were examined in greater detail, some differences were detected. It was noted that many of the parameters exhibited worse mean values for the inotersen group compared to the placebo group, particularly for the components of the composite scores for assessing disease severity.

Table C8 shows the baseline disease and efficacy parameters for each group, with bold numbers indicating a greater severity.

These differences suggest that the patients in the inotersen group had more advanced autonomic neuropathy, sensorimotor neuropathy, and CM at baseline. The duration of disease from hATTR-PN diagnosis was also longer for the inotersen group in comparison to the placebo group. This indicates that the magnitude of the treatment effect observed in the study may under-represents the actual treatment benefit of inotersen.

Table C7. NEURO-TTR baseline disease characteristics (SS)

	Placebo (N=60)	Inotersen (N=112)	Total (N=172)
TTR genotype observed in >1 patient†, n (%)			
Type VAL30MET	33 (55.0)	56 (50.0)	89 (51.7)
Type THR60ALA	8 (13.3)	14 (12.5)	22 (12.8)
Type LEU58HIS	3 (5.0)	7 (6.3)	10 (5.8)
Type SER77TYR	5 (8.3)	4 (3.6)	9 (5.2)
Type PHE64LEU	3 (5.0)	5 (4.5)	8 (4.7)
Type SER50ARG	1 (1.7)	5 (4.5)	6 (3.5)
Type GLU89GLN	0	5 (4.5)	5 (2.9)
Type VAL122ILE	1 (1.7)	2 (1.8)	3 (1.7)
Type THR49ALA	0	2 (1.8)	2 (1.2)
Duration of disease from hATTR-PN diagnosis (months)‡			
Mean (SD)	39.3 (40.30)	42.4 (51.19)	41.3 (47.58)
Median	24.0	23.0	23.0
Minimum, maximum	1, 159	2, 297	1, 297
Duration from onset of hATTR-PN symptoms (months)‡			
Mean (SD)	64.0 (52.34)	63.9 (53.16)	63.9 (52.72)
Median	48.0	50.5	49.5
Minimum, maximum	8, 277	5, 372	5, 372
Patients diagnosed with hATTR-CM, n (%)			
Yes	22 (36.7)	45 (40.2)	67 (39.0)
No	38 (63.3)	67 (59.8)	105 (61.0)
Duration of disease from hATTR-CM diagnosis (months)			
N	22	44	66
Mean (SD)	21.0 (22.52)	25.1 (28.62)	23.7 (26.63)
Median	15.0	15.0	15.0
Minimum, maximum	1, 81	1, 132	1, 132
Duration from onset of hATTR-CM symptoms (months)			
N	18	36	54
Mean (SD)	34.1 (29.33)	44.7 (58.00)	41.1 (50.23)
Median	29.5	26.5	29.0
Minimum, maximum	1, 114	1, 300	1, 300
mNIS+7 composite scores			

	Placebo (N=60)	Inotersen (N=112)	Total (N=172)
Mean (SD) Median Minimum, maximum	74.75 (39.003) 74.89 13.2, 156.7	79.16 (36.958) 76.15 11.2, 174.7	77.62 (37.629) 75.60 11.2, 174.7
Norfolk QoL-DN total scores N Mean (SD) Median Minimum, maximum	 59 48.68 (26.746) 48.11 -1.0, 111.0	 111 48.22 (27.503) 45.00 -2.0, 127.0	 170 48.38 (27.165) 47.00 -2.0, 127.0
PND score, n (%) I II III IV V	 23 (38.3) 19 (31.7) 15 (25.0) 3 (5.0) 0	 32 (28.6) 42 (37.5) 30 (26.8) 8 (7.1) 0	 55 (32.0) 61 (35.5) 45 (26.2) 11 (6.4) 0
BMI (kg/m^2) N Mean (SD) Median Minimum, maximum	 60 24.21 (4.858) 23.81 14.5, 39.8	 111 23.99 (4.896) 23.50 13.3, 40.2	 171 24.07 (4.869) 23.60 13.3, 40.2
NT-proBNP (pmol/L) N Mean (SD) Median Minimum, maximum	 60 81.98 (159.151) 30.50 2.0, 872.0	 108 121.55 (255.420) 44.50 1.0, 2252.0	 168 107.42 (226.076) 34.00 1.0, 2252.0
NYHA score, n (%) I II III IV	 40 (66.7) 20 (33.3) 0 0	 71 (63.4) 41 (36.6) 0 0	 111 (64.5) 61 (35.5) 0 0
Karnofsky score Karnofsky performance status ≤50 Mean (SD) Median Minimum, maximum	 0 76.8 (10.81) 80.0 60, 90	 0 76.2 (11.20) 80.0 60, 100	 0 76.4 (11.04) 80.0 60, 100
TTR concentration (g/L) Mean (SD) Median Minimum, maximum	 0.2186 (0.04696) 0.2245 0.106, 0.304	 0.2134 (0.06108) 0.2080 0.086, 0.397	 0.2153 (0.05647) 0.2115 0.086, 0.397

† Eighteen other TTR mutations were observed in 1 patient each, including ALA109SER, ALA97SER, ASP38ALA, GLU54SER, GLU61LYS, GLU89LYS, GLY47ALA, GLY67ARG, ILE107PHE, ILE107VAL, ILE84SER, LYS35THR, LYS70ASN, PHE33LEU, PRO24SER, SER77PHE, THR59LYS, and TYR114CYS.

‡ Only year and month were collected for hATTR-PN diagnosis and onset of hATTR-PN symptoms. The duration from hATTR-PN diagnosis and onset of hATTR-PN symptoms was calculated relative to the informed consent date.

Abbreviations: BMI, body mass index; g/L, grams per litre; hATTR-CM, hereditary transthyretin amyloidosis with 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; SS, safety set; TTR, transthyretin.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

Table C8. Summary of baseline scores and values for efficacy parameters and select laboratory parameters, with percent difference for the placebo group relative to the inotersen group (NEURO-TTR FAS, SS, and Randomised populations)

Parameters	Components, sub-components, or laboratory parameter	Population	Placebo	Inotersen	Percent difference (placebo group relative to inotersen group)
mNIS+7 (mean)	Composite score	FAS	74.12	79.35	-6.59
	NIS	FAS	43.40	46.59	-6.85
	modified +7 composite score	FAS	30.73	32.76	-6.20
	NIS muscle weakness score	FAS	19.99	21.20	-5.71
	NIS sensory score	FAS	13.31	14.41	-7.63
	NIS reflex score	FAS	10.10	10.95	-7.76
	Heat-pain sensory score	FAS	7.25	7.91	-8.34
	Touch-pressure sensory score	FAS	10.80	11.40	-5.26
	Heart rate to deep breathing score	FAS	1.814	1.962	-7.54
	Nerve conduction score	FAS	10.868	11.492	-5.43
Norfolk QoL-DN (mean)	Total score	FAS	48.60	48.57	0.06
	Symptoms score	FAS	10.68	10.65	0.28
	Physical functioning/Large fibre neuropathy score	FAS	24.42	24.09	1.37
	Activities of daily living score	FAS	6.41	6.52	-1.69
	Small fibre neuropathy score	FAS	5.24	5.09	2.95
	Autonomic neuropathy score	FAS	1.84	2.22	-17.12

Parameters	Components, sub-components, or laboratory parameter	Population	Placebo	Inotersen	Percent difference (placebo group relative to inotersen group)
SF-36 PCS score (mean)		FAS	37.19	35.65	4.32
SF-36 MCS Score (mean)		FAS	50.61	51.04	-0.84
	Mental health domain score	FAS	71.19	72.24	-1.45
NSC (mean)	Total score	FAS	22.92	24.92	-8.03
	Muscle weakness	FAS	7.68	8.31	-7.58
	Sensory (hypo/loss of sensation)	FAS	4.31	4.42	-2.49
	Sensory (paraesthesia, hypersensation)	FAS	6.21	6.31	-1.58
	Autonomic (GI/urinary incontinence)	FAS	0.91	1.67	-45.51
	Autonomic (other than GI/urinary incontinence)	FAS	3.81	4.21	-9.50
BMI (kg/m^2) (mean)		FAS	24.25	24.27	-0.08
mBMI		FAS	1053.7	1025.33	2.77
PND score	I (%)	SS	38.3	28.6	33.92
ECHO (mean)	GLS (%)	Randomised	-16.49	-15.92	3.58
	Interventricular septum thickness (cm)	Randomised	1.321	1.445	-8.58
	LV mass (g)	Randomised	195.808	223.734	-12.48
NT-proBNP (pmol/L)		SS	81.98	121.55	-32.55
NYHA I (%)		SS	66.7	63.4	5.21
Karnofsky performance status score (mean)		SS	76.8	76.2	0.79
Duration from onset hATTR-PN symptoms (mean, months)		SS	64.0	63.9	0.16

Parameters	Components, sub-components, or laboratory parameter	Population	Placebo	Inotersen	Percent difference (placebo group relative to inotersen group)
Duration of disease from hATTR-PN diagnosis (mean, months)		SS	39.3	42.4	-7.31
Duration from onset hATTR-CM symptoms (mean, months)		SS	34.1	44.7	-23.71
Duration of disease from hATTR-CM diagnosis (mean, months)		SS	21.0	25.1	-16.33
CM-ECHO Set (% included)		Randomised	55.0	66.4	-17.17
Laboratory (baseline mean values)					
	Platelets	SS	212.19	223.39	-5.01
	Serum creatinine	SS	77.3	76.2	1.44
	eGFR	SS	87.4	88.9	-1.69
	Urine albumin/creatinine	SS	3.152	7.273	-56.66
	Urine protein/creatinine	SS	14.6	24.8	-41.13
	Haemoglobin	SS	137.8	135.9	1.40

Note: Bold indicates greater severity.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FAS, full analysis set; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy mBMI, modified body mass index; GLS, global longitudinal strain; I, improved; LV, left ventricle; MCS, mental component summary; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NSC, neuropathy symptoms and change score; NT-proBNP, N terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PCS, physical component summary; PND, polyneuropathy disability; SF-36 short form-36; SS, safety set.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

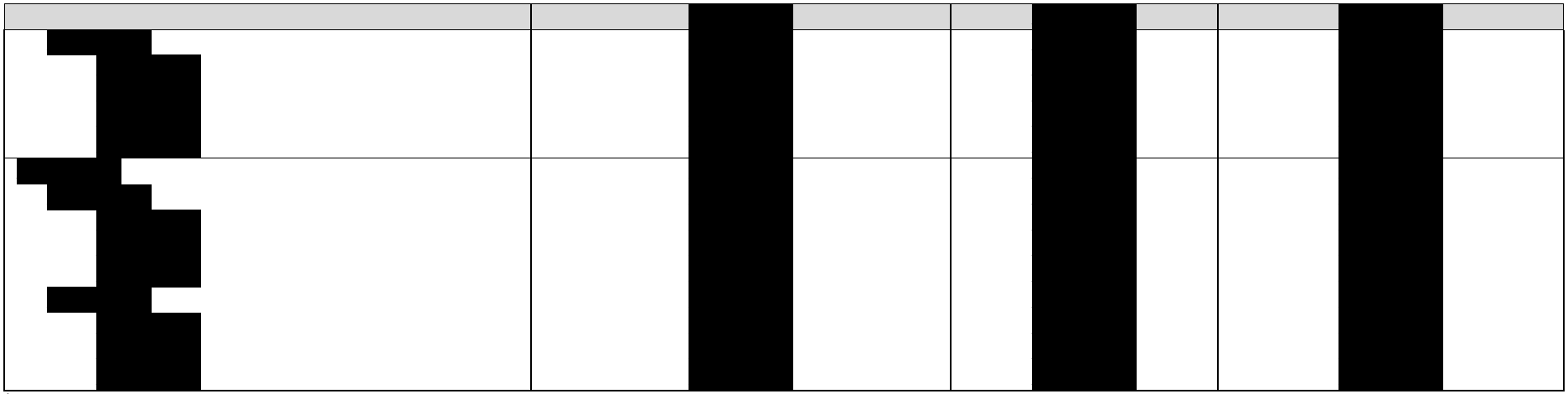
9.4.3.4 Baseline disease characteristics (NEURO-TTR Extension)

Baseline disease characteristics in NEURO-TTR Extension (see Table C9), were generally balanced between treatment groups [redacted] This is consistent with placebo-inotersen patients having experienced a faster rate of disease progression as a consequence of receiving placebo during NEURO-TTR.

Table C9. NEURO-TTR Extension baseline disease characteristics (SS)

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

[redacted]



† Seventeen other TTR mutations were observed in one patient each, including ALA109SER, ALA97SER, ASP38ALA, GLU89LYS, GLY47ALA, GLY67ARG, ILE107PHE, ILE107VAL, ILE84SER, LYS35THR, LYS70ASN, PHE33LEU, PRO24SER, SER77PHE, THR49ALA, TYR114CYS, and VAL122ILE

Abbreviations: BMI, body mass index; 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; SS, safety set; TTR, transthyretin.

Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Changes from baseline in mNIS+7 composite score and Norfolk QoL-DN total score were examined in the following pre-planned subgroups in NEURO-TTR, including:

- V30M TTR mutation (Yes, No)
- Age (<65 years old, ≥65 years old)
- Race (White, non-White)
- Sex (Male, Female)
- Region (North America, Europe, South America/Australasia)
- Previous treatment with tafamidis or diflunisal (Yes, No)
- Disease stage (Stage 1, Stage 2)
- CM-ECHO Set (Included, Not included)

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

NEURO-TTR patient disposition is shown in Table C10. 81% of the study cohort completed treatment according to the protocol. The proportion of patients who discontinued study treatment was higher in the inotersen group (23.0%) compared with the placebo group (13.3%) primarily due to adverse events (AEs).

Table C10. NEURO-TTR patient disposition

	Placebo (N=60) n (%)	Inotersen (N=113) n (%)	Total (N=173) n (%)
Randomised	60 (100)	113 (100)	172 (100)
Dosed	60 (100)	112 (99.1)	172 (99.4)
Completed†	52 (86.7)	87 (77.0)	139 (80.3)
Discontinued	8 (13.3)	26 (23.0)	34 (19.7)
Primary reason for early treatment discontinuation, n (%)			
AE or SAE	1 (1.7)	16 (14.2)	17 (9.8)
Stopping rule met	1 (1.7)	2 (1.8)	3 (1.7)
Investigator judgement	0	0	0
Voluntary withdrawal	3 (5.0)	2 (1.8)	5 (2.9)
Pregnancy	0	0	0
Ineligibility	0	1 (0.9)	1 (0.6)
Significant protocol deviation	0	0	0
Liver transplant	0	1 (0.9)	1 (0.6)
Disease progression	3 (5.0)	2 (1.8)	5 (2.9)
Other	0	2 (1.8)	2 (1.2)
Entered NEURO-TTR Extension, n (%)	49 (81.7)	84 (74.3)	133 (76.9)

Abbreviations: AE, adverse event; SAE, serious adverse event.
† Number of patients who completed up to the week 66 visit, even if individual visits were not done or doses were not taken.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

NEURO-TTR Extension patient disposition is shown in Table C11 [redacted]. Approximately [redacted] of patients that completed treatment in NEURO-TTR elected to enrol in NEURO-TTR Extension.

Table C11. NEURO-TTR Extension patient disposition [redacted]

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

Abbreviations: AE, adverse event; SAE serious adverse event.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

The rate of withdrawal from NEURO-TTR and NEURO-TTR Extension was low (see Table C10 and Table C11).

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study.

The quality assessment for the NEURO-TTR randomised clinical trial (RCT) (8) based on the data sources available for the trial is provided in Table C12.

Table C12. Critical appraisal of randomised control trials

Study name	NEURO-TTR	
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.
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.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Results of the relevant studies

NEURO-TTR study

- **In patients with hATTR-PN, inotersen treatment resulted in a clinical meaningful, substantial, and highly statistically significant improvement in neurological disease progression and QoL, versus placebo (primary outcomes LSM difference: mNIS+7, p<0.001; Norfolk QoL-DN, p<0.001) at 15 months**
    - Statistically significant improvements for both primary outcomes were achieved despite inotersen patients having a greater disease severity at baseline (more advanced autonomic neuropathy, sensorimotor neuropathy, and CM), versus patients in the placebo group.
    - This indicates that the magnitude of the treatment effect observed in the study may underrepresent the actual treatment benefit of inotersen.
    - The magnitude of treatment benefit of inotersen, as per both primary outcome measures, increases over time on treatment, suggesting that the maximally achievable treatment effect may not have been captured during the study duration.

  Primary outcome - mNIS+7

    - Significant improvements in disease progression were seen as early as 8 months after treatment initiation (LSM difference: p<0.001).
    - Progression of disease was slowed or arrested in 36.5% of inotersen-treated patients (demonstrated by improvement [negative change] or no worsening in the mNIS+7, p=0.033).
    - Response rate was consistently higher in the inotersen group than the placebo group across all thresholds evaluated, with an approximate 2-fold difference observed between the inotersen and placebo groups at each threshold.

- Statistical significance in favour of inotersen treatment was demonstrated at all thresholds beyond a 0-point change.
    - Pre-specified sensitivity analyses of the mNIS+7 demonstrated a robust and beneficial treatment under all assumptions.

  Primary outcome - Norfolk QoL-DN

    - Significant improvements in QoL were seen as early as 8 months after treatment initiation (LSM difference: p=0.032).
    - Improvement or no worsening in QoL was seen in 50% inotersen-treated patients (demonstrated by improvement [negative change] or no worsening in Norfolk QoL-DN, p=0.008).
    - Pre-specified sensitivity analyses of the Norfolk QoL-DN demonstrated a robust and beneficial treatment effect of inotersen under all assumptions.

- **Results across the components of mNIS+7 and domains of Norfolk QoL-DN composite scores (secondary outcomes) were consistent with the primary outcome analysis, showing benefit in motor, sensory, and autonomic neuropathies, and QoL functional domains**
    - Norfolk QoL-DN symptom domain score in patients with Stage 1 hATTR-PN (LSM difference versus placebo: p=0.012).
    - Norfolk QoL-DN physical functioning/large fibre neuropathy domain score in patients with Stage 2 hATTR-PN (LSM difference versus placebo: p=0.013).
    - NIS composite score (LSM difference versus placebo: p<0.001).
    - Modified +7 composite score (LSM difference versus placebo: p=0.001) compared with placebo.
    - NIS+7 composite score (LSM difference versus placebo: p<0.001)
- **Several tertiary and exploratory outcomes demonstrated a statistically significant improvement in neuropathy and QoL with inotersen treatment**
    - SF-36 PCS score: (LSM difference versus placebo: p=0.006).
    - Individual components of NIS and modified +7: LSM differences versus placebo in muscle strength (p<0.001), sensation of the big toe and index finger (p<0.001), reflexes (p=0.040), nerve conduction (p=0.025) and heat-pain (small fibre), (p=0.001).
    - Individual Norfolk QoL-DN domain scores; LSM differences versus placebo in physical functioning (p<0.001), large fibre symptoms (p=0.001), and activities of daily living (p=0.001).
    - Change in the neuropathy and symptoms change (NSC) score; LSM difference versus placebo (p<0.001).
- **Inotersen treatment resulted in robust reductions in circulating TTR**
    - Over 80% of patients in the inotersen study arm showed a ≥60% decrease in TTR plasma levels by week 13 through to week 66.
    - The differences in LSMs for change from baseline in TTR were statistically significant in favour of inotersen (p<0.001) at all time points.

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

9.6.1.1 NEURO-TTR results

Table C13. NEURO-TTR summary of results (FAS)

	Placebo (N=59) Change from baseline	Inotersen (N=106) Change from baseline	Difference
	N Mean (SD) LSM (SE) 95% CI	N Mean (SD) LSM (SE) 95% CI	LSM 95% CI p-value
Primary outcome			
mNIS+7composite score (week 66)	52 23.89 (24.190) 25.53 (2.690) 20.21, 30.85	85 4.16 (15.672) 5.80 (2.127) 1.59, 10.00	-19.73 -26.43, -13.03 <0.001
Norfolk QoL-DN (week 66)	52 10.77 (21.134) 12.67 (2.666) 7.40, 17.94	84 -0.08 (18.967) 0.99 (2.117) -3.19, 5.18	-11.68 -18.29, -5.06 <0.001
Secondary outcomes			
Norfolk QoL-DN symptoms domain score Stage 1 (week 66)	33 1.18 (5.270) 1.11 (0.778) -0.43, 2.66	55 -1.40 (4.763) -1.42 (0.608) -2.63, -0.21	-2.53 -4.49, -0.57 0.012
Norfolk QoL-DN PF/LF domain score Stage 2 (week 66)	19 8.74 (9.689) 9.04 (2.481) 4.04, 14.03	29 1.05 (11.924) 0.78 (2.021) -3.28, 4.85	-8.25 -14.71, -1.80 0.013
mBMI (week 65)	49 -8.57 (9.159) -85.32 (14.047) -113.11, -57.52	82 -7.08 (9.386) -82.50 (10.979) -104.21, -60.78	2.82 -32.12, 37.76 0.873
BMI (week 65)	49 -0.87 (1.202) -0.80 (0.204) -1.21, -0.40	82 -0.24 (1.521) -0.30 (0.159) -0.61, 0.02	0.50 0.00, 1.01 0.051
NIS composite score (week 66)	52 17.29 (16.986) 18.65 (1.762) 15.16, 22.13	85 4.47 (10.329) 5.40 (1.403) 2.62, 8.17	-13.25 -17.65, -8.85 <0.001
Modified +7 composite score (week 66)	52 6.60 (12.770) 6.95 (1.540) 3.91, 10.00	85 -0.31 (11.134) 0.46 (1.221) -1.95, 2.87	-6.49 -10.32, -2.66 0.001
NIS+7 composite score (week 66)	52 19.00 (16.824) 20.39 (1.815) 16.80, 23.98	85 5.10 (10.709) 5.90 (1.444) 3.04, 8.75	-14.50 -19.03, -9.96 <0.001
GLS (week 65) CM-ECHO Set	25 0.46 (2.702)‡ 0.94 (0.588) -0.23, 2.11	50 0.69 (3.134)‡ 1.14 (0.497) 0.15, 2.13	0.20 -1.17, 1.56 0.771

	Placebo (N=59) Change from baseline	Inotersen (N=106) Change from baseline	Difference
	N Mean (SD) LSM (SE) 95% CI	N Mean (SD) LSM (SE) 95% CI	LSM 95% CI p-value
ECHO subgroup	16 1.05 (2.745)‡ 1.61 (0.747) 0.10, 3.11	30 0.25 (3.163)‡ 0.72 (0.577) -0.44, 1.88	-0.89 -2.67, 0.90 0.322
Tertiary outcomes			
SF-36 PCS score† (week 65)	51 -3.71 (8.509) -3.65 (1.011) -5.65, -1.65	84 0.30 (6.627) -0.05 (0.802) -1.64, 1.53	3.59 1.07, 6.12 0.006
SF-36 MCS score† (week 65)	51 -0.97 (9.239) -1.35 (1.121) -3.57, 0.87	84 1.02 (7.721) 1.07 (0.888) -0.68, 2.83	2.42 -0.37, 5.22 0.088
SF-36 mental health domain score† (week 65)	51 -1.67 (17.795) -2.48 (2.079) -6.60, 1.63	84 2.32 (14.405) 2.59 (1.645) -0.67, 5.84	5.07 -0.11, 10.25 0.055
Individual components of NIS and modified +7 (week 66)	See **Error! Reference source not found.**		
Individual domains of Norfolk QoL-DN (week 66)	See **Error! Reference source not found.**		
Exploratory outcomes			
NSC total score† (week 66)	52 7.75 (9.138) 8.10 (1.121) 5.89, 10.32	85 1.20 (7.624) 1.77 (0.891) 0.01, 3.53	-6.33 -9.12, -3.55 <0.001
PND score† (week 65) N Improved, n (%) Not changed, n (%) Worsened, n (%)	 52 2 (3.8) 37 (71.2) 13 (25.0)	 86 9 (10.5) 56 (65.1) 21 (24.4)	Not applicable

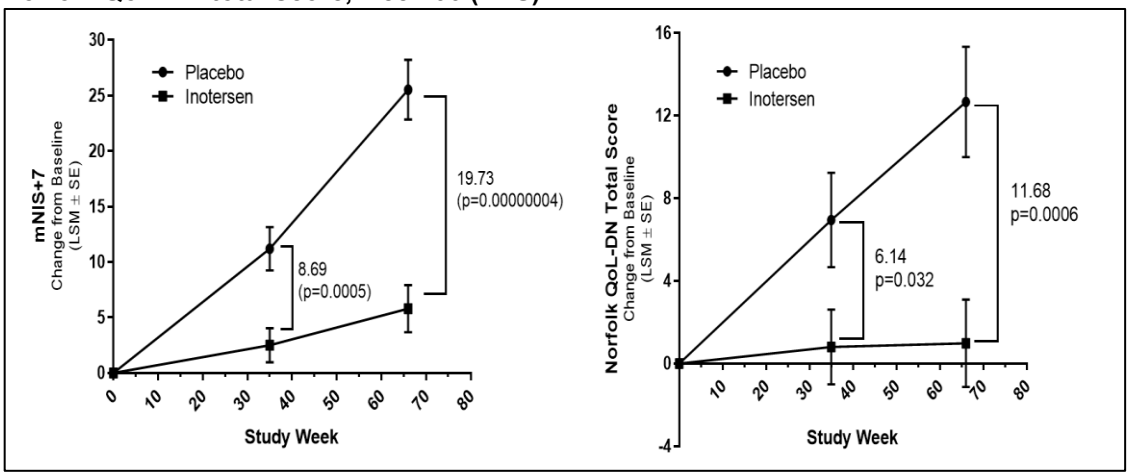
† Analysis based on data collected up to 52 days after last dose of study drug.
‡ Percentage.
Abbreviations: BMI, body mass index; CM, cardiomyopathy; ECHO, echocardiogram; FAS, full analysis set; GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; mBMI, modified body mass index; 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; PCS, physical component summary; PND, polyneuropathy disability; SF-36, short form-36; SD, standard deviation; SE, standard error; TTR, transthyretin.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32, 38).

Co-primary outcomes: Change from baseline to week 66 in the mNIS+7 composite score and the Norfolk QoL-DN total score (increase in mNIS+7 composite score and Norfolk QoL-DN total score indicates a worsening of disease).

NEURO-TTR met both primary outcomes. Over the 15-month study period of the study (66 weeks), inotersen-treated patients achieved a highly statistically significant improvement in neurological disease progression (mNIS+7) (p<0.001) and QoL

(Norfolk QoL-DN) (p<0.001) compared to placebo (Figure 6). Statistically significant differences were also observed for both outcomes at 8 months (week 35) (LSM change from baseline -8.69 points, p<0.001 and -6.14 points, p=0.032, respectively). Statistical significance was maintained at week 35 and week 66 for all pre-specified sensitivity analyses, including all missing data sensitivity analyses. The magnitude of difference between the treatment groups increases with time (Figure 6).

Figure 6: NEURO-TTR LSM change from baseline in mNIS+7 composite score and Norfolk QoL-DN total score, week 66 (FAS)



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.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

In a further analysis, progression of disease at week 66 was slowed or arrested in 36.5% of patients treated with inotersen, as demonstrated by improvement (negative change) or no worsening in the mNIS+7 (p=0.032). In 50% of patients treated with inotersen, there was improvement (negative change) or no worsening in the Norfolk QoL-DN (p=0.008), - see Table C14.

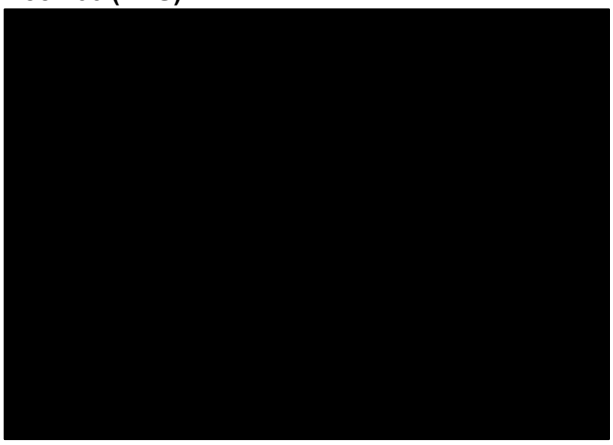
Table C14. NEURO-TTR patients with no disease progression, week 66

Treatment group†	mNIS+7		Norfolk QoL-DN	
	Placebo N=52	Inotersen N=85	Placebo N=52	Inotersen N=84
No disease progression‡ (week 66 change from baseline), n (%) p-value	10 (19.2)	31 (36.5) p=0.032	14 (26.9)	42 (50) p=0.008

Abbreviations: mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy
† All patients with non-missing value at baseline and week 66 efficacy assessment.
‡ Change from baseline to week 66 was less than or equal to zero.
(38)Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (38).

In a responder analysis of mNIS+7 composite score (thresholds ranging from a 0- to 30-point increase from baseline), the inotersen group had approximately a 2-fold higher response rate than the placebo group at each threshold tested, demonstrating consistency of response (Figure 7). A responder was defined as a patient who had a change from baseline that was less than or equal to the pre-specified threshold value. Statistical significance in favour of inotersen was demonstrated at all thresholds beyond a 0-point change.

Figure 7: NEURO-TTR mNIS+7 composite score response rate versus threshold value, week 66 (FAS)



Abbreviations: FAS, full analysis set; mNIS+7, modified neuropathy impairment score.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (38).

Results across multiple disease characteristics at week 66 showed a statistically significant benefit in all subgroups based on mNIS+7 composite score, except one in the Norfolk QoL-DN (see Table C15). Results across the components of mNIS+7 and domains of Norfolk QoL-DN composite scores were consistent with the primary outcome analysis, showing benefit in motor, sensory, and autonomic neuropathies and QoL functional domains (see

).

Table C15. NEURO-TTR summary of efficacy results by subgroup, week 66 (FAS)

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.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (38).

Secondary, tertiary, and exploratory outcomes

Table C13 provides a summary of the results of secondary, tertiary, and exploratory outcomes.

Secondary outcome: Change from baseline to week 66 in the Norfolk QoL-DN symptom domain score in Stage 1 patients and the Norfolk QoL-DN physical functioning/large fibre score in Stage 2 patients

Inotersen showed a statistically significant benefit versus placebo at week 66 (Table C13) for Stage 1 patients in terms of symptoms and physical functioning (difference

in LSM: -2.53, p=0.012; -8.25 p=0.013), for Stage 1 and Stage 2 patients, respectively.

The symptom domain score measures the presence of neuropathy symptoms such as numbness, tingling, electric shocks, pain, and weakness; predominant early features of hATTR-PN (Stage 1).

The physical functioning/large fibre domain score measures deficits in gross motor movements such as walking, getting out of a chair, walking down stairs, and limitations to normal work or activities, which are aspects typically impacted later in disease (Stage 2).

Secondary outcome: Change from baseline to week 66 in the NIS composite score and modified +7 composite score

The analysis of change from baseline in the NIS composite score and modified +7 composite score in NEURO-TTR showed a statistically significant benefit of inotersen treatment at week 66 (LSM difference: -13.25, p<0.001; -6.49, p=0.001, respectively), and is consistent with the mNIS+7 primary outcome results (Table C13).

Secondary outcome: Change from baseline to week 66 in the NIS+7 composite score

The analysis of change from baseline in NIS+7 composite score showed a statistically significant difference (LSM difference: -14.50, p<0.001) in favour of inotersen treatment at week 66, consistent with the mNIS+7 primary endpoint results (Table C13).

Tertiary outcome: Change from baseline to week 66 in the Short Form-36 health survey

A statistically significant difference in favour of inotersen treatment (LSM difference 3.59, p=0.006) was observed in the PCS score of the SF-36 health survey at week 65 (Table C13). This benefit is clinically meaningful for patients in terms of physical functioning.

Clinically significant worsening in the mean change from baseline in PCS score, defined as a change of at least -3, was noted in the placebo group at week 65.

Improvements in the mental component summary (MCS) score and the mental health domain score were observed at week 65 in the inotersen group compared to a worsening in the placebo group (LSM difference: 2.42, p=0.088; 5.07, p=0.055) (Table C13).

Tertiary outcome: Change from baseline to week 66 in the individual components of NIS and modified +7

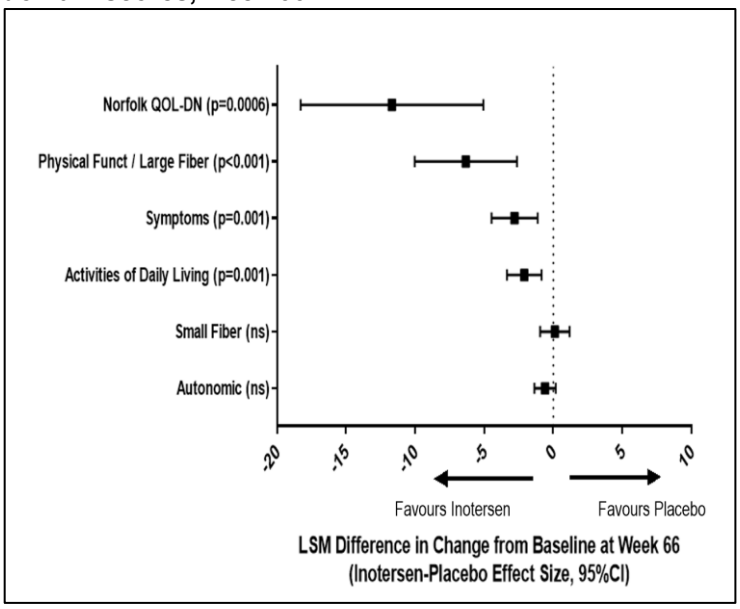
In the analyses of modified +7 sub-component scores, nerve conduction and heat-pain (small fibre) showed a statistically significant difference in favour of inotersen treatment compared with placebo at week 66. The touch pressure sub-component (large fibre) showed a trend in favour of inotersen. No difference was observed between treatment groups in the heart rate response to deep breathing (HRDB) score, an autonomic test. However, HRDB cannot be assessed in patients with active pacing or in atrial fibrillation, both common in hATTR-PN patients. In patients with

non-missing data, a numerical trend in favour of inotersen treatment was observed in HRDB change from baseline, although statistical analysis was not performed.

Tertiary outcome: Change from baseline to week 66 in individual Norfolk QoL-DN domain scores

A statistically significant difference in favour of inotersen was seen in physical functioning/large fibre symptoms, and activities of daily living at week 66 in the FAS - see Figure 8.

Figure 8: NEURO-TTR LSM differences in change from baseline for Norfolk QoL-DN domain scores, week 66



Abbreviations: CI, confidence interval; LSM, least squares mean; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (38).

Exploratory outcome: Changes from baseline to week 66 in the Neuropathy symptoms and change score (NSC)

Changes in the NSC score demonstrated a statistically significant difference (LSM difference: -6.33, p<0.001) in favour of inotersen treatment at week 66 (Table C13) which was consistent with the results for other QoL measures. Four of the five NSC domain scores showed significant differences between treatment groups or trends in favour of inotersen treatment compared with placebo. No difference between treatment groups was observed in the hypo/loss of sensation sensory domain score.

The NSC score is a health questionnaire designed to collect signs and symptoms of neuropathy that is administered by the neurologist during the NIS exam.

Exploratory outcome: Change from baseline to week 65 in the polyneuropathy disability (PND) score

Improved PND scores were observed at week 65 in a higher proportion of patients in the inotersen group (10.5%) compared with the placebo group (3.8%) (Table C13).

The PND score rates patients' ambulatory status in five broad categories, ranging from no motor impairment to wheelchair required/confined to bed.

Exploratory outcome: Echocardiogram (ECHO) parameters and N-terminal prohormone of Brain Natriuretic Peptide (NT-proBNP)

No statistically significant differences were observed between the inotersen group and the placebo group in the NEURO-TTR CM-ECHO set in selected parameters (see Table C16). None of these parameters changed meaningfully from baseline in either treatment group.

The lack of statistical significance is not surprising, given the relatively short treatment period. Furthermore, only patients in earlier stages of cardiac disease were included (New York Heart Association [NYHA] I and II). The CHMP considered that the outcome measurement time points of 35 and 62 weeks may indeed be too short to detect relevant effects on cardiac parameters in the CM-ECHO Set.

[redacted]

[redacted]

Table C16. [redacted]

[redacted]

[redacted]

Exploratory outcome: Proportion of patients with ≥60% decrease in TTR levels (week 66)

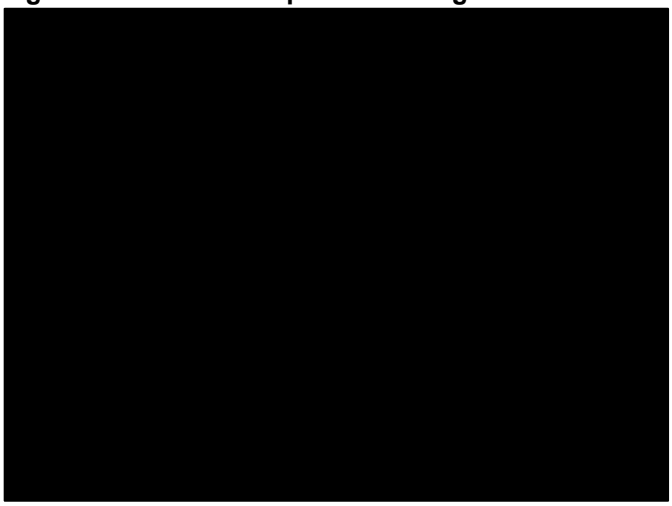
The proportion of patients in the inotersen group with ≥60% decrease in TTR levels exceeded 80% by week 13 through to week 66.

Robust reduction in circulating TTR levels was observed throughout the 15-month treatment period, with mean percent changes from baseline in serum TTR ranging from 68.41% to 74.03% (median range: 74.64% to 78.98%) from week 13 to week 65

as seen in Figure 9. In the placebo group, mean serum TTR concentration decreased by 8.50% at week 3 and then remained fairly constant throughout the remaining study period.

The differences in LSMs between the treatment groups for change from baseline in TTR were statistically significant (p<0.001) at all time points.

Figure 9: NEURO-TTR percent change from baseline in serum TTR over time



Abbreviations: LSM, least squares mean; SE, standard error; TTR, transthyretin.
Source: Benson *et al.*(8)

9.6.1.2 NEURO-TTR Extension interim results [redacted]

NEURO-TTR Extension study

- **[redacted] of patients that completed treatment in NEURO-TTR elected to enrol in the NEURO-TTR Extension study.**
- **Improvement in neurological disease progression (continued slowing of disease progression) and QoL were maintained in the long-term [redacted] with inotersen treatment.**

  [redacted]

  [redacted]

  [redacted]

- [redacted]

[redacted]

The interim analysis data [redacted] comprise of summary statistics only and do not include the primary statistical analysis; the mixed model for repeated measures (MMRM) analyses will be completed at the end of the study. The NEURO-TTR Extension study is expected to be completed in [redacted]

Change from baseline in the mNIS+7 composite score and Norfolk QoL-DN total score

From baseline in NEURO-TTR to the NEURO-TTR Extension, changes in the mean of the mNIS+7 composite score [redacted] and the Norfolk QoL-DN total score [redacted] were observed in the [redacted] This demonstrates that patients continued to receive benefit with extended dosing (i.e. continued slowing of disease progression) (see Table C17).

Within the placebo-inotersen group, changes in both the mNIS+7 and Norfolk QoL-DN total scores were observed from baseline in NEURO-TTR Extension. The rate of disease progression, following inotersen treatment, was slower for those patients in NEURO-TTR Extension compared to the rate of progression observed in NEURO-TTR.

[redacted] This indicates that there was increased benefit with earlier treatment of which persisted over time, with continued treatment.

Table C17. NEURO-TTR Extension changes from baseline mNIS+7 composite score and Norfolk QoL-DN total score, [redacted] (FAS)

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

Abbreviations: FAS, full analysis set; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; SD standard deviation.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file(40) .

In the responder analysis for NEURO-TTR Extension, the response rates [redacted], based on NEURO-TTR baseline, [redacted]

This observation is not unexpected, given that all patients received inotersen in NEURO-TTR Extension. Taken together, these data not only are consistent with increased benefit from early initiation of treatment but also suggest that once both groups received inotersen, the differences in disease progression rate diminished.

Norfolk QoL-DN symptom domain score in Stage 1 patients and Norfolk QoL-DN physical functioning/large fibre score in Stage 2 patients

Mean changes from baseline in Norfolk QoL-DN symptoms domain score in patients with Stage 1 hATTR-PN showed that patient QoL continued to improve with extended dosing in NEURO-TTR Extension [redacted] (see Table C18). [redacted]

Table C18. [redacted]

[redacted]						
[redacted]						
[redacted]						

Abbreviations: FAS, full analysis set; SD, standard deviation.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

In NEURO-TTR Extension, mean changes from baseline in the Norfolk QoL-DN physical functioning/large fibre neuropathy score in patients with Stage 2 disease continued to show benefit [redacted]

Table C19. NEURO-TTR Extension changes from baseline in the Norfolk QoL-DN physical functioning/large fibre neuropathy domain score, [redacted] (FAS) – Patients with Stage 2 hATTR-PN at NEURO-TTR baseline

[redacted]						
[redacted]						
[redacted]						

Note: Analysis based on data collected up to 52 days after the last dose of study drug in NEURO-TTR or NEURO-TTR Extension.
Abbreviations: FAS, full analysis set; SD, standard deviation.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

BMI

In NEURO-TTR, the placebo group had a [redacted] respectively. In NEURO-TTR Extension the changes in BMI [redacted] relative to the NEURO-TTR Extension baseline [redacted] (see Table C20). This is not surprising since all patients were receiving inotersen).

Table C20. NEURO-TTR Extension, changes from baseline in body mass index, [redacted] (FAS)

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

Abbreviations: FAS, full analysis set; kg/m^2, kilograms per square metre; SD, standard deviation.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

NIS composite score

In NEURO-TTR Extension, mean changes from baseline in the NIS composite score showed continued benefit [redacted] (see Table C21)**Error! Reference source not found.**. In addition, the [redacted] compared with their progression in NEURO-TTR where the patients were receiving placebo.

Table C21. NEURO-TTR Extension changes from baseline in the NIS composite score, [redacted] (FAS)

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

Abbreviations: FAS, full analysis set; SD, standard deviation.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

SF-36 health survey

Patients in the [redacted] showed continued benefit with inotersen extended dosing [redacted] from NEURO-TTR Extension baseline to [redacted] (see Table C22).

The changes observed in the [redacted] than those observed over 65 weeks in NEURO-TTR. Patients in the placebo-inotersen group also [redacted] (mean change from NEURO-TTR Extension baseline to [redacted]).

Changes from baseline in MCS and mental health domain scores were observed in NEURO-TTR Extension. [redacted] (see Table C22)Error! Reference source not found.. However, [redacted]

[redacted]

Table C22. NEURO-TTR Extension changes from baseline in SF-36 scores, [redacted] (FAS)

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

Note: Includes data collected up to 52 days after the last dose of study drug in NEURO-TTR or NEURO-TTR Extension.
Abbreviations: FAS, full analysis set; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-36, short form-36.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

PND score

In NEURO-TTR Extension, changes in the PND score [redacted] relative to NEURO-TTR baseline, showed that a greater proportion of patients [redacted] remained stable (not changed) or improved [redacted]. These findings suggest that early initiation of inotersen treatment is beneficial.

Table C23. NEURO-TTR Extension changes from baseline in the PND score, [redacted] (FAS)

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

Note: Includes data collected up to 52 days after the last dose of study drug in NEURO-TTR or NEURO-TTR Extension.
Abbreviations: FAS, full analysis set; PND, polyneuropathy disability; SD, standard deviation.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

NT-proBNP

The [redacted] (see Table C9), respectively. The geometric mean was used due to the high spread of values observed in individual patients. [redacted] The changes observed using the median values were consistent with the geometric mean.

TTR

As expected, TTR levels decreased in the placebo-inotersen group when inotersen treatment was started. This reduction was maintained during NEURO-TTR Extension and is consistent with the reductions [redacted] during NEURO-TTR. [redacted].

9.6.2 Justify the inclusion of outcomes in Error! Reference source not found. and Error! Reference source not found. from any analyses other than intention-to-treat

The efficacy data for NEURO-TTR and NEURO-TTR Extension were analysed on the FAS: all randomised patients who received at least one injection of study drug (inotersen or placebo) and who had a baseline and at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QoL-DN questionnaire total score.

The FAS was used for the principle analyses of efficacy data in CS2 in compliance with ICH E9 (Note for guidance on statistical principles for clinical trials) and represents the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects. Subjects were required to have a baseline value and at least one post baseline result in order to be included in the FAS because the primary endpoint is change from baseline. Subjects with either baseline or all post-baseline values missing will result in missing change from baseline and no results from those subjects can be used in the analysis.

9.7 Adverse events

NEURO-TTR and NEURO-TTR Extension(8)

- **Inotersen has a predictable and manageable safety profile,**
  - The majority of drug-related treatment-emergent adverse events (TEAEs) were mild to moderate in severity and many were consistent with known symptoms or complications of hATTR-PN (e.g. nausea, vomiting and anaemia).
  - The proportion of subjects with TEAEs that led to permanent discontinuation of study drug was higher in the inotersen group (14.3%) compared with the placebo group (3.3%), and primarily due to adverse events.
  - Serious TEAEs considered related to study drug were infrequent overall,
  - SC injection of inotersen was well-tolerated, with the majority of adverse events at the injection site were mild in severity, transient and self-resolving. No patients permanently discontinued inotersen due to adverse events at the injection site.
  - The principal safety concerns identified for inotersen treatment were glomerulonephritis and thrombocytopenia. Both of these were effectively detected with enhanced monitoring introduced in NEURO-TTR demonstrating that these events can be effectively detected with routine monitoring in clinical practice. This is reflected with the routine monitoring of platelet counts, UPCR, eGFR and hepatic enzymes included in the SmPC for inotersen.

- There were no new signals or safety concerns from the interim analysis of the NEURO-TTR Extension study, suggesting no additional toxicities related to longer-term exposure of inotersen.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The systematic literature review outlined in section 9.1 to 9.3 was used to identify related data. The relevant studies identified were NEURO-TTR and NEURO-TTR Extension. The study design, methodology, critical appraisal and efficacy results are summarised in sections 9.4 to 9.6.

9.7.2 Provide details of all important adverse events reported for each study.

9.7.2.1 NEURO-TTR

As shown in Table C24

, treatment-emergent adverse events (TEAEs) were observed in almost all patients participating in either the placebo or inotersen arm of the NEURO-TTR. The majority of events were mild or moderate in severity.

In the inotersen group, 16 (14.3%) TEAEs led to permanent discontinuation of study treatment, over one-third of these TEAEs were associated with thrombocytopenia (four inotersen patients) or glomerulonephritis (two inotersen patients), which are identified risks of inotersen treatment. The only TEAE leading to withdrawal from the study observed in >1 patient in the inotersen group was cachexia, which is a known complication of hATTR-PN.

There were five deaths in NEURO-TTR, all in the inotersen group. Four of the five deaths were consistent with progression or complication of the underlying disease (cachexia n=2; intestinal perforation n=1; congestive heart failure n=1) and were reported as unrelated to study treatment by the investigator. One patient in the inotersen group had a fatal TEAE of intracranial haemorrhage, in association with Grade 4 thrombocytopenia with a platelet count ~10 $x10^9$/L that was considered possibly related to study treatment by the investigator. This case occurred prior to the implementation of more frequent platelet monitoring during the study.

The death rate in inotersen-treated patients in NEURO-TTR (4.5%) is comparable with that reported in the placebo and active treatment groups of randomised clinical studies in comparable patient populations (41, 42). Therefore, it is likely that the numerical imbalance in the death rate between placebo and inotersen patients is due to a combination of 1) the 2:1 randomisation of patients in NEURO-TTR; 2) the fact that patients randomised to inotersen in NEURO-TTR had more severe disease, in particular cardiac disease and autonomic neuropathy, than those randomised to placebo; and 3) chance events since two of the deaths relate to surgical/post-surgical complications or complications of infection.

Table C24. NEURO-TTR incidence of TEAEs (SS)

	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.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

The majority of patients with TEAEs had events that were mild or moderate in severity. The most frequently reported study drug-related TEAEs in the inotersen group (≥10% of patients) were injection site erythema, nausea, fatigue, diarrhoea, headache, and injection site pain (Table C25). The majority of adverse events at the

injection site were mild in severity, transient and self-resolving. No adverse events at the injection site resulted in permanent discontinuation of inotersen.

Table C25. NEURO-TTR frequently reported TEAEs (≥10% incidence) (SS)

Preferred Term	Placebo (N=60)		Inotersen (N=112)	
	Patients n (%)	Number of events	Patients n (%)	Number of events
Injection site erythema	0	0	35 (31.3)	116
Nausea	7 (11.7)	9	35 (31.3)	44
Fatigue	12 (20.0)	14	28 (25.0)	43
Diarrhoea	12 (20.0)	16	27 (24.1)	29
Headache	7 (11.7)	10	26 (23.2)	34
Injection site pain	4 (6.7)	7	23 (20.5)	47
Pyrexia	5 (8.3)	6	22 (19.6)	32
Urinary tract infection	12 (20.0)	14	21 (18.8)	47
Oedema peripheral	6 (10.0)	6	21 (18.8)	23
Chills	2 (3.3)	3	20 (17.9)	40
Fall	13 (21.7)	16	19 (17.0)	26
Myalgia	6 (10.0)	7	17 (15.2)	25
Vomiting	3 (5.0)	3	17 (15.2)	22
Thrombocytopenia	1 (1.7)	2	15 (13.4)	21
Constipation	6 (10.0)	7	15 (13.4)	17
Anaemia	2 (3.3)	2	15 (13.4)	16
Asthenia	8 (13.3)	11	14 (12.5)	17
Arthralgia	5 (8.3)	8	13 (11.6)	20
Injection site pruritus	0	0	13 (11.6)	16
Dizziness	7 (11.7)	7	12 (10.7)	14
Platelet count decreased	0 (0.0)	0	12 (10.7)	14
Muscular weakness	6 (10.0)	7	11 (9.8)	11
Pain in extremity	8 (13.3)	11	10 (8.9)	12
Cough	8 (13.3)	8	10 (8.9)	11
Hypoaesthesia	6 (10.0)	7	10 (8.9)	11
Nasopharyngitis	6 (10.0)	7	9 (8.0)	9
Thermal burn	6 (10.0)	6	6 (5.4)	6
Neuralgia	9 (15.0)	9	3 (2.7)	3

Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

The principal safety concerns identified for inotersen treatment were glomerulonephritis and thrombocytopenia (Table C24 and Table C26**Error! Reference source not found.**). As these were identified in NEURO-TTR, enhanced monitoring with frequent testing of urine P/C and A/C ratio in at-risk patients and routine hematological testing of platelet counts was implemented. 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. For most patients, platelet count remained above 75 x 10^9/L and no specific intervention was necessary. Patients with lower platelet count can be managed with dose pause and adjustment of dose regimen. In the most severe cases, treatment with corticosteroids may hasten platelet count recovery.

Table C26. NEURO-TTR serious TEAEs considered related to study drug (SS)

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

† Patient was subsequently diagnosed with glomerulonephritis upon renal biopsy.
Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (32).

As demonstrated, the principal safety risks associated with inotersen can be effectively monitored with routine laboratory testing in clinical practice as per the SmPC (7), allowing the early detection and management of adverse events. The SmPC recommends platelet counts should be monitored every two weeks, urine protein to creatinine ratio (UPCR) and eGFR testing monitored at least every 3 months during treatment with inotersen and hepatic enzymes measured 4 months after initiation of inotersen and annually thereafter.

9.7.2.2 NEURO-TTR Extension

As of the latest safety data [redacted] a total of [redacted] patients were enrolled in the NEURO-TTR Extension and [redacted] patients had been dosed; [redacted] patients had received placebo and [redacted] patients had received inotersen in the NEURO-TTR study.

There were no new signals or safety concerns from a review of NEURO-TTR Extension data, suggesting no toxicities related to longer-term exposure of inotersen. In particular, there were no further cases of acute glomerulonephritis or Grade 4 thrombocytopenia.

Similar to NEURO-TTR, most patients in NEURO-TTR Extension experienced at least one TEAE as shown in Table C27, the majority of which were mild to moderate in severity. The percentage of patients who had a TEAE considered related to study treatment by the investigator was smaller in the inotersen-inotersen group than in the placebo-inotersen group. [redacted]

[redacted] in NEURO-TTR Extension. All were consistent with progression or complication of the underlying disease or chance infections and

reported as not related to study treatment by the investigator [redacted]

Table C27. NEURO-TTR Extension incidence of TEAEs (SS)

		[redacted]			[redacted]	
[redacted]						

† Includes two patients who had fatal TEAEs
Abbreviations: SS, safety set; TEAEs, treatment-emergent adverse events.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (39).

The most frequently reported study drug-related TEAEs (≥10% of patients) in NEURO-TTR Extension were fatigue, nausea, diarrhea, thrombocytopenia, peripheral edema, urinary tract infection, vomiting, chills, injection site pain, fall, and injection site erythema. Similar to the observations in NEURO-TTR, the majority of TEAEs were mild or moderate in severity.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Inotersen had an acceptable safety and tolerability profile in both NEURO-TTR and NEURO-TTR Extension (study ongoing) in a diverse population of patients with hATTR-PN. The majority of adverse events were mild to moderate in severity. Most common adverse events were often known symptoms or complications of the underlying disease. In many cases, the event or a predisposing factor was reported in the patient's medical history. The majority of adverse events at the injection site were mild in severity, transient and self-resolving. No patients permanently discontinued inotersen due to AEs at the injection site.

The principal safety concerns identified for inotersen treatment were thrombocytopenia and glomerulonephritis. 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. These key identified events can be effectively detected and monitored with routine laboratory tests as specified in the inotersen SmPC (7).

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Evidence synthesis is not required, as only one relevant controlled trial for inotersen was identified, which is compared to current standard of care in England (i.e. no active treatment).

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

In the NEURO-TTR study, inotersen treatment resulted in a statistically significant and clinically meaningful improvement in slowing, arresting and in some cases reversing neurological disease progression (mNIS+7) and QoL (Norfolk QoL-DN). Statistical significance was seen as early as 8 months (week 35) after treatment initiation in patients with hATTR-PN. Statistical significance was also achieved in the individual subdomains of these outcomes, in the sensitivity analyses and subgroup analyses, as well as multiple other outcomes, suggesting a consistent and robust treatment benefit of inotersen on both the neurological components of the disease and on QoL.

The results from the primary outcomes were supported by consistent effects in secondary, tertiary and exploratory outcomes (either statistically significant or trends in favour of inotersen).

Overall, the results from NEURO-TTR demonstrated that inotersen treatment provides clinical benefit to multiple aspects of disease including motor and sensory and neuropathies and QoL functional domains. These benefits were consistent across the pre-specified sub-groups of hATTR-PN patients included in NEURO-TTR.

In the NEURO-TTR Extension study, inotersen treatment resulted in slowing or arresting of disease progression in all patients. Throughout NEURO-TTR Extension, patients that received placebo in NEURO-TTR showed more severe disease than those that received inotersen in NEURO-TTR. Throughout the NEURO-TTR Extension study, inotersen benefits were observed in both groups.

The majority of adverse events observed in the NEURO-TTR and NEURO-TTR Extension studies were mild to moderate in severity. The principal safety concerns associated with inotersen treatment were thrombocytopenia and glomerulonephritis. These can be detected early via monitoring of platelet counts, urine protein/creatinine ratio, eGFR and hepatic enzymes – as reflected in the safety results of NEURO-TTR study once enhanced monitoring was introduced.

There were no new signals or safety concerns from a review of NEURO-TTR Extension data (to date), suggesting that longer-term exposure of inotersen does not trigger additional toxicities. Overall, the CHMP deemed the safety risks to be manageable by implementing risk-minimisation measures which are expected to be

both effective and feasible in clinical practice. These include specific monitoring, dose reduction as well as stopping rules. These risk minimisation measures are thoroughly described in the respective sections of the SmPC. Post-marketing measures will be in place to further collect data on the main identified safety concerns in a real-world treatment setting

Inotersen has a positive benefit:risk ratio in patients with hATTR-PN. Inotersen treatment significantly improves neurological disease progression and QoL in a wide population of patients with hATTR-PN.

hATTR-PN is a multi-system, progressively debilitating, and fatal neurodegenerative disease. Current treatment options are limited, and most patients only receive symptomatic therapies, that do not address the underlying cause of disease. By inhibiting hepatic production of both mutant and wild type (normal) TTR, inotersen represents a step-change in treatment, for a diverse population of hATTR-PN patients who have a short life expectancy, high morbidity, and a high unmet medical need.

[redacted]

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The pivotal study, NEURO-TTR, is a robust, well-conducted randomised clinical study based on 173 patients, which incorporates clinically relevant and accepted efficacy measures. Both primary outcomes, mNIS+7 and Norfolk QoL-DN, demonstrated the significant benefits of inotersen (slowing or arresting neurological disease progression and QoL as early as week 35).

The NEURO-TTR study included a relevant population of patients with hATTR-PN, generalisable to England. Any medications that were deemed necessary by the investigator were allowed in NEURO-TTR (symptomatic treatments), except diflunisal and tafamidis. Diflunisal is not currently approved for the treatment of hATTR-PN. Tafamidis is indicated for the treatment of adult patients with Stage 1 hATTR-PN, it is not currently recommended for use in England. Therefore, the placebo arm of

NEURO-TTR reflects the symptomatic treatments used in current clinical practice in England.

Long-term data for inotersen's clinical effectiveness and safety profile has further demonstrated the sustained benefits of the drug with a predictable and manageable safety profile. Efficacy measured in NEURO-TTR Extension demonstrated that the benefit of inotersen is maintained in the longer-term [redacted] in those patients that received inotersen in NEURO-TTR, and that inotersen slowed disease progression in those patients that received placebo in NEURO-TTR.

NEURO-TTR and NEURO-TTR Extension studies evaluated the use of inotersen in earlier stages of the disease, and therefore the use of inotersen is restricted to Stages 1 and 2 only.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base for inotersen is relevant to the decision problem defined in the scope. The NEURO-TTR and NEURO-TTR Extension studies included a diverse population of hATTR-PN generalisable to clinical practice in England. These studies included a relevant comparator arm (placebo) and the outcomes aligned with the scope. Evidence from these studies demonstrates a slowing, arresting or reversing of disease progression with inotersen. In addition, about half of patients experienced improvement of their HRQoL.

The benefits associated with inotersen treatment are expected to dramatically improve patients' lives in a population that currently has a significant unmet medical need due to a lack of effective treatment alternatives that address the underlying cause of the disease. The inclusion of inotersen in the treatment paradigm for hATTR-PN patients will radically change the way the disease is treated, leading to direct health and non-health benefits (outlined in further detail in Section 0) for patients, their carers and families by helping them to remain independent and productive members of their family, community and society for longer.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

There are no known factors that may influence the external validity of study results. The proposed indication for inotersen is for the treatment of adult patients with hATTR-PN including Stage 1 and Stage 2 of the disease. The patient population in NEURO-TTR and NEURO-TTR Extension reflects the population of patients with hATTR-PN that will be treated with inotersen in clinical practice in England.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

The loss of motor function has the highest impact on HRQoL, as the patient eventually loses the ability to walk or becomes bedridden at more advanced stages of the disease. However, patients suffer from numerous symptoms which also negatively impact HRQoL. These symptoms vary between patients and with disease stage (outlined previously in section 7), and include the following:

- Sensory and motor neuropathies
- Autonomic neuropathy (dizziness or fainting, vomiting, severe diarrhoea and/or constipation and neurogenic bladder).
- Body weight is often lost early in the disease, and life-threatening cachexia is common
- Focal lesions at onset, for example carpal tunnel syndrome
- Erectile dysfunction (males)
- Cardiac involvement (heart failure, episodes of arrhythmias, and severe conduction disorders, including atrioventricular block with faintness, syncopes, or even sudden death)
- Ocular manifestations (vitreous opacities, chronic open-angle glaucoma and scalloped pupils)
- Renal manifestations (nephritic syndrome and renal failure)

[redacted](9).

10.1.2 Please describe how a patient's health-related quality of life (HRQoL) is likely to change over the course of the condition.

The symptoms of hATTR-PN worsen as the disease progresses, resulting in a progressive decline in HRQoL over time and disease stage (see Figure 10). The symptom burden associated with disease progression has previously been described in Section 7.1.

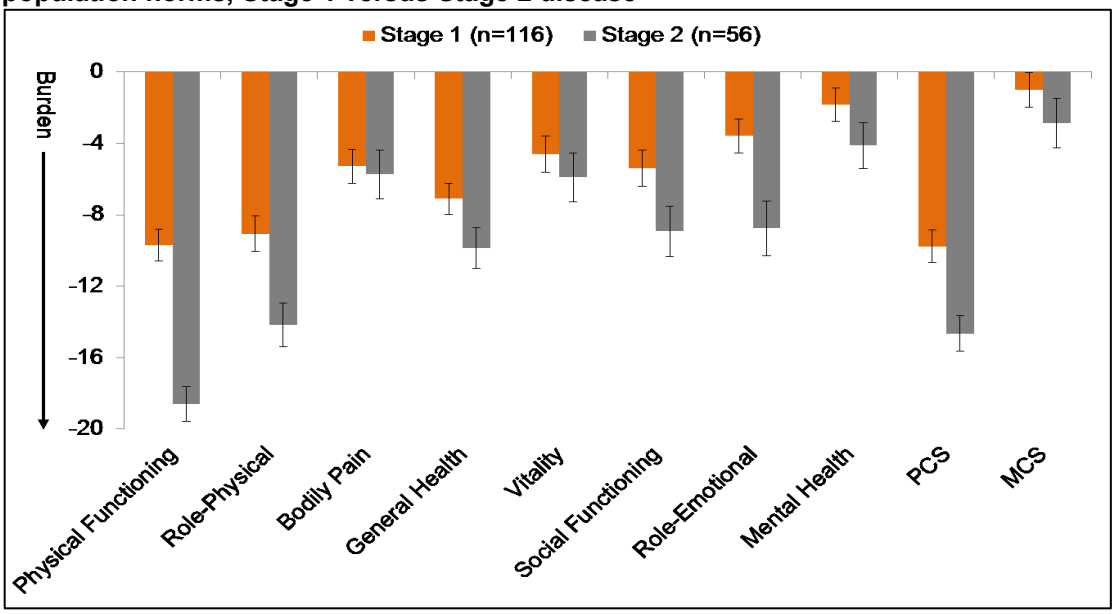
To estimate the burden of hATTR on patients' HRQoL, post-hoc analyses were conducted on baseline SF-36v2 scores from patients enrolled in the NEURO-TTR study and compared with scores from population-based benchmark samples.

When compared to a general population, patients with Stage 2 ambulatory disability report a markedly higher HRQoL burden than hATTR patients with Stage 1 ambulatory disability (see Figure 10).

Differences in burden for each of the two subgroups on most SF-36v2 domains (excepting all but bodily pain, vitality, and mental health) and PCS exceeded group-level MID thresholds, highlighting the additional HRQoL deficits that correspond with progression from Stage 1 to Stage 2 ambulatory disability.

As hATTR-PN progresses from Stage 2 to Stage 3, patients lose the ability to walk, become bedridden and lose their independence. Patients may be hospitalised at this stage due to severe symptoms such as cachexia, leading to a further dramatic decline in HRQoL.

Figure 10: Baseline burden of disease for hATTR patients relative to US general population norms, Stage 1 versus Stage 2 disease



Abbreviations: MCS, mental component summary; PCS, physical component summary.
Error bars represent standard errors of means.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (40).

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

In the NEURO-TTR study, Norfolk QoL-DN and SF-36v2 were used to assess patients' HRQoL at baseline and week 65. Utilities consistent with the NICE

reference case were therefore not collected in the trial and could not be used to inform the cost-effectiveness analysis robustly.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

There are no published mapping algorithms to map Norfolk QoL-DN to EuroQoL-5 Dimensions (EQ-5D).

Whilst the SF-36 can be converted into SF-6D utilities and mapped to EQ-5D, patients with Stage 3 disease were not enrolled. Therefore, it is not possible to generate robust health-state utility data from the NEURO-TTR study that matches the health state definitions used by Coutinho *et al.*

As such, published literature was used to inform health state utilities in the cost-effectiveness analysis, which conform to the NICE reference case.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in the appendix.

Details of the SLR to capture HRQL data are provided in Appendix 18. Inclusion and exclusion criteria are provided in section 18.1.6, Table 8.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

A total of 16 publications reporting HRQL were included in the SLR (see Section 9.2.2; Figure 3 provides for numbers included and excluded at each stage). Fifteen of these publications did not contain data to inform the economic model (see Table C28).

One publication, Stewart *et al.* reported HRQoL according to clinical stage for 1,205 symptomatic patients with hATTR-PN included in the THAOS registry (43). The cohort consisted of 970 patients with the V30M mutation and 235 patients with a non-

V30M mutation having a median age of 40 years and 54 years, respectively. EQ-5D-3L data were available for 77.5% of the recruited population including 618 (V30M) vs 113 (non-V30M) patients with Coutinho Stage 1 disease, 58 vs 22 with Stage 2 disease and 31 vs 15 with Stage 3. The publication reports data for 93 Brazilian patients by Coutinho Stage (Stage 1: n=55; Stages 2: n=15; and Stage 3: n=8).

Utility values in each were combined for the V30M and non-V30M cohort from this publication and applied in the economic model. Health state utilities for patients are outlined in Error! Reference source not found.. These are calculated as the weighted average of the V30M and non-V30M cohorts reported in Stewart *et al.* (43).

Table C28. Summary of publications reporting HRQoL (not suitable for use in the in the economic model)

Reference	Population	Instruments	Reported
Adams *et al.*, 2015 (44) (Poster)	hATTR-PN	EQ-5D, EQ-VAS	Mean EQ-5D-5L and EQ-VAS scores according to PND score (I and >II) at baseline
Denoncourt *et al.*, 2015 (45) (Poster)	hATTR-PN	EQ-5D-5L, EQ-VAS	Mean EQ-5D and EQ-VAS scores according to PND score (I and >II) at baseline
Denoncourt *et al.*, 2016 (11) (Abstract)	hATTR-PN	EQ-5D, EQ-VAS, Norfolk-DN and R-ODS	Mean EQ-5D, EQ-VAS, Norfolk-DN and R-ODS scores according to PND score I and >II at baseline
Telles-Correia *et al.*, 2009 (46) (Full paper)	hATTR-PN	SF-36, physical and mental and DIFQL	Mean SF-36 scores (MCS and PCS) and DIFQL scores before versus after liver transplantation
Drent *et al.*, 2009 (47) (Full paper)	hATTR-PN	SF-36	SF-36 scores post liver transplantation (at 1,2,3 and 4 years)
Ines *et al.*, 2015 (48) (Abstract)	hATTR-PN	EQ-5D-3L	Mean EQ-5D-3L utility score for patients with hATTR-PN compared with asymptomatic carriers and the general population
Ines *et al.*, 2015 (49) (Abstract)	hATTR-PN	EQ-5D-3L	Mean EQ-5D-3L utility score for symptomatic hATTR-PN patients
Lopes *et al.*, 2017 (5) (Full paper)	hATTR-PN	BSI-53	Mean BSI-53 (GSI, PST, and PSI) scores
Lopes *et al.*, 2018 (6) (Full paper)	hATTR-PN (V30M only)	None	Two questionnaires developed specifically to investigate the impact of the disease on individuals and their families

Reference	Population	Instruments	Reported
Lane *et al.*, 2017 (50) (Abstract)	hATTR-CM and ATTRwt	SF-36	Analysis of SF-36 data no scores presented (population not relevant to this submission)
Grogan *et al.*, 2017 (51) (Abstract)	hATTR-CM and ATTRwt	EQ-5D, EQ-VAS	Mean EQ-5D score (SD) and EQ-VAS score (SD), ATTRwt vs hATTR-CM overall and by NHYA class (population not relevant to this submission)
Coelho *et al.*, 2013 (52) (Full paper)	hATTR-PN	EQ-5D	Mean (SD) EQ-5D score for symptomatic, asymptomatic ATTR-PN patients and general population (US) by age
Stewart *et al.*, 2013 (53) (Abstract)	hATTR-PN and hATTR-CM	EQ-5D	Mean EQ-5D scores (with versus without transplant) for patients and carers
Lattanzi *et al.*, 2016 (54) (Abstract)	Familial ATTR	SF-36	Mean SF-36 MCS and PCS scores
Dodet *et al.*, 2015 (55) (Abstract)	hATTR-PN	Pittsburgh sleep quality index (PSQI)	Mean PSQI score hATTR-PN patients versus healthy subjects

Abbreviations: ATTRwt, wild-type transthyretin amyloidosis; BSI-53, Brief Symptom Inventory; DIFQL, variable to measure the difference between quality of life measured 6 months after transplantation (QL6M) and before transplantation (QLBT) [DIFQL = QL6M-QLBT]; EQ-5D, EuroQoL-5 Dimensions; hATTR-PN, hereditary transthyretin amyloidosis polyneuropathy; hATTR-CM, hereditary transthyretin amyloidosis cardiomyopathy; MCS, mental component summary; Norfolk QOL-DN, Norfolk Quality of Life Diabetic Neuropathy; PCS, physical component summary; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale; SF-36, short form-36; VAS, visual analogue scale; V30M, valine replaced by ethionine at amino acid position number 30.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

N/A.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

Most of the NEURO-TTR study drug-related TEAEs were mild to moderate in severity and many were consistent with known symptoms or complications of hATTR-PN (e.g. nausea, vomiting and anaemia). Other key risks, such as thrombocytopenia and renal impairment, are effectively managed via monitoring guidance, as per the SmPC (7). As such, adverse events have been assumed to have a minimal impact HRQoL and therefore have not been included in the economic model.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Health state utilities for patients are outlined in **Error! Reference source not found.**. These are calculated as the weighted average of the V30M and non-V30M cohorts reported in Stewart *et al.* (43).

Table C29. Summary of patient quality-of-life values for cost-effectiveness analysis

Health state	Patient EQ-5D-3L utility
Stage 1	0.697
Stage 2	0.429
Stage 3	0.084

Source: Stewart *et al.* (43).
Abbreviations: EQ-5D, EuroQoL-5 Dimensions.

As outlined in Section 7.1.4, the quality of life impact on carers in hATTR is significant and substantial. However, no studies have formally assessed the impact on carer quality of life by the health states described in the health economic model.

A systematic literature review of carer disutilities in other diseases has described studies which have found carer disutility to be as large as 0.14 in multiple sclerosis and stroke patients (56). In addition, Gani *et al*. (39) developed an algorithm which calculated carer disutility by Expanded Disability Status Scale (EDSS) severity score in multiple sclerosis, which attributed a rising disutility for carers as severity worsened. This has been used in previous NICE submissions (technology appraisal guidance TA533) (57) for calculating carer disutility in multiple sclerosis, and represents an appropriate approximation for hATTR carer disutility given the similarities in mobility, disability and symptomology as the disease progresses.

Table C30 outlines the disutility per carer in hATTR. In line with what has been previously accepted by the HST and NHS England in a similarly devastating disease, Duchenne Muscular Dystrophy, it is assumed that each patient has two full-time carers (58).

Table C30. Summary of carer quality-of-life values for cost-effectiveness analysis

Health state	EQ-5D-3L disutility per carer	Total disutility applied in model (2 x 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)

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[a]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[a] 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.

One clinical expert validated the disutilities assumed in the model and agreed that the approach adopted in the base case, was the most suitable approach in light of the paucity of data in hATTR.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQoL remains constant within each individual health state.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The impact of adverse events on HRQoL were excluded from the analysis. Adverse events were excluded from the model as no significant differences were observed for any one SAE, and the overall treatment-related SAE rates were very low in absolute terms (<5%)

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQoL varies over time according to disease stage – see section 10.1.9. However, HRQoL is assumed to be constant within each health state.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

The utility values from Stewart *et al.* for V30M and non-V30M patients have been averaged (43).

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

Not applicable. No treatment continuation or stopping rules are included in this submission.

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

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

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 18.3.

Details of the SLR to capture relevant health economic studies are provided in Appendix 18.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in Table 8 in the Appendices

Inclusion and exclusion criteria are provided in Section 18.1.6, Table 8.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Three publications (one poster and two abstracts) were identified from the SLR (59-61) - see Section 9.2.2, Figure 3 for numbers included and excluded at each stage.

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope.

All three publications explored the costs associated with hATTR-PN in Portugal and none contained data to inform the economic model. No publications reporting cost-utility analyses were identified.

Ines *et al.* estimated total costs for medicines dispensed in an ambulatory setting for management of hATTR-PN to be €1,612,673 overall; liver transplant patients accounted for approximately half (48%) of the total costs(59). In a second study, Ines *et al.* used a stochastic Markov model to predict healthcare costs for Portuguese patients diagnosed with hATTR-PN and estimated mean life-time healthcare costs per patient at €125,645 (60). In the third study, Ines *et al.* compared the annual healthcare costs for patients with hATTR-PN according clinical stage of disease (Stage 1, 2, and 3) (61). Average annual healthcare costs increased with disease progression from €4,859 for Stage 1 to €9,062 for Stage 2 and €12,425 for Stage 3 (61). None of these publications informed the model.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

N/A. All studies were posters or abstracts and none of the three studies informed the economic model.

12 Economic analysis

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The base-case population in the model consisted of a cohort of adult patients with hATTR-PN. This is in line with the scope and licenced indication.

The average age was 59 years, with [redacted] entering the model in Stage 1 and [redacted] entering the model in Stage 2, based on the demographics observed in the NEURO-TTR study.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

The comparator was established clinical management (without inotersen), as per the scope. This is described as BSC throughout. Current treatment options are limited to symptomatic treatment as described in Section 2.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

A cohort-based Markov state-transition model was developed to estimate the costs and health effects of inotersen and BSC in adult patients with hATTR-PN. The model includes four health states based on Coutinho staging (10);

(i) Disease Stage 1, where the patient can walk without assistance

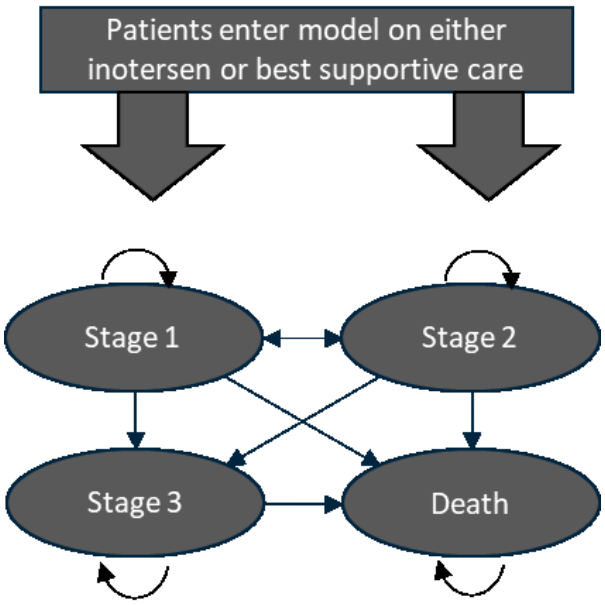
(ii) Disease Stage 2, where the patient requires assistance to walk

(iii) Disease Stage 3, where the patient needs a wheelchair or is bedridden

(iv) Death

The model structure is illustrated in Figure 11. The arrows represent the possible movements (transitions) between health states in any given cycle. Regardless of stage, a transition into the death state is always possible.

Figure 11: Model structure



Note: The cycle length is 4 weeks.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model structure has been developed around a similar model submitted to the AGNSS in a related condition (62). The structure was largely accepted by the ERG, however the ERG report on this model criticised the inclusion of liver transplant health states and therefore liver transplant has been omitted from the model structure. The Institute for Clinical and Economic Review (ICER) in the US are also using a similar model structure for their review of inotersen (63).

The purpose of the model is to demonstrate progression through the stages outlined and reflect the severity of symptoms increase as the disease progresses, resulting in a decline in HRQoL. A cohort-based Markov structure has therefore been selected as the clinical pathway of care is stochastic and chronic. Alternative simulation model would involve unacceptable levels of assumptions, as there is a paucity of data in hATTR-PN.

Disease stages defined by Coutinho *et al.* reflect the clinical pathway of care in England (10). The cycle length of four weeks was selected to reflect the approximate length of time between healthcare system contacts in UK clinical practice.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table D1 outlines the assumptions used in the model.

Table D1. Model assumptions

Model structure	Justification
Patients were assumed to discontinue treatment on entering Stage 3	This is in line with the license
Patients cannot move back from Stage 3 to Stage 2 or Stage 1	Inotersen is not given in Stage 3, and this assumption also aligns with the tafamidis model (62).
All patients will die on or before reaching the age of 100	Standard modelling assumption
Clinical inputs	
TQoL score used to estimate Coutinho disease stage.	Norfolk QoL-DN, one of the primary endpoints in the Phase 3 NEURO-TTR study, has been validated to be a reliable indicator of the impact of disease severity on HRQoL in patients with hATTR-PN. Thus, the Total Norfolk QoL-DN score (TQoL score) recorded in the NEURO-TTR study was used to estimate Coutinho disease transition during the trial observation period. This is aligned with the published literature: Vinik *et al.* study (35). In Vinik's study, a cross-sectional study in Portugal, the authors found that the Norfolk TQoL, a composite score from Norfolk QoL-DN, discriminated between hATTR-PN disease stage groups as well as a healthy population. The cut-off scores used align with the tafamidis model (62).
Disease stage transition probabilities vary over time.	The trial gives data for transition probabilities between 0 and 35 weeks, and 35 and 66 weeks. The first 35 weeks of data are estimated using the first set of transition probabilities, and all subsequent weeks (including extrapolation weeks) are estimated using the second set of transition probabilities. Section 9.6 demonstrates that the magnitude of benefit increases with time on treatment; as such the extrapolation phase was based on weeks 35 to 66.
Mortality rates estimated using Weibull curve fitted to trial data	Only long-term evidence available to model mortality in hATTR; the cohort in the Sattianayagam study had the same median age as that of the NEURO-TTR study (63 years) and as such should follow similar survival trajectories.

	NICE Decision Support Unit (DSU) guidance (64) was followed to select the curves. The Weibull curve was the best fit in the V30m cohort and a reasonable fit in the non-V30m cohort; it was judged that the same curve should be selected for each cohort to avoid over estimation in the non-V30m group.
Discontinuation rates estimated using a Gompertz curve fitted to trial data	NICE DSU guidance was followed to select the curve (64). The Gompertz curve was not statistically significantly different from the curve with the lowest AIC and BIC and was judged to better reflect the clinical pathway where patients would gradually become less likely to discontinue as their time on treatment increased.
Compliance rates estimated at [redacted] using comparison of expected and actual dose from the trial.	Compliance (defined as those who miss a dose for any reason - other than discontinuation - which is not later made up) was included in the model as it more accurately reflects the real-world setting in which the drug will be used, as well as the modelled benefit from treatment.
A carer disutility of -0.005 was applied to Stage 1 patients A carer disutility of -0.055 was applied to Stage 2 patients A carer disutility of -0.250 was applied to Stage 3 patients	Based on Gani *et al (39)*., which developed an algorithm which calculated carer disutility by Expanded Disability Status Scale (EDSS) severity score in multiple sclerosis, which attributed a rising disutility for carers as severity worsened. This has been used in previous NICE submissions (57) for calculating carer disutility in multiple sclerosis, and represents an appropriate approximation for hATTR carer disutility given the similarities in mobility, disability and symptomology as the disease progresses. **Error! Reference source not found.** outlines the disutility per carer in hATTR. In line with what has been accepted by the HST and NHS England in a similarly devastating disease, Duchenne Muscular Dystrophy, it is assumed that each patient has two full-time carers.(39, 58)
Cost inputs	
One off event costs are triggered every time a transition is made to a worsening health state	Representing changes that must be made to their lifestyle (for example, altering the frequency of their healthcare system contacts). This assumption aligns with the tafamidis model (62).
Adverse events not individually costed	There is no statistically significant difference between serious adverse event rates, and

	the absolute rate of serious adverse events is very low (<5%).

Abbreviations: ERG, evidence review group; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; HRQoL, health-related quality of life; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; THAOS, Transthyretin Amyloidosis Outcomes Survey; TQoL, total quality of life.

12.1.6 Define what the model's health states are intended to capture.

Each health state captures the costs and utilities associated with inotersen and BSC and reflects the increase in costs and the decline in HRQoL as patients' progress through the disease stages.

Stage 1 state: The Stage 1 state captures the proportion of patients at each point in time that do not required any assistance with ambulation. The Stage 1 state can be modified as either being 'On treatment', 'Discontinued' or 'BSC' to represent someone entering the state as part of the inotersen arm, previously part of the inotersen arm, or part of the BSC arm respectively.

Stage 2 state: The Stage 2 state captures the proportion of patients at each point in time that do require assistance with ambulation (excluding wheelchair). The Stage 2 state can be modified as either being 'On treatment', 'Discontinued' or 'BSC' to represent someone entering the state as part of the inotersen arm, previously part of the inotersen arm, or part of the BSC arm respectively.

Stage 3 state: The Stage 3 state captures the proportion of patients at each point in time that need a wheelchair or are bedridden. The Stage 3 state can only be further modified as being 'Discontinued' or 'BSC', since no Stage 3 patient receives inotersen.

Death state: The death state captured the proportion of patients that are dead at each point in time.

Two cohorts (inotersen and BSC) enter the model in the Stage 1 state. For each cohort, patients could transition between health states as illustrated in **Error! Reference source not found.**.

- From Stage 1 to Stage 2, Stage 3 or death (or remain in the Stage 1 state)
- From Stage 2 to Stage 1, Stage 3 or death (or remain in the Stage 2 state)
- From Stage 3 to death (or remain in the Stage 3 state)
- Death is an absorbing state, therefore remaining in the death state is the only transition available.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table D2. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime (41 years)	Average life expectancy of patients with hATTR-PN ranges from 3 to 15 years from symptom onset, and average age in the model is 59. The base case therefore uses a lifetime horizon to fully capture the impact of disease progression and mortality. Patients are limited by the model from surviving past 100 years as a standard modelling assumption.	Gertz *et al.(1)*. Sattianaygam *et al (2).*

Discount costs and outcomes	1.5%	1.5% is considered appropriate in line with the NICE Reference Case, which states that 1.5% discount rates can be considered if: • Treatment restores people who would die or have severely impaired health to life or near full health • This is sustained over a very long period • This would not commit the NHS to significant irrecoverable costs 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'. 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). As inotersen is taken weekly and can be safely discontinued, this would not commit the NHS to significant irrecoverable costs.	NICE Reference Case (65)
Perspective (NHS/PSS)	NHS/PSS	As per the NICE reference case	NICE (65).

Cycle length	4-week cycles	Patients on inotersen need to be monitored on platelet count at least every 2 weeks. UPCR test and eGFR test should be monitored at least every 12 weeks. Therefore, a moderate assumption of 4-week cycle length was made. No half-cycle correction is required; patients receive full course of treatment at the beginning of each cycle.	Inotersen SmPC (7) Briggs *et al.* (66).

Abbreviations: eGFR, estimated glomerular filtration rate; hATTR-PN, hereditary transthyretin amyloidosis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; SmPC, summary of product characteristics; UPCR, urine protein to creatinine ratio.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

12.2.1.1 Disease state transition probabilities

Transition probabilities (4-week) were calculated using TQoL data from the NEURO-TTR study. Norfolk QoL-DN, one of the primary outcomes in this study, has been validated to be a reliable indicator of the impact of disease severity on HRQoL in patients with hATTR-PN (35). In this cross-sectional study in Portugal it was shown that the Norfolk TQoL score, a composite score from Norfolk QoL-DN, discriminated between hATTR-PN disease stage groups as well as a healthy population. Based on this validation, the TQoL score recorded in the study (week 35 and week 65) was used to estimate the disease transition during the study period.

There is a lack of published literature on the TQoL cut-off score for hATTR-PN according to disease stage, and thus the cut-off scores from the tafamidis ERG report were used in the base case (see Table D3). The cut-off score in the tafamidis ERG report (62) were based on the THAOS registry, a global, multicentre, longitudinal observational registry for all patients with ATTR.

Table D3. TQoL cut-off scores for each disease stage

Disease Stage	TQoL cut-off score
Stage 1	2.6
Stage 2	54
Stage 3	91
Maximum TQoL	135

Abbreviations: TQoL, total quality of life.
Source: Faria *et al.* (62).

Based on the TQoL cut-off scores in Table D3, disease transition data from the NEURO-TTR study were summarised for each patient cohort by treatment arm – see Table D4 to Table D7. Patients with no TQoL data reported at week 35 or 65 were

excluded from the summary. Patients in Stage 3 remained in Stage 3, and so are excluded from the tables.

The conversion from the probabilities taken from the trial into the 4-week probability (to correspond with the cycle length) is given by the formula(66):

$$= 1 - EXP(-(-LN(1 - "Population\ in\ subsequent\ state"/"Population\ in\ initial\ state")/("Time\ to\ be\ converted\ from"/"Time\ to\ be\ converted\ to")))$$

So, for example, the Stage 1 to Stage 2 transition given in **Error! Reference source not found.** would be:

$$= 1 - EXP(-(-LN(1 - \frac{10}{49})/(\frac{35}{4})))$$

Table D4. Patients receiving inotersen – 0-35 weeks

	Population in initial state	Population in subsequent state	Probability (35 weeks)	Probability (4 weeks)
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]

Table D5. Patients receiving inotersen – 35-66 weeks

	Population in initial state	Population in subsequent state	Probability (31 weeks)	Probability (4 weeks)
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]

Table D6. Patients receiving BSC – 0-35 weeks

	Population in initial state	Population in subsequent state	Probability (35 weeks)	Probability (4 weeks)
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]

Table D7. Patients receiving BSC – 35-66 weeks

	Population in initial state	Population in subsequent state	Probability (31 weeks)	Probability (4 weeks)
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]

Transitions for 4-week probabilities post week 66 (i.e. the extrapolation phase) were based on those derived in weeks 35-66, since it was observed that the magnitude of benefit is larger the longer patients remain on treatment (see Section 9.6).

12.2.1.2 Mortality

Mortality data was immature in the NEURO-TTR study, and literature is sparse describing long-term mortality outcomes in hATTR due the rare nature of the condition (see Section 6.3). Specifically, mortality data has not been collected by Coutinho staging.

Long-term follow-up data only exists for Sattianayagam *et al.* 2012 (2) this was based on 78 patients with hATTR split by V30m and non-V30m mutations. To align with the tafamidis ERG's criticism of the manufacturer's model submitted for tafamidis, time since diagnosis was used to calculate mortality, as opposed to time since onset. Although the ERG tafamidis report criticised that age-related mortality was not included, the median age of the cohort in Sattianayagam *et al.* 2012 (2) (63 years) is the same as the NEURO-TTR study (8) (63 years); as such any deaths due to age in Sattianayagam *et al.* 2012 would be similar to that of NEURO-TTR study.

To reflect the population under consideration in the cost-effectiveness analysis, survival data from the Sattianayagam *et al.* 2012 study was calculated in both the V30M and non-V30M mutation population separately and then combined by a weighted average using the split of V30M mutation in the NEURO-TRR study (51.7% V30M; 49.3% non-V30M).

To calculate survival in each population, Kaplan Meier data for survival from diagnosis was collected from Sattianayagam *et al.* 2012 (2) and digitised using GetData Graph Digitizer (67). In order to extrapolate survival from diagnosis over a lifetime horizon, NICE DSU guidance was followed in which parametric distributions

were fit to both sets of Kaplan Meier data using the following standard parametric distributions with R: Exponentional, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma (64).

The best fitting distribution was chosen by statistical consideration (Akaike's Information Criterion [AIC] and Bayesian Information Crierion [BIC]) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed survival and clinical plausibility. The lower the AIC and BIC, the better fit the distribution is to the observed data. Table D8**Error! Reference source not found.** summarises the AIC and BIC scores for each survival distribution. The distributions for the populations are presented in Figure 12 and Figure 13, respectively. The statistical goodness of fit measures found that that Weibull and Log-logistic distribution were the best fit for the V30M and non-V30M populations, respectively. For the V30M population, this was appropriate since the distribution closely estimated the survival of the population. For the non-V30M population, the Log-logistic distribution was not deemed clinically plausible since it has a long tail which would lead to a clinically unviable average survival time compared to V30M projected survival. All distributions other than Gompertz and Weibull also gave unrealistically long tails. Therefore, given its superior fit compared to the Gompertz distribution, the Weibull distribution was also selected for the non-V30M population; it fitted the Kaplan Meier data reasonably well. The survival distributions applied in the model are presented in Figure 14.

Table D8. Goodness of fit statistics for V30M and non-V30M survival from diagnosis parametric distributions curve

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. **Selected curves.**

Figure 12: Kaplan Meier and parametric distributions for the V30M population

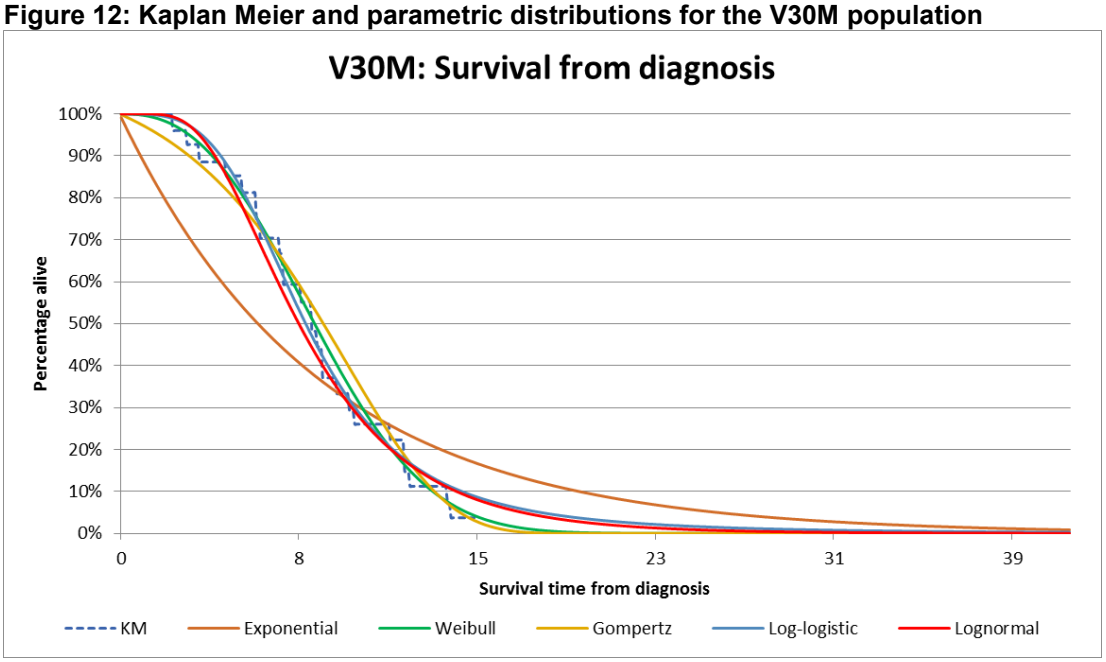


Figure 13: Kaplan Meier and parametric distributions for the non-V30M population

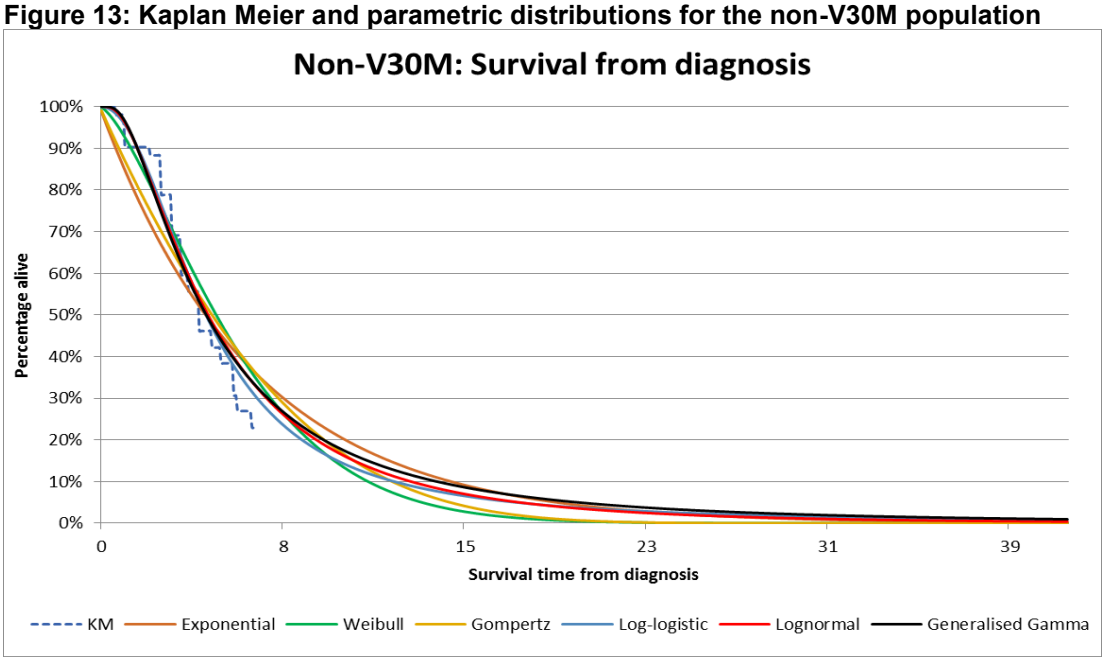
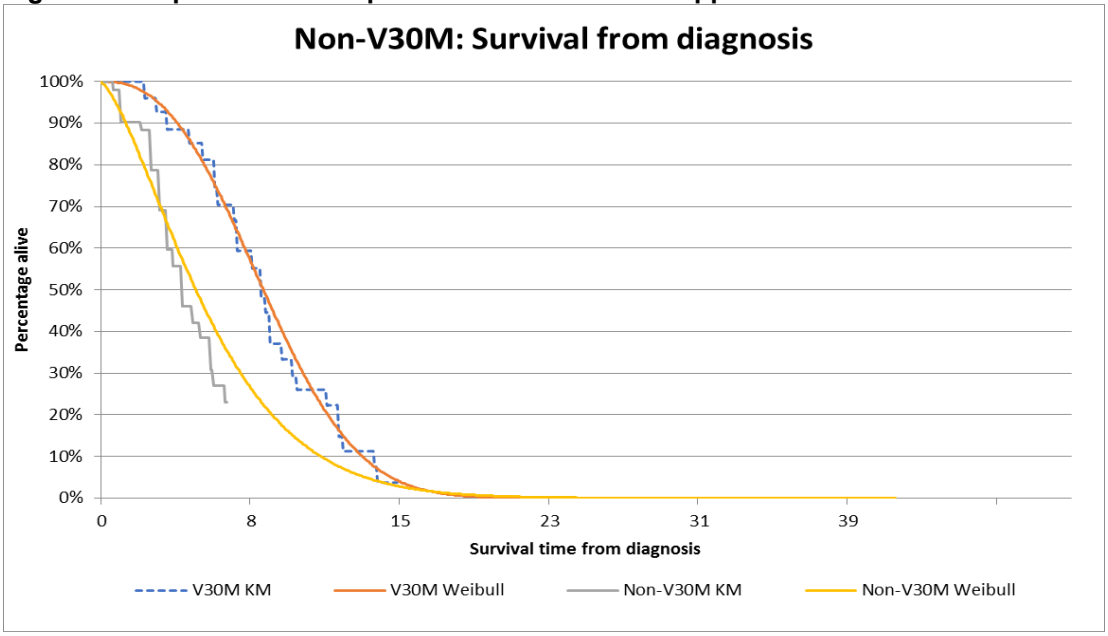


Figure 14: Kaplan Meier and parametric distributions applied in the model



12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Yes. Transition probabilities are assumed to be the same as those between weeks 35 to 66 of the NEURO-TTR study. This is justified as there is no evidence that inotersen becomes less effective over time, and it was observed that the magnitude of benefit is larger the longer patients remain on treatment (see Section 9.6).

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Yes. Norfolk QoL-DN, one of the primary endpoints in the Phase 3 NEURO-TTR study, has been validated to be a reliable indicator of the impact of disease severity on HRQoL in patients with hATTR-PN. Thus, the TQoL score recorded in the NEURO-TTR study was used to estimate the disease transition during the trial observation period. The cut-off TQoL scores from the tafamidis ERG report were used in model default setting to define a patient's disease stage.

This is aligned with the published literature: Vinik *et al.* study (35). In Vinik's study, a cross-sectional study in Portugal, the authors found that the Norfolk TQoL, a composite score from Norfolk QoL-DN, discriminated between hATTR-PN disease stage groups as well as a healthy population.

This assumption also aligns with the tafamidis model (62).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The majority of adverse events observed with inotersen in the clinical trial programme were mild to moderate to events. The absolute rate of serious adverse events is very low (<5%).The principal safety concerns identified for inotersen treatment were glomerulonephritis and thrombocytopenia. Both of these are effectively managed with enhanced monitoring as reflected in the SmPC for inotersen (see section 8.7 and 9.7 for further details) (7). As such, adverse events are not included in the cost-effectiveness model because the impact is expected to minimal.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Expert opinion was sought to understand the current management of patients with hATTR-PN, key modelling assumptions and model parameters via two advisory boards held in 2018. The first advisory board, held in April 2018, had eight attendees with the following backgrounds:

- Consultant clinicians with specialisms in cardiology, haematology, nephrology and neurology
- Representative from Public Health, NHS Scotland
- A Professor of Clinical Epidemiology & Biostatistics from UCL
- Two attendees from Amyloidosis Research Consortium (ARC) UK.

The second advisory board, held in May 2018, had six attendees including the following backgrounds:

- 4 health economists, three of which based in key academic centres for health economist and one independent health economist
- A member of ARC UK
- A consultant cardiologist.

The topics that were covered across the advisory boards included understanding current treatment pathway for patients with hATTR-PN, the impact of introducing inotersen based on the clinical trial data, cost-effectiveness modelling approach and relevant parameters.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in Error! Reference source not found. below.

For ease of presentation, clinical transition probabilities are given in Table D9 while all other variables are given in Table D10.

Table D9. Clinical transition probabilities

Transition from…	Transition to…	4-weekly probability (Week 0 – 35)	Lower bound (for DSA)	Upper bound (for DSA)	4-weekly probability (Week 35-death)	Lower bound (for DSA)	Upper bound (for DSA)	Reference
Inotersen Stage 1	Inotersen Stage 1	[redacted]	N/A	N/A	[redacted]	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 1	Inotersen Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 1	Inotersen Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 2	Inotersen Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 2	Inotersen Stage 2	[redacted]	N/A	N/A	[redacted]	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 2	Inotersen Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 3	Inotersen Stage 1	N/A	N/A	N/A	N/A	N/A	N/A	1. Welton *et al.* (68)

								2. NEURO-TTR study (32)
Inotersen Stage 3	Inotersen Stage 2	N/A	N/A	N/A	N/A	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
Inotersen Stage 3	Inotersen Stage 3	[redacted]	N/A	N/A	[redacted]	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 1	BSC or treatment discontinued Stage 1	[redacted]	N/A	N/A	[redacted]	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 1	BSC or treatment discontinued Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 1	BSC or treatment discontinued Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 2	BSC or treatment discontinued Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 2	BSC or treatment discontinued Stage 2	[redacted]	N/A	N/A	[redacted]	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)

BSC or treatment discontinued Stage 2	BSC or treatment discontinued Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 3	BSC or treatment discontinued Stage 1	N/A	N/A	N/A	N/A	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 3	BSC or treatment discontinued Stage 2	N/A	N/A	N/A	N/A	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)
BSC or treatment discontinued Stage 3	BSC or treatment discontinued Stage 3	[redacted]	N/A	N/A	[redacted]	N/A	N/A	1. Welton *et al.* (68) 2. NEURO-TTR study (32)

Table D10. Summary of variables applied in the cost-effectiveness model

Variable	Value	Standard Error (for PSA)	Distribution (for PSA)	Lower bound (for DSA)	Upper bound (for DSA)	Source
Initial patient distribution – Stage 1	[redacted]	Not varied				NEURO-TTR study (32)
Initial patient distribution – Stage 2	[redacted]					NEURO-TTR study (32)

Initial patient distribution – Stage 3	0.00%		NEURO-TTR study (32)
Initial patient distribution – Average age	59		NEURO-TTR study (32)
Mortality: Weibull shape parameter for V30M patients	[redacted]	N/A – different distributions to be tested as scenario analyses	Sattianayagam *et al.* 2012 (2)
Mortality – Weibull scale parameter for V30M patients	[redacted]	N/A – different distributions to be tested as scenario analyses	Sattianayagam *et al.* 2012 (2)
Mortality – Weibull shape parameter for non-V30M patients	[redacted]	N/A – different distributions to be tested as scenario analyses	Sattianayagam *et al.* 2012 (2)
Mortality – Weibull scale parameter for non-V30M patients	[redacted]	N/A – different distributions to be tested as scenario analyses	Sattianayagam *et al.* 2012 (2)
Treatment discontinuation Gompertz	[redacted]	N/A – different distributions to be tested as scenario analyses	NEURO-TTR study (32)

curve – Shape factor						
Treatment discontinuation Gompertz curve – Rate factor	[redacted]					NEURO-TTR study (32)
Treatment compliance	[redacted]	[redacted]	Beta	[redacted]	[redacted]	NEURO-TTR study (32)
Utility score at Stage 1	0.697	0.035	Beta	0.662	0.732	Stewart *et al.* (43)
Utility score at Stage 2	0.429	0.021	Beta	0.408	0.450	Stewart *et al.* (43)
Utility score at Stage 3	0.084	0.004	Beta	0.080	0.088	Stewart *et al.* (43)
Utility score at Death	0.000	0.000	Beta	0.000	0.000	Assumption
Carer disutility at Stage 1	-0.0050	0.000	Beta	-0.0048	-0.0053	TA533 (57)
Carer disutility at Stage 2	-0.0550	-0.003	Beta	-0.0523	-0.0578	TA533 (57)
Carer disutility at Stage 3	-0.2500	-0.013	Beta	-0.2375	-0.2625	TA533 (57)
Number of carers	2	N/A	N/A	N/A	N/A	Assumption

Inotersen cost (per 4-week of treatment)	[redacted]	N/A	N/A	N/A	N/A	Akcea Therapeutics
Vitamin A costs (per 4-week of treatment)	£0.65	N/A	N/A	N/A	N/A	NHS Electronic Drug Tariff, accessed 27/07/18(69)
Unit cost of platelet count test (per 2 weeks of treatment)	£1.69	£0.08	Gamma	£1.60	£1.77	NHS reference costs 2016/17, DAPS03
Unit cost of eGFR (per 3 months of treatment)	£1.69	£0.08	Gamma	£1.60	£1.77	NHS reference costs 2016/17, DAPS03
Unit cost of UPCR (per 3 months of treatment)	£1.13	£0.06	Gamma	£1.07	£1.18	NHS reference costs 2016/17, DAPS04
Unit cost of hepatic enzyme testing (per 12 months of treatment)	£1.69	£0.08	Gamma	£1.60	£1.77	NHS reference costs 2016/17, DAPS03
HRU cost at Stage 1 per 4-week	£393.33	£19.67	Gamma	£373.66	£413.00	Faria *et al.* (62)

HRU cost at Stage 2 per 4-week	£1,306.86	£65.34	Gamma	£1,241.52	£1,372.20	Faria *et al.* (62)
HRU cost at Stage 3 per 4-week	£1,744.63	£87.23	Gamma	£1,657.39	£1,831.86	Faria *et al.* (62)
HRU one-off cost Stage 1	£0.00	£0.00	Gamma	£0.00	£0.00	Assumption
HRU one-off cost Stage 2	£1,218.88	£60.94	Gamma	£1,157.94	£1,279.82	Faria *et al.* (62)
HRU one-off cost Stage 3	£4,525.50	£226.27	Gamma	£4,299.23	£4,751.78	Faria *et al.* (62)
HRU one-off cost death	£0.00	£0.00	Gamma	£0.00	£0.00	Assumption

Abbreviations: BSC, best supportive care; eGFR, estimated glomerular filtration rate; HRU, healthcare resource use; NHS, National Health Service; UPCR, urine protein to creatinine ratio

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Patients present with a wide variety of manifestations which makes it challenging to list all the relevant reference costs and payment by results (PbR) tariffs. Some examples of relevant tariffs are shown in Table D11 and Table D12.

Table D11. Relevant national tariff costs

Description	Combined day case/ordinary elective spell	Reference
Heart failure or shock	£1,382 - £5,901	2017/18 and 2018/19 National tariff (code EB03A – EB03E)
Arrythmia or conduction disorders	£527 - £3,624	2017/18 and 2018/19 National tariff (code EB07A – EB07E)
Syncope or collapse	£430 - £3,611	2017/18 and 2018/19 National tariff (code EB08A – EB08E)
Chronic kidney disease	£2,734 - £7,332	2017/18 and 2018/19 National tariff (code LA08G – LA08J)
Glaucoma	£324 - £447	2017/18 and 2018/19 National tariff (code BZ94A – BZ94B)
Minor, cataract or lens procedures (vitrectomy)	£231	2017/18 and 2018/19 National tariff (code BZ94A – BZ33Z)

Table D12. Relevant NHS reference costs

Description	Unit cost	Reference
Kidney or urinary tract infection	£808 - £7,406	National Schedule of reference costs 2016/17 (code LA04H – LA04S)
Minor bladder procedures (catheterisation)	£328	National Schedule of reference costs 2016/17 (code LB15E)
Intravenous nutrition	£379	National Schedule of reference costs 2016/17 (code XD26Z)

Urology (face to face consultant led first appointment)	£130	National Schedule of reference costs 2016/17 (code 101)
Ophthalmology (face to face consultant led first appointment)	£116	National Schedule of reference costs 2016/17 (code 130)
Gastroenterology (face to face consultant led first appointment)	£176	National Schedule of reference costs 2016/17 (code 301)
Cardiology (face to face consultant led first appointment)	£158	National Schedule of reference costs 2016/17 (code 320)
Nephrology (face to face consultant led first appointment)	£204	National Schedule of reference costs 2016/17 (code 361)

Resource use costs for the model were taken from the tafamidis ERG report and updated to 2018 costs (62). The unit costs reported in the tafamidis ERG report were sourced from UK sources i.e. the British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and National Health Service (NHS) reference costs.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

An SLR was undertaken to identify resource use data and relevant cost effectiveness studies (see section 11.2.1). Three studies examined the resource use associated with patients with hATTR-PN and the associated costs to the Portuguese healthcare system (59-61). However, these did not contain sufficient information to inform the model.

Therefore, resource use and associated costs for the model were taken from the only other available source – the tafamidis ERG report (62). According to the report, data on resource use was obtained from a group of clinicians based in Sweden (Pfizer stated they received no responses from the UK-based specialists consulted) and unit costs applied from UK sources i.e. the BNF, PSSRU and NHS reference costs. The UK clinicians contacted by the ERG during the tafamidis submission process considered the data on resource use provided by the Swedish clinicians as generally applicable to the UK clinical setting.**Error! Reference source not found.** The costs from tafamidis ERG report were updated to 2018 costs and applied in the model.

12.3.3 Clinical advisor assessment of resource input

12.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model2.

For information on how clinical advisors were approach and their input extracted and included, please see Section **Error! Reference source not found.**

The UK clinicians contacted by the ERG during the tafamidis submission process considered the data on resource use provided by the Swedish clinicians as generally applicable to the UK clinical setting.

Technology and comparators' costs

12.3.5 Provide the list price for the technology.

The list price for iontersen is £5,925 per weekly dose.

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

The patient access scheme price is used in the model. The patient access scheme price for inotersen is [redacted] per weekly dose.

12.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. D7 should be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Table D13. Costs per treatment/patient associated with inotersen in the cost-effectiveness model

Items	Value	Source
Cost of inotersen per patient per cycle (4-week)	[redacted]	Akcea Therapeutics
Cost of vitamin A per treatment/patient cycle per cycle (4-week)	£0.65	Assumed to be equal to 'Vitamins capsules' on NHS Electronic Drug Tariff, accessed 27/07/18
Administration cost	£0.00	The administration costs were assumed to be zero due to the fact that inotersen can be self-injected or injected by a carer
Monitoring costs		

[2] 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.

Unit cost of platelet count test per patient every 2 weeks	£1.69	NHS reference costs 2016/17, DAPS03
Unit cost of eGFR test per patient every 3 months	£1.69	NHS reference costs 2016/17, DAPS03
Unit cost of UPCR test per patient every 3 months	£1.13	NHS reference costs 2016/17, DAPS04
Unit cost of hepatic enzyme testing (yearly)	£1.69	NHS reference costs 2016/17, DAPS03

Abbreviations: eGFR, estimated glomerular filtration rate; NHS, National Health Service; UPCR, urine protein to creatinine ratio.

Health-state costs

12.3.8 If the cost- effectiveness model presents health states, table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

The HRU recurrent costs reported in the tafamidis ERG report were updated to 2018 costs and applied in the economic model**Error! Reference source not found.**. In addition to recurrent costs, the model applies a one-off cost at the progression to Stage 2 and subsequently at progression to Stage 3 (these costs were sourced from the ERG report and updated to reflect 2018 costs). **Error! Reference source not found.** The clinicians contacted by the ERG considered the resource use that these one-off costs refer to be reasonable and applicable to the UK setting.

Table D14. List of health states and associated costs in the cost-effectiveness model

Health states	Items	Value	Reference
Health state 1 per cycle (4-week)	Primary care	£24.17	Faria *et al.* (62)inflated to 16/17 using PSSRU inflation indices (70)
	Aids	£0.56	
	Homecare	£138.66	
	Symptom treatment costs	£229.94	
	Total	£393.33	
Health state 2 per cycle (4-week)	Primary care	£104.38	Faria *et al.* (62) inflated to 16/17 using PSSRU inflation indices (70)
	Aids	£1.63	
	Homecare	£818.08	
	Symptom treatment costs	£382.77	
	Total	£1,306.86	
Health state 3 per cycle (4-week)	Primary care	£49.43	Faria *et al.* (62) inflated to 16/17 using PSSRU inflation indices (70)
	Aids	£0.00	
	Homecare	£953.06	
	Symptom treatment costs	£742.14	
	Total	£1,744.63	
One-off cost Stage 2	-	£1,218.88	Faria *et al.* (62) inflated to 16/17 using PSSRU inflation indices (70)
One-off cost Stage 3	-	£4,525.50	Faria *et al.* (62) inflated to 16/17 using PSSRU inflation indices (70)

Adverse-event costs

12.3.9 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Not applicable (see Section 12.2.4).

Miscellaneous costs

12.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Not all patients in the trial took every dose of inotersen. Compliance for patients receiving inotersen was [redacted] %, therefore the cost of inotersen was adjusted by the actual dose consumed (since a higher dose may well have provided better outcomes).

In addition, the cost and efficacy of inotersen was adjusted based on those who continued or discontinued treatment. Patients who discontinued treatment received zero cost of inotersen and the effectiveness of BSC. Discontinuation was estimated by taking the discontinuation patient level data observed in the trial and fitting six standard parametric distributions in line with the NICE DSU guidelines (64) (Figure 15). Table D15 presents the goodness of fit statistics for the 6 distributions modelled. No curve was significantly better fitting than any other based on AIC and BIC criteria, and therefore the modelled curve was selected based on clinical plausibility as well as fit statistics. The Gompertz curve was selected because it demonstrated a rapid decline over the trial period and then a steadier decline over the next several hundred cycles, as shown in Figure 16. This was thought to more accurately reflect patients discontinuing early due to side effects, but those who could tolerate the drug easily being unlikely to discontinue.

Figure 15. KM and standard parametric discontinuation curves for inotersen

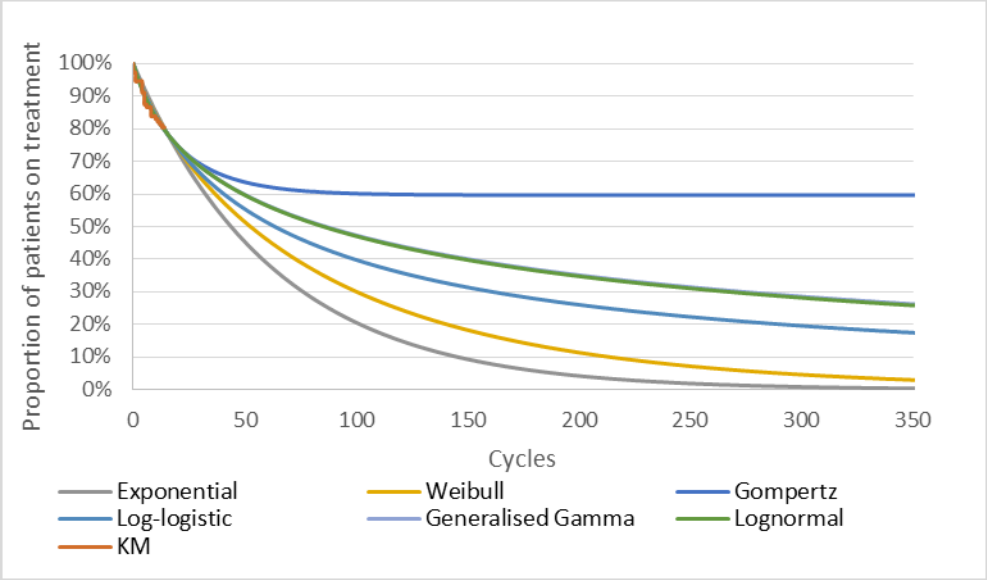
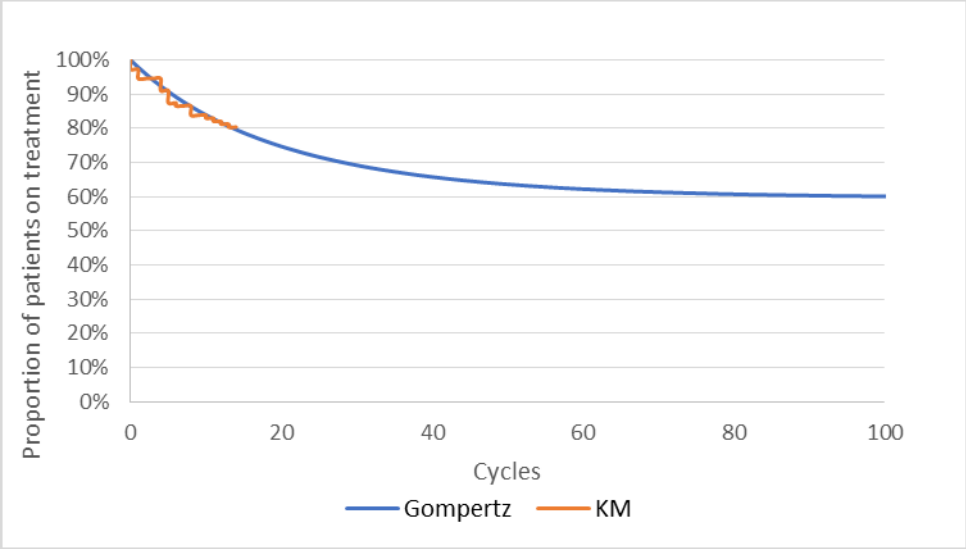


Table D15. Goodness of fit statistics for inoteren disconinutation standard parametric curves

Distribution	AIC	BIC
Exponential	259.471	262.189
Weibull	260.779	266.216
Gompertz	**260.548**	**265.985**
Log-logistic	260.625	266.062
Lognormal	260.221	265.658
Generalised	262.220	270.376

Figure 16: Discontinuation curve given by Gompertz curve fitted to trial data



Treatment discontinuation was varied in a scenario analyses. The Lognormal distribution was chosen to model discontinuation as it was the next curve which produced a rapid decline over the trial period before plateauing out over the next hundred cycles (**Error! Reference source not found.**). In addition, the goodness of fit statistics suggests that the Lognormal curve is a statistically good fit to the observed data (Table D15).

12.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Clinical engagement showed that patients with hATTR-PN regard the diagnosis as a 'death sentence' in the sense that there is no effective treatment available and the disease is inherently progressive. Access to psychological services (and mental health care generally) would be expected to be higher in the BSC group compared to the inotersen group, which offers the possibility of halting or reversing progression of the disease. This cannot be quantified, nor can the concomitant increase in QALY associated with the feeling of 'rescue' from the otherwise incurable condition (as the trial was double-blinded).

12.4 Approach to sensitivity analysis

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

The following sensitivity analyses were conducted in the model:

- Deterministic one-way sensitivity analysis on all applicable parameters, using 5% variation.

- Deterministic multi-way sensitivity analysis on all parameters where there is reasonable ground to expect a complex relationship which cannot fully be captured with one-way sensitivity analysis.
- Scenario analyses were conducted to assess the impact of varying cost and benefit discount rates and parametric distributions for mortality and discontinuation.
- Probabilistic sensitivity analysis (PSA). Distributions were selected in line with recommendations made by Briggs *et al*. incorporating uncertainty around parameter estimates into cost-effectiveness modelling (66). PSA was conducted using 10,000 monte-carlo simulations ensure stable results.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic, scenario and probabilistic sensitivity analyses were undertaken, as described above. Variables were varied in the PSA according to their reported standard deviation, and according to an assumed standard deviation of 5% in the absence of recorded values. Values were varied in the DSA according to a rule of +/- 5%. Distributions and their sources are stated in Table D9 and Table D10.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

See Table D9 and Table D10.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

The initial distribution of patient by stage and the average age of these patients were excluded from the the sensitivity analyses. In addition, the treatment cost of inotersen remained fixed in the model.

12.5 Results of economic analysis

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with

the patient access scheme. A suggested format is available in Error! Reference source not found..

The base-case cost-effectiveness results are presented in Table D16. Inotersen accrued [redacted] incremental QALYs and £[redacted] incremental costs. This corresponds to ICER of £324,054.44 per QALY gained.

Table D16. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	6.806	[redacted]	-	-	-	-
Inotersen	[redacted]	6.806	[redacted]	[redacted]	0.000	[redacted]	324,054.44

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The following outcomes from the decision problem are modelled:

- symptoms of polyneuropathy (as measured by disease stage in the model)
- mortality
- health-related quality of life (for patients and carers).

For symptoms of polyneuropathy, transition probabilities from the first 66 weeks of the trial are used to estimate subsequent transition probabilities. The transition probabilities in the first 66 weeks exactly mirror that of the trial.

Trial data demonstrates no statistically significant difference in mortality and adverse events between the treatment and BSC arm, therefore the adverse events are not modelled (see section 8.7 and 9.7 for further details).

In light of a lack of quality of life data from the trial, published literature was used to source utilities for health states and carer disutilities.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of patients in Stage 1, 2, and 3 health states and Dead for both Inotersen and BSC for the first ten years are presented in Table D17. Corresponding graphical respresentations are presented in Figure 17 and Figure 18, and Figure 19 and Figure 20 for the first ten years and the full time horizon, respectively.

Table D17. Markov trace for each state by comparator (first ten years only)

	Inotersen				BSC			
Year	**Stage 1**	**Stage 2**	**Stage 3**	**Dead**	**Stage 1**	**Stage 2**	**Stage 3**	**Dead**
0.08	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.00	[redacted]							
5.54	[redacted]							
6.00	[redacted]							
6.54	[redacted]							
7.00	[redacted]							
7.54	[redacted]							
8.00	[redacted]							
8.54	[redacted]							
9.00	[redacted]							
9.54	[redacted]							
10.00	[redacted]							

Figure 17: Ten-year trace diagram for inotersen

Figure 18: Ten-year trace diagram for BSC

Figure 19: Full trace diagram for inotersen

Figure 20: Full trace diagram for BSC

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The QALYs accrued over time per health state for the first 10 years for both Inotersen and BSC are presented in Table D18.

Table D18. Markov trace for QALYs accrued in each state by comparator (first ten years only)

	Inotersen			BSC		
Year	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
0.08						

0.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Total QALYs and LYGS accrued per health state over the full time horizon for both Inotersen and BSC are presented in Table D19.

Table D19. Model outputs by clinical outcomes

Outcome	LYG	QALY
Inotersen – Stage 1	[redacted]	[redacted]
Inotersen – Stage 2	[redacted]	[redacted]
Inotersen – Stage 3	[redacted]	[redacted]
Inotersen – All Stages	[redacted]	[redacted]
BSC – Stage 1	[redacted]	[redacted]
BSC – Stage 2	[redacted]	[redacted]
BSC – Stage 3	[redacted]	[redacted]
BSC – All Stages	[redacted]	[redacted]

Abbreviations: LYG, life years; QALY, quality-adjusted life year

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

As clinical outcomes also correspond to the health states assigned in the model, disaggregated QALYs by health state are already presented in Table D18.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

The undiscounted base-case cost-effectiveness results are presented in Table D20**Error! Reference source not found.Error! Reference source not found.**. Inotersen accrued [redacted] incremental QALYs and [redacted] incremental costs. This corresponds to ICER of £309,563.49 per QALY gained.

Table D20. Undiscounted results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	7.297	[redacted]	-	-	-	-
Inotersen	[redacted]	7.297	[redacted]	[redacted]	0.000	[redacted]	309,563.49

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Error! Reference source not found..

A summary of costs by category per patient are provided in Table D21 for both inotersen and BSC.

Table D21. Summary of costs by category of cost per patient

Item	Cost intervention Inotersen	Cost comparator BSC	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	106.1%
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	0.0%
Vitamin A cost	[redacted]	[redacted]	[redacted]	[redacted]	0.0%
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	0.0%
Transition costs	[redacted]	[redacted]	[redacted]	[redacted]	0.2%
HRU costs	[redacted]	[redacted]	[redacted]	[redacted]	5.9%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.0%
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					

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Error! Reference source not found..

A summary of cost by health state per patient for both inotersen and BSC are provided in Table D22.

Table D22. Summary of costs by health state per patient

Health state	Treatment costs	Administration costs	Vitamin A costs	Monitoring costs	HRU costs	Transition costs	All costs
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, health resource utilization

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Error! Reference source not found..

N/A

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

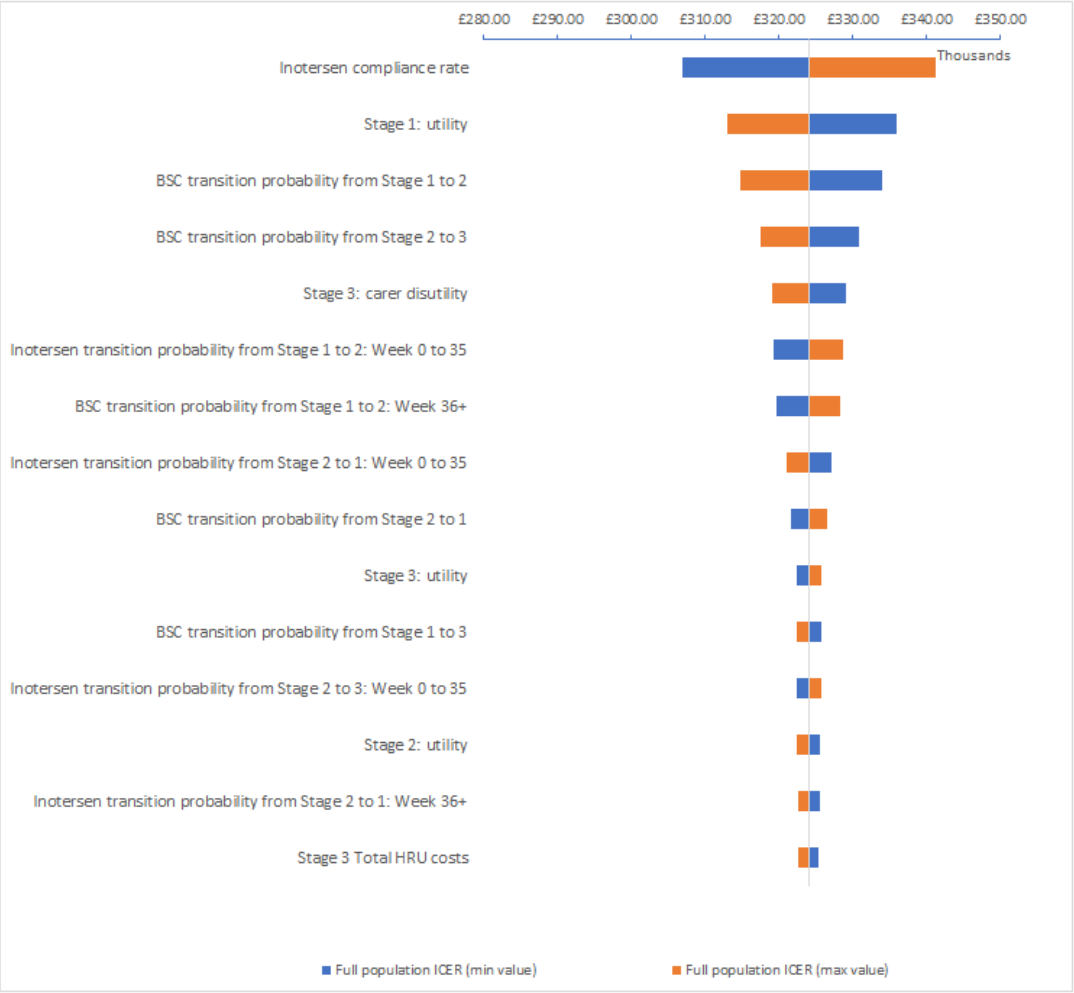
Table D23 shows the results for the top 15 most sensitive parametes from the one-way sensitivity analysis. In addition, Figure 21 demonstrates graphically the magnitudes of these effects in relation to the ICER. The variables less significant than these 15 contribute very little uncertainty to the results.

Table D23. One-way sensitivity analysis results

Variable	ICER (min value)	ICER (max value)	Difference
Inotersen compliance rate	£306,867.57	£341,241.30	£34,373.73
Stage 1: utility	£335,985.48	£312,941.69	£23,043.79
BSC transition probability from Stage 1 to 2	£334,071.43	£314,763.98	£19,307.45
BSC transition probability from Stage 2 to 3	£330,818.09	£317,622.49	£13,195.60
Stage 3: carer disutility	£329,203.13	£319,064.31	£10,138.81
Inotersen transition probability from Stage 1 to 2: Week 0 to 35	£319,387.44	£328,814.93	£9,427.49
BSC transition probability from Stage 1 to 2: Week 36+	£319,684.13	£328,291.11	£8,606.99
Inotersen transition probability from Stage 2 to 1: Week 0 to 35	£327,075.68	£321,109.13	£5,966.54
BSC transition probability from Stage 2 to 1	£321,642.49	£326,486.00	£4,843.51
Stage 3: utility	£322,366.54	£325,760.10	£3,393.56
BSC transition probability from Stage 1 to 3	£325,749.26	£322,378.57	£3,370.69
Inotersen transition probability from Stage 2 to 3: Week 0 to 35	£322,420.71	£325,702.07	£3,281.36
Stage 2: utility	£325,675.83	£322,449.11	£3,226.71
Inotersen transition probability from Stage 2 to 1: Week 36+	£325,579.99	£322,559.65	£3,020.34
Stage 3 Total HRU costs	£325,473.29	£322,635.58	£2,837.71

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio

Figure 21: One-way sensitivity analysis graphical results



Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; max, maximum; min, minimum

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in in table D10.2.

The most sensitive parameters are those relating to transition probabilities (particularly when on inotersen) and QALYs accrued in each state. Consequently, Table D24 presents results from multi-way sensitivity analyses where transition probabilities, health state utilities and carer disutilities are varied simultaneously.

Table D24 shows how the ICERs change as transition probabilities and utility values are varied from low to high. Of note is that there is no simple relationship between transition probabilities and ICER, which is consistent with the complex clinical pathway of the disease. The ICER remains below £350,000 for all scenarios modelled.

Table D24. Multi-way sensitivity analysis; transition probabilities vs utilities

	Carers and patients use minimum-value utilities	Patient uses minimum-value utilities, carers use base case	Base case	Patient uses maximum-value utilities, carers use base case	Carers and patients use maximum-value utilities
Low-end transition probabilities	£349,724.12	£344,384.93	£332,237.91	£320,918.58	£316,417.06
Base transition probabilities	£341,109.93	£335,895.83	£324,054.44	£313,019.50	£308,623.27
High-end transition probabilities	£333,404.91	£328,302.85	£316,734.66	£305,953.97	£301,652.06

Abbreviations: ICER, incremental cost-effectivness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALY, quality adjusted life year

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Mean PSA results are presented in Table D25. Inotersen was associated with [redacted] incremental QALYs and [redacted] incremental costs. This corresponds with an ICER of £324,963.15 per QALY. The corresponding incremental cost-effectiveness plane is presented in Figure 22.

Table D25. PSA results

	Base case	PSA	Difference (absolute)	Difference (proportional)
Incremental cost	[redacted]	[redacted]	[redacted]	0.02%

Incremental LYG	0.00	0.00	0.00	N/A
Incremental QALY	[redacted]	[redacted]	[redacted]	0.07%
ICER	£324,054.44	£324,963.15	£908,71	0.28%

Abbreviations: ICER, incremental cost-effectivness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALY, quality adjusted life year

Figure 22: PSA incremental cost-effectiveness plane

Abbreviations: PSA, probabilistic sensitivity analyses

12.5.14 Scenario analyses

Scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model. Scenario analyses modelled and their corresponding ICERs are presented in Table D26.

Table D26. Scenario analyses results

Parameter	Base case	Scenario	ICER
Base case			£324,054.44
Discount rate for costs and benefit	1.5%	0%	£309,563.49
	1.5%	3.5%	£343,282.18
Discoutinuation distribution	Gompertz	Lognormal	£323,677.58
Survival distribution	Weibull	Gompertz	£327,150.88

Abbreviations: ICER, incremental cost-effectiveness ratio

12.5.15 What were the main findings of each of the sensitivity analyses?

The one-way sensitivity analysis (OWSA) demonstrates that the compliance rate and utility valued applied to stage 1 are of the most sensitive parameters. Transition probabilities for both inotersen and BSC are also sensitive in the OWSA. The ICER is less sensitive to changes in health state costs (including monitoring) and discount rates. The ICER remained below £342,000 in all scenarios modelled.

Multi-way sensitivity analyses investigated the relationship between transition probabilities for both inotersen and BSC, and utility values applied to health states and carers. In all scenarios modelled in the ICER remained below £350,000.

The mean PSA results lie very close to the deterministic base-case results (Table D16). Inotersen accrued [redacted] QALYs at cost of [redacted] compared to BSC. The corresponding ICER was £324,963.15 per QALY gained.

Scenario analyses demonstrated that the ICER is not sensitive to changing the treatment discontinuation distributions from a Gompertz to Lognormal. In addition, the model is not sensitive to changing the survival distribution from a Weibull to a Gompertz. As anticipated, the ICER changes slightly when discount rates are increased and decreased.

12.5.16 What are the key drivers of the cost results?

The key drivers of cost are the price of inotersen and the time-in-state HRU costs. An important driver of the cost result is that inotersen prevents patients from entering the highly expensive Stage 3 state for much longer than BSC. This drives considerable savings for the NHS.

Miscellaneous results

12.5.17 Describe any additional results that have not been specifically requested in this template. If none, please state.

There are no additional results of relevant to the submission.

12.6 Subgroup analysis

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in Error! Reference source not found..

No subgroup analysis was undertaken.

12.6.2 Define the characteristics of patients in the subgroup(s).

N/A

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

N/A

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7.

N/A

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

N/A

Validation

12.6.6 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model was developed in close collaboration with clinical experts in hATTR-PN and validated by an external modelling agency. Two health economists checked each input and formula, and numerous checksum formulae were included in different stages of the model. In addition to DSA, PSA, scenario analyses and extreme value testing was used to identify inputs that behaved unintuitively. Face validity appears high, with life expectancy matching that of the hATTR-PN population and QoL in each stage approximately corresponding to descriptions given in patient engagement literature.

Interpretation of economic evidence

12.6.7 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The economic model represents the most valid and reliable characterisation of hATTR. Modelling decisions are primarily based on a previous AGNSS submission for a related compound. Where modelling decisions were made in contradiction of the tafamidis submission, this was typically in response to ERG criticism of aspects of the model.

12.6.8 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The only group of patients to which this model may not be applicable is those undergoing liver transplant. Clinical expert opinion is that this represents a negligible number of patients in the UK (probably zero) and that this is unlikely to change in the near future.

12.6.9 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The main strengths of the cost-effectivness analysis and hence the results are that they are relevant and generasible to clinical practice in England base on the following reasons:

- The patient population considered as adult patients with hATTR-PN. This population is in line with the population defind in the NICE scope and decision problem (**Error! Reference source not found.**) and falls within the anticipated license for Inotersen.
- The compartors considered are in line with the comparators defined in the NICE scope and decision problem (**Error! Reference source not found.**).
- The clinical evidence population can be considered representative of English patients as UK patients were enrolled in the NEURO-TTR trial.
- The modelled clinical outcomes are of high face validity, with patients decline to Stage 3 over the course of around 10 to 15 years.
- Monitoring resource use in the model is based up the SmPC.
- All costs and resource use in the model have been sourced from UK sources.

The main weakness of the cost-effectiveness analysis is a lack of high quality literature giving long-term mortality and transition probabilities for people with hATTR-PN.

12.6.10 What further analyses could be undertaken to enhance the robustness/completeness of the results?

At this stage, there is no further data available to enhance robustness of the model.

13 Cost to the NHS and Personal Social Services

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

It is anticipated there are around [redacted] patients in the UK eligible for treatment, based on UK expert opinion. Over the next five years, this is expected to increase to [redacted] patients (see Table D27).

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

Market share is anticipated to rise from [redacted] in year 1 to [redacted] in year 5. Table D27 demonstrates how this is distributed.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

There are no other significant costs associated with inotersen treatment.

13.4 Describe any estimates of resource savings associated with the use of the technology.

There are likely to be two major resource savings associated with the technology which are modelled:

- Inotersen can delay or reverse transition through disease states, with the tendency that patients will spend longer in less costly disease states. This benefit is doubly valuable, since not only is there a direct saving associated with being in a less expensive disease state, the longer one spends in lower-cost disease states, the higher expected mortality in the more costly disease states, meaning that fewer years are spent in Stage 3 overall compared to BSC.
- Inotersen can delay transition into disease states which carry a one-off cost of transition. As a result, the net present value of such transitions is diminished (potentially all the way to 0 if the patient has a high risk of mortality before transition). This is a minor resource saving but is accounted for in the model.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The model currently assumes care is given by a family member or is otherwise delivered in an unpaid setting. For patients without a family member who can offer the near round-the-clock support required for a Stage 3 patient, a significant PSS cost will be incurred as PSS are required to provide a carer. This will also be true – to a lesser extent – of patients in the care of family members who require respite care for a period. It is not possible to quantify the extent of this paid care in hATTR-PN, so a conservative assumption has been made to exclude it from the model.

In addition, clinical engagement showed that patients with hATTR-PN regard the diagnosis as a ‘death sentence’ in the sense that no effective treatment alternative exists and the disease being inherently progressive. Access to psychological services (and mental health care generally) would be expected to be higher in the BSC group compared to the inotersen group, which offers the possibility of halting or reversing progression of the disease. This cannot be quantified, nor can the concomitant increase in QALY associated with the feeling of ‘rescue’ from the otherwise incurable condition (as the trial was double-blinded).

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Productivity loss associated with the disease is thought likely to be high impact for a short length of time. The average age of patients diagnosed with hATTR-PN is around 59, meaning that they are quite near the age of retirement. This indicates that the total number of years the disease affects productivity is small, but that the years affected will be the most valuable of the working life of the individual. There is likely a small effect of Stage 1 disease, and then a significant effect of Stage 2 and 3 disease, but there is no evidence to confirm this.

In addition, Section 7 outlines that the burden of care for carers is significant; this displaces productive economic activity which will be a further extra-NHS/PSS source of savings associated with the technology.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The estimated budget impact over 5 years is described in Table D27.

Table D27. Estimated budget impact parameters

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

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The main weakness with the budget impact analysis is the very volatile nature of the disease coupled with the low number of patients with hATTR-PN.

Section E – Impact of the technology beyond direct health benefits

Summary

- Given the progressively debilitating nature of the disease, patients with hATTR-PN suffer extensively in terms of their health and emotional wellbeing; however, the impact of patients' progressive loss of independence and dignity extends into many other aspects of their lives and the lives of their carers. This includes a high financial burden, loss of productivity at work (including their ability to work), and a detrimental impact of patient's ability to actively participate in family life and social activities.
- Patients' ability to undertake paid work is significantly reduced, given the progressively debilitating nature of the disease and poor life expectancy, resulting in around two-thirds of patients unable to work (11).
- Family members are often carers for patients with hATTR-PN, providing medical support and care and assisting with activities of daily living, including household chores such as shopping and cooking. At advanced stages of the disease, carers also provide daily personal care. Consequently, carers' own ability to work and work productivity is significantly impaired.
- Inotersen has the potential to slow, arrest or reverse disease progression, with patients remaining in earlier stages of the disease (stage 1 or 2) for longer.
    - In turn, this allows patients to stay in a better health state and retain their independence for longer via the preservation of their ambulatory ability and key health domains, providing patients the opportunity to continue with employment, as well as actively participate in family life and social activities.
    - Inotersen also has the potential to reduce the burden falling on carers, in terms of their wellbeing, work productivity and participation in family and social activities.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and

personal social services, or are associated with significant benefits other than health.

Given the progressively debilitating nature of the disease, patients with hATTR-PN suffer extensively in terms of their health and emotional wellbeing. However, the impact of patients' progressive loss of independence and dignity also extends into many other aspects of their lives and lives of their carers. [redacted] (9). These additional detrimental impacts of hATTR-PN are not currently captured in the economic modelling.

The financial impact of the disease is substantial to the patient and their family. Patients' ability to undertake paid work is significantly reduced, given the progressively debilitating nature of the disease and the poor life expectancy. Denoncourt *et al.* reported that almost two-thirds of patients (64%) were unable to work because of hATTR-PN (11). [redacted] (9). This is supported further by a published data by Stewart *et al.* (71).

Family members often act as carers for patients with hATTR-PN. They typically provide medical support and care and assist with activities of daily living, including household chores such as cleaning, shopping and cooking. At advanced stages of the disease, carers also provide daily personal care. Consequently, the disease has a significant knock-on impact on carers' productivity at work as well as their ability to work. Berk *et al.* reported that 12% of carers limited work to part-time and 15% were unable to continue employment altogether, with the ability to hold employment falling from 22% to 6% for those caring for a patient with Stage 1 and Stage 2 hATTR-PN, respectively (21). [redacted] (9).

Patients' ability to engage in family life and social activities is impacted. In the early stages of disease, patients are likely to be able to continue with many aspects of family life and social activities such as hobbies or sport. As the disease progresses, the severity of symptoms increases to such an extent that family life and social activities are severely impacted. This can lead to feelings of guilt, depression and anxiety. The progressive loss of patients' independence in areas of life is detrimental, with some patients eventually confined to a wheelchair or bedridden, unable to leave the house.

The significant amount of time spent caring for patients means that carers also have to relinquish their own social activities and can become socially withdrawn due to the emotional and physical demands of caring.

Inotersen has the potential to slow, arrest or reserve disease progression with patients remaining in earlier stages of the disease (Stage 1 or 2) for longer. In turn, this allows patients to retain their independence for longer, thereby continuing with employment, actively participating in family life and social activities. In addition, carers are also likely to remain in paid employment and enjoy social activities for longer.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

None.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Costs borne by patients and carers include travel expenses for bi-annual visits to the NAC, in addition to other travel costs incurred to local centres post and prior to diagnosis e.g. general practitioner, secondary care.

Furthermore, inotersen offers the advantage of being administered subcutaneously and therefore can be self-administered avoiding unnecessary travel expenses to the hospital for treatment and any associated carer costs (including travel or fees for a private carer to escort a patient to the hospital). It also avoids patients and their family members taking unnecessary time off work to attend or escort patients to the appointment.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The burden on family members who provide care to patients with hATTR-PN is substantial. Due to the inherited nature of the disease it is common for multiple family members to be affected by the disease, and therefore the burden is often compounded by dual patient and carer roles. A study by Stewart *et al.* found that the median amount of time spent per week caring for h-ATTR-PN patients was reported at 144 hours (~6 days) for carers who had not been diagnosed with hATTR-PN themselves and estimated at a median of 100 hours weekly (~4 days) in carers who also had hATTR-PN, resulting in moderate to high levels of fatigue (1).

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The efficacy and safety profile for inotersen has been demonstrated via the clinical study programme. The NEURO-TTR study is one of the largest studies (n=172) of hATTR-PN patients to date demonstrating early and sustained benefit to patients treated with inotersen. Based on the results of this study, regulatory authorities have recognised the unmet need for effective treatments in this disease and the significant potential for inotersen to address this with both Priority Review and Accelerated Assessment being granted the by regulatory bodies in the US and EU respectively. Both the FDA and EMA have granted licenses for inotersen.

The open-label extension study (NEURO-TTR Extension) is ongoing and is collecting long-term safety and efficacy data (see section 0 for further details).

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Inotersen is the first licensed medicine for the treatment of hATTR-PN to target the underlying cause of the disease (formation of TTR amyloid deposits), and provides a step-change in the management of hATTR-PN. As a result, inotersen has the potential to dramatically improve patients' lives via slowing, arresting or reversing disease progression (8), which has not been achievable before.

The UK is one of the world-leaders for innovation in life sciences, many scientists from other countries come to the UK to research and develop innovative drugs and technologies. To remain world-leaders, it is critical to ensure that these innovative drugs and technologies are adopted for use in the UK as early as possible for the benefit of patients. Positive NICE recommendations for new innovative medicines demonstrate to potential investors that innovative treatments can achieve reimbursement in the UK, allowing the UK to continue to play a leading role at the forefront of medical innovation globally.

As a first-in-class treatment that targets the underlying cause of the disease and not just its symptoms, inotersen meets a high unmet medical need for patients with hATTR-PN. The inclusion of inotersen in the treatment paradigm for hATTR-PN patients has the potential to radically change the way the disease is treated and may allow patients to live a full and fulfilling life for longer.

Akcea is committed to developing and commercialising further innovative medical technologies in disease areas of high unmet need. The availability of inotersen would positively impact the ability of Akcea to invest in further innovation and to forge collaborations with other UK-based innovators and to undertake further collaborative research into hATTR and other diseases and their treatment.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

Akcea Therapeutics are committed to further strengthening the evidence base of inotersen and are planning a product registry in the US and EU to collate further information on the efficacy and safety of inotersen.

As part of our post authorisation development plans, agreed with the EMA, Akcea Therapeutics shall establish an Inotersen registry. This non-interventional, multinational, observational cohort study in the form of product registry in patients receiving Tegsedi for the treatment of hATTR with symptoms of polyneuropathy to prospectively assess platelet count decreases, acute renal failure including glomerulonephritis, ocular toxicities due to vitamin A deficiency, discontinuations during treatment including follow-up of patients after discontinuation, adverse events, SAEs, dose reductions, corticosteroid treatment, treatment pauses and treatment re-initiation compared to external data sources or similar patients not exposed to inotersen. Existing hATTR natural history data set(s) will be leveraged as a comparator for analysis of incidence rates of select events of interest (ESI) to help

differentiate effects of inotersen from those of underlying disease. A planned feasibility analysis will seek to identify additional sources of data that can address any remaining research gaps.

A retrospective chart review will also be conducted (as a PASS) with the specific objective of evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, the cut-off points proposed, dose adaptation, and initiation of corticosteroid therapy on thrombocyte recovery.

Lastly, the clinical study ISIS 420915-CS3, An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP), will serve as an additional Pharmacovigilance Activity. The safety results from this study, especially platelet and renal safety data, will be carefully evaluated periodically and at the conclusion of the study.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

It is anticpipated that the clinical effectiveness of inotersen will be reviewed as part of the existing pathway of care at specialist centres.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

Treatment should be initiated by and remain under the supervision of a physician experienced in the treatment of patients with hATTR-PN. Standard monitoring should be adhered to as per the summary of product characteristics (7). Inotersen is self-administered after treatment initiation at an expert centre, and Akcea Therapeutics will provide home-based nurse-led injection training when requested by the patient.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure would be required as inotersen is administered by the patient or their carer after treatment initiation.

[redacted]

Section F - Managed Access Arrangements

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA.

Not applicable.

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*
- *What evidence will be collected to reduce uncertainty*
- *How this evidence will be collected and analysed*
- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*
- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*
- *Funding arrangement, including any commercial proposals or financial risk management plans*
- *The roles and responsibilities of clinical and patient groups during the MAA*
- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

Not applicable.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA.

Not applicable

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18 Appendices

18.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

18.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The electronic databases and the platforms searched are outlined in Table 1.

Table 1: Electronic databases searched in the SLR

Database	Platform	Span of search	Date searched
Medline	www.ncbi.nlm.nih.gov/pubmed/	2008-2018	31-January-2018
Embase	Embase.com	2008-2018	7-Feburary-2018
Cochrane Library	http://onlinelibrary.wiley.com/cochranelibrary/search/	2008-2018	2-Feburary-2018

Abbreviations: SLR, systematic literature review.

18.1.2 The date on which the search was conducted.

The dates on which the electronic searches were conducted are shown in Table 1.

18.1.3 The date span of the search.

Electronic databases: 2008-2018.

18.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 2: PubMed search strings and the number of hits (31 Jan 2018)

Search	Query	Items found
#27	#1 AND #26	1246
#26	#19 OR #21 OR #23 OR #25	7097719
#25	Incidenc*[tiab] OR "Prevalence"[tiab] OR epidem*[tiab] OR mortalit*[tiab] OR natural histor*[tiab] OR demograph*[tiab] OR morbid*[tiab] OR risk[tiab] OR survival[tiab] OR etiology[tiab] OR aetiology[tiab] OR distribution[tiab] OR Frequency[tiab] OR pattern[tiab]	5572811
#24	#11 AND #23	2
#23	"resource use"[tiab] OR resource utili*[tiab] OR "resource usage"[tiab] OR "nursing cost"[tiab] OR "resource allocation"[tiab] OR "resource management"[tiab] OR "Health Care"[tiab] OR Health Care cost*[tiab] OR "direct	614300

	cost"[tiab] OR "indirect cost"[tiab] OR "Economic burden"[tiab] OR "economic impact"[tiab] OR "Disease Burden"[tiab] OR "Burden of illness"[tiab] OR "Burden of sickness"[tiab] OR "Sickness Burden"[tiab] OR "burden of disease"[tiab] OR productivit*[tiab] OR "productivity"[tiab] OR "work day"[tiab] OR "working days"[tiab] OR "length of stay"[tiab] OR "duration of stay"[tiab] OR "extended stay"[tiab] OR "prolonged stay"[tiab] OR "duration of stay"[tiab] OR "prolonged stay"[tiab] OR "duration of hospitalisation"[tiab] OR "bed-days"[tiab] OR "bed days"[tiab] OR re-admi*[tiab] OR readmi*[tiab] OR "readmission"[tiab] OR "hospital readmission"[tiab] OR "ICU stay"[tiab] OR "ICU day"[tiab] OR absent*[tiab] OR "absenteeism"[tiab] OR "presenteeism"[tiab] OR "work day"[tiab] OR "working days"[tiab] OR "Lost Work productivity"[tiab]	
#22	#11 AND #21	25
#21	"Quality of life" OR "HRQOL" OR "QOL" OR "HRQL" OR "health related quality of life" OR "health utilities index" OR "HUI"	284766
#20	#11 AND #19	6
#19	#12 OR #15 OR #16 OR #17 OR #18	1544027
#18	Economics[Mesh] OR Economic*[Mesh] OR Economic*[tiab] OR Cost[Mesh] OR cost[tiab] OR "costs and cost analysis"[Mesh] OR "costs and cost analysis"[tiab] OR "Cost allocation"[tiab] OR "Cost-allocation"[tiab] OR "Cost-benefit analysis"[tiab] OR "Cost control"[tiab] OR "Cost savings"[tiab] OR "Cost of illness"[tiab] OR "Cost sharing"[tiab] OR "deductibles and coinsurance"[tiab] OR "Medical savings accounts"[tiab] OR "Health care costs"[tiab] OR "Direct service costs"[tiab] OR "Drug costs"[tiab] OR "Employer health costs"[tiab] OR "Hospital costs"[tiab] OR "Health expenditures"[tiab] OR "Capital expenditures"[tiab] OR "Value of life"[tiab] OR "fees and charges"[tiab] OR charg*[tiab] OR fees[tiab] OR budget[Mesh] OR budget[tiab] OR "fiscal"[tiab] OR fund*[tiab] OR financ*[tiab] OR "cost estimate"[tiab] OR "cost-estimate"[tiab] OR "cost variable"[tiab] OR "cost-variable"[tiab] OR "variable cost"[tiab] OR "variable-cost"[tiab] OR "unit cost"[tiab] OR "unit-cost"[tiab] OR pharmacoeconomic[tiab] OR "pharmaco economic"[tiab] OR "pharmaco-economic"[tiab] OR pric*[tiab] OR cost-effectiv*[tiab] OR cost effectiv*[tiab] OR cost-effectiv*[tiab] OR "cost effectiveness"[tiab] OR "cost-effectiveness"[tiab] OR "Socioeconomic"[tiab] OR "Cost utility"[tiab] OR "cost minimization"[tiab] OR "cost-minimization"[tiab] OR "health care utilisation"[tiab] OR "economic aspect"[tiab]	1523372

	OR "financial management"[tiab] OR "health economics"[tiab] OR reimburse*[tiab] OR re-imburse*[tiab]	
#17	"fiscal"[tiab] OR "funding"[tiab] OR "financial"[tiab] OR "finance"[tiab] OR economic*[tiab] OR pharmacoeconomi*[tiab] OR price*[tiab] OR "pricing"[tiab]	365001
#16	"Low cost"[tiab] OR "High cost"[tiab] OR "Low costs"[tiab] OR "High costs"[tiab] OR "Health care cost"[tiab] OR "healthcare cost"[tiab] OR "health-care cost"[tiab] OR "Health care costs"[tiab] OR "healthcare costs"[tiab] OR "health-care costs"[tiab] OR "Estimated cost"[tiab] OR "Estimated costs"[Tiab] OR cost-Estimat*[tiab] OR "Cost-Estimate"[tiab] OR "Cost-Estimates"[tiab] OR "Variable cost"[tiab] OR "Unit cost"[tiab] OR "Variable costs"[tiab] OR "Unit costs"[tiab] OR "cost-Estimation"[tiab] OR "Cost per unit"[Tiab]	82953
#15	#13 AND #14	154062
#14	Economic*[tiab] OR Cost*[tiab]	675306
#13	"hospital" [tiab] OR "medical" [tiab] OR "nursing" [tiab] OR "pharmaceutical" [tiab]	1958642
#12	Economic*[tiab] OR "Economic"[MeSH] OR "Economics"[tiab] OR "Economics"[MeSH] OR "costs and cost analysis"[tiab] OR "Cost allocation"[tiab] OR "Cost-benefit analysis"[tiab] OR "Cost control"[tiab] OR "Cost savings"[tiab] OR "Cost of illness"[tiab] OR "Cost sharing"[tiab] OR "deductibles and coinsurance"[tiab] OR "deductibles"[tiab] OR "coinsurance"[tiab] OR "Medical savings accounts"[tiab] OR "Health care costs"[tiab] OR "Direct service costs"[tiab] OR "Drug costs"[tiab] OR "Employer health costs"[tiab] OR "Hospital costs"[tiab] OR "Health expenditures"[tiab] OR "Capital expenditure"[tiab] OR "Value of life"[tiab] OR "fees and charges"[tiab] OR "budget"[tiab]	741930
#11	#1 AND #10	229
#10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	32666
#9	"Liver transplant" OR "hepatic transplant"	16375
#8	"Doxycycline/tauroursodeoxycholic acid" OR "Doxy-TUDCA" OR "Tauroursodeoxycholic Acid and Doxycycline" OR "Doxycycline and tauroursodeoxycholic Acid" OR "Doxycycline and tau-URSO" OR "Doxycycline + tau-URSO" OR "Doxycycline + tauroursodeoxycholic acid"	14864
#7	"revusiran" OR "Revusiran [INN]"	4
#6	"IONIS-TTRRx" OR "ISIS 420915" OR "IONIS-TTR" OR Inotersen OR "GSK2998728" OR "UNII-950736UC77" OR "IONISTTRRx" OR "ISIS420915" OR "IONISTTR" OR	185

	"GSK-2998728" OR "UNII950736UC77" OR "IONIS TTRRx" OR "ISIS-420915" OR "IONIS TTR" OR "UNII 950736UC77"	
#5	"tolcapone" OR "SOM-0226" OR "SOM0226"	424
#4	"patisiran" OR "ALN-TTR02" OR "ALN-18328" OR "UNII-50FKX8CB2Y" OR "ALNTTR02" OR "ALN18328" OR "UNII50FKX8CB2Y" OR "ALN TTR02" OR "ALN 18328" OR "UNII 50FKX8CB2Y"	194
#3	"diflunisal" OR "Dolobid" OR "Algobid" OR "MK 647" OR "MK-647" OR "Diflunisalum" OR "MK647"	750
#2	"Tafamidis" OR "2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid" OR "Vyndaqel" OR "Fx-1006"	106
#1	"Familial Amyloid Polyneuropathy" OR "hereditary TTR amyloid polyneuropathy" OR "hATTR-Polyneuropathy" OR "hATTR-PN" OR "hATTR Polyneuropathy" OR "hATTR PN" OR "Transthyretin amyloidosis" OR "transthyretin-related hereditary amyloidosis" OR "TTR-FAP" OR "transthyretin familial polyneuropathy" OR "Transthyretin amyloid neuropathy" OR "Amyloidosis Transthyretin related" OR "Neuropathic heredofamilial amyloidosis" OR "Neuropathic heredofamilial amyloidosis" OR "Transthyretin amyloid polyneuropathy" OR "TTR amyloid neuropathy" OR "Familial transthyretin amyloidosis" OR "Familial amyloid neuropathies" OR “Amyloid Polyneuropathy” OR “Amyloid Polyneuropathies” OR “transthyretin polyneuropathy” OR “transthyretin polyneuropathies” OR "Familial polyneuropathies" OR “Familial polyneuropathy" OR “Amyloid neuropathy” OR “Amyloid neuropathies” OR “transthyretin neuropathy” OR “transthyretin neuropathies” OR "Familial neuropathies" OR “Familial neuropathy" OR “Amyloid cardiomyopathy” OR “Amyloid cardiomyopathies” OR “transthyretin cardiomyopathy” OR "transthyretin cardiomyopathies” OR "Familial cardiomyopathies" OR “Familial cardiomyopathy” OR "hATTR cardiomyopathy" OR "hATTR cardiomyopathies" OR "hATTR neuropathy" OR "hATTR neuropathies"OR "hATTR polyneuropathy" OR "hATTR polyneuropathies" OR “Familial Amyloid Cardiomyopathy” OR “Cardiac amyloidosis”	4122

Table 3: Embase search strings and the number of hits (7 Feb 2018)

Search	Query	Items found
#29	('familial amyloid polyneuropathy' OR 'hereditary ttr amyloid polyneuropathy' OR 'hattr-polyneuropathy' OR 'hattr-pn' OR 'hattr pn' OR 'transthyretin amyloidosis' OR 'transthyretin-related hereditary amyloidosis' OR 'ttr-fap' OR 'transthyretin familial	1513

	polyneuropathy' OR 'transthyretin amyloid neuropathy' OR 'amyloidosis transthyretin related' OR 'neuropathic heredofamilial amyloidosis' OR 'transthyretin amyloid polyneuropathy' OR 'ttr amyloid neuropathy' OR 'familial transthyretin amyloidosis' OR 'familial amyloid neuropathies' OR 'amyloid polyneuropathy' OR 'amyloid polyneuropathies' OR 'transthyretin polyneuropathy' OR 'transthyretin polyneuropathies' OR 'familial polyneuropathies' OR 'familial polyneuropathy' OR 'amyloid neuropathy' OR 'amyloid neuropathies' OR 'transthyretin neuropathy' OR 'transthyretin neuropathies' OR 'familial neuropathies' OR 'familial neuropathy' OR 'amyloid cardiomyopathy' OR 'amyloid cardiomyopathies' OR 'transthyretin cardiomyopathy' OR 'transthyretin cardiomyopathies' OR 'familial cardiomyopathies' OR 'familial cardiomyopathy' OR 'hattr cardiomyopathy' OR 'hattr cardiomyopathies' OR 'hattr neuropathy' OR 'hattr neuropathies' OR 'hattr polyneuropathy' OR 'hattr polyneuropathies' OR 'familial amyloid cardiomyopathy' OR 'cardiac amyloidosis') AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [2008-2018]/py	
#28	#1 AND #27	2152
#27	#20 OR #22 OR #24 OR #26	7571489
#26	(incidenc*:ab,ti OR 'prevalence':ab,ti OR epidem*:ab,ti OR mortalit*:ab,ti OR natural) AND histor*:ab,ti OR demograph*:ab,ti OR morbid*:ab,ti OR risk:ab,ti OR survival:ab,ti OR etiology:ab,ti OR aetiology:ab,ti OR distribution:ab,ti OR frequency:ab,ti OR pattern:ab,ti	6111335
#25	#12 AND #24	26
#24	(('resource use':ab,ti OR resource) AND utili*:ab,ti OR 'resource usage':ab,ti OR 'nursing cost':ab,ti OR 'resource allocation':ab,ti OR 'resource management':ab,ti OR 'health care':ab,ti OR health) AND care AND cost*:ab,ti OR 'direct cost':ab,ti OR 'indirect cost':ab,ti OR 'economic burden':ab,ti OR 'economic impact':ab,ti OR 'disease burden':ab,ti OR 'burden of illness':ab,ti OR 'burden of sickness':ab,ti OR 'sickness burden':ab,ti OR 'burden of disease':ab,ti OR productivit*:ab,ti OR 'productivity':ab,ti OR 'length of stay':ab,ti OR 'extended stay':ab,ti OR 'duration of stay':ab,ti OR 'prolonged stay':ab,ti OR 'duration of hospitalisation':ab,ti OR 'bed-days':ab,ti OR 'bed days':ab,ti OR 're admi*':ab,ti OR readmi*:ab,ti OR 'readmission':ab,ti OR 'hospital readmission':ab,ti OR 'icu stay':ab,ti OR 'icu day':ab,ti OR absent*:ab,ti OR 'absenteeism':ab,ti OR 'presenteeism':ab,ti OR 'work day':ab,ti OR 'working days':ab,ti OR 'lost work productivity':ab,ti	596060
#23	#12 AND #22	95
#22	'quality of life' OR 'hrqol' OR 'qol' OR 'hrql' OR 'health related quality of life' OR 'health utilities index' OR 'hui'	641286
#21	#12 AND #20	15

#20	#13 OR #16 OR #17 OR #18 OR #19	1168997
#19	(('economics'/exp OR economic*:ab,ti OR 'cost'/exp OR cost:ab,ti OR 'costs and cost analysis'/exp OR 'costs and cost analysis':ab,ti OR 'cost allocation':ab,ti OR 'cost-allocation':ab,ti OR 'cost-benefit analysis':ab,ti OR 'cost control':ab,ti OR 'cost savings':ab,ti OR 'cost of illness':ab,ti OR 'cost sharing':ab,ti OR 'deductibles and coinsurance':ab,ti OR 'medical savings accounts':ab,ti OR 'health care costs':ab,ti OR 'direct service costs':ab,ti OR 'drug costs':ab,ti OR 'employer health costs':ab,ti OR 'hospital costs':ab,ti OR 'health expenditures':ab,ti OR 'capital expenditures':ab,ti OR 'value of life':ab,ti OR 'fees and charges':ab,ti OR charg*:ab,ti OR fees:ab,ti OR 'budget'/exp OR budget:ab,ti OR 'fiscal':ab,ti OR fund*:ab,ti OR financ*:ab,ti OR 'cost estimate':ab,ti OR 'cost-estimate':ab,ti OR 'cost variable':ab,ti OR 'cost-variable':ab,ti OR 'variable cost':ab,ti OR 'variable-cost':ab,ti OR 'unit cost':ab,ti OR 'unit-cost':ab,ti OR pharmacoeconomic:ab,ti OR 'pharmaco economic':ab,ti OR 'pharmaco-economic':ab,ti OR pric*:ab,ti OR cost-) AND effectiv*:ab,ti OR cost) AND effectiv*:ab,ti OR 'cost effectiv*':ab,ti OR 'cost effectiveness':ab,ti OR 'cost-effectiveness':ab,ti OR 'socioeconomic':ab,ti OR 'cost utility':ab,ti OR 'cost minimization':ab,ti OR 'cost-minimization':ab,ti OR 'health care utilisation':ab,ti OR 'economic aspect':ab,ti OR 'financial management':ab,ti OR 'health economics':ab,ti OR reimburse*:ab,ti OR 're imburse*':ab,ti	419486
#18	'fiscal':ab,ti OR 'funding':ab,ti OR 'financial':ab,ti OR 'finance':ab,ti OR economic*:ab,ti OR pharmacoeconomi*:ab,ti OR price*:ab,ti OR 'pricing':ab,ti	448615
#17	'low cost':ab,ti OR 'high cost':ab,ti OR 'low costs':ab,ti OR 'high costs':ab,ti OR 'health care cost':ab,ti OR 'healthcare cost':ab,ti OR 'health-care cost':ab,ti OR 'health care costs':ab,ti OR 'healthcare costs':ab,ti OR 'health-care costs':ab,ti OR 'estimated cost':ab,ti OR 'estimated costs':ab,ti OR 'cost estimat*':ab,ti OR 'cost-estimate':ab,ti OR 'cost-estimates':ab,ti OR 'variable cost':ab,ti OR 'unit cost':ab,ti OR 'variable costs':ab,ti OR 'unit costs':ab,ti OR 'cost-estimation':ab,ti OR 'cost per unit':ab,ti	105709
#16	#14 AND #15	227566
#15	economic*:ab,ti OR cost*:ab,ti	851444
#14	'hospital':ab,ti OR 'medical':ab,ti OR 'nursing':ab,ti OR 'pharmaceutical':ab,ti	2755068
#13	economic OR 'economic' OR 'economics':ab,ti OR 'economics'/exp OR 'costs and cost analysis':ab,ti OR 'cost allocation':ab,ti OR 'cost-benefit analysis':ab,ti OR 'cost control':ab,ti OR 'cost savings':ab,ti OR 'cost of illness':ab,ti OR 'cost sharing':ab,ti OR 'deductibles and coinsurance':ab,ti OR 'deductibles':ab,ti OR 'coinsurance':ab,ti OR 'medical savings accounts':ab,ti OR 'health care costs':ab,ti OR 'direct service costs':ab,ti OR 'drug costs':ab,ti OR 'employer health costs':ab,ti OR 'hospital costs':ab,ti OR 'health expenditures':ab,ti	602711

	OR 'capital expenditure':ab,ti OR 'value of life':ab,ti OR 'fees and charges':ab,ti OR 'budget':ab,ti	
#12	#1 AND #11	646
#11	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	41795
#10	'liver transplant' OR 'hepatic transplant'	37153
#9	'doxycycline/tauroursodeoxycholic acid' OR 'doxy-tudca' OR 'tauroursodeoxycholic acid and doxycycline' OR 'doxycycline and tauroursodeoxycholic acid' OR 'doxycycline and tau-urso' OR 'doxycycline + tau-urso' OR 'doxycycline + tauroursodeoxycholic acid'	7
#8	'revusiran' OR 'revusiran [inn]'	23
#7	'ionis-ttrrx' OR 'isis 420915' OR 'ionis-ttr' OR inotersen OR 'gsk2998728' OR 'unii-950736uc77' OR 'ionisttrrx' OR 'isis420915' OR 'ionisttr' OR 'gsk-2998728' OR 'unii950736uc77' OR 'ionis ttrrx' OR 'isis-420915' OR 'ionis ttr' OR 'unii 950736uc77'	20
#6	'tolcapone' OR 'som-0226' OR 'som0226'	1684
#5	'patisiran' OR 'aln-ttr02' OR 'aln-18328' OR 'unii-50fkx8cb2y' OR 'alnttr02' OR 'aln18328' OR 'unii50fkx8cb2y' OR 'aln ttr02' OR 'aln 18328' OR 'unii 50fkx8cb2y'	78
#4	'diflunisal' OR 'dolobid' OR 'algobid' OR 'mk 647' OR 'mk-647' OR 'diflunisalum' OR 'mk647'	2670
#3	'tafamidis' OR '2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid' OR 'vyndaqel' OR 'fx-1006'	373
#2	('familial amyloid polyneuropathy' OR 'hereditary ttr amyloid polyneuropathy' OR 'hattr-polyneuropathy' OR 'hattr-pn' OR 'hattr pn' OR 'transthyretin amyloidosis' OR 'transthyretin-related hereditary amyloidosis' OR 'ttr-fap' OR 'transthyretin familial polyneuropathy' OR 'transthyretin amyloid neuropathy' OR 'amyloidosis transthyretin related' OR 'neuropathic heredofamilial amyloidosis' OR 'transthyretin amyloid polyneuropathy' OR 'ttr amyloid neuropathy' OR 'familial transthyretin amyloidosis' OR 'familial amyloid neuropathies' OR 'amyloid polyneuropathy' OR 'amyloid polyneuropathies' OR 'transthyretin polyneuropathy' OR 'transthyretin polyneuropathies' OR 'familial polyneuropathies' OR 'familial polyneuropathy' OR 'amyloid neuropathy' OR 'amyloid neuropathies' OR 'transthyretin neuropathy' OR 'transthyretin neuropathies' OR 'familial neuropathies' OR 'familial neuropathy' OR 'amyloid cardiomyopathy' OR 'amyloid cardiomyopathies' OR 'transthyretin cardiomyopathy' OR 'transthyretin cardiomyopathies' OR 'familial cardiomyopathies' OR 'familial cardiomyopathy' OR 'hattr cardiomyopathy' OR 'hattr cardiomyopathies' OR 'hattr neuropathy' OR 'hattr neuropathies' OR 'hattr polyneuropathy' OR 'hattr polyneuropathies' OR 'familial amyloid cardiomyopathy' OR 'cardiac amyloidosis') AND ([young adult]/lim OR [adult]/lim OR	2706

	[middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim	
#1	'familial amyloid polyneuropathy' OR 'hereditary ttr amyloid polyneuropathy' OR 'hattr-polyneuropathy' OR 'hattr-pn' OR 'hattr pn' OR 'transthyretin amyloidosis' OR 'transthyretin-related hereditary amyloidosis' OR 'ttr-fap' OR 'transthyretin familial polyneuropathy' OR 'transthyretin amyloid neuropathy' OR 'amyloidosis transthyretin related' OR 'neuropathic heredofamilial amyloidosis' OR 'transthyretin amyloid polyneuropathy' OR 'ttr amyloid neuropathy' OR 'familial transthyretin amyloidosis' OR 'familial amyloid neuropathies' OR 'amyloid polyneuropathy' OR 'amyloid polyneuropathies' OR 'transthyretin polyneuropathy' OR 'transthyretin polyneuropathies' OR 'familial polyneuropathies' OR 'familial polyneuropathy' OR 'amyloid neuropathy' OR 'amyloid neuropathies' OR 'transthyretin neuropathy' OR 'transthyretin neuropathies' OR 'familial neuropathies' OR 'familial neuropathy' OR 'amyloid cardiomyopathy' OR 'amyloid cardiomyopathies' OR 'transthyretin cardiomyopathy' OR 'transthyretin cardiomyopathies' OR 'familial cardiomyopathies' OR 'familial cardiomyopathy' OR 'hattr cardiomyopathy' OR 'hattr cardiomyopathies' OR 'hattr neuropathy' OR 'hattr neuropathies' OR 'hattr polyneuropathy' OR 'hattr polyneuropathies' OR 'familial amyloid cardiomyopathy' OR 'cardiac amyloidosis'	6286

Table 4: Cochrane search strings and the number of hits (2 Feb 2018)

Search	Query	Items found
#1	Familial Amyloid Polyneuropathy or "hereditary TTR amyloid polyneuropathy" or "hATTR-Polyneuropathy" or "hATTR-PN" or "hATTR Polyneuropathy" or "hATTR PN" or "Transthyretin amyloidosis" or "transthyretin-related hereditary amyloidosis" or "TTR-FAP" or "transthyretin familial polyneuropathy" or "Transthyretin amyloid neuropathy" or "Amyloidosis Transthyretin related" or "Neuropathic heredofamilial amyloidosis" or "Neuropathic heredofamilial amyloidosis" or "Transthyretin amyloid polyneuropathy" or "TTR amyloid neuropathy" or "Familial transthyretin amyloidosis" or "Familial amyloid neuropathies" or "Amyloid Polyneuropathy" or "Amyloid Polyneuropathies" or "transthyretin polyneuropathy" or "transthyretin polyneuropathies" or "Familial polyneuropathies" or "Familial polyneuropathy" or "Amyloid neuropathy" or "Amyloid neuropathies" or "transthyretin neuropathy" or "transthyretin neuropathies" or "Familial neuropathies" or "Familial neuropathy" or "Amyloid cardiomyopathy" or "Amyloid cardiomyopathies" or "transthyretin cardiomyopathy" or "transthyretin cardiomyopathies" or "Familial cardiomyopathies" or "Familial cardiomyopathy" or "hATTR cardiomyopathy" or "hATTR cardiomyopathies" or "hATTR neuropathy" or "hATTR neuropathies" or "hATTR polyneuropathy" or "hATTR polyneuropathies" or "Familial Amyloid Cardiomyopathy" or "Cardiac amyloidosis" (Word variations have been searched)	109

#2	Tafamidis or "2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid" or "Vyndaqel" or "Fx-1006"	46
#3	diflunisal or "Dolobid" or "Algobid" or "MK 647" or "MK-647" or "Diflunisalum" or "MK647"	301
#4	patisiran or "ALN-TTR02" or "ALN-18328" or "UNII-50FKX8CB2Y" or "ALNTTR02" or "ALN18328" or "UNII50FKX8CB2Y" or "ALN TTR02" or "ALN 18328" or "UNII 50FKX8CB2Y"	15
#5	tolcapone or "SOM-0226" or "SOM0226"	112
#6	IONIS-TTRRx or "ISIS 420915" or "IONIS-TTR" or Inotersen or "GSK2998728" or "UNII-950736UC77" or "IONISTTRRx" or "ISIS420915" or "IONISTTR" or "GSK-2998728" or "UNII950736UC77" or "IONIS TTRRx" or "ISIS-420915" or "IONIS TTR" or "UNII 950736UC77"	4
#7	revusiran or "Revusiran [INN]"	2
#8	Doxycycline/tauroursodeoxycholic acid or "Doxy-TUDCA" or "Tauroursodeoxycholic Acid and Doxycycline" or "Doxycycline and tauroursodeoxycholic Acid" or "Doxycycline and tau-URSO" or "Doxycycline + tau-URSO" or "Doxycycline + tauroursodeoxycholic acid"	0
#9	Liver transplant or "hepatic transplant"	1368
#10	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	1824
#11	#1 and #10	60
#12	Economic* or "Economic" or "Economics" or "Economics" or "costs and cost analysis" or "Cost allocation" or "Cost-benefit analysis" or "Cost control" or "Cost savings" or "Cost of illness" or "Cost sharing" or "deductibles and coinsurance" or "deductibles" or "coinsurance" or "Medical savings accounts" or "Health care costs" or "Direct service costs" or "Drug costs" or "Employer health costs" or "Hospital costs" or "Health expenditures" or "Capital expenditure" or "Value of life" or "fees and charges" or "budget":ti,ab,kw (Word variations have been searched)	41523
#13	hospital or "medical" or "nursing" or "pharmaceutical":ti,ab,kw (Word variations have been searched)	182341
#14	Economic* or Cost*	88696
#15	#13 and #14	26467
#16	Low cost or "High cost" or "Low costs" or "High costs" or "Health care cost" or "healthcare cost" or "health-care cost" or "Health care costs" or "healthcare costs" or "health-care costs" or "Estimated cost" or "Estimated costs" or cost-Estimat* or "Cost-Estimate" or "Cost-Estimates" or "Variable cost" or "Unit cost" or "Variable costs" or	13710

	"Unit costs" or "cost-Estimation" or "Cost per unit":ti,ab,kw (Word variations have been searched)	
#17	fiscal or "funding" or "financial" or "finance" or economic* or pharmacoeconomi* or price* or "pricing":ti,ab,kw (Word variations have been searched)	30849
#18	Economics or Economic* or Economic* or Cost or cost or "costs and cost analysis" or "costs and cost analysis" or "Cost allocation" or "Cost-allocation" or "Cost-benefit analysis" or "Cost control" or "Cost savings" or "Cost of illness" or "Cost sharing" or "deductibles and coinsurance" or "Medical savings accounts" or "Health care costs" or "Direct service costs" or "Drug costs" or "Employer health costs" or "Hospital costs" or "Health expenditures" or "Capital expenditures" or "Value of life" or "fees and charges" or charg* or fees or budget or budget or "fiscal" or fund* or financ* or "cost estimate" or "cost-estimate" or "cost variable" or "cost-variable" or "variable cost" or "variable-cost" or "unit cost" or "unit-cost" or pharmacoeconomic or "pharmaco economic" or "pharmaco-economic" or pric* or cost-effectiv* or cost effectiv* or cost-effectiv* or "cost effectiveness" or "cost-effectiveness" or "Socioeconomic" or "Cost utility" or "cost minimization" or "cost-minimization" or "health care utilisation" or "economic aspect" or "financial management" or "health economics" or reimburse* or re-imburse*:ti,ab,kw (Word variations have been searched)	90606
#19	#12 or #15 or #16 or #17 or #18	94052
#20	#11 and #19	3
#21	Quality of life or "HRQOL" or "QOL" or "HRQL" or "health related quality of life" or "health utilities index" or "HUI"	67424
#22	#11 and #21	20
#23	resource use or resource utili* or "resource usage" or "nursing cost" or "resource allocation" or "resource management" or "Health Care" or Health Care cost* or "direct cost" or "indirect cost" or "Economic burden" or "economic impact" or "Disease Burden" or "Burden of illness" or "Burden of sickness" or "Sickness Burden" or "burden of disease" or productivit* or "productivity" or "work day" or "working days" or "length of stay" or "duration of stay" or "extended stay" or "prolonged stay" or "duration of stay" or "prolonged stay" or "duration of hospitalisation" or "bed-days" or "bed days" or re-admi* or readmi* or "readmission" or "hospital readmission" or "ICU stay" or "ICU day" or absent* or "absenteeism" or "presenteeism" or "work day" or "working days" or "Lost Work productivity":ti,ab,kw (Word variations have been searched)	76491
#24	#11 and #23	5
#25	Incidenc* or "Prevalence" or epidem* or mortalit* or natural histor* or demograph* or morbid* or risk or survival or etiology or aetiology or distribution or Frequency or pattern:ti,ab,kw (Word variations have been searched)	397501

#26	#19 or #21 or #23 or #25	497830
#27	#1 and #26	64

18.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Electronic searches were supplemented by hand searching registries – see Table 5, congresses – see Table 6 and websites – see Table 7. The searches were conducted on 5th February 2018.

Table 5: Registries

Database	Platform	Search strategy
US NIH registry & results database	https://clinicaltrials.gov	Advanced search / Search terms: Hereditary transthyretin amyloidosis, hATTR, polyneuropathy, cardiac amyloidosis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, Inotersen
WHO ICTRP registry	http://apps.who.int/trialsearch/	Advanced search / Search terms: Hereditary transthyretin amyloidosis, hATTR, polyneuropathy, cardiac amyloidosis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, Inotersen
CEA-registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx	Search terms: Hereditary transthyretin amyloidosis, hATTR, polyneuropathy, cardiac amyloidosis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, Inotersen

Abbreviations: CEA, Cost-effectiveness analysis; ICTRP, International Clinical Trials Registry Platform; NIH, National Institutes of Health; US, United States; WHO, World Health Organization.

Abstract titles were searched using the keywords mentioned in Table 6 to identify relevant abstracts from the listed congresses.

Table 6: List of congresses searched in the SLR (2015-2017)

Research meeting	Abstract source	Search terms
European congress of hereditary ATTR amyloidosis & ATTR Amyloidosis meeting for patients and doctors (2015, 2017)	https://www.attr-meeting.com	Hereditary transthyretin amyloidosis, hATTR, polyneuropathy, cardiac amyloidosis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, Inotersen
International symposium on amyloidosis (2016)	http://www.amyloidosis.nl/	Same as above
European Academy of Neurology (2015, 2016, 2017)	https://www.ean.org/	Same as above

Research meeting	Abstract source	Search terms
American Academy of Neurology (2015, 2016, 2017)	https://www.aan.com/	Same as above
International Society for Pharmacoeconomics and Outcomes Research US and Europe (2015, 2016, 2017)	https://www.ispor.org/	Same as above
American Association of Neuromuscular & Electrodiagnostic Medicine (2015, 2016, 2017)	http://www.aanem.org/Home	Same as above
Peripheral Nerve Society (2015, 2017)	https://www.pnsociety.com/i4a/pages/index.cfm?pageid=1	Same as above
American Neurological Association (2015, 2016, 2017)	https://myana.org/	Same as above
American College of Cardiology (2015, 2016, 2017)	http://www.acc.org/#sort=%40fcommonsortdate86069%20descending	Same as above
Heart Failure Society of America (2015, 2016, 2017)	http://meeting.hfsa.org	Same as above
European Society of Cardiology (2015, 2016, 2017)	https://www.escardio.org/The-ESC	Same as above

Abbreviations: ATTR, Transthyretin amyloidosis; SLR, systematic literature review.

Table 7: Websites searched in the SLR

Database	Search field	Search terms
NICE	https://www.nice.org.uk/	Hereditary transthyretin amyloidosis, hATTR, polyneuropathy, cardiac amyloidosis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, Inotersen
RePEc website	http://repec.org/	Same as above
EQ-5D website	https://euroqol.org/	Same as above
The University of Sheffield's ScHARRHUD database of health utilities' evidence	https://www.scharrhud.org/	Same as above
HERC-maintained mapping algorithm database	https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies	Same as above

Abbreviations: hATTR, hereditary transthyretin amyloidosis; HERC, Health Economics Research Centre; NICE, National Institute for Health and Care Excellence; RePEc, Research Papers in Economics; SLR, systematic literature review.

18.1.6 The inclusion and exclusion criteria

The inclusion and exclusion criteria for first pass screening are shown in Table 8.

Table 8: Eligibility criteria used in search / screening strategy

Study characteristics	Inclusion	Exclusion
Population	Adults >18 years with confirmed diagnosis of hATTR-PN. FAP type I & II Cardiac amyloidosis FAC	• CIPD • ALS • Motor polyradiculoneuropathy • Carpal tunnel syndrome • Idiopathic polyneuropathy • Paraneoplastic neuropathy • Motor neuron diseases • Charcot-Marie-Tooth disease • Alcoholic neuropathy • Diabetic neuropathy • Immunoglobulin light chain amyloidosis • Amyloid A Amyloidosis • Hypertensive Heart Disease • Hypertrophic Cardiomyopathy • Wild-type ATTR • FAP type III & IV

Study characteristics	Inclusion	Exclusion
Interventions	Inotersen Tafamidis (Pfizer) Diflunisal Patisiran (Alnylam) Liver transplant BSC	• Monoclonal antibodies • Fibril disrupters • Herbal medicines • Homoeopathic medicines • Alternative therapies • Any other intervention
Study design/ Type of studies	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	Case reports Case series In-vitro studies Pre-clinical studies

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	

Study characteristics	Inclusion	Exclusion
	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	Before 2008
Publication	Primary publications, secondary publications / sub group analysis, pooled data analysis, Congress abstracts corresponding to the above	Systematic reviews (flag), network meta-analysis (flag), narrative reviews (flag), editorials, letters and commentaries • Congress abstracts that do not report sufficient data • Report data for n ≤5 Small studies
Language	English	Any other language

Abbreviations: FAC, familial amyloid cardiomyopathy; FAP, familial amyloid polyneuropathy; GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NSC, neuropathy symptoms and change; PND, polyneuropathy disability; RCT, randomised clinical trial; SF-36, short form-36.

Full text articles were reviewed for final selection of the references to be included in the SLR. The inclusion criteria used during first pass screening was modified to include the following additional criteria as shown in Table 9.

Table 9: Additional criteria for full text review

Study type	Changes to inclusion/exclusion criteria
Costs	None
HRQoL	As above, including no intervention (registry data)
Inotersen	None
Patisiran	None
Diflunisal	None
Tafamidis	In addition to the criteria above, exclusion of: • Abstracts with limited data • Publications reporting laboratory parameters such as total protein, albumin, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, • Reports of nutritional status • Studies involving n<10
Liver transplant	Inclusion of publications meeting the criteria above plus the following additional inclusion criteria: • Published as full paper • Included n>20 • Reports survival/long-term outcomes, not just short-term outcomes of LT Additional exclusion criteria were: • Inclusion of heart transplant and LT • Reporting ocular effects/outcomes • Not specific for hATTR • Reporting data for domino LT • LT procedure outcomes • Nutritional status/body composition • Occurrence of ESRD
Disease background, management and epidemiology (targeted search)	• Aimed only to include full papers, except for epidemiology. • Only included most recent study/data where a number of papers report similar data • Excluded papers before 2012 if more recent data available • Excluded papers with smaller patient numbers if larger studies available • Excluded: • Genetics/genetic counselling • Studies without clinical outcomes • Studies of new diagnostic techniques/prognostic factors which are not in current use

Abbreviations: ALS, amyotrophic lateral sclerosis; CIPD, chronic inflammatory demyelinating polyradiculoneuropathy; ESRD, end stage renal disease, hATTR, hereditary transthyretin amyloidosis; LT, liver transplant.

18.1.7 The data abstraction strategy

The relevant data from the included studies were extracted into predefined data extraction tables (DET) by one analyst. All the data points were verified in a quality check of the DET by a second analyst.

18.2 Appendix 2: Search strategy for adverse events

The following information should be provided:

18.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See section 18.1.1.

18.2.2 The date on which the search was conducted.

See section18.1.2.

18.2.3 The date span of the search.

See section 18.1.3.

18.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 18.1.4.

18.2.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

See section 18.1.5.

18.2.6 The inclusion and exclusion criteria.

See section 18.1.6.

18.2.7 The data abstraction strategy.

See section 18.1.7.

18.3 Appendix 3: Search strategy for HRQL

The following information should be provided.

18.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- EconLIT
- NHS EED.

See section 18.1.1.

18.3.2 The date on which the search was conducted.

See section 0.

18.3.3 The date span of the search.

See section 18.1.3.

18.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 18.1.4.

18.3.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

See section 18.1.5.

18.3.6 The inclusion and exclusion criteria

See section 18.1.6.

18.3.7 The data abstraction strategy

See section 18.1.7.

18.4 Appendix 4: Search strategy for economic evidence

The following information should be provided.

18.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

See section 18.1.1

18.4.2 The date on which the search was conducted.

See section 18.1.2.

18.4.3 The date span of the search.

See section 18.1.3.

18.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 18.1.4.

18.4.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

See section 18.1.5.

18.4.6 The inclusion and exclusion criteria

See section 18.1.6

18.4.7 The data abstraction strategy

See section 18.1.7.

18.5 Appendix 5: Resource identification, measurement and valuation

18.5.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

See section 18.1.1.

18.5.2 The date on which the search was conducted.

See section 0

18.5.3 The date span of the search.

See section 18.1.3.

18.5.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 18.1.4.

18.5.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

See section 18.1.5.

18.5.6 The inclusion and exclusion criteria

See section 18.1.6.

18.5.7 The data abstraction strategy

See section 18.1.7.

18.6 Appendix 6: Study design and methodology for NEURO-TTR and NEURO-TTR extension

Table 10: Composite scores and individual components of the mNIS+7 score

NIS Composite Score (individual components)	Maximum Scores	Modified +7 Composite Score (individual components)	Maximum Scores
Cranial nerves	40	HRDB	3.72
Muscle weakness	152	Nerve conduction tests	18.6
Reflexes	20	Touch-pressure	40
Sensation	32	Heat-pain (i.e., heat as pain)	40
NIS maximum score	**244**	**Modified +7 maximum score**	**102.32**
mNIS+7 maximum score			**346**

Abbreviations: HRDB, heart rate response to deep breathing; mNIS+7, modified neuropathy impairment score; NIS, neuropathy impairment score.
Source: Ionis Pharmaceuticals/Akcea Therapeutics, data on file (37).

Table 11: The Norfolk Quality of Life – Diabetic Neuropathy Questionnaire (TQoL)

Part I: Symptoms **Have you had any of the following symptoms in the past 4 weeks? Please check all that apply.**				
	Feet	Legs	Hands	Arms
1. Numbness				
2. Tingling, pins and needles				
3. Electric shocks				
4. Other unusual sensations				
5. Superficial pain				
6. Deep pain				
7. Weakness				
Part II: Activities of daily life: Answer these questions according to the following scale: 0 - not a problem; 1 - very mild problem; 2 - mild problem; 3 - moderate problem; 4 - severe problem				
8. In the past 4 weeks has the pain kept you awake or woken you at night?				
9. In the past 4 weeks has the touch of bed sheets, clothes or wearing shoes bothered you?				
10. In the past 4 weeks have you burned or injured yourself and been unable to feel it?				
11. In the past 4 weeks have any symptoms kept you from doing your usual activities during the day?				
12. In the past 4 weeks have you had difficulty doing fine movements with your fingers, like buttoning your clothes, turning pages in a book, picking up coins from a table?				
13. In the past 4 weeks have you felt unsteady on your feet when you walk?				

14. In the past 4 weeks have you had any problems getting out of a chair without pushing with your hands?
15. In the past 4 weeks have you had a problem walking down stairs?
16. In the past 4 weeks have you been unable to feel your feet when walking?
17. In the past 4 weeks Have you been unable to tell hot/cold water **with your hands**?
18. In the past 4 weeks have you been unable to tell hot/cold water **with your feet**?
19. In the past 4 weeks have you had a problem with vomiting, particularly after meals (but not due to flu or other illness)?
20. In the past 4 weeks have you had a problem with diarrhoea and/or loss of bowel control?
21. In the past 4 weeks have you had a problem with fainting or dizziness when you stand?

How much difficulty have you had performing the following activities:

22. Bathing/showering?
23. Dressing?
24. Walking?
25. Getting on or off the toilet?
26. Using eating utensils?

Answer these questions according to the following scale: 0 - not at all; 1 – a little; 2 – somewhat; 3 – moderately; 4 - severely

In the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical or emotional health?

27. Cut down the amount of time you spent on work or other activities?
28. Accomplished less than you would like?
29. Were limited in the kind of work or activities that you could perform?
30. Had difficulty performing the work or other activities (it took extra effort)?
31. In general, would you say your health now is: Excellent; Very good; Good; Fair; Poor
32. Compared with 3 months ago, how would you rate your health in general now? Excellent; Very good; Good; Fair; Poor
33. In the past 4 weeks, to what extent has your physical health interfered with your normal social activities with family, friends, neighbours or groups?
34. In the past 4 weeks, how much did **pain** interfere with your normal work (including work both outside the home and housework?
35. In the past 4 weeks, how much did **weakness or shakiness** interfere with your normal work (including work both outside the home and housework)?

19 Related procedures for evidence submission

19.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may

request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

19.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

19.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technologies (HST)

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Dear Luke,

The Evidence Review Group, Aberdeen HTA Group and the technical team at NICE have looked at the submission received on 14th August from Akcea Therapeutics. The ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **20th September 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/60481.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (Orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely,

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. Please clarify what modified BMI represents and why it is required in addition to standard BMI.

A2. Please clarify the difference in definition between the safety set (SS) and the full analysis set (FAS). The NEURO-TTR SS and FAS differed by seven patients. Could you please clarify why those seven people were excluded from the FAS?

A3. Table C5 (page 48): The n (%) reported for (i) previous treatment with tafamidis or diflunisal (ii) disease stage 1 and stage 2 and (iii) V30M TTR mutation differ to those reported in the main trial publication, Benson et al (2018). Please explain the difference in numbers reported.

A4. Page 67 mentions pre-specified missing data analyses. Please provide detail on what these where and the results produced.

A5. Section 9.2, Study selection, and Figure 3, schematic for the SLR (page 36). For the review of clinical evidence, search strategies for Pubmed in Section 18.1.4 indicate that you first performed a search relating to the condition (search line #1, n = 4222), and then applied a range of filters relating to interventions other than inotersen (tafamidis, difunisal, patisiran, liver transplant, BSC), economic analysis, quality of life, and epidemiology studies. The same strategy was applied to the Embase and Cochrane searches. However, Figure 3 appears to show that only the first search (#1), relating to the clinical condition, was used for each of the databases. Can you please clarify if this was the case. Please also clarify the purpose of the various search filters. How was the subset of literature identified by these filters used in the submission?

A6. Section 9.3.2. (page 38) asks to "state the rationale behind excluding any of the published studies listed in table C5 and C6", while you refer to Tables C1 and C2 in your response. Please clarify.

A7. Section 9.4, Summary of methodology of relevant studies, Table C3, NEURO-TTR summary of methodology (page 40). The sections on the 'duration of study' and 'duration of follow-up' mention 6-month post-treatment evaluation. Please clarify how the post-treatment data are used in the current submission.

A8. Section 9.4.3.2, baseline demographic characteristics (Neuro-TTR Extension). It is stated on page 48 that "[redacted] had stage 1 hATTR-PN", while Table C6, NEURO-TTR Extension baseline demographic characteristics (SS) (page 49), suggests that [redacted] of people had stage 1 hATTR-PN. Could you please clarify the reason for the difference in numbers reported?

A9. Section 9.4.3.3. It is stated on page 50 that "Table C8 shows the baseline disease and efficacy parameters for each group, with bold numbers indicating a greater severity."

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However, there are no bold numbers in Table C8. Please provide an updated version of the table.

A10. Section 9.6.1.1, NEURO-TTR results, Table C13 (page 65), NEURO-TTR summary of results (FAS). The results for BMI, mBMI and GLS in Table C13 are not referred to in the text, whereas results for other variables are discussed (page 69-70). Please clarify the reason for this omission and provide short summary for BMI, mBMI and GLS.

A11. Section 9.6.1.1, NEURO-TTR results, Table C13 (page 65), NEURO-TTR summary of results (FAS). Individual components of NIS and modified +7 and Norfolk QoL-DN are referred to Figures 9 and 10, respectively, but these appear incorrect (Figures 9 and 10 do not seem relevant). Please clarify and provide relevant figures.

A12. Section 9.6.1.1, NEURO-TTR results, Table C15 (page 69), NEURO-TTR summary of efficacy results by subgroup, week 66 (FAS). The text on page 68 suggests that "Results across multiple disease characteristics at week 66 showed a statistically significant benefit in all subgroups based on mNIS+7 composite score, except one in the Norfolk QoL-DN". However, more than one subgroup in Table C15 show p>0.05. Could you please clarify why those results were not considered statistically significant?

A13. Section 9.7.2, adverse events (AE). Please provide a breakdown of each AE in Tables C24, 25 and 26 (page 82, 83 and 84), by grade of severity (e.g. mild, moderate and severe).

A14. Section 9.7.2, adverse events. On page 83, it is stated that "As these were identified in NEURO-TTR, enhanced monitoring with frequent testing of urine P/C and A/C ratio in at-risk patients and routine hematological testing of platelet counts was implemented." Please explain what the abbreviations P/C and A/C stand for.

Section B: Clarification on cost-effectiveness data

B1. Section 12.1.7. The economic model currently uses a discount rate of 1.5% per annum for costs and outcomes.

i) Please provide an explanation for how the proposed case meets NICE's criteria for consideration of this rate – NICE criteria: '*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), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant*

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irrecoverable costs'. Please see Guide to the methods of technology appraisal Section 6.2.19

ii) In addition, please provide base case and corresponding sensitivity analyses using 3.5% discount rate for costs and QALYs.

B2. Section 8.2, [redacted] (page 31). Please provide further details of the proposed [redacted]:

i) [redacted]?

ii) [redacted].

iii) Have the additional costs of eGFR and UPCR testing every three months been fully captured in the economic model? In particular, will these require any additional visits to health care providers?

B3. Section 12.3.10. Discontinuation of inotersen has been modelled based on parametric survival analysis of the NEURO-TTR discontinuation data. Could you please use the data on time to discontinuation observed in the Neuro-TTR extension study to support your chosen extrapolation curve?

B4. **Priority:** The chosen treatment discontinuation curve (Figure 16 of the CS [page 128], worksheet 'Data Store', cell 'M40') suggests that 80.67% of the surviving cohort should remain on treatment by the end of year 1, but only 23% of the cohort are incurring treatment costs by cycle 13 in the model (Worksheet 'Trace', Cells F17:G17). This may be because the survival function (indicating the probability of remaining on treatment up to given time points) is being treated as cycle specific probabilities of remaining on treatment; rather the selected curve in the 'Data Store' worksheet (M27:M580) should first be converted into cycle specific probabilities of remaining on treatment (=S(t)/(S(t-1)) before feeding into the formulas in the "Engine" worksheet.

i) Please confirm if this is an error in the implementation of treatment discontinuation in the economic model?

ii) Can you please amend the modelling of treatment discontinuation as described and provide the revised model and a full set of analyses based on it?

iii) Can you please also provide a set of scenario analyses that explore the impact of using each of the alternative parametric distributions for time to discontinuation?

B5. Changing the treatment compliance rate in the model impacts on the costs of treatment but not affect QALYs.

i) Please comment on the counter-intuitive results seen when reducing the compliance parameter in the model.

ii) Can you please revise your model to incorporate both the cost and QALY implications of changing treatment compliance?

B6. The cost and utility implications of adverse events have not been included in the model. Can you please provide an analysis that explores the impact of incorporating the implications of moderate and severe adverse events as defined and observed in the NEURO-TTR trial?

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B7. The modelling approach involved mapping from the Norfolk QoL-DN score to Coutinho disease states (based on total score cut-offs), and then applying mean EQ-5D values by Coutinho stage obtained from an observational study using the Brazilian valuation tariff.

i) Please comment on the uncertainties that arise from this approach.
ii) Please provide utility values for the modelled health states by mapping observed SF-36 in NEURO-TTR to EQ-5D; a repeated measures model could also potentially allow for the impact of progression to stage three disease to be assessed.
iii) Please cross-validate the values used in your base case against those produced by the above analysis

B8. The model assumes that mortality is not correlated with Coutinho stage. Please comment on the validity of this assumption. Can you please provide a scenario where mortality is correlated with disease stage, and inotersen generates a mortality benefit through its impact on slowing disease progression.

B9. Section 10.1.9. The model assumes that all patients will have two full time carers, and cites the HST evaluation of ataluren for Duchenne muscular dystrophy in the justification; however, that evaluation considered a paediatric population. Please provide further justification for the assumption of disutility being applied to multiple carers in the specific population considered in the current evaluation, taking into account the level of home care accounted for in the health state costs. Please provide an analysis where the carer disutility is applied to only one carer, rather than two.

B10. The costs from Faria et al seem to be inflated, as opposed to re-costed using appropriate Healthcare Resource Groups (HRGs). Please explain why this approach was appropriate, and whether it was possible to obtain resource level data from which to recalculate costs?

B11. Section 13.7, page 147. Please provide full details of all the calculations and assumptions underpinning the budget impact analysis.

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Highly Specialised Technologies (HST)

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Dear Luke,

The Evidence Review Group, Aberdeen HTA Group and the technical team at NICE have looked at the submission received on 14th August from Akcea Therapeutics. The ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **20th September 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/60481.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (Orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely,

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. Please clarify what modified BMI represents and why it is required in addition to standard BMI.

Response:

Modified BMI is not necessarily 'required' in addition to standard BMI, but it is often measured in hATTR clinical trials. Measurement of 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, the modified BMI measurement, which adjusts for low serum albumin (BMI x albumin g/L), is often used instead of BMI.

A2. Please clarify the difference in definition between the safety set (SS) and the full analysis set (FAS). The NEURO-TTR SS and FAS differed by seven patients. Could you please clarify why those seven people were excluded from the FAS?

Response:

The Full Analysis Set (FAS) included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) and who had a baseline and at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QoL-DN questionnaire total score. The FAS was the primary population for analysis of efficacy and pharmacodynamic outcomes. Results were summarised according to randomised treatment.

The Safety Set (SS) included all randomised subjects who received at least 1 injection of study drug (irrespective of whether they had any efficacy assessments performed). The SS was used for analyses of all safety measures. Results were summarised according to the actual treatment that was received.

Seven subjects were excluded from the FAS population as they did not have post-baseline assessments of mNIS+7 or Norfolk QoL-DN.

A3. Table C5 (page 48): The n (%) reported for (i) previous treatment with tafamidis or diflunisal (ii) disease stage 1 and stage 2 and (iii) V30M TTR mutation differ to those reported in the main trial publication, Benson et al (2018). Please explain the difference in numbers reported.

Response:

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 (2018) were randomised by CRF whereas patients in the submission were randomised by IXRS. This is due to IXRS being the

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most appropriate randomisation stratification when modelling primary efficacy, which is the purpose of the cost-effectiveness model developed for the NICE submission.

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A4. Page 67 mentions pre-specified missing data analyses. Please provide detail on what these where and the results produced.

Response:

Detail on the analyses are included in the Appendix (see Appendix 2). Results produced from these analyses are reproduced in Table 1. Rows in bold are the missing data analyses requested. There are no new conclusions from the missing data; they are all statistically significant.

Table 1 Sensitivity analyses of change from baseline in mNIS+7 composite score

	Week 35 LSM Change from Baseline			Week 66 LSM Change from Baseline		
	Difference	95% CI	p-value	Difference	95% CI	p-value
Non-parametric analysis (SA1)	-8.26	-12.96, -3.61	0.001	-18.81[a]	-26.66, -10.79	<0.001
Conservative assessment level imputation (SA2)	**-8.80**	**-13.54, -4.07**	**<0.001**	**-19.60**	**-26.18, -13.02**	**<0.001**
Excluding assessments done at early termination (SA3)	**-9.04**	**-13.78, -4.30**	**<0.001**	**-20.04**	**-26.72, -13.37**	**<0.001**
Multiple imputation assuming missing at random (SA4)	**-8.57**	**-13.28, -3.87**	**<0.001**	**-19.43**	**-26.55, -12.30**	**<0.001**
Multiple imputation assuming copy increments from reference (SA5)	**-7.57**	**-12.30, -2.84**	**0.002**	**-15.74**	**-23.30, -8.17**	**<0.001**
Multiple imputation assuming jump to reference (SA6)	**-7.57**	**-12.30, -2.84**	**0.002**	**-14.89**	**-22.55, -7.22**	**<0.001**
Data at withdrawal visit included (time continuous) (SA7)	**-8.14**	**-13.12,-3.16**	**0.002**	**-19.19**	**-25.93,-12.45**	**<0.001**
Per protocol set (SA8)	-7.54	-12.38, -2.70	0.003	-18.80	-25.66, -11.94	<0.001
Adjusting for pooled site (SA9)	-9.07	-14.27, -3.87	<0.001	-19.91	-26.70, -13.12	<0.001
Excluding NIS-sensation (SA11)	-7.13	-11.73, -2.53	0.003	-16.32	-22.19, -10.45	<0.001
Excluding heart rate to deep breathing score (HRDB) (SA12)	-8.82	-13.59, -4.06	<0.001	-19.57	-26.29, -12.85	<0.001
Modified Baseline definition (SA13)	-8.57	-13.39, -3.74	<0.001	-19.60	-26.28, -12.92	<0.001

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A5. Section 9.2, Study selection, and Figure 3, schematic for the SLR (page 36). For the review of clinical evidence, search strategies for Pubmed in Section 18.1.4 indicate that you first performed a search relating to the condition (search line #1, n = 4222), and then applied a range of filters relating to interventions other than inotersen (tafamidis, difunisal, patisiran, liver transplant, BSC), economic analysis, quality of life, and epidemiology studies. The same strategy was applied to the Embase and Cochrane searches. However, Figure 3 appears to show that only the first search (#1), relating to the clinical condition, was used for each of the databases. Can you please clarify if this was the case. Please also clarify the purpose of the various search filters. How was the subset of literature identified by these filters used in the submission?

Response:

We acknowledge this could have been made clearer in the submission, and we can confirm that only the first search (#1, n=4222) was used. Additional search filters were not applied. Search filters were originally planned, however, given that the number of items found was within a reasonable range, the search strategy was intentionally kept broad. The only filters used in this instance were date (2008-2018) and age (adult) filters.

A6. Section 9.3.2. (page 38) asks to "state the rationale behind excluding any of the published studies listed in table C5 and C6", while you refer to Tables C1 and C2 in your response. Please clarify.

Response:

This appears to be a linking error, where references to the corresponding tables did not update correctly. This should read '9.3.2 State the rationale behind excluding any of the published studies listed in Table C1 and Table C2'.

A7. Section 9.4, Summary of methodology of relevant studies, Table C3, NEURO-TTR summary of methodology (page 40). The sections on the 'duration of study' and 'duration of follow-up' mention 6-month post-treatment evaluation. Please clarify how the post-treatment data are used in the current submission.

Response:

Post-treatment data were collected for those who did not enter the extension study, described in detail in the CSR[1]. The only data used in the submission was ongoing safety data collected until week 91. Only 14 patients completed post-treatment follow-up at the time of submission (Table 4 of CSR), and therefore the impact on the submission of post-treatment follow-up data is minimal.

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Data was collected at week 91 on study endpoints, including mNIS+7 assessment and Norfolk QoL-DN questionnaire performed at Week 91. As those in the post-treatment period were not on the study drug, analyses of these data are not relevant to the submission and were consequently not included.

Data were also collected for the purpose of safety monitoring (Section 12.1 in the CSR). This was included in the submission in Tables C24, C25 and C26 (that is, events which occurred both on- and off-treatment were recorded for both arms). Question A13 in this document requests more detail on the breakdown of these events by minor / moderate / severe and relates to the same group. As safety events occurring after treatment could have been caused by earlier treatment these data were considered relevant to the submission.

A8. Section 9.4.3.2, baseline demographic characteristics (Neuro-TTR Extension). It is stated on page 48 that "[redacted] had stage 1 hATTR-PN", while Table C6, NEURO-TTR Extension baseline demographic characteristics (SS) (page 49), suggests that [redacted] of people had stage 1 hATTR-PN. Could you please clarify the reason for the difference in numbers reported?

Response:

This is an error and should read "[redacted]" Therefore, there is no actual difference in numbers reported.

A9. Section 9.4.3.3. It is stated on page 50 that "Table C8 shows the baseline disease and efficacy parameters for each group, with bold numbers indicating a greater severity." However, there are no bold numbers in Table C8. Please provide an updated version of the table.

Response

Please find an updated version of the table in question below, in Table 2.

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Table 2: Summary of baseline scores and values for efficacy parameters and select laboratory parameters, with percent difference for the placebo group relative to the inotersen group (NEURO-TTR FAS, SS, and Randomised populations)

Parameters	Components, sub-components, or laboratory parameter	Population	Placebo	Inotersen 300 mg	Percent difference (placebo group relative to inotersen group)
mNIS+7 (mean)	Composite score	FAS	74.12	**79.35**	-6.59
	NIS	FAS	43.40	**46.59**	-6.85
	Modified +7 composite score	FAS	30.73	**32.76**	-6.20
	NIS muscle weakness score	FAS	19.99	**21.20**	-5.71
	NIS sensory score	FAS	13.31	**14.41**	-7.63
	NIS reflex score	FAS	10.10	**10.95**	-7.76
	Heat-pain sensory score	FAS	7.25	**7.91**	-8.34
	Touch-pressure sensory score	FAS	10.80	**11.40**	-5.26
	Heart rate to deep breathing score	FAS	1.814	**1.962**	-7.54
	Nerve conduction score	FAS	10.868	**11.492**	-5.43
Norfolk QoL-DN (mean)	Total score	FAS	**48.60**	48.57	0.06
	Symptoms score	FAS	**10.68**	10.65	0.28
	Physical functioning/Large fibre neuropathy score	FAS	**24.42**	24.09	1.37
	Activities of daily living score	FAS	6.41	**6.52**	-1.69
	Small fibre neuropathy score	FAS	**5.24**	5.09	2.95
	Autonomic neuropathy score	FAS	1.84	**2.22**	-17.12

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Parameters	Components, sub-components, or laboratory parameter	Population	Placebo	Inotersen 300 mg	Percent difference (placebo group relative to inotersen group)
SF-36 PCS score (mean)		FAS	37.19	**35.65**	4.32
SF-36 MCS Score (mean)		FAS	**50.61**	51.04	-0.84
	Mental health domain score	FAS	**71.19**	72.24	-1.45
NSC (mean)	Total score	FAS	22.92	**24.92**	-8.03
	Muscle weakness	FAS	7.68	**8.31**	-7.58
	Sensory (hypo/loss of sensation)	FAS	4.31	**4.42**	-2.49
	Sensory (paraesthesia, hypersensation)	FAS	6.21	**6.31**	-1.58
	Autonomic (GI/urinary incontinence)	FAS	0.91	**1.67**	-45.51
	Autonomic (other than GI/urinary incontinence)	FAS	3.81	**4.21**	-9.50
BMI (kg/m^2) (mean)		FAS	**24.25**	24.27	-0.08
mBMI		FAS	1053.7	**1025.33**	2.77
PND score	I (%)	SS	38.3	**28.6**	33.92
ECHO (mean)	GLS (%)	Randomised	-16.49	**-15.92**	3.58
	Interventricular septum thickness (cm)	Randomised	1.321	**1.445**	-8.58
	LV mass (g)	Randomised	195.808	**223.734**	-12.48
NT-proBNP (pmol/L)		SS	81.98	**121.55**	-32.55
NYHA I (%)		SS	66.7	**63.4**	5.21
Karnofsky performance status score (mean)		SS	76.8	**76.2**	0.79
Duration from onset hATTR-PN symptoms (mean, months)		SS	**64.0**	63.9	0.16

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Parameters	Components, sub-components, or laboratory parameter	Population	Placebo	Inotersen 300 mg	Percent difference (placebo group relative to inotersen group)
Duration of disease from hATTR-PN diagnosis (mean, months)		SS	39.3	**42.4**	-7.31
Duration from onset hATTR-CM symptoms (mean, months)		SS	34.1	**44.7**	-23.71
Duration of disease from hATTR-CM diagnosis (mean, months)		SS	21.0	**25.1**	-16.33
CM-ECHO Set (% included)		Randomised	55.0	**66.4**	-17.17
Laboratory (baseline mean values)					
	Platelets	SS	**212.19**	223.39	-5.01
	Serum creatinine	SS	**77.3**	76.2	1.44
	eGFR	SS	**87.4**	88.9	-1.69
	Urine albumin/creatinine	SS	3.152	**7.273**	-56.66
	Urine protein/creatinine	SS	14.6	**24.8**	-41.13
	Haemoglobin	SS	137.8	**135.9**	1.40

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A10. Section 9.6.1.1, NEURO-TTR results, Table C13 (page 65), NEURO-TTR summary of results (FAS). The results for BMI, mBMI and GLS in Table C13 are not referred to in the text, whereas results for other variables are discussed (page 69-70). Please clarify the reason for this omission and provide short summary for BMI, mBMI and GLS.

Response

Discussion surrounding the variables for BMI, mBMI and GLS were omitted as they were not statistically significant, and we were wary of the page limit advised in the HST submission template. A short summary for each of BMI, mBMI and GLS is provided below.

Secondary outcome: Change from baseline to week 66 in body mass index and modified body mass index

Changes from baseline in body mass index (BMI) showed a trend in favour of inotersen treatment to slow weight loss over time (difference in LSM: 0.50 kg/m^2, p=0.051) at week 66 (Table C13). There were no statistically significant differences in modified body mass index (mBMI) at week 66 between treatment groups (difference in LSM: 2.82 kg/m^2, p=0.873).

Secondary outcome: Change from baseline to week 66 in global longitudinal strain in the ECHO subgroup and CM-ECHO Set

Mean global longitudinal strain (GLS) values were abnormal at baseline in both groups in the CM-ECHO Set (placebo, -14.63; inotersen, -14.44) as compared with established ranges. No statistically significant differences in GLS were observed between treatment groups in the CM-ECHO Set or the ECHO subgroup at week 66 (Table C13). Based on ranges utilised in other cardiovascular conditions, no clinically significant worsening of GLS was observed in either treatment group.

A11. Section 9.6.1.1, NEURO-TTR results, Table C13 (page 65), NEURO-TTR summary of results (FAS). Individual components of NIS and modified +7 and Norfolk QoL-DN are referred to Figures 9 and 10, respectively, but these appear incorrect (Figures 9 and 10 do not seem relevant). Please clarify and provide relevant figures.

Response

The figures describing individual component scores were removed from the company submission, but the references to their place in the text were not updated. Please see Figure 1 for a depiction of individual components of NIS and modified +7 (week 66) and Figure 2 for individual domains of Norfolk QoL-DN (week 66).

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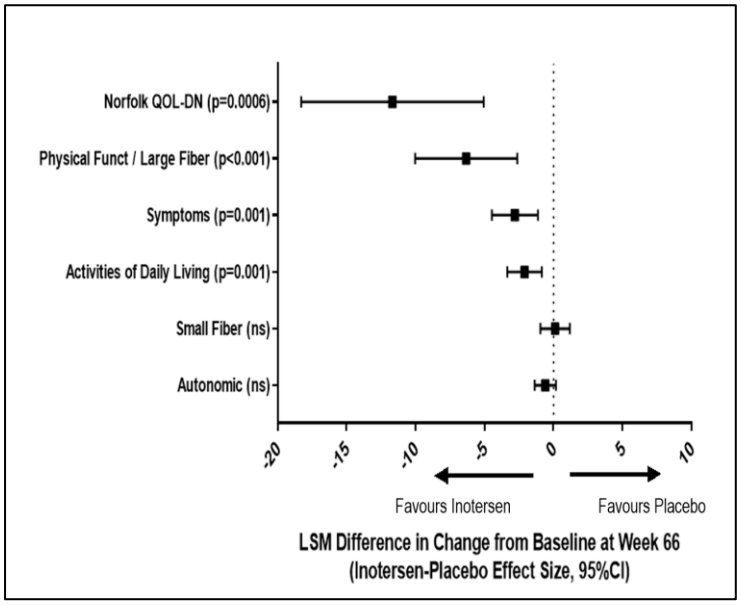
Figure 1: NEURO-TTR LSM differences in change from baseline for mNIS+7, NIS, and modified +7 composite scores, and individual components, week 66

Figure 2: NEURO-TTR LSM differences in change from baseline for Norfolk QoL-DN domain scores, week 66



A12. Section 9.6.1.1, NEURO-TTR results, Table C15 (page 69), NEURO-TTR summary of efficacy results by subgroup, week 66 (FAS). The text on page 68 suggests that "Results across multiple disease characteristics at week 66 showed a statistically significant benefit in all subgroups based on mNIS+7 composite score, except one in the Norfolk QoL-DN". However, more than one subgroup in Table C15 show p>0.05. Could you please clarify why those results were not considered statistically significant?

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Response

All results with p<0.05 are considered statistically significant, and therefore every result for mNIS+7 is statistically significant by this criterion. However, as identified in the question, not every result is significant by this criterion for Norfolk QoL-DN and therefore this section is mis-worded. The results which are statistically significant in the Norfolk QoL-DN subgroups are: V30 mutation present and absent, disease stage 1 and 2, CM-ECHO set or non-CM-ECHO set, no previous treatment (previous treatment close to significance [p=0.052]), age <65, male sex, white and being in region North America or South America/Australasia.

The intended meaning of the original sentence was that the result of the Norfolk QoL-DN is statistically significant for the group as a whole; the implication that all subgroups are statistically significant in Norfolk QoL-DN was not intended.

A13. Section 9.7.2, adverse events (AE). Please provide a breakdown of each AE in Tables C24, 25 and 26 (page 82, 83 and 84), by grade of severity (e.g. mild, moderate and severe).

Response:

Please see Table 3, Table 4 and Table 5, corresponding to Tables C24, C25 and C26 respectively.

Table 3: NEURO-TTR incidence of TEAEs (SS)

	Placebo (N=60) n (%)			Inotersen (N=112) n (%)		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Any TEAEs	7 (11.67)	40 (66.67)	13 (21.67)	20 (17.86)	60 (53.57)	31 (27.68)
TEAEs related to study treatment	16 (26.67)	6 (10.00)	1 (1.67)	50 (44.64)	29 (25.89)	8 (7.14)
TEAEs leading to permanent discontinuation of study drug	0 (0.00)	1 (1.67)	1 (1.67)	0 (0.00)	6 (5.36)	10 (8.93)
TEAEs leading to withdrawal from study	0 (0.00)	1 (1.67)	0 (0.00)	0 (0.00)	1 (0.89)	7 (6.25)
Any serious TEAEs	0 (0.00)	8 (13.33)	5 (8.33)	2 (1.79)	9 (8.04)	25 (22.32)
Serious TEAEs related to study treatment	0 (0.00)	1 (1.67)	0 (0.00)	0 (0.00)	1 (0.89)	7 (6.25)
Fatal TEAEs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (4.46)
Fatal TEAEs related to study treatment	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)

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Table 4: NEURO-TTR frequently reported TEAEs (≥10% incidence) (SS)

Preferred Term	Placebo (N=60)			Inotersen (N=112)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Injection site erythema	0 (0.00)	0 (0.00)	0 (0.00)	35 (31.25)	0 (0.00)	0 (0.00)
Nausea	3 (5.00)	4 (6.67)	0 (0.00)	22 (19.64)	12 (10.71)	1 (0.89)
Fatigue	9 (15.00)	3 (5.00)	0 (0.00)	18 (16.07)	10 (8.93)	0 (0.00)
Diarrhoea	7 (11.67)	5 (8.33)	0 (0.00)	18 (16.07)	7 (6.25)	2 (1.79)
Headache	4 (6.67)	3 (5.00)	0 (0.00)	24 (21.43)	2 (1.79)	0 (0.00)
Injection site pain	4 (6.67)	0 (0.00)	0 (0.00)	21 (18.75)	2 (1.79)	0 (0.00)
Pyrexia	5 (8.33)	0 (0.00)	0 (0.00)	17 (15.18)	5 (4.46)	0 (0.00)
Oedema peripheral	4 (6.67)	2 (3.33)	0 (0.00)	16 (14.29)	5 (4.46)	0 (0.00)
Urinary tract infection	6 (10.00)	6 (10.00)	0 (0.00)	12 (10.71)	9 (8.04)	0 (0.00)
Chills	1 (1.67)	1 (1.67)	0 (0.00)	15 (13.39)	5 (4.46)	0 (0.00)
Fall	8 (13.33)	4 (6.67)	1 (1.67)	15 (13.39)	4 (3.57)	0 (0.00)
Myalgia	5 (8.33)	1 (1.67)	0 (0.00)	14 (12.50)	3 (2.68)	0 (0.00)
Vomiting	0 (0.00)	3 (5.00)	0 (0.00)	11 (9.82)	5 (4.46)	1 (0.89)
Anaemia	1 (1.67)	1 (1.67)	0 (0.00)	9 (8.04)	6 (5.36)	0 (0.00)
Constipation	4 (6.67)	2 (3.33)	0 (0.00)	9 (8.04)	5 (4.46)	1 (0.89)
Thrombocytopenia	1 (1.67)	0 (0.00)	0 (0.00)	8 (7.14)	5 (4.46)	2 (1.79)
Asthenia	4 (6.67)	4 (6.67)	0 (0.00)	9 (8.04)	5 (4.46)	0 (0.00)
Arthralgia	2 (3.33)	3 (5.00)	0 (0.00)	9 (8.04)	3 (2.68)	1 (0.89)
Injection site pruritus	0 (0.00)	0 (0.00)	0 (0.00)	13 (11.61)	0 (0.00)	0 (0.00)
Dizziness	5 (8.33)	2 (3.33)	0 (0.00)	8 (7.14)	3 (2.68)	1 (0.89)
Platelet count decreased	0 (0.00)	0 (0.00)	0 (0.00)	8 (7.14)	4 (3.57)	0 (0.00)
Muscular weakness	1 (1.67)	5 (8.33)	0 (0.00)	7 (6.25)	4 (3.57)	0 (0.00)
Cough	7 (11.67)	1 (1.67)	0 (0.00)	8 (7.14)	2 (1.79)	0 (0.00)
Hypoaesthesia	4 (6.67)	2 (3.33)	0 (0.00)	6 (5.36)	4 (3.57)	0 (0.00)
Pain in extremity	3 (5.00)	5 (8.33)	0 (0.00)	5 (4.46)	5 (4.46)	0 (0.00)
Nasopharyngitis	6 (10.00)	0 (0.00)	0 (0.00)	9 (8.04)	0 (0.00)	0 (0.00)
Thermal burn	4 (6.67)	2 (3.33)	0 (0.00)	4 (3.57)	2 (1.79)	0 (0.00)
Neuralgia	5 (8.33)	3 (5.00)	1 (1.67)	2 (1.79)	1 (0.89)	0 (0.00)

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Table 5: NEURO-TTR serious TEAEs considered related to study drug (SS)

Preferred Term	Placebo (N=60)			Inotersen (N=112)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Nervous System Disorders	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**3 (2.68)**
Embolic stroke	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)
Haemorrhage intracranial	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)
Myelopathy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)
Renal and Urinary Disorders	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**1 (0.89)**	**2 (1.79)**
Glomerulonephritis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)	1 (0.89)
Acute kidney injury	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)
Tubulointerstitial nephritis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)
Blood and Lymphatic System Disorders	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**2 (1.79)**
Thrombocytopenia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.79)
Vascular Disorders	**0 (0.00)**	**1 (1.67)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**1 (0.89)**
Deep vein thrombosis	0 (0.00)	1 (1.67)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)
Respiratory, Thoracic and Mediastinal Disorders	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**1 (0.89)**
Pulmonary embolism	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.89)

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A14. Section 9.7.2, adverse events. On page 83, it is stated that "As these were identified in NEURO-TTR, enhanced monitoring with frequent testing of urine P/C and A/C ratio in at-risk patients and routine hematological testing of platelet counts was implemented." Please explain what the abbreviations P/C and A/C stand for.

Response:

P/C stands for protein / creatinine ratio and A/C for albumin / creatinine ratio. Both are measures of kidney function.

Section B: Clarification on cost-effectiveness data

Following review of the ERG questions and the availability of a NEURO-TTR extension data cut not available at the time of the original submission, we propose that the base case should be updated based on the following:

- Monitoring costs increased to account for phlebotomist time, as per response to question B2
- Use of extended discontinuation data, as per response to question B3
- Corrected discontinuation formula, as per response to question B4
- Use of 90% compliance rate, as per response to question B5
- Use of differential mortality by health state, as per response to question B8

The results of this new base case are provided in Table 6. Sensitivity analyses (probabilistic, one-way, and scenario as presented in the original submission) can be found in Appendix 1.

Table 6: Proposed new base case results

Intervention	Total costs	Total QALYs	Total LYG	Δ costs	Δ QALY	Δ LYG	ICER
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470

B1. Section 12.1.7. The economic model currently uses a discount rate of 1.5% per annum for costs and outcomes.

i) Please provide an explanation for how the proposed case meets NICE's criteria for consideration of this rate – NICE criteria: '*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), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely*

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that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs'. Please see Guide to the methods of technology appraisal *Section 6.2.19*

ii) *In addition, please provide base case and corresponding sensitivity analyses using 3.5% discount rate for costs and QALYs.*

Response:

The justification for considering a 1.5% discount rate is given in Table D2 of the original submission. This text is reproduced below for convenience:

"1.5% [as the selected discount rate] is considered appropriate in line with the NICE Reference Case, which states that 1.5% discount rates can be considered if:

- *Treatment restores people who would die or have severely impaired health to life or near full health*
- *This is sustained over a very long period*
- *This would not commit the NHS to significant irrecoverable costs*

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'.

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).

As inotersen is taken weekly and can be safely discontinued, this would not commit the NHS to significant irrecoverable costs."

Upon discussion with NICE and ERG during the clarification call on 11 September 2018, it was clarified to Akcea that further discussion was required around whether patients receiving inotersen would return to near full health, the length of time this is expected to be sustained, and the potential for irrecoverable costs to the NHS. Further to the original justification, a more extensive justification addressing each of the criteria is provided below. No further discussion has been undertaken on whether people with hATTR would die or have a severely impaired health, as this is clearly outlined in our original submission and was not raised during the clarification call with NICE and the ERG as an area that required further consideration .

i. Inotersen has been shown to maintain quality of life in hATTR patients based on the clinical evidence demonstrated in the submission. With inotersen, there is a significantly higher probability of stage 1 hATTR patients remaining in stage 1, and stage 2 patients reverting back to stage 1. Since stage 1 of the disease is attributed with quality of life close to the national average, and stage 3 is attributed with quality of life worse than death when including carer disutilities, increasing the length of time to transition from

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stage 1 to stage 3 will increase overall quality of life significantly. As demonstrated in the original submission, preventing the inevitable significant decline in health demonstrates a significant benefit attributable to treatment with inotersen compared to standard of care.

ii. Secondly, we believe the NEURO-TTR extension data (unavailable at the time of submission) further bears out the second point. The treatment effect of inotersen does not wane over the NEURO-TTR extension period for patients remaining on treatment, which demonstrates that the benefits of inotersen are expected to be sustained over a lifelong period, provided patients remain on treatment. As the average age of an individual in the model is 59 years, for those individuals who live 30+ years from disease onset, inotersen satisfies this criterion.

iii. Finally, as stated in the submission, inotersen is taken weekly and self-administered by the patient. Thus, the NHS commits to no significant capital or infrastructure costs, as there are no upfront costs of treatment (such as the purchase of equipment or training to facilitate treatment). Additionally, should it be necessary, treatment can be safely discontinued ceasing all other associated costs.

While we believe the application of 1.5% for costs and outcomes to be fully justified, both in the original submission and further in this response, we have provided a base case assuming a 3.5% discount rate and associated sensitivity analyses as requested. These are recorded in Table 7 - Table 9.

Table 7: Base case results for scenario B1

Proposed new base case results							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470
Scenario (new base case + 3.5% discounting)							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.01	£389,105

Table 8: Probabilistic results for question B1 on discounting: incremental results of inotersen relative to base supportive care

Scenario	**Δ costs**	**Δ QALY**	**ICER**
Proposed new base case	[redacted]	[redacted]	£368,592
Scenario	[redacted]	[redacted]	£390,251

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Table 9: Ten most sensitive parameters in the one-way sensitivity analyses for scenario B1

Parameter	Lower bound ICER	Upper bound ICER	Difference
Proposed new base case			
Inotersen compliance rate	£350,669.05	£388,270.79	£37,601.75
Stage 1: utility	£384,426.28	£355,633.75	£28,792.52
BSC transition probability from Stage 1 to 2	£373,323.39	£365,761.21	£7,562.18
Inotersen transition probability from Stage 2 to 1: Week 36+	£373,109.14	£366,051.17	£7,057.97
Stage 3: carer disutility	£372,946.11	£366,057.93	£6,888.18
Inotersen transition probability from Stage 1 to 2: Week 36+	£366,131.76	£372,805.35	£6,673.59
BSC transition probability from Stage 2 to 3: Week 36+	£372,699.65	£366,522.14	£6,177.51
BSC transition probability from Stage 2 to 3	£371,845.62	£367,149.04	£4,696.58
Stage 2: utility	£371,675.37	£367,290.49	£4,384.87
BSC transition probability from Stage 2 to 1: Week 36+	£367,685.86	£371,255.20	£3,569.34
Scenario			
Inotersen compliance rate	£369,268.96	£408,941.90	£39,672.94
Stage 1: utility	£404,895.17	£374,500.98	£30,394.19
BSC transition probability from Stage 1 to 2	£393,319.66	£385,052.25	£8,267.41
Stage 3: carer disutility	£392,914.55	£385,369.45	£7,545.10
Inotersen transition probability from Stage 2 to 1: Week 36+	£392,925.72	£385,513.69	£7,412.03
BSC transition probability from Stage 2 to 3: Week 36+	£392,803.34	£385,719.94	£7,083.39
Inotersen transition probability from Stage 1 to 2: Week 36+	£385,620.57	£392,587.75	£6,967.18
Discount rates: QALYs	£385,679.08	£392,542.67	£6,863.59
BSC transition probability from Stage 2 to 3	£391,710.49	£386,561.67	£5,148.82
Stage 2: utility	£391,274.88	£386,959.91	£4,314.97

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B2. Section 8.2, [redacted] (page 31). Please provide further details of the proposed [redacted]

i) [redacted]?

Response:

[redacted]

Response:

[redacted]

A scenario analysis is presented in Table 10 [redacted]

Table 10: Base case results for scenario B2

Proposed new base case results							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470
[redacted]							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£369,131

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iii) Have the additional costs of eGFR and UPCR testing every three months been fully captured in the economic model? In particular, will these require any additional visits to health care providers?

Response:

We acknowledge the question posed by the ERG, and can confirm that only the costs of tests were included in the original submission to calculate monitoring costs. All tests would be conducted by a phlebotomist, and therefore the base case has been updated to include the phlebotomist's time in performing the tests; this is assumed to be a grade 3 in-hospital nurse costing £25 per hour[2], and the time spent with the phlebotomist is assumed to be 10 minutes every two weeks.

B3. Section 12.3.10. Discontinuation of inotersen has been modelled based on parametric survival analysis of the NEURO-TTR discontinuation data. Could you please use the data on time to discontinuation observed in the Neuro-TTR extension study to support your chosen extrapolation curve?

Response:

We acknowledge the question posed by the ERG, and have updated the base case based on the NEURO-TTR discontinuation data.

Figure 3 represents the fitted time-to-discontinuation curves and Kaplan Meier data from the NEURO-TTR and NEURO-TTR extension studies. Note for clarity that all curves represent discontinuation following the correction suggested in question B4, and therefore more accurately represent the trial data. Table 11 shows the AIC and BIC statistics for both sets of curves.

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Figure 3: [redacted]

Table 11: Goodness-of-fit statistics for two modelled curves

	Original data		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

Distributions' fit-to-data from the NEURO-TTR and NEURO-TTR extension studies have fairly similar goodness-of-fit in terms of AIC. However, the exponential distribution appears to have a significantly better fit compared to other distribution when considering BIC. In addition, the Kaplan Meier data does not appear to suggest that discontinuation will taper over time. Therefore, the exponential distribution fit to data from the NEURO-TTR and NEURO-TTR extension studies was used in the updated base case.

B4. ***Priority:*** *The chosen treatment discontinuation curve (Figure 16 of the CS [page 128], worksheet 'Data Store', cell 'M40') suggests that 80.67% of the surviving cohort should remain on treatment by the end of year 1, but only 23% of the cohort are incurring treatment costs by cycle 13 in the model (Worksheet 'Trace', Cells F17:G17). This may be because the survival function (indicating the probability of remaining on treatment up to given time points) is being treated as cycle specific probabilities of remaining on treatment; rather the selected*

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curve in the 'Data Store' worksheet (M27:M580) should first be converted into cycle specific probabilities of remaining on treatment (=S(t)/(S(t-1)) before feeding into the formulas in the "Engine" worksheet.

i) *Please confirm if this is an error in the implementation of treatment discontinuation in the economic model?*
ii) *Can you please amend the modelling of treatment discontinuation as described and provide the revised model and a full set of analyses based on it?*
iii) *Can you please also provide a set of scenario analyses that explore the impact of using each of the alternative parametric distributions for time to discontinuation?*

Response:

Thank you for your suggested correction to the model. This is an error of implementation which affects the CEM but not the BIM, where the correct formula was used (see answer to question B11). Table 12 shows the updated base case with this error corrected, and the impact of using alternative parametric distributions.

Table 12: Scenario analyses for question B4 based on preferred parametric fit

Proposed new base case result (with Exponential distribution)							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470
Proposed new base case result with Weibull distribution							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.660				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.120	£379,151
Proposed new base case result with Gompertz distribution							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.993				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.453	£408,802
Proposed new base case result with Log-logistic distribution							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.819				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.278	£393,684
Proposed new base case result with Lognormal distribution							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.914				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.373	£400,199
Proposed new base case result with Generalised Gamma distribution							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	9.393				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.852	£474,143

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B5. Changing the treatment compliance rate in the model impacts on the costs of treatment but not affect QALYs.

i) Please comment on the counter-intuitive results seen when reducing the compliance parameter in the model.

ii) Can you please revise your model to incorporate both the cost and QALY implications of changing treatment compliance?

Response:

We acknowledge the ERG's concern but would reiterate that treatment effectiveness and compliance are modelled as observed in the NEURO-TTR study. A relationship between compliance and effectiveness could not be established from the study, since compliance was relatively high in NEURO-TTR study, and as such one-way sensitivity analyses investigate the impact of varying individual parameters (compliance and effectiveness) only. Therefore, we are unable to revise the model to incorporate the cost and QALY implications of changing compliance.

However, we would like to highlight that the compliance rate submitted in the original submission [redacted] is inaccurate, and we have since received updated data demonstrating a compliance rate of [redacted] Previously the model incorrectly counted the compliance of discontinuers, who will likely have a different compliance profile to those who are stable on drug. This has been incorporated into the updated base case.

B6. The cost and utility implications of adverse events have not been included in the model. Can you please provide an analysis that explores the impact of incorporating the implications of moderate and severe adverse events as defined and observed in the NEURO-TTR trial?

Response:

The costs and consequences of adverse events were not included in the model as there was not a significant difference in the number of each event observed between arms in the study. Therefore, a meaningful comparison between the rates of adverse events cannot be made due to the level of uncertainty attributed to them. Additionally, as the rates of adverse events are so low across the trial there is a minimal impact on the ICER. As such, their inclusion was not meaningful.

However, a scenario analysis has been performed, including the costs and consequences of serious adverse events in the model. The results are presented in Table 13. Note that there is missing data on cost of myelopathy and disutilities of myelopathy, glomerulonephritis, tubulointerstitial nephritis and thrombocytopenia. The overall impact on the ICER is negligible.

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Table 13: Scenario analysis for question B6 based on adverse events

Proposed new base case result							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470
Scenario case (proposed new base case + adverse events)							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559,				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£370,731

B7. The modelling approach involved mapping from the Norfolk QoL-DN score to Coutinho disease states (based on total score cut-offs), and then applying mean EQ-5D values by Coutinho stage obtained from an observational study using the Brazilian valuation tariff.

i) Please comment on the uncertainties that arise from this approach.

Response:

There are two potential uncertainties:

1. Mapping the Norfolk QoL-DN score to Coutinho disease states based on total score cut-offs. However, this is based on a registry study of Transthyretin Familial Amyloid Polyneuropathy[3]. This method has been used in a previous submission to the AGNSS in a related condition, and was therefore considered appropriate despite this potential uncertainty.
2. The key uncertainty is the use of the Brazilian valuation tariff. It is unclear whether this would provide similar results were the UK valuation tariff used (the preferred NICE reference case). Unfortunately, this is an ultra-orphan disease and therefore quality of life estimates conforming precisely to the NICE reference case are not well reported.

ii) Please provide utility values for the modelled health states by mapping observed SF-36 in NEURO-TTR to EQ-5D; a repeated measures model could also potentially allow for the impact of progression to stage three disease to be assessed.

iii) Please cross-validate the values used in your base case against those produced by the above analysis

Response:

No stage 3 patients were recorded in NEURO-TTR, and as such no SF-36 data are available for these patients. Therefore, as mentioned in the original submission, it is not possible to generate robust health-state utility data from the NEURO-TTR study that matches the health state definitions used by Coutinho et al[4].

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B8. The model assumes that mortality is not correlated with Coutinho stage. Please comment on the validity of this assumption. Can you please provide a scenario where mortality is correlated with disease stage, and inotersen generates a mortality benefit through its impact on slowing disease progression.

Response:

No trial information was uncovered on the difference in mortality rates by disease stage. Therefore, our initial approach was to assume no difference in mortality rates as a base case and to seek secondary information on differential rates of mortality (which was not available at the time of submission). However, we agree with the ERG that a differential mortality benefit should be modelled through inotersen's impact on slowing disease progression.

A Delphi panel has since been conducted with four clinical experts to gain consensus on the relationship between disease stage and mortality[5]. Table 14 details the hazard ratios associated with the increased hazard of mortality compared to the general population by Coutinho stage.

Table 14: Delphi panel hazard ratios for mortality by disease stage compared to general population

hATTR stage	Hazard ratio
Stage 1	[redacted]
Stage 2	[redacted]
Stage 3	[redacted]

A differential rate of mortality was generated in the model by applying the hazard ratios in Table 14 to the general all-cause mortality rates for the UK population provided by the Office of National Statistics[6]. That is, if the odds of dying in a particular year are X:1 for a typical member of the public, the odds of death for a hATTR patients in the model are [redacted]X:1 for Stage 1, [redacted]X:1 for Stage 2 and [redacted]X:1 for Stage 3.

The new proposed base case incorporates this method of calculating differential mortality using the Delphi panel results.

B9. Section 10.1.9. The model assumes that all patients will have two full time carers, and cites the HST evaluation of ataluren for Duchenne muscular dystrophy in the justification; however, that evaluation considered a paediatric population. Please provide further justification for the assumption of disutility being applied to multiple carers in the specific population considered in the current evaluation, taking into account the level of home care accounted for in the health state costs. Please provide an analysis where the carer disutility is applied to only one carer, rather than two.

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Response:

In the submission, it was reported that the average hATTR patient received a median of 144 hours of care per week[7]. Assuming a median full-time week over 7-days of 52.5 hours (aligned with a median 37.5 hour work-week as reported by the Office of National Statistics[8]), this equates to almost three full time carers per patient. A scenario analysis based on three carers in presented in Table 9.

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.

As requested, a scenario analysis for one carer is presented in Table 15.

Table 15: Scenario analyses for question B9 based on one carer and three carers

Scenario case (proposed new base case + three carers)							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£341,214
Proposed new base case result (with Exponential distribution fit to extension data)							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470
Scenario case (proposed new base case + one carer only)							
Intervention	**Total costs**	**Total QALYs**	**Total LYG**	**Δ costs**	**Δ QALY**	**Δ LYG**	**ICER**
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£402,828

B10. The costs from Faria et al seem to be inflated, as opposed to re-costed using appropriate Healthcare Resource Groups (HRGs). Please explain why this approach was appropriate, and whether it was possible to obtain resource level data from which to recalculate costs?

Response:

This approach was deemed appropriate as it is not possible to obtain resource-level data for each cost category, as the relevant section in Faria et al (Table 30 of the ERG response to the tafamidis submission[9]) only reports the total cost and proportion of patients attributed to that cost. As no indication is given as to what costs or resource use went in to compiling these estimates, we believe it is appropriate to inflate these costs using standard sources.

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B11. Section 13.7, page 147. Please provide full details of all the calculations and assumptions underpinning the budget impact analysis.

Response:

The budget impact model (BIM) is based on three disease states – Stage 1, Stage 2 and Stage 3 and the 'engine' of the BIM is the same as the 'engine' of the cost-effectiveness model. Please see section 12 of the main submission for details on the cost-effectiveness model methodology and cost inputs used. The following information explains the specific aspects of the calculations used in the budget impact model to estimate the eligible population and budget impact over the first five years from the introduction of inotersen.

In the BIM, the eligible patient population is calculated by taking the total number of hATTR-PN patients each year based on the prevalent and incident population[10] and stratifying them by disease severity (i.e. Stage 1, 2 and 3). The only patients that are considered eligible for inotersen treatment are patients in Stage 1 and 2, which is consistent with the population for the cost-effectiveness model. As such, the number of patients commencing the model in Stage 3 is not relevant to the cost-effectiveness model, and it is assumed that no patients commence the model in Stage 3. In the BIM, a proportion of new diagnoses will be Stage 3, and therefore an approximation of this population is made from the NEURO-TTR data, although these patients are excluded from the eligible population estimates. Table 16 shows the distribution applied in the BIM and the data form NEURO-TTR.

Table 16 – Distribution of existing and new hATTR patients by disease stage

Stage	% distribution (model)	% distribution (NEURO-TTR)
Stage 1	[redacted]	65.70%
Stage 2	[redacted]	34.30%
Stage 3	[redacted]	N/A

The market share of inotersen has been included in the calculations for the BIM. Estimates of the market share of inotersen are given in Table 17, and based on internal Akcea sales projections. While these are necessarily estimates, they are thought to represent a plausible case.

Table 17 – Market share of inotersen by year

Stage	% market share
Year 1	[redacted]
Year 2	[redacted]
Year 3	[redacted]
Year 4	[redacted]
Year 5	[redacted]

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In the budget impact model, discontinuation is treated as a static percentage for the five-year time horizon. The annual rate of discontinuation used in the BIM is [redacted] which is based on a linear extrapolation of the discontinuation rate of the NEURO-TTR trial.

As with discontinuation, mortality is also a static percentage. Unlike discontinuation, there were too few deaths in the trial to inform a robust estimate of the annual mortality risk over the first five years, and hence a large database study[11] is used to generate an annual risk of 0.55%.

References

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2. Curtis, L. and A.J.U.o.K. Burns, PSSRU Unit Costs of Health & Social Care 2017. 2017.
3. European Medicines Agency. European Medicines Agency. Assessment report: Vyndaqel - tafamidis meglumine. 2011.
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7. Gertz, M.A., Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care, 2017. 23(7 Suppl): p. S107-S112.
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9. Faria. R, W.S., Palmer S., Tafamidis for Transthyretin Familial Polyneuropathy (TTR-FAP): Evidence Review Group assessment of manufacturer submission. University of York, 2012.
10. Pinney, J.H., et al., Systemic Amyloidosis in England: an epidemiological study. Br J Haematol., 2013. 161(4): p. 525-532.
11. Coelho, T., et al. The natural history of transthyretin familial amyloid polyneuropathy: An analysis from the transthyretin amyloidosis outcomes survey. in J Peripher Nerv Syst 2016. Wiley-Blackwell.

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Appendix 1: Updated base case results

Base case results

The base-case cost-effectiveness results are presented in Table A1.

Table A1: New base case results

Intervention	Total costs	Total QALYs	Total LYG	Δ costs	Δ QALY	Δ LYG	ICER
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£369,470

The proportion of patients in Stage 1, 2, and 3 health states and Dead for both Inotersen and BSC for the first ten years are presented in Table A2. Corresponding graphical representations are presented in Figure A1 - Figure A4 for the first ten years.

Table A2: Markov trace for each state by comparator (first ten years only)

	Inotersen				BSC			
Year	Stage 1	Stage 2	Stage 3	Dead	Stage 1	Stage 2	Stage 3	Dead
0.08	[redacted]							
0.54	[redacted]							
1.00	[redacted]							
1.54	[redacted]							
2.00	[redacted]							
2.54	[redacted]							
3.00	[redacted]							
3.54	[redacted]							
4.00	[redacted]							
4.54	[redacted]							
5.00	[redacted]							

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5.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure A1: Ten-year trace diagram for inotersen

[redacted]

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Figure A2: Ten-year trace diagram for base supportive care

Figure A3: Full trace diagram for inotersen

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Figure A4: Full trace diagram for base supportive care

The QALYs accrued over time per health state for the first ten year for both inotersen and base supportive care are presented in Table A3.

Table A3: Markov trace for QALYs accrued in each state by comparator (first ten years only)

	Inotersen			BSC		
Year	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
0.08	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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3.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9.54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The total QALYs and LYG accrued per health state over the full time horizon for both inotersen and base supportive care are presented in Table A4.

Table A4: Model outputs by clinical outcome

Outcome	LYG	QALY
Inotersen – Stage 1	3.944	[redacted]
Inotersen – Stage 2	2.164	[redacted]
Inotersen – Stage 3	2.450	[redacted]
Inotersen – All Stages	8.559	[redacted]
BSC – Stage 1	2.288	[redacted]
BSC – Stage 2	1.732	[redacted]

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BSC – Stage 3	3.520	[redacted]
BSC – All Stages	7.541	[redacted]

The undiscounted results of the base case are presented in Table A5.

Table A5: New base case results (undiscounted)

Intervention	Total costs	Total QALYs	Total LYG	Δ costs	Δ QALY	Δ LYG	ICER
Inotersen	[redacted]	[redacted]	8.559				
BSC	[redacted]	[redacted]	7.541	[redacted]	[redacted]	1.018	£354,816

A summary of the costs by category per patients are provided in Table A6 for both inotersen and base supportive care.

Table A6: Summary of costs by category per patient

Item	Cost intervention Inotersen	Cost comparator BSC	Increment
Technology cost	[redacted]	[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 summary of cost by health state per patient for both inotersen and base supportive care are provided in Table A7.

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Table A7: Summary of costs by health state per patient

Health state	Treatment costs	Administration costs	Vitamin A costs	Monitoring costs	HRU costs	Transition costs	All costs
Inoterse n – Stage 1	[redacted]	£0	£15	£321	£18,883	£0	[redacted]
Inoterse n – Stage 2	[redacted]	£0	£6	£143	£34,327	£1,481	[redacted]
Inoterse n – Stage 3	[redacted]	£0	£0	£464	£49,132	£2,458	[redacted]
Inoterse n - Total	[redacted]	£0	£21	£163	£102,342	£3,939	[redacted]
BSC – Stage 1	[redacted]	£0	£0	£0	£11,075	£0	[redacted]
BSC – Stage 2	[redacted]	£0	£0	£0	£27,901	£1,276	[redacted]
BSC – Stage 3	[redacted]	£0	£0	£0	£72,257	£3,189	[redacted]
BSC - Total	[redacted]	£0	£0	£0	£111,234	£4,463	[redacted]

Abbreviations: BSC, best supportive care; HRU, health resource utilization

One-way sensitivity analysis results

Table A8 shows the results for the top 15 most sensitive parameters from the one-way sensitivity analysis. Figure A5 demonstrates graphically the magnitude of these effects in relation to the ICER.

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Table A8: One-way sensitivity analysis results

Parameter	Lower bound ICER	Upper bound ICER	Difference
Inotersen compliance rate	£350,669	£388,270	£37,601
Stage 1: utility	£384,426	£355,633	£28,792
BSC transition probability from Stage 1 to 2	£373,323	£365,761	£7,562
Inotersen transition probability from Stage 2 to 1: Week 36+	£373,109	£366,051	£7,057
Stage 3: carer disutility	£372,946	£366,057	£6,888
Inotersen transition probability from Stage 1 to 2: Week 36+	£366,131	£372,805	£6,673
BSC transition probability from Stage 2 to 3: Week 36+	£372,699	£366,522	£6,177
BSC transition probability from Stage 2 to 3	£371,845	£367,149	£4,696
Stage 2: utility	£371,675	£367,290	£4,384
BSC transition probability from Stage 2 to 1: Week 36+	£367,685	£371,255	£3,569
Discount rates: QALYs	£367,979	£370,962	£2,983
Inotersen transition probability from Stage 1 to 2: Week 0 to 35	£368,073	£370,867	£2,793
Stage 3: utility	£368,320.58	£370,626.45	£2,305
BSC transition probability from Stage 1 to 2: Week 36+	£370,645	£368,408	£2,237
BSC transition probability from Stage 2 to 1	£368,535	£370,403	£1,867

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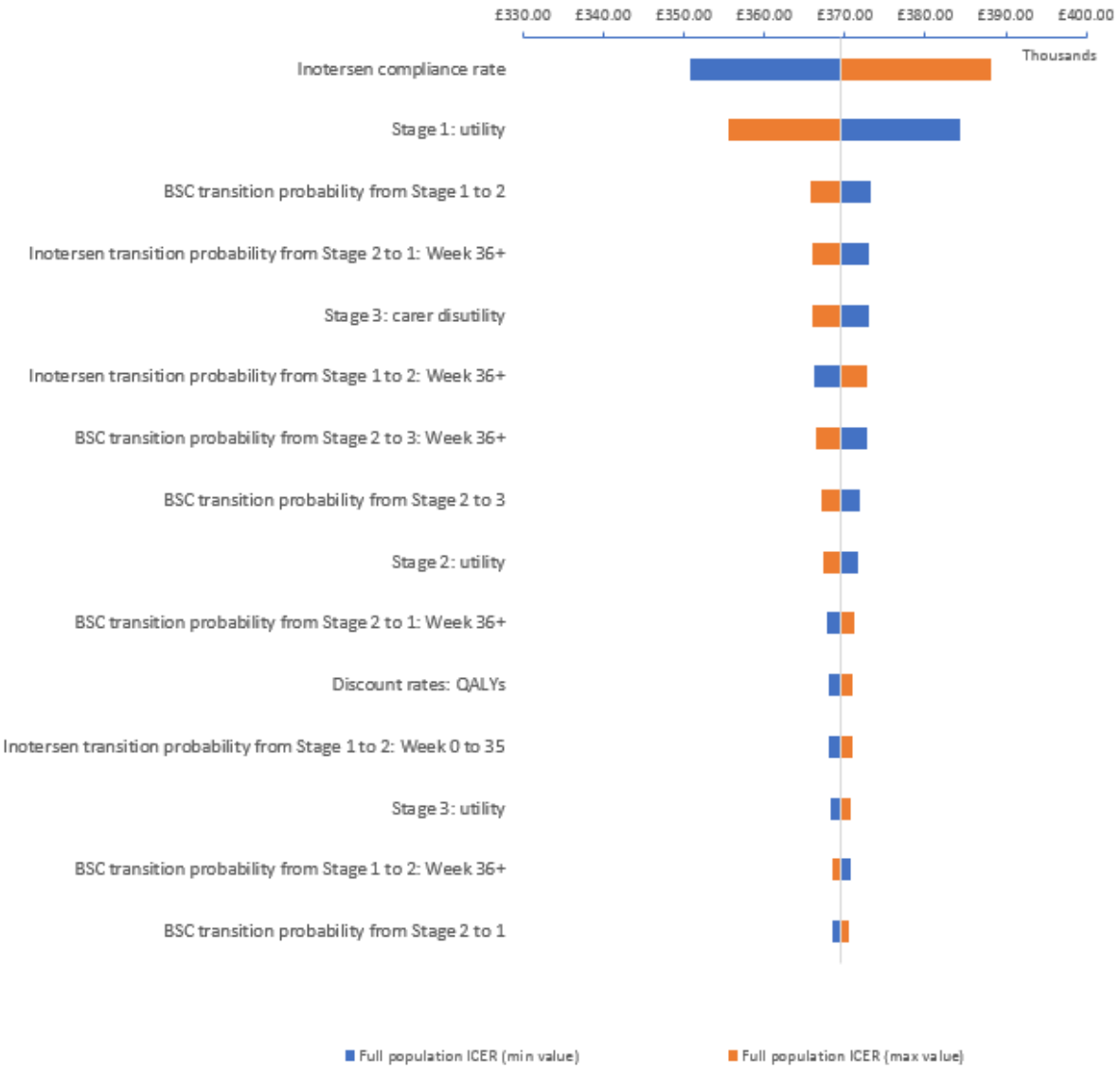
Figure A5: One-way sensitivity analysis graphical results



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Multiway sensitivity analysis

The results of the multi-way sensitivity analysis are presented in Table A9.

Table A9: Multi-way sensitivity analysis; transition probabilities vs utilities

	Carers and patients use minimum-value utilities	Patient uses minimum-value utilities, carers use base case	Base case	Patient uses maximum-value utilities, carers use base case	Carers and patients use maximum-value utilities
Low-end transition probabilities	£396,015	£392,603	£376,215	£361,140	£358,300
Base transition probabilities	£388,916	£385,555	£369,470	£354,673	£351,876
High-end transition probabilities	£382,545	£379,230	£363,417	£348,870	£346,112

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

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Probabilistic results

The mean probabilistic sensitivity analyses (PSA) are presented in Table A10. The corresponding incremental cost-effectiveness plane is presented in Figure A6.

Table A10: PSA results

	Base case	PSA	Difference (absolute)	Difference (proportional)
Incremental cost	[redacted]	[redacted]	£10	<0.001%
Incremental LYG	1.018	1.018	0.00	N/A
Incremental QALY	[redacted]	[redacted]	0.007	0.005%
ICER	£369,470	£368,592	£878	0.002%

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

Figure A6: Incremental cost-effectiveness plane

[redacted]

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Scenario analyses

Scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model. The scenario analyses originally presented were: varying the discount rate to 0% and 3.5%, varying the discontinuation distribution applied and varying the survival distribution. Since the discontinuation has been varied, the method of applying mortality has changed and discontinuation has been tested at 3.5% in the response to the ERG questions, only the discontinuation at 0% is presented in Table A11.

Table A11: Scenario analysis

Parameter	Base case	Scenario	ICER
Base case			£369,470
Discount rate for costs and benefit	1.5%	0%	£354,691

Appendix 2: Details of sensitivity analysis

In response to question A4, please see below for details of each sensitivity analysis undertaken, including those excluded from the original text. Please note that Sensitivity Analysis 10 is not reproduced in Table 1 of the clarification letter – it needs to be provided in a separate table, which is Table 14 in the CSR.

- Sensitivity Analysis 1 (Non-Parametric Analysis): to example robustness of MMRM model
- Sensitivity Analysis 2 (Conservative Assessment Level Imputation) – To examine whether the primary analysis results are robust to the strategy for imputing missing assessment level data, an alternative strategy that results in a conservative estimate of the treatment effect will be implemented.
- Sensitivity Analysis 3 (Excluding Assessments done at Early Termination Visits) – In order to examine the robustness of the primary analysis to the inclusion of premature termination data, the primary efficacy analysis will be repeated excluding data collected at early termination visits which are included in the primary analysis.
- Sensitivity Analysis 4 – Multiple Imputation assuming Missing at Random, to investigate the impact of alternative missing data assumptions. Analysis is based on Safety Set.
- Sensitivity Analysis 5 – Multiple Imputation assuming Copy Increments from Reference, to investigate the impact of alternative missing data assumptions. Analysis is based on Safety Set.
- Sensitivity Analysis 6 – Multiple Imputation assuming Jump to Reference, to investigate the impact of alternative missing data assumptions. Analysis is based on Safety Set.

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- Sensitivity Analysis 7 – Data at Withdrawal Visit Included, to investigate the impact of alternative missing data assumptions. Analysis is based on Safety Set.
- Sensitivity Analysis 8 (Per Protocol Set) – The primary efficacy analysis will be repeated, using the PPS population.
- Sensitivity Analysis 9 (Adjustment for Pooled Site) – The primary efficacy analysis will be repeated, but with the addition of pooled investigative site as a fixed categorical effect in the model.
- Sensitivity Analysis 10 (Responder Analysis) – A responder analysis based on the change in mNIS +7 score will be conducted to examine whether improvement in response is consistent over a range of response thresholds. A responder is defined as a patient whose mNIS +7 score change from baseline to Week 66 is less than or equal to the threshold value. The relationship between response rate and thresholds will be summarized using a cumulative distribution plot. In addition, comparison of response rates for specific threshold values will be done. Thresholds that will be tested will include 0, 2, 4, 6, 8, 10, 15, 20, 30 points above the baseline value. Patients that terminate treatment early irrespective of the reason or had missing Week 66 data will be considered a non-responder.
- Sensitivity Analysis 11 (HRDB and Nerve Conductions Scored Using Points and NIS-Sensation Excluded) – Additional sensitivity analysis on mNIS+7 composite score will be performed using the points (instead of Normal Dev) from heart rate deep breathing and nerve conduction and also removing the sensation part of the NIS.
- Sensitivity Analysis 12 (HRDB Component Excluded) – Additional sensitivity analysis on mNIS+7 composite score will be performed, with HRDB not included as a component.
- Sensitivity Analysis 13 (Modified mNIS+7 Baseline Definition) –the primary efficacy analysis for mNIS+7 will be repeated using a modified baseline definition, defined as the average of two assessments taken within 60 days prior to the first dose of Study Drug.

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Patient organisation submission

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

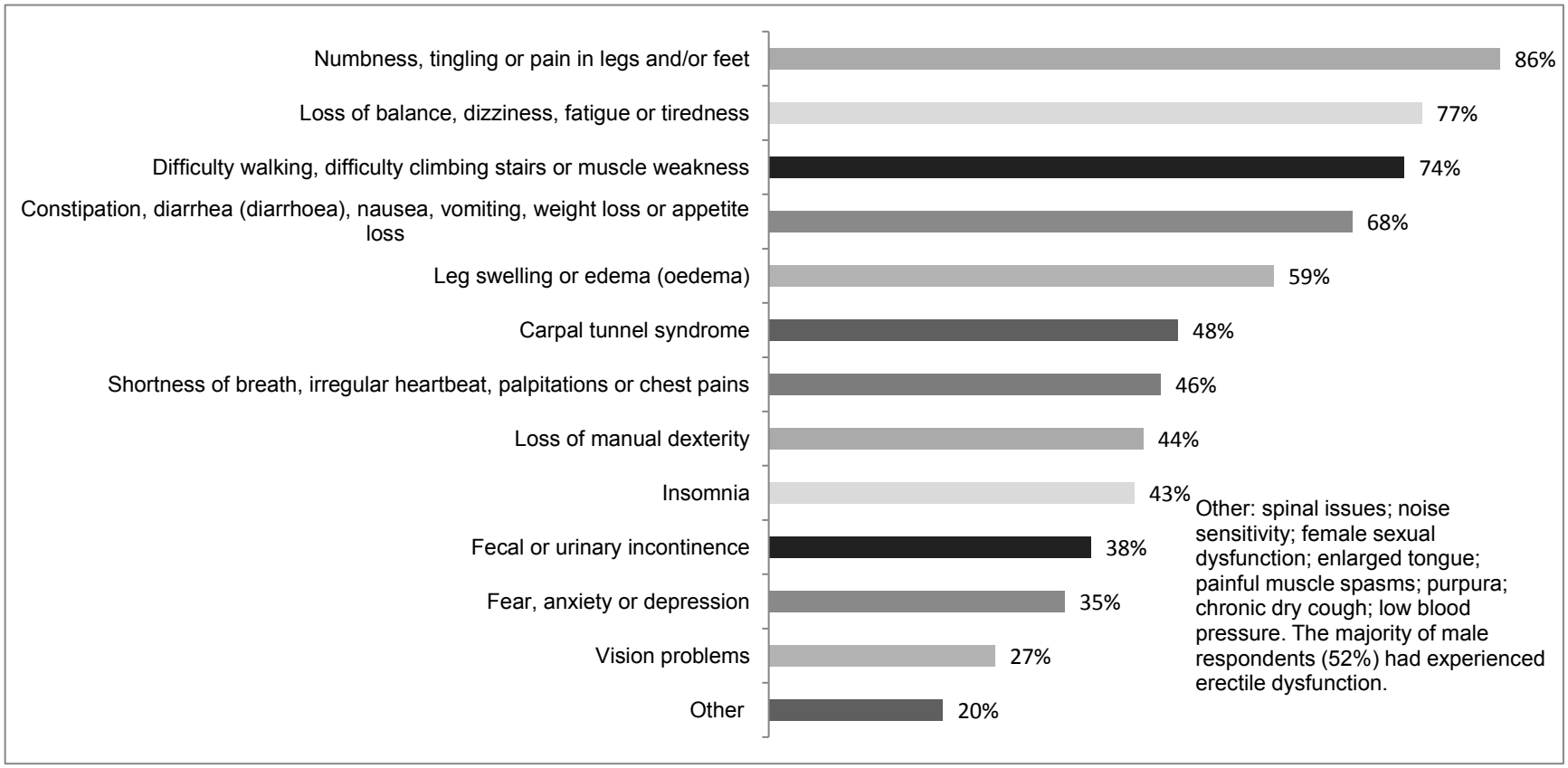
- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Amyloidosis Research Consortium UK (ARC UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	ARC UK aims to tackle the most pressing unmet needs in systemic amyloidosis and improving the lives of amyloidosis patients and their families. In building links between patients, academia, the pharmaceutical industry, regulators and other stakeholders we hope to advance the best research and accelerate new treatments to patients. We aim to address the challenges in diagnosis and research to ensure that patients benefit from the most important advances, while at the same time driving forward priority areas of research and innovation in amyloidosis. We have four strategic objectives that inform everything we do: early and accurate diagnosis; better research for better outcomes; access to effective treatments; and access to quality care, information and support. We are a patient representative organisation which, as part of our day to day work, sets out to support and represent amyloidosis patients and families from across the UK. However, we are not a membership organisation. We currently receive funding from various sources including from a range of pharmaceutical companies, patients and their families as well as grant-giving bodies.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and their families drive everything we do. This submission draws on conversations with patients and carers with whom we are in everyday contact. In addition, we have included information from survey-based research we conducted with hATTR patients and carers in Spring 2018. 101 patients and 51 carers provided information about their experiences, the impact of the disease on their lives and their goals and concerns about treatment. In parallel, we held two online focus groups, involving nine patients and carers to explore aspects of this topic in more depth. We also interviewed five patients and carers by telephone. The research was not limited to UK patients, due to practical reasons, although 25 (16%) of the survey participants and five (56%) of the focus group participants reside in the UK and Republic of Ireland. Evaluation of the responses by country of residence showed no geographic associations. All but five patients (95%) in our research had experienced symptoms associated with polyneuropathy in the last 12 months. A copy of the summary report is attached. *Burden of disease and perspectives on treatment: summary report from research with hereditary transthyretin amyloidosis (hATTR) patients and carers.* ARC UK. July 2018 (unpublished). In addition to our own research,

	we have included information from other published sources, including research by Stewart et al. *Characterizing the high disease burden of transthyretin amyloidosis for patients and caregivers.* Neurol Ther. August 2018. While based on a US and Spanish survey, the findings provide some additional insight into the burden of disease and closely correlate with ARC UK's research.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The patient population covered by inotersen's indication is hATTR patients with symptoms of polyneuropathy. We are limiting our comments, where relevant, to polyneuropathy. However, hATTR is a multi-system disease and while some patients have predominantly polyneuropathy or cardiomyopathy phenotypes, many patients have mixed symptomology. **hATTR has a very high burden on patients: the multi-systemic nature of the disease affects all aspects of life** Patients usually experience multiple symptoms, including sensory, motor and autonomic deficits and, for some patients, cardiac involvement. These translate into numerous effects on daily living, including mobility issues, insomnia, pain, intermittent diarrhoea, sexual dysfunction, vision and motility problems, imbalance and instability and an effect on patients' abilities to undertake daily activities. *Figure 1* below shows the range of symptoms reported by patients to our survey.

Figure 1. Symptom burden over the last 12 months (ARC UK survey 2018)



Each of these symptoms can be individually highly problematic for patients as well as contributing to an overall cumulative burden, as shown in the examples from *Table 1* below.

Table 1. Examples reported by patients of how symptoms affect their daily lives (ARC UK survey 2018)

Mobility problems	"I was an avid runner, having completed 22 marathons. Now I walk slowly with the help of a cane." "Because not too long ago I led an active, athletic lifestyle that now I can only dream of."
Chronic pain	"Keeps me awake and/or awakens me. It also affects my driving, household chores, and is a constant reminder that I have this disease." "It hurts all the way up to my belt."
Loss of manual dexterity	"Difficult to do things (buttons, zips, earrings). Dropping things, turning pages in a book. So many things that require tactile sense."
Diarrhoea	"I am never sure when I will get diarrhoea, so I cannot go out in case. Or I won't eat in case it happens." "It has brought my life to a complete standstill." "I'm afraid to eat out of home away from bathroom. Diarrhoea comes on suddenly."
Insomnia	"If I cannot sleep, I steadily decline in all aspects."
Neuropathy in hands	"I can't cook anymore as I'll burn myself and not even notice". "I can no longer make quilts because I can't pick up the fabric and pins."
Confusion / mental functioning	"Other things I can live with, even the constipation and diarrhoea."
Combination of symptoms	"Anything I like to do is gone."

In Stewart's study, almost half of all patients (48%) reported they were unable to complete typical household chores and many patients reported impairments in mobility, self-care and usual activities. An earlier study by Stewart et al found that SF-12 physical health summary scores were substantially lower in hATTR patients compared with age-matched controls (Stewart et al 2013).

Patients also reported missing more than a working day on average a week due to their disease, as well as high levels of productivity impairment while working (Stewart et al 2018).

Our survey findings largely reflect this. As well the effects on their physical health, patients reported a considerable impact from the disease on their work or professional lives. When asked to rate the impact of the disease on different domains of their lives over the previous 12 months (on a scale where 0 is no impact and 10 is a very significant impact):

- 50% patients gave a ≥8 impact on their work/professional life
- 40% patients gave a ≥8 impact on their physical health
- 32% patients gave a ≥8 impact on their social/family relationships
- 29% patients gave a ≥8 impact on their emotional wellbeing
- 25% patients gave a ≥8 impact on their financial wellbeing

Patients tell us that one of the most challenging aspects of having the disease is losing independence and becoming dependent on other family members. As symptoms deteriorate, patients may lose the ability to walk, drive and work, leading to additional financial, emotional and carer burden. Another common theme is losing the ability to undertake 'normal' day to day activities that others take for granted, such as participating in family life, socialising with friends or enjoying hobbies.

The hereditary nature of the disease contributes to the emotional burden of the disease. Many patients have been carers for loved ones before succumbing to the disease themselves and they know 'what is to come'. They also live with the knowledge that they may pass, or have already passed, the disease onto their children, and experience feelings of guilt and anxiety for future generations of their family.

hATTR considerably impacts on carers and other family members

The disease has a substantial lifelong impact on entire families. It places a significant burden on family members as they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own in dealing with the realities of the disease. Family members often become full or part-time unpaid carers with consequences on their work, social and financial situation.

Carers of hATTR patients tell us that dealing with gastrointestinal problems (especially diarrhoea), patients' mental functioning and the combination of multiple symptoms are particularly problematic for them in their caring capacity. As carers they experience the burden of the disease on their own lives and similarly to patients, multiple domains of their lives are affected by hATTR.

	When asked to rate the impact of the disease on different domains of their lives over the previous 12 months (on a scale where 0 is no impact and 10 is a very significant impact): • 55% carers gave a ≥8 impact on their social/family relationships (compared to 32% patients) • 54% carers gave a ≥8 impact on their emotional wellbeing (compared to 29% patients) • 37% carers gave a ≥8 impact on their physical health • 31% carers gave a ≥8 impact on their work/professional life • 22% carers gave a ≥8 impact on their financial wellbeing These are similar to Stewart et al's findings that the greatest impacts on carers related to their mental health, although they too observed impacts on physical health. Key themes that emerged from our survey related to fatigue and anxiety. Carers told us they feel exhausted from worry and from taking on an additional burden of household chores, juggling work and informal caring. Some carers told us they could no longer have a social life because of exhaustion and feeling unable to leave the patient alone. Many carers said that their career or work productivity had suffered because of their caring responsibilities and fatigue. In Stewart's study, carers reported spending an average of 46 hours a week providing care, which is more than the equivalent of a full-time job. There is also a considerable emotional burden experienced by carers. Some feel anger or sadness that their life is no longer their own; carers also commonly reported they were anxious about seeing the patient deteriorate further and were further worried about their children and future generations of the family who could have the disease.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are no other licensed disease-modifying treatments available on the NHS, although patients may be offered off-label treatments, including diflunisal and doxycycline. A very small number of patients have liver transplants. Beyond this, treatment is primarily aimed at managing the symptoms of the disease. Several participants in our survey had tried an off-label treatment. These patients generally indicated that they did not feel certain that their disease had improved.

	Patients report varying levels of efficacy in relation to symptom management approaches. In responses to our survey, there was considerable dissatisfaction with the effectiveness of treatment to manage neuropathic pain and fatigue. Seven in 10 patients who had tried treatment to deal with fatigue were dissatisfied or very dissatisfied with treatment; and six in 10 were similarly dissatisfied or very dissatisfied with approaches to manage neuropathic pain. Around four in 10 patients were also dissatisfied or very dissatisfied with treatments to manage gastrointestinal symptoms, cardiac symptoms or blood pressure. The symptoms mentioned here are often highly problematic for patients and can have a very negative impact on their ability to live 'a normal life.'
8. Is there an unmet need for patients with this condition?	Yes. While existing treatments can offer a degree of symptomatic relief, there is very high unmet need for new effective and safe disease-modifying treatments that could have a lasting and/or deeper positive impact on patients' disease and symptoms. Even marginal improvements in symptomology can be transformational for patients. Patients told us, for example, that slowing further deterioration in their neuropathy would enable them to maintain hobbies for longer, take on more of a share of household chores and maintain a healthy family dynamic. Others explained that achieving a small improvement in the symptoms they found to be most problematic could dramatically transform their lives: "Success is being able to participate in my life rather than be a bystander… To do up to three errands a day instead of one. I can walk my kids to school multiple days in a row instead of paying for it the next day with pain." "If we could go out for a whole day without worrying where the nearest toilet is – it will change our lives completely to go back to some normality which we haven't had for many years, and take the pressure off our families who are supporting us."
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Many factors are important to hATTR patients and their carers when it comes to thinking about treatment. The prospect of new treatments designed for slowing/stabilising hATTR offers significant hope to patients and their families. This is especially so given the context of the disease being hereditary, the negative impact it has on patients and carers' quality of life, and there being no other licensed alternatives available with which to treat the disease. Our recent research explored in some depth the question of what value new treatments have for hATTR patients and their families. Unsurprisingly, the most important factors for treatment relate to the impact a treatment can have on slowing the underlying disease and improving symptoms. Alongside this there was a strong preference for a local or home-based treatment option. Patients and carers expressed concern about fatigue and taking time off work should frequent travel be required. However, they also said that a current lack of alternatives means they would be willing to put up with some inconvenience and that efficacy is the most important

	consideration overall. Similarly, while they would desire significant outcomes, they still highly value what might be perceived as 'modest' improvements in their health condition. Overall, current treatment preferences and values are influenced by a lack of effective alternatives and high unmet need/symptom burden; whereas choice is likely to become an increasingly important consideration in the future. As a treatment that can stabilise the disease and be self-administered at home, inotersen therefore offers a highly valuable potential treatment option to patients and carers. Seven patients in our research had had direct experience of inotersen. We asked these patients additional questions about how well it managed their disease, any experiences they had of side-effects and their views on its (in)convenience. All these patients indicated that they considered inotersen to have had a positive effect on managing their disease and minimising their symptoms. They also rated it highly for convenience, as an injectable treatment that can be self-administered at home.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The need for regular platelet monitoring could be perceived as a disadvantage. We understand, however, that the proposed inotersen service design aims to minimise the possible burden this could have on patients by ensuring that blood tests for monitoring platelet levels are done at the patient's home. To the extent that it is possible, we urge NICE to ensure that the company has a comprehensive service delivery model in place that is not just practical from a feasibility perspective but is built around the specific needs of patients. Further, we would expect the company to carry out patient/ carer experience/satisfaction surveys throughout the duration of treatment and for this data to be provided (where permissible) to the patient's clinical team to inform ongoing needs assessment. Evidence from our survey suggests that patients felt comfortable with the idea of self-injecting treatment – with appropriate training and guidance. Some patients, however, may not be comfortable with self-injections; or their neuropathy may preclude them from being physically able to self-inject inotersen. These patients are therefore likely to require other options.
Patient population	
11. Are there any groups of patients who might benefit more or less from	From the available evidence, it is our view that the technology would benefit patients with either stage 1 or stage 2 polyneuropathy in terms of achieving the potential for delaying disease progression and improving the symptoms caused by the disease.

the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues. However, we believe it is important for this patient community to have accessible, convenient treatment options available to them and not have choices limited to them according to where they live.
Other issues	
13. Are there any other issues that you would like the committee to consider?	There are several contextual issues we wish to emphasise. **A treatment that involves minimal inconvenience for this patient population ought to carry a value premium** Although in the current context patients are willing to endure some inconvenience in order to slow or stabilise their disease, the issue of convenience should also reflect on a treatment's value. Due to the symptom burden patients often give up work or reduce their hours. Those who do work often say it is a struggle to manage and are concerned about their ability to continue working. Carers, providing informal care, also experience an impact on their ability to work. Patient and carers are concerned about losing more working time should they need to travel frequently for treatment. Furthermore, the common symptoms experienced by this population such as gastrointestinal symptoms, peripheral neuropathy and fatigue can make it hard to travel or prevent travel altogether. Finally, hATTR patients often lose their independence, increasingly relying on family members to care for them. Having a treatment that does not bear an additional burden on family members and, by its nature, supports patients to be independent is incredibly important.

	Patients' suitability and preferences for treatment options need formal assessment and evaluation Having a treatment that can be taken at home is extremely positive and welcome. However, there are risks of non-compliance. Patients told us they want to have a clear point of contact within the specialist clinical team to whom they can ask questions and they want training and support to self-administer treatment. The criteria patients apply to choosing between treatments or whether to have treatment are very individual and can change over time in response to disease-related, family, social and personal factors. Holistic needs assessment to support patients in making decisions about treatment and care should be carried out prior to and routinely throughout treatment, ideally as a condition of prescribing and reflected in NICE guidance. This will have the added benefit of ensuring that only patients who are both clinically eligible and otherwise suitable for treatment receive it. **Accounting for benefits not fully captured by the clinical trial data** There are numerous health benefits that are not fully captured by the clinical data. hATTR is a heterogenous disease and patients are affected by symptoms in different ways. Fatigue, peripheral neuropathy, gastrointestinal events, incontinence, sexual dysfunction, muscle weakness, pain, insomnia and vision problems are particularly cited by patients and family members in our research as having a significant impact on their quality of life. Not all of these are captured by the clinical data or quality of life tools, yet it is important to recognise that control of the disease could improve the specific symptoms that matter most to patients. **The need for a flexible approach to deal with uncertainty** ARC UK recognises that inotersen has some limitations, including a lack of long term data and the need for regular platelet monitoring. We also anticipate that as a treatment for an ultra-rare disease demonstrating value for money may be a challenge. We would urge NICE, NHS England and Akcea to find a solution that achieves both access and affordability and that is a fair reflection of inotersen's value. It is critical that NICE can be flexible in considering both the available evidence and the additional benefits / pertinent contextual issues. Alongside this, it is vital that inotersen is appropriately priced according to its value.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- hATTR is a devastating disease. The heavy symptom burden *affecting all areas of life* and hereditary nature of the disease are two crucial factors contributing to the quality of life deficit experienced by patients and carers.
- There is significant unmet need – no other available licensed treatments are approved and symptom management approaches have variable / limited effectiveness.

- Inotersen offers a significant step change in the management of this disease: the fact that it offers a convenient method of administration is especially positive.
- This is a situation where there are clearly additional benefits (e.g. on carers, productivity, convenience, independence etc) that may not be captured in either the clinical evidence or modelling; and these need to be factored in.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Burden of disease and perspectives on treatment

Summary report from research with hereditary transthyretin amyloidosis (hATTR) patients and carers

Amyloidosis Research Consortium UK

www.arci.org

July 2018

Contents

Amyloidosis Research Consortium UK

Background

Rationale

- An absence of burden of disease research for hereditary transthyretin amyloidosis (hATTR)
- Few available treatment options; no routinely available, licensed disease-modifying treatments in the UK and US
- Two new treatments exiting phase III studies and due for regulatory and health technology assessment reviews
- Need for patient and carer-level data to better understand preferences and values in relation to potential new treatments for this disease

The study sought to obtain perspectives of hATTR patients and caregivers on key issues

- Disease symptom burden
- Impact of the disease on day to day life
- Views on existing treatments
- Goals and concerns for future treatment: through exploratory and stated preference elicitation methods

Methods

Design

- ARC UK designed two online surveys with input from patients, carers, NICE and ICER
- The surveys were tested extensively with patients and carers

Survey recruitment

- ARC UK sent the surveys to hATTR patients and carers from ARC / ARC UK's database
- The surveys were promoted through social media and the web
- The National Amyloidosis Centre (UK) and Amyloidosis Support Groups (USA) publicised them on online forums
- The surveys were open from April – June 2018
- **101 patients and 51 carers provided valid data**

Focus groups / interviews

- Survey participants who opted in were invited to take part in an online focus group or telephone interview to explore perspectives on the benefits and risks of treatment in more depth
- **Nine patients and carers participated in one of two online focus groups** (5 UK; 4 US participants)
- **Five individual telephone interviews** were conducted with patients and carers who preferred an interview format

Analysis

- The focus groups and telephone interviews were audio-recorded and thematically analysed
- The surveys were analysed for summary statistics and the free text thematically analysed

Summary findings

1. hATTR has a very high burden on patients and families. A multi-systemic disease, it affects *all* aspects of life
2. hATTR significantly impacts on patients' independence and sense of normality: their ability to work, participate in family and social life, be mobile and undertake daily activities and hobbies
3. hATTTR considerably impacts on carers: the emotional burden of 'knowing what's to come', practical caring burden and the effect on their own ability to work
4. Patients have mixed experiences of symptom and disease management approaches: there is unmet need with regard to efficacy, side-effect burden and convenience/choice
5. New treatments specifically for hATTR offer significant hope to patients and their families, especially in the context of the disease being hereditary, high impact on quality of life, and no/few alternatives
6. Patients and carers value multiple factors as important for treatment, including efficacy, convenience, risk of side-effects and knowledge of benefits-risks
7. The most important factors for treatment are related to impact on the disease. Patients are likely to accept risks of side-effects for 'modest' gains
8. Treatment preferences and values are influenced by a lack of effective alternatives and high unmet need/symptom burden; as choice increases, convenience and side-effects are likely to become increasingly important considerations

Patient survey demographics

115 survey responses were received. Of these 14 were excluded as duplicates or because no useable data was provided.

Of the 101 valid responses, 91 patients completed all sections of the survey and 10 partially completed the survey.

Time since diagnosis (n=101)			
Less than 12 months ago	1-2 years ago	2-5 years ago	More than 5 years ago
11	17	44	29

Age (n=101)					
39 and under	40-49	50-59	60-69	70-79	80 and over
6	11	18	36	27	3

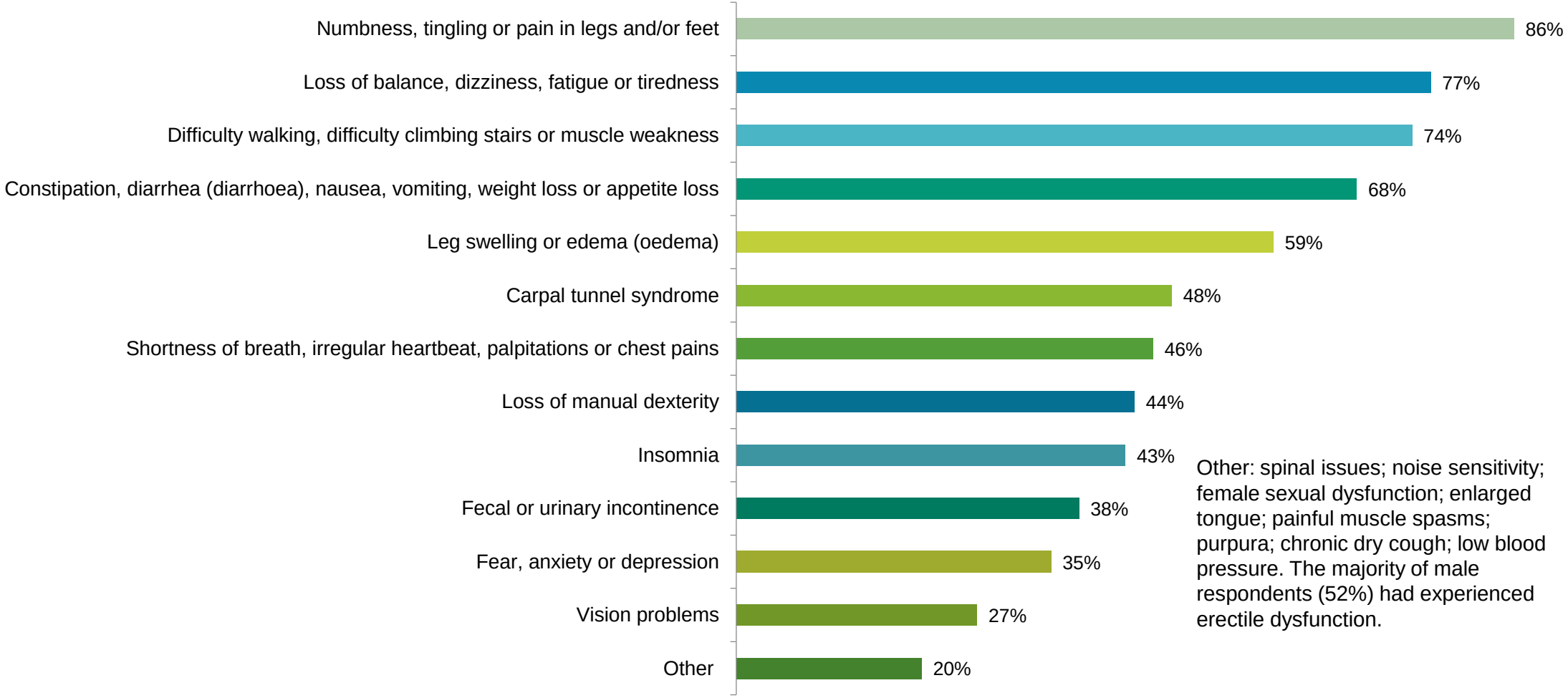
Employment status (n=100)				
Employed full-time	Employed part-time	Not employed, looking for work	Not employed, currently unable to work	Retired
20	18	1	13	48

Live with dependents (n=100)			
Yes, child dependents	Yes, adult dependents	Yes, both adult and child dependents	No
17	19	7	57

Place of residence (n=101)		
USA	UK and Republic of Ireland	Other
65	14	Netherlands (3), Canada (3), Mexico (3), Australia (2), New Zealand (2), Malaysia (2), Colombia (1), Spain (1), Italy (1), Portugal (1), Brail (1), France (1) and Denmark (1)

Genetic mutation (if known) (n=101)	
Val30Met	15
Val122 Ile	11
Glu89Gln	2
Gly53Glu	0
Glu54Gly	3
Ile68Leu	0
Thr60Al	18
Leu111Met	1
not typed	2
Not sure	21
Other	28

Patients experience a high, multi-systemic symptom burden



Other: spinal issues; noise sensitivity; female sexual dysfunction; enlarged tongue; painful muscle spasms; purpura; chronic dry cough; low blood pressure. The majority of male respondents (52%) had experienced erectile dysfunction.

Q. In the last 12 months which symptoms have you experienced? (n=98)

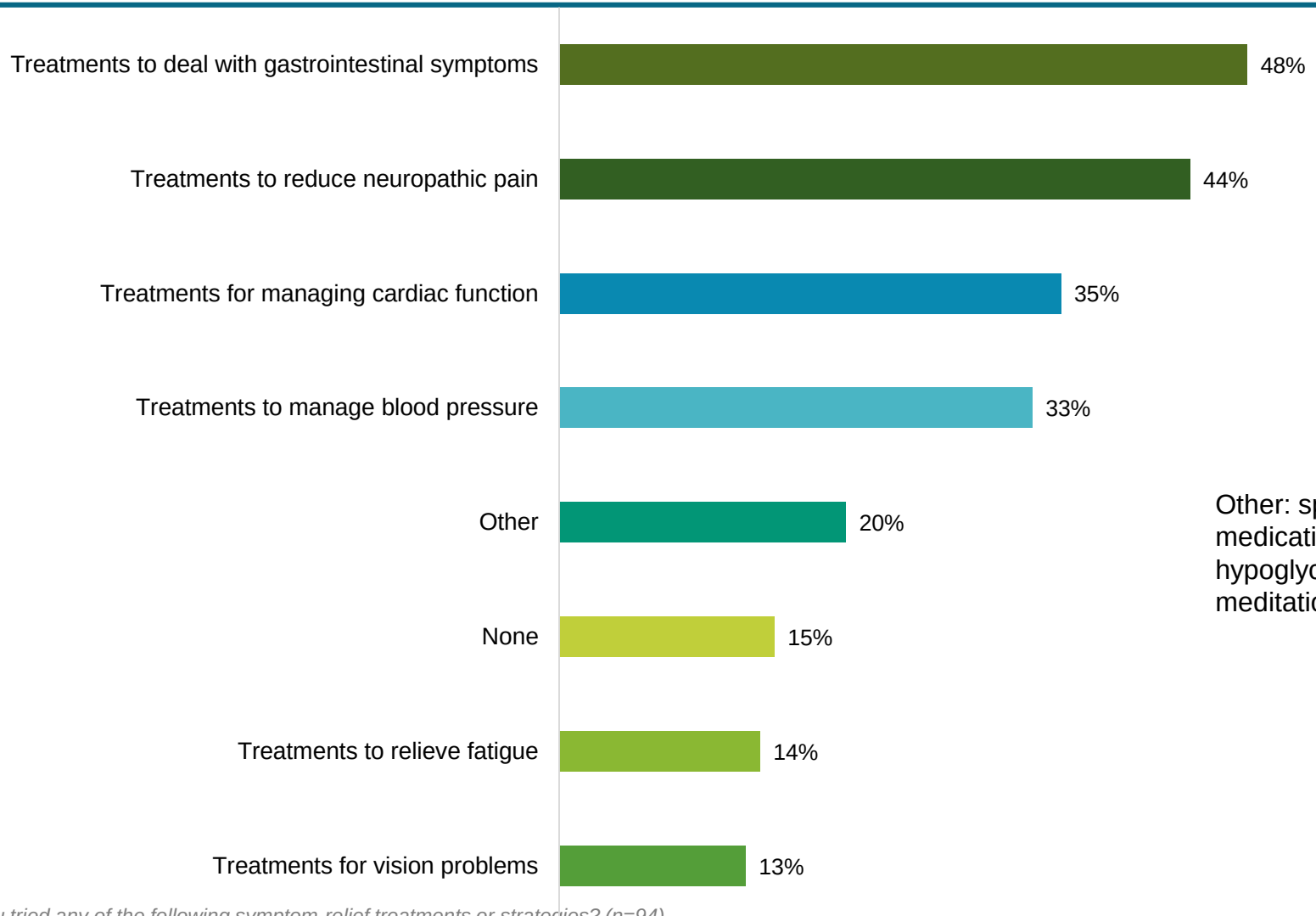
Symptoms have a pervasive impact on patients' ability to lead 'a normal life'

Amyloidosis Research Consortium UK

Which symptom is the most problematic for you?	Why?
Shortness of breath	"Makes me very anxious that my heart is going to stop working." "She feels like she is passing out, she can't go for a walk or enjoy some of the very simple things in life."
Mobility problems	"I was an avid runner, having completed 22 marathons. Now I walk slowly with the help of a cane." "Because not too long ago I led an active, athletic lifestyle that now I can only dream of."
Chronic pain	"Keeps me awake and/or awakens me. It also affects my driving, household chores, and is a constant reminder that I have this disease." "It hurts all the way up to my belt."
Loss of manual dexterity	"Difficult to do things (buttons, zippers, earrings). Dropping things, turning pages in a book. So many things that require tactile sense."
Diarrhoea	"I am never sure when I will get diarrhoea so I can not go out in case. Or I won't eat in case it happens." "It has brought my life to a complete standstill." "I'm afraid to eat out of home away from bathroom. Diarrhoea comes on suddenly."
Insomnia	"If I cannot sleep, I steadily decline in all aspects."
Neuropathy in hands	"I can't cook anymore as I'll burn myself and not even notice". "I can no longer make quilts because I can't pick up the fabric and pins."
Confusion / mental functioning	"Other things I can live with, even the constipation and diarrhoea."
Combination of symptoms	"Anything I like to do is gone."

Q. Which of these symptoms is the most problematic for you? Why?

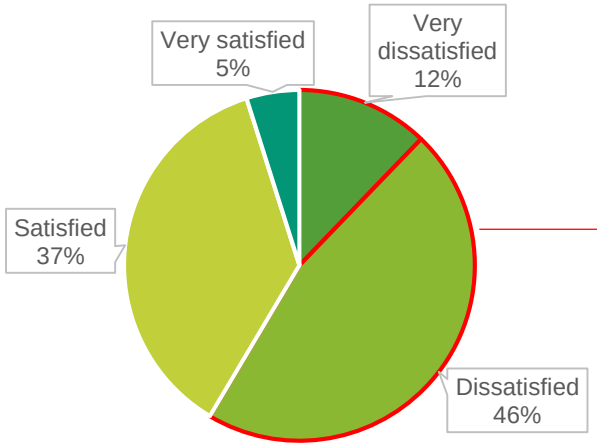
Most patients have tried a range of treatments or strategies to help manage their symptoms



Other: spine surgery; defibrillator; depression medication; edema treatment; dialysis; hypoglycaemia treatment; migraine meds; meditation; PT/OT

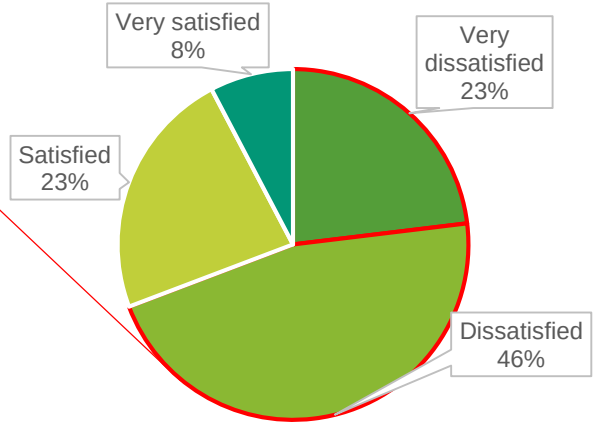
Q. Have you tried any of the following symptom-relief treatments or strategies? (n=94)

There is variable satisfaction with symptom-relief treatments and strategies

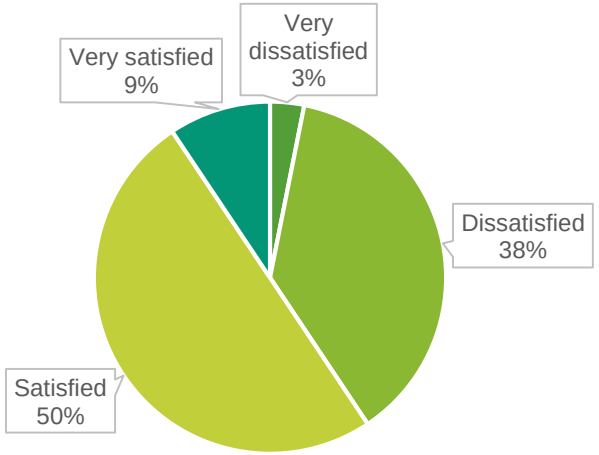


Treatments to reduce neuropathic pain (n=41)

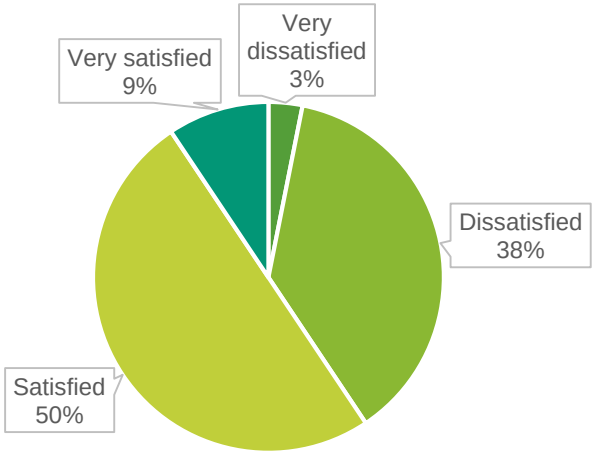
Considerable dissatisfaction with treatments to relieve neuropathic pain and fatigue



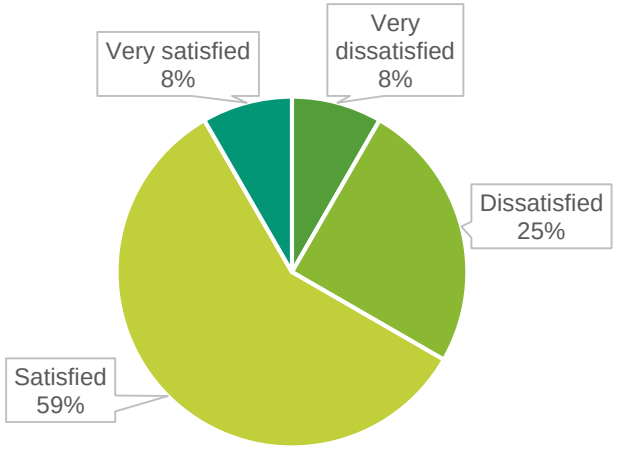
Treatments to relieve fatigue (n=13)



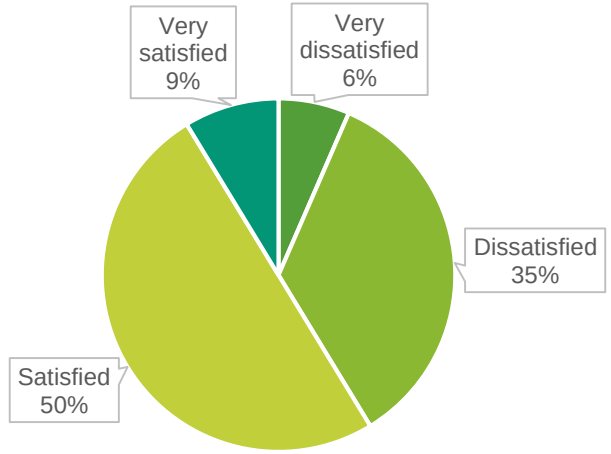
Treatments for managing cardiac function (n=32)



Treatments for managing blood pressure (n=31)



Treatments for vision problems (n=12)

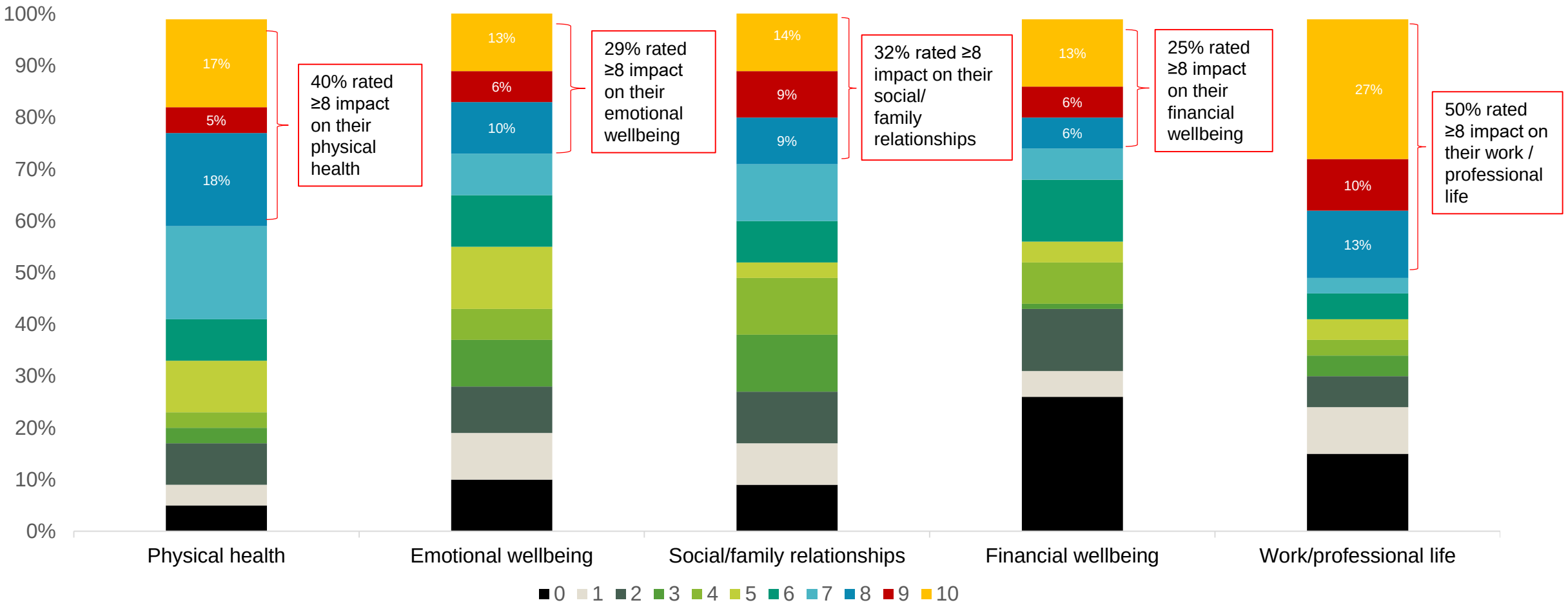


Treatments for gastro-intestinal symptoms (n=46)

Q. How satisfied have you been with symptom relief treatments?

Many different areas of patients' lives are affected by hATTR

Respondents rated the impact hATTR had on different aspects of their life over the last 12 months using a scale between 0 and 10 (0=no impact and 10=extreme impact)



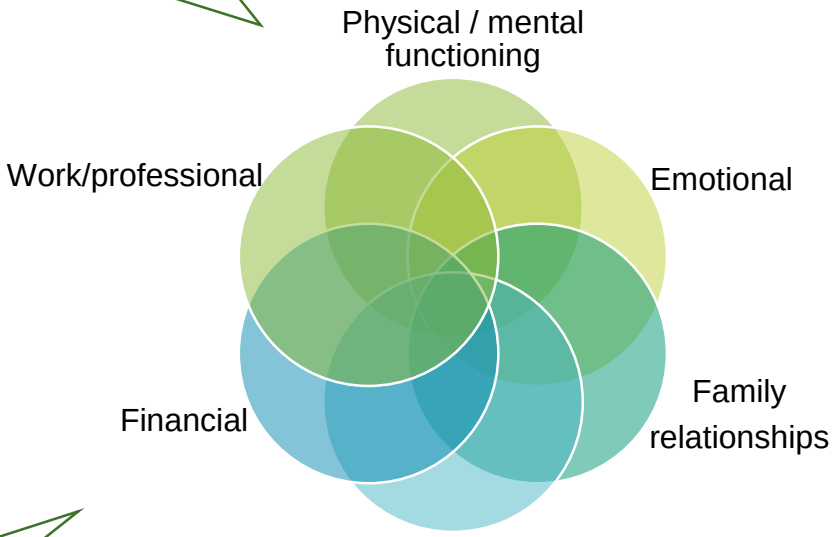
Q. Over the last 12 months how have the following aspects of your life been affected by hATTR? Please indicate between 0 and 10 where 0=no impact and 10=extreme impact (n=93)

Impacts on quality of life domains are inextricably linked

Amyloidosis Research Consortium UK

"Physically I'm not as strong, can't run or do anything in a hurry, I won't holiday abroad, financially I can't work as an investigator as I use to do."

"Overall, being diagnosed with hATTR has meant a huge change in my life. Sadly, my mother passed away from the disease two years ago and two days later I got my diagnosis. It has been a very traumatic time in my life and has massively affected all of my life and relationships."



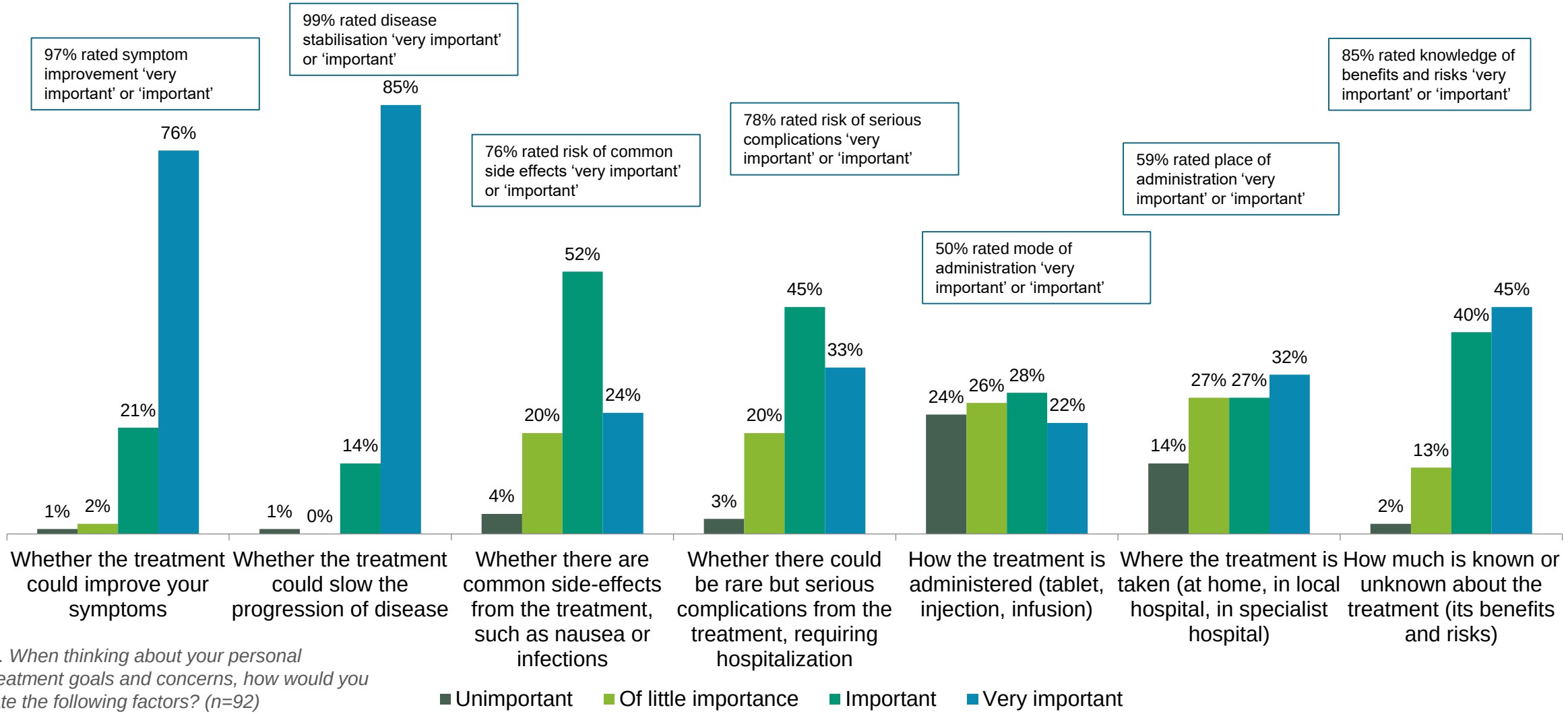
"I only have energy to work and then I come home and rest. I don't have much energy for family or a social life."

I am still able to work. My energy level is dropping as well as my productivity. I usually will avoid social engagements after work so I can rest instead. I try to keep a positive attitude and have solid relationships with my family and friends. Unfortunately I have not seen a lot of my loved ones because of fatigue."

"Had to give up work and with no bowel control we had quite a lot of expenses for hygiene products and personal stuff such as clothing, bed pans and bedding."

"Unable to work or lead a meaningful life . Family is affected by my illness for they are taking care of me. This has affected their social life as well as mine."

Patients' treatment attribute ratings favour efficacy; however, many different factors are important



Q. When thinking about your personal treatment goals and concerns, how would you rate the following factors? (n=92)

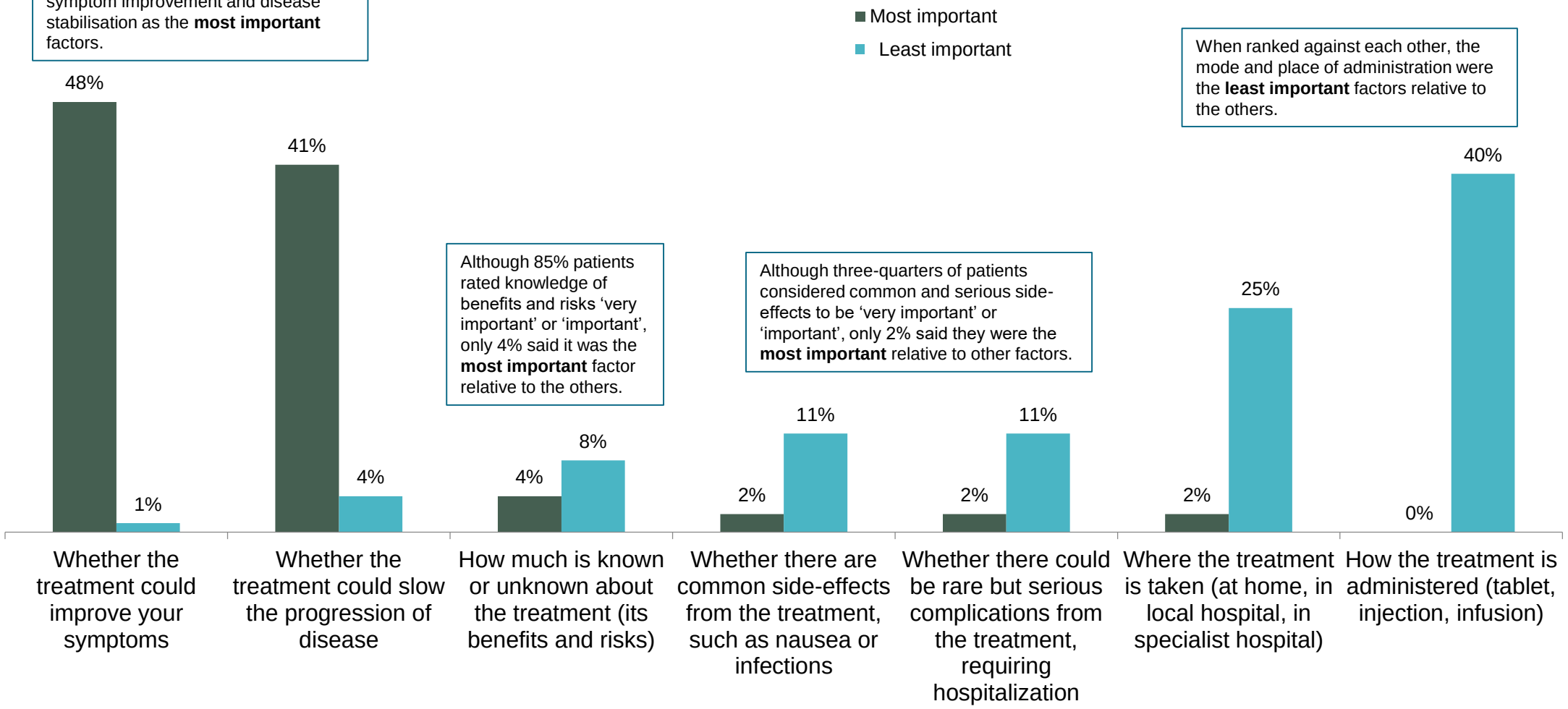
Forced ranking shows patients give greatest weight to efficacy and least to convenience

A clear preference emerged for symptom improvement and disease stabilisation as the **most important** factors.

Although 85% patients rated knowledge of benefits and risks 'very important' or 'important', only 4% said it was the **most important** factor relative to the others.

Although three-quarters of patients considered common and serious side-effects to be 'very important' or 'important', only 2% said they were the **most important** relative to other factors.

When ranked against each other, the mode and place of administration were the **least important** factors relative to the others.



Q. Which of these is the single most important and the single least important factor to you? (n=92)

Patients' preferences take into account complex trade-offs, individual goals and concerns for the future

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"I don't care about minor side effects. I'm dying."

"If it helps at all, I want it. I do prefer not to travel."

"I understand about rare complications but I would not want more digestive problems."

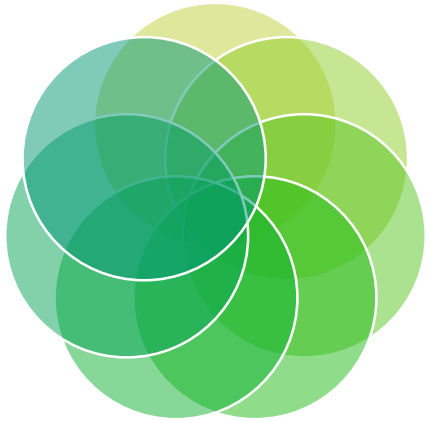
Trade-offs between efficacy, convenience and risks

"The most important thing is to stop this disease before quality of life becomes so deteriorated that you become a burden on your family."

Desire to see any improvement on current situation

Desire to improve functioning in daily life

"It is extremely important to find something that will stop the numbness and help me become mobile again."



Desire to remain / retain independence

Desire to improve overall symptom burden / particular symptoms

"Would like to reclaim some of my prior abilities to take care of my home and reduce the time it takes to do tasks I never thought about."

Desire to repair existing damage

Concern about disease progression

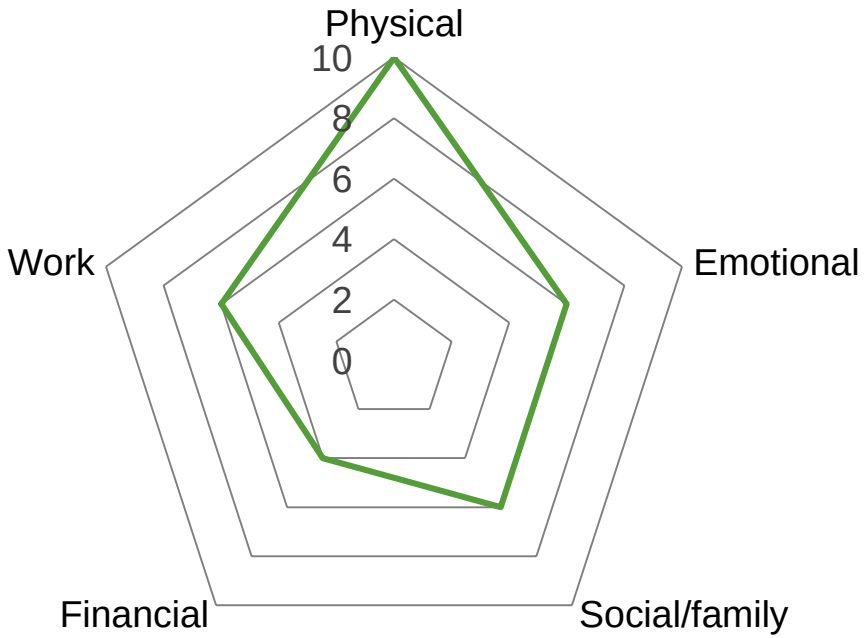
"My wife is experiencing loss of short-term memory. There is a history of Alzheimer's in her family. I must remain functional and able to provide care."

"Time commitment. I still have a part time job, and if I lose that, then its just the disease I have to think about."

Patient case study 1

- Male, diagnosed 2-5 years ago
- Late forties
- Full-time caregiver to his wife who has dementia
- First in family with hATTR diagnosis
- Symptoms in last 12 months: Difficulty walking, difficulty climbing stairs or muscle weakness; Numbness, tingling or pain in legs and/or feet; Constipation, diarrhoea, nausea, vomiting, weight loss or appetite loss; Loss of balance, dizziness, fatigue or tiredness
- Most problematic: **Dizziness** ‘every time I stand’
- Negative experiences on all amyloid-targeting treatments to date
- Can’t easily travel away from home due to caring responsibilities
- Most important factor: where treatment is taken
- Least important factor: risk of mild or common side-effects

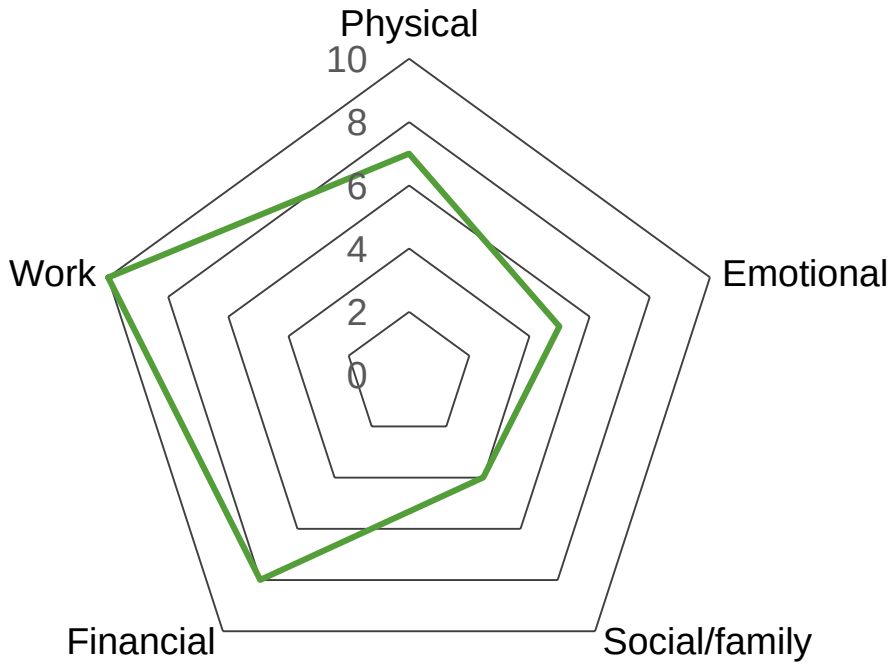
Impact of hATTR on your life over last 12 months



Patient case study 2

- Male, diagnosed more than 5 years ago
- Mid sixties
- Employed part-time
- Mother, uncle and brother with hATTR diagnosis
- Symptoms in last 12 months: Difficulty walking, difficulty climbing stairs or muscle weakness; Numbness, tingling or pain in legs and/or feet; Constipation, diarrhoea, nausea, vomiting, weight loss or appetite loss; Loss of balance, dizziness, fatigue or tiredness; Fecal or urinary incontinence; Erectile dysfunction; Loss of manual dexterity
- Most problematic: **Loss of balance/endurance** is the ‘biggest hindrance from doing normal things’
- No bad effects from prior treatment; seeing positive signs on disease on current treatment
- Most important factor: symptom improvement
- Least important factor: risk of severe side-effects requiring hospitalisation

Impact of hATTR on your life over the last 12 months



Carer survey demographics

52 survey responses were received. Of these 1 was excluded because no useable data was provided.

Of the 51 valid responses, 46 carers completed all sections of the survey and 5 partially completed the survey.

Time since diagnosis (n=51)			
Less than 12 months ago	1-2 years ago	2-5 years ago	More than 5 years ago
5	12	16	18

Age (n=51)					
39 and under	40-49	50-59	60-69	70-79	80 and over
3	15	8	16	8	1

Employment status (n=50)				
Employed full-time	Employed part-time	Not employed, looking for work	Not employed, currently unable to work	Retired
14	13	2	3	18

Relationship to the patient (n=50) *could select more than one				
Parent	Child	Spouse/partner	Sibling	Other
0	6	40	5	1

Place of residence (n=51)		
USA	UK and Republic of Ireland	Other
36	9	Canada (2), Australia (2), New Zealand (1), Spain (1)

Genetic mutation of patient (if known) (n=51)	
Val30Met	8
Val122 Ile	4
Glu89Gln	2
Gly53Glu	0
Glu54Gly	1
Ile68Leu	1
Thr60Al	13
Leu111Met	0
not typed	0
Not sure	15
Other	7

GI, mental function and the combination of multiple symptoms are particularly problematic for carers

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Which symptoms do you think are the most problematic?	Why?
Symptoms can have a different impact on caregivers	"For me, it's that he can't go on walks anymore. That's the time we spoke the most. For him, it's wearing a diaper." "For my husband, the numbness and difficulty in walking and dizziness....although the bowel issues are getting more regular. For me it's not knowing how long I have him for....and the coughing."
Combination of symptoms	"All symptoms because they affect everyday life." "Everything is devastating." "Cannot leave home, cannot do ordinary tasks. Must have help with everything as symptoms worsen. Hard on caregivers physically.." "Difficulty feeding himself, holding items, picking up things, loss of strength to do every day functions."
Mental / emotional functioning	"Unable to process information quickly enough to function effectively in daily life - can't work, perform any complex tasks or make difficult decisions." "It worries me. He's become more unstable mentally."
Insomnia	"He says its the diarrhoea, but for me its that he's depressed and cant sleep. It worries me."
Anxiety	"Shortness of breath and chest pains which feed into anxiety attacks. My dad is increasingly more frightened."
Pain, balance, weakness	"Constant nerve pain arms, hands, legs spine and loss of balance, weakness."
Gastro-intestinal	"The passing out and the inability to keep any nutrients down. My husband is slowly starving to death." "The GI issues seem to be the most that interfere with her lifestyle and well-being." "Intermittent diarrhoea – embarrassing in public." "Diarrhoea takes a lot of strength away."

Carers experience a significant practical and emotional everyday burden

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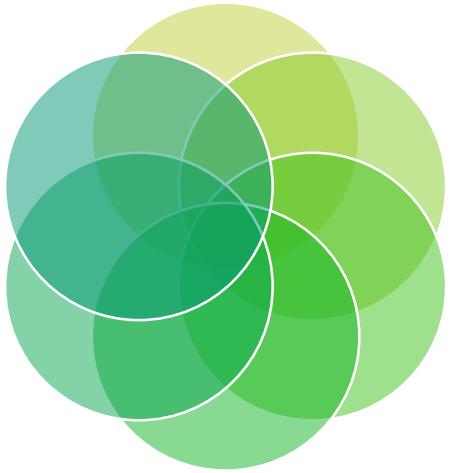
"Supporting him with his disappointment and frustration regarding the increased symptoms."

Providing emotional support to deal with patient's disappointment

"Accompanying my husband to London for each infusion, which takes a whole day including travel. It's a very long and tiring day."

I've gone part-time to fully support him during the various hospital appointments he attends."

Dealing with own worries, concerns and disappointment



Accompanying to appointments

"Had to give him the injection, which was so painful, it made me cry causing him so much pain."

Taking time off work

Administering treatment

"It's very hard to see when medicine does not work and you don't have any hope. Some days I feel very low."

Managing treatment regimen

"Ongoing changes in medications keep me on my toes, as I am the one who arranges meds daily."

Carers report a higher impact on their emotional wellbeing and social/family relationships than patients

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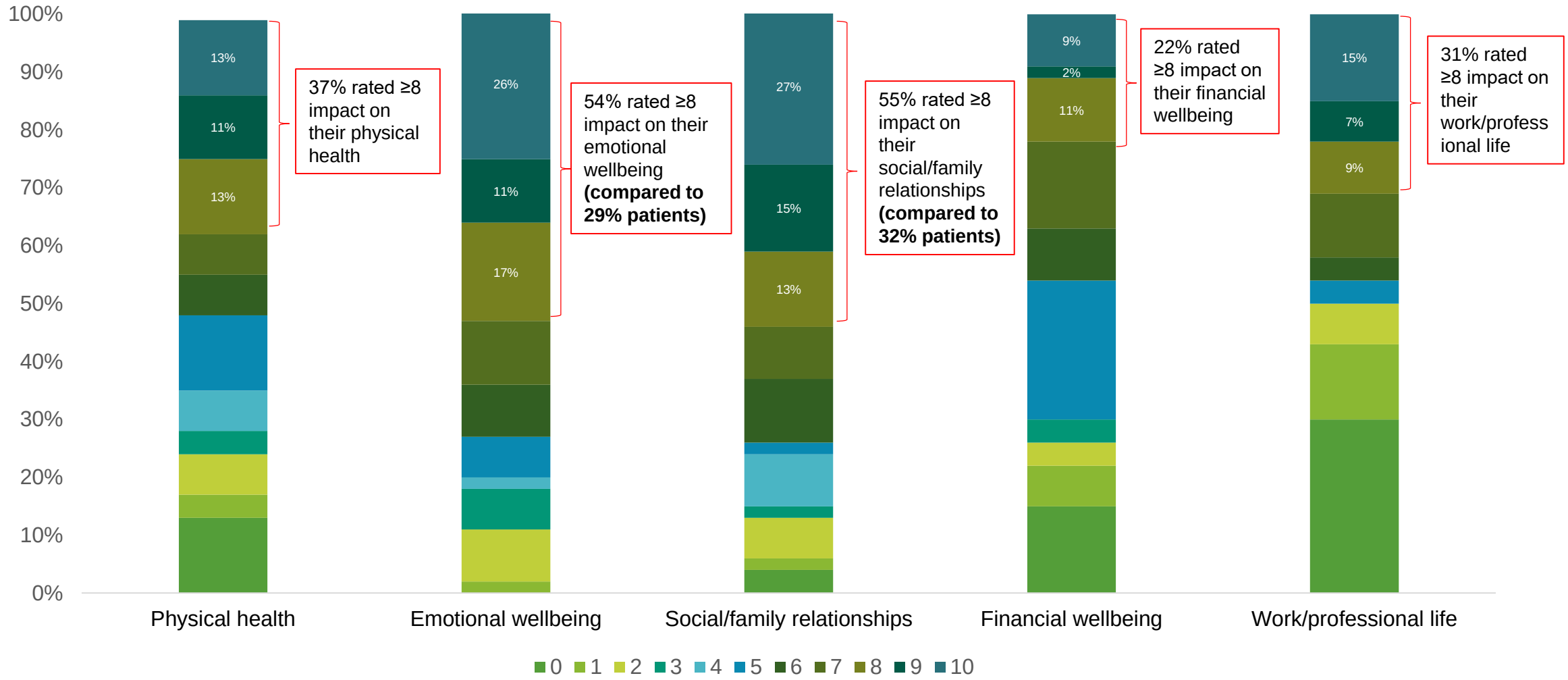
Respondents rated the impact hATTR had on different aspects of their life over the last 12 months using a scale between 0 and 10 (0=no impact and 10=extreme impact)



Q. Over the last 12 months how have the following aspects of your life been affected by hATTR? Please indicate between 0 and 10 where 0=no impact and 10=extreme impact (n=45)

Fatigue and anxiety affect many carers' quality of life

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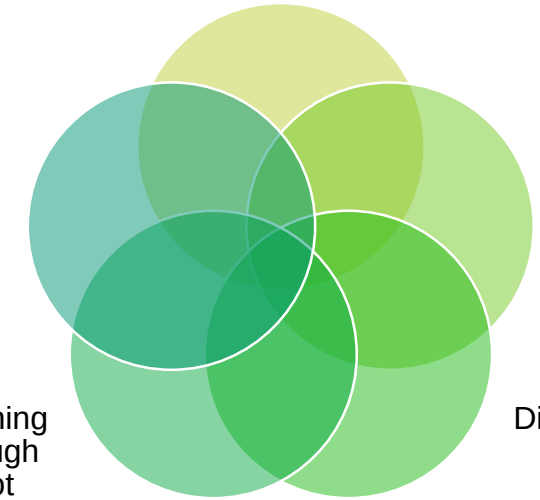
"It's just super sad watching the deterioration and depression then thinking that your nephew could be next, heart-breaking."

Worrying about children / grandchildren who have or may have the disease

"I no longer have any social life because I don't want to leave him alone at night when he's been alone all day. He is emotionally dependent on me so he gets sad when I am not around."

Feeling that their life is no longer their own / having to focus all energy on the patient



Exhaustion from worrying and taking on a greater burden of caring / chores

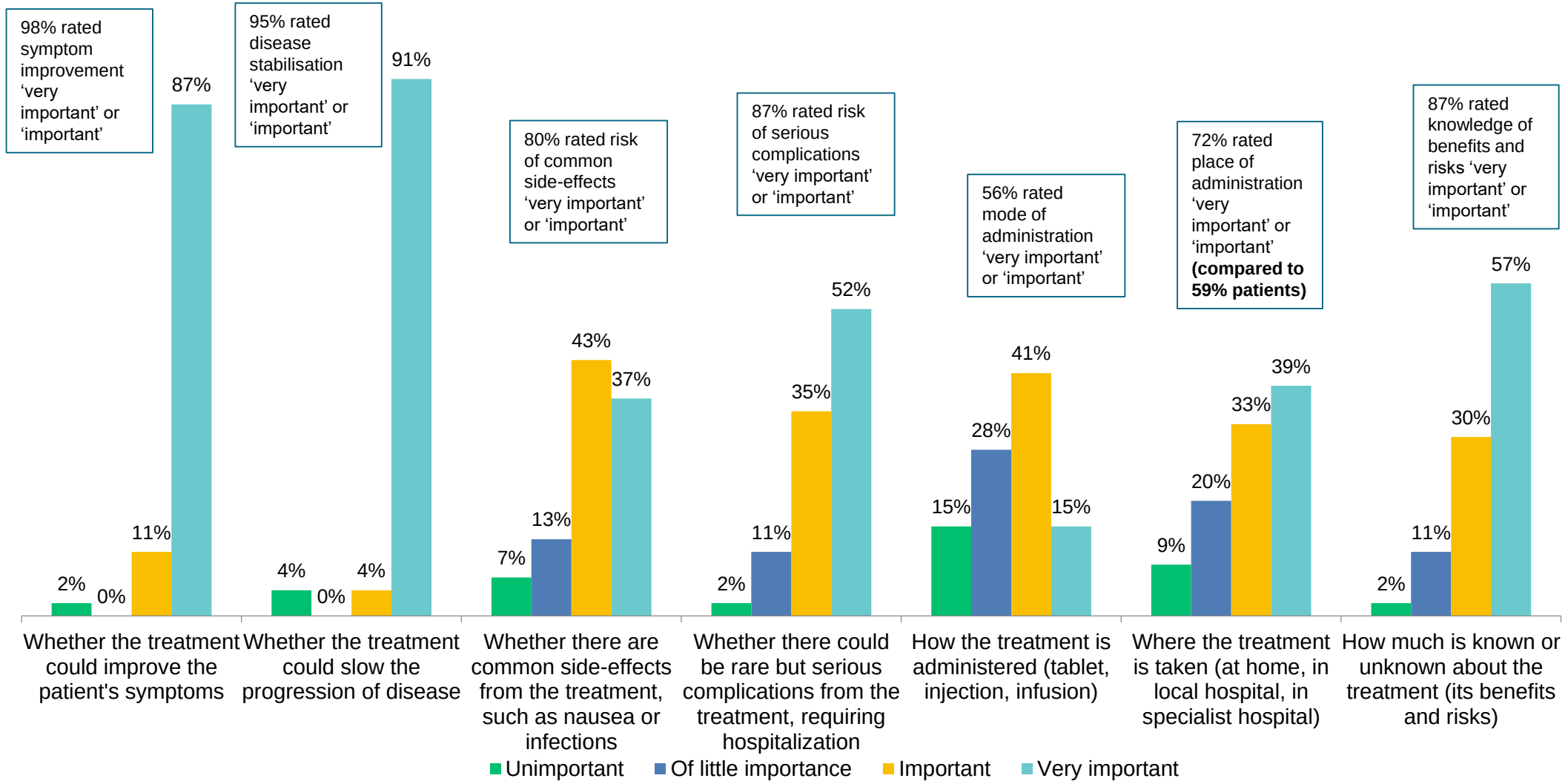
"There has been little support offered to my father and my mother, who cares for him full time. Their mental health has been mostly ignored. I too have had no support and I have had to bear the burden of working full time, caring for my dad and caring for my mum as her mental health has been significantly impacted by my dad's diagnosis."

Difficulty maintaining a social life through exhaustion / not feeling able to leave the patient

Difficulty maintaining a career through caring responsibilities / fatigue

"I recently got a promotion at work which was great because we needed the salary increase, but now the higher level of responsibility is causing me stress because I can't work late or be mentally "present" as much as I should be. He can't help out at home at all so I have to do everything. It's exhausting having to work full time, care for him all night and take care of the rest of the families needs."

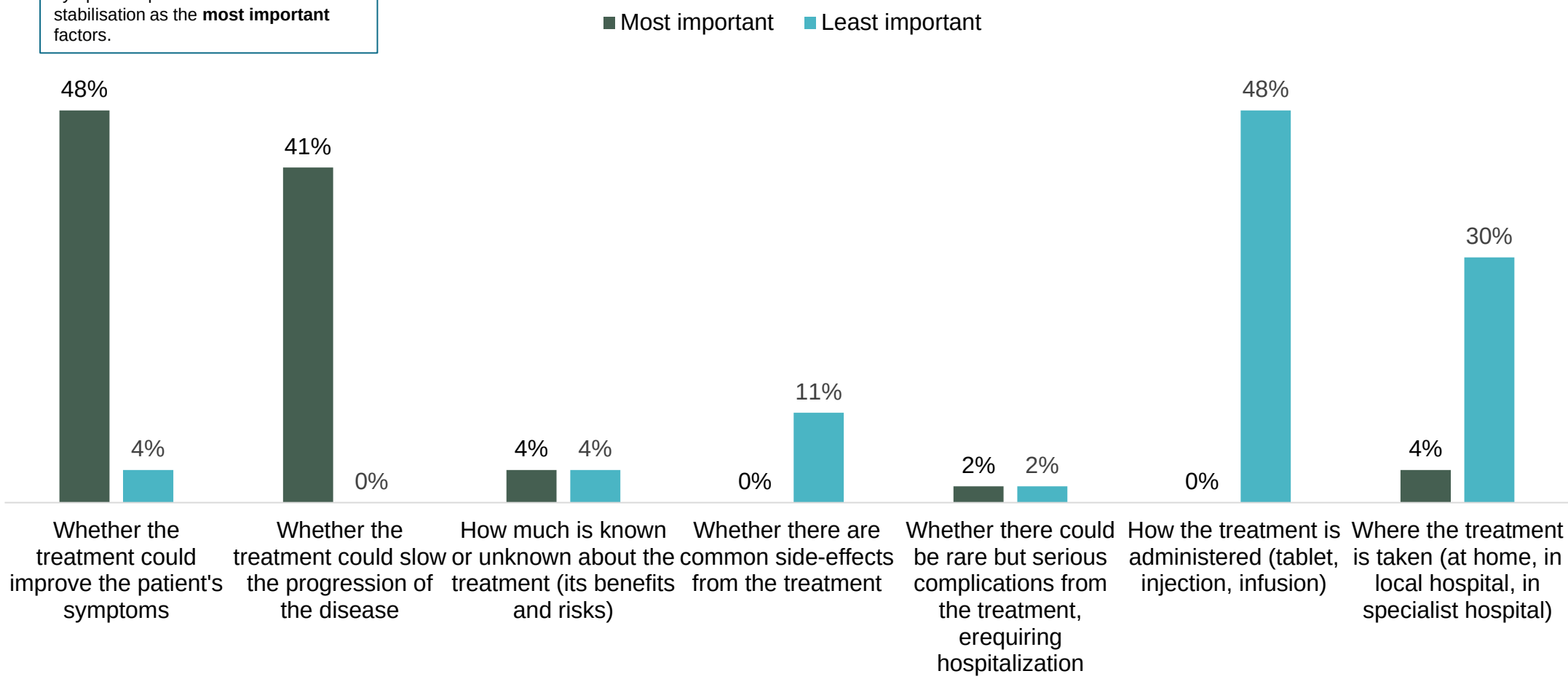
Carers rate the importance of most treatment factors similarly to patients



Q. When thinking about your personal treatment goals and concerns, how would you rate the following factors? (n=46)

Forced ranking shows that carers, like patients, prioritise efficacy over convenience

A clear preference emerged for symptom improvement and disease stabilisation as the **most important** factors.



Q. Which of these is the single most important and the single least important factor to you? (n=46)

Like patients, carers view modest improvements to be a significant outcome in the current context

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"Things are so bad right now that he is willing to try anything to relieve his symptoms and slow it down even to the point that we don't care what possible complications or side effects there are. He has no other choice."

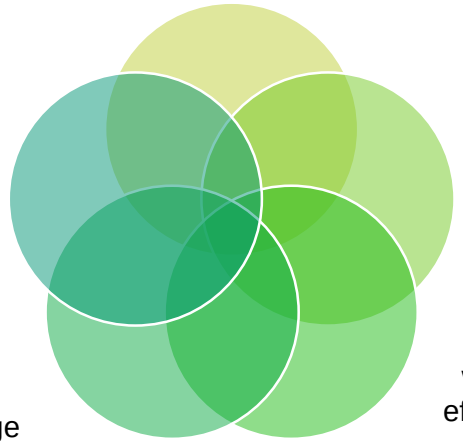
"We want a cure - but right now we are fighting for slowing down the disease progression."

"Would prefer not to have to travel to a special hospital for treatment. Also would prefer an injection to a five hour infusion."

"That this disease can be maintained until a cure is found or the disease is able to be maintained by the use of medication. With having children we worry that our sons and grandchildren will be at risk."

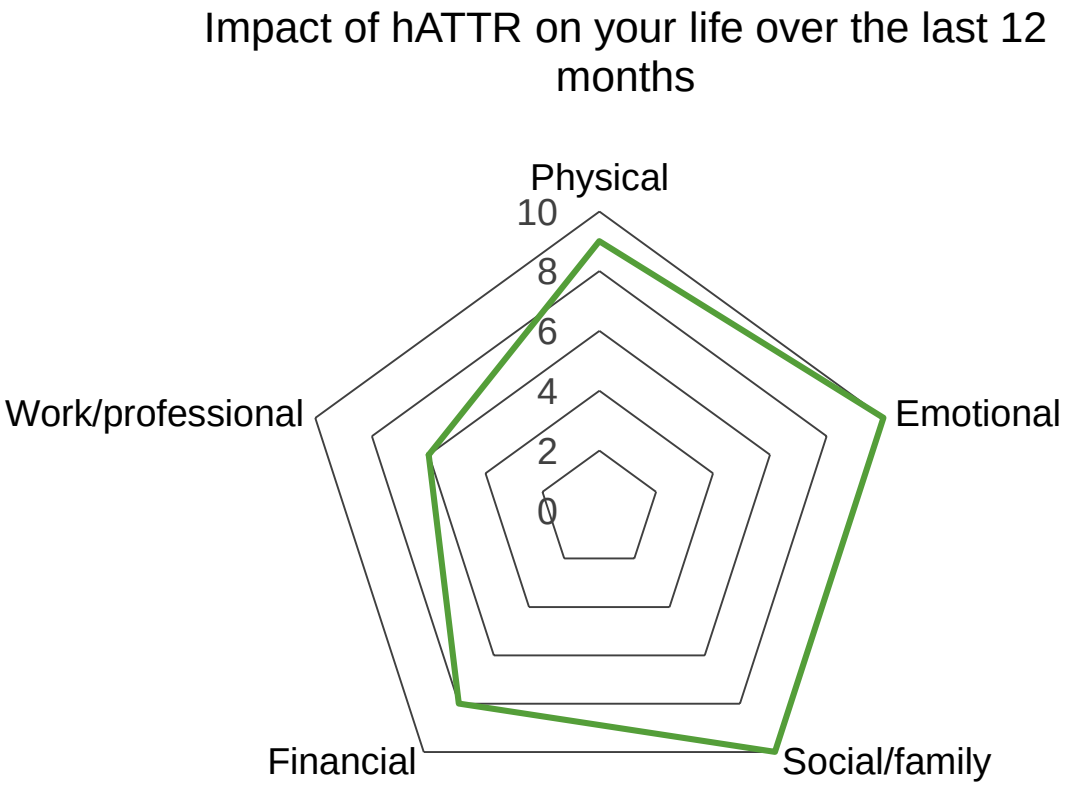
"My goal is for his life to not only be prolonged, but for him to have a good quality of life for as long as possible - for him to be able to live, not just be alive."

"Living longer and lifestyle are by far the top issues. Amyloidosis patients (and caregivers) will put up with a lot of other factors in order for the patient to live longer and with a better quality-of-life."



Carer case study

- Spouse, mid fifties.
- Full-time employment.
- “I no longer have any social life because I don't want to leave him alone at night when he's been alone all day. He is emotionally dependent on me so he gets sad when I am not around. He can't help out at home at all so I have to do EVERYTHING. It's exhausting having to work full time, care for him all night and take care of the rest of the families needs. I am in a constant state of stress and worry about everything from his declining health, to the thought of losing him, to our finances, to my work life. Just constantly worrying.”
- Most important factor: slowing disease progression
- Least important factor: how treatment is administered



Analysis of treatment preferences qualitative sub-study: focus groups and interviews

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Aim: to explore four key issues in depth around values and preferences for treatment, including trade-offs and relative importance of different factors

Themes:

A. The first disease-modifying treatments offer major hope for a disease that has destroyed families' lives
B. Treatment value relates to functional improvements, retaining/regaining 'normality' and independence
C. Side effect concerns are relative to patients' existing symptom burden
D. Convenience is likely to have a significant influence in a context of multiple treatment options

A. The first disease-modifying treatments offer major hope for a disease that has destroyed families' lives

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Key theme	Example
Patients and families talk of having hope and a brighter outlook for the future, in the context of there being no other effective alternatives at the moment	• "We didn't plan to have a family because of the disease. We might adopt in the future.. We didn't even think we had that option." • "It's exciting to know there are options. I've been grasping at straws. Nothing is helping me." • "I'm not feeling so dark about my future. There's a lot more light."
Patients express hope that they may not experience / or may delay experiencing the 'fate' of family members who have died from the disease	• "The prospect of what's facing us down the road isn't good. We've all seen family members go through it." • "I'm now looking at not absolutely going down the same path my dad did." • "Mum's final years were horrendous."
Patients and carers also expressed the significance of having new treatments for future generations, including their own children	• "The timing is hopefully right for us. And not just for us, it's huge for our families and children."

B. Treatment value relates to functional improvements, retaining/regaining ‘normality’ and independence

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Key theme	Example
Value in stopping progression of the disease in order to regain functionality / normality	• “[Success is] being able to participate in my life rather than be a bystander… To do up to three errands a day instead of one. I can walk my kids to school multiple days in a row instead of paying for it the next day with pain.” • “To get back to doing normal things, back into the garden or out for a walk..” • “If we could go out for a whole day without worrying where the nearest toilet is – it will change our lives completely to go back to some normality which we haven’t had for many years, and take the pressure off our families who are supporting us.”
Value in slowing progression to prevent further loss of functionality or deterioration	• “Slowing or stopping disease progression is still progress.” • “If it stops me where I am at now in my disease, that’s success. That’s good enough for me. If it will let me carry on doing what I can do now.” • “One day I would love to see it improved; but at this point I’m just focused on slowing.”
Value in maintaining independence for as long as possible	• “I would hate my independence to be taken away and for my wife to be my 100% carer. I don’t want to burden anyone with that.”
Modest benefits are meaningful	• “Even a small effect would build upon your quality of life. The measurement scales don’t take account of pain, embarrassment or social impact. If there is any small benefit it would be worth it.”

C. Side effect concerns are relative to patients' existing symptom burden

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Key theme	Example
Side effects are a consideration but it depends on their severity and how manageable they are	• "As long as it's not to the point where it's a detriment to your health i.e. you're not going to land up in hospital, it's a risk worth rolling the dice on." • "Sometimes your body recovers or gets used to it. Or you find mechanisms to cope with them." • "If it causes you not to live then 'no', but if seeing the results working then 'yes'." • "You have to ask yourself are they inhibiting quality of life?" • "It's important to be knowledgeable about the risks, vigilant and have a back up plan"
A risk of side effects is acceptable and 'worth it' for a potential improvement, however small	• "The side-effects would have to be pretty bad to be worse than the disease." • "I'll try to stop the disease first and then deal with the side-effects."
If side effects become unmanageable or begin to outweigh the benefits / disease effect then it wouldn't be 'worth it'	• "You don't want side-effects that are going to make you worse than you already are." • "I'd probably try it as some people don't get the side-effects. But if it got really bad and I couldn't see any improvement in my condition I'd come off it." • "If it becomes too oppressive I'm out."

D. Convenience is likely to have a significant influence in a context of multiple treatment options

Amyloidosis Research Consortium UK

Key theme	Example
A clear preference for oral medication, followed by self-injection, followed by infusion (when all other things are equal)	• "If all other factors were equal I'd go for a pill, then injection, then travel to hospital.. But side-effects would come into it and so would the benefits."
Place of administration / reducing the need to travel for treatment is more important than method of administration	• "Administration isn't the issue, it's the time taken to get there and come back. We're all ill and have weariness and lots of other issues." • I'd prefer patisiran at home if the effects were just as good."
Convenience is not as important as other issues e.g. efficacy; however, over a period of time travelling for treatment could be problematic for some	• "I'm working full-time. I have to take time off work or arrange for someone to take him." • "If you have GI, then logistics are everything… You have to factor in the bathroom or not feeling well. It's something you have to logistically plan with everything else you have going on." • "I appreciate what the drug is doing but the three-weekly travel… I'm anxious the day before, the day you're there you're wiped out and the day after I don't sleep well."
Patients want choice and they want treatments to be convenient; however, at the moment – with no alternatives – convenience is less important than it might be in the future	• "If you've seen what this disease can do you take whatever you can get." • "As choice increases, convenience will become a bigger factor." • "It would be a nice dream for a treatment to be convenient. But we're not at that point. We're still at life-saving and halting disease progression."

Conclusions

Amyloidosis Research Consortium UK

1. hATTR has a very high burden on patients and families. A multi-systemic disease, it affects *all* aspects of life
2. hATTR significantly impacts on patients' independence and sense of normality: their ability to work, participate in family and social life, be mobile and undertake daily activities and hobbies
3. hATTTR considerably impacts on carers: the emotional burden of 'knowing what's to come', practical caring burden and the effect on their own ability to work
4. Patients have mixed experiences of symptom and disease management approaches: there is unmet need with regard to efficacy, side-effect burden and convenience/choice
5. New treatments specifically for hATTR offer significant hope to patients and their families, especially in the context of the disease being hereditary, high impact on quality of life, and no/few alternatives
6. Patients and carers value multiple factors as important for treatment, including efficacy, convenience, risk of side-effects and knowledge of benefits-risks
7. The most important factors for treatment are related to impact on the disease. Patients are likely to accept risks of side-effects for 'modest' gains
8. Treatment preferences and values are influenced by a lack of effective alternatives and high unmet need/symptom burden; as choice increases, convenience and side-effects are likely to become increasingly important considerations

Referencing the report and ARC UK contacts

The findings here are pre-publication and should not be published or shared without prior permission from the Amyloidosis Research Consortium UK.

Any use of the findings in the report should be referenced as follows:

Amyloidosis Research Consortium UK. *Burden of disease and perspectives on treatment: summary report from research with hereditary transthyretin amyloidosis (hATTR) patients and carers.* July 2018 (unpublished).

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Association of British Neurologists and the British Peripheral Nerve Society

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Based on the recent study by Schmidt et al. (PMID 29211930), the mid estimated prevalence of hATTR is 97 patients. I would expect the majority to receive treatment with the technology.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The condition is currently managed by the national amyloidosis centre, a NHS commissioned highly specialised service. The national amyloid centre receives patient referrals from throughout the UK. Patients with hATTR and significant neuropathy are also seen at the National Hospital for Neurology, UCLH.

The current treatment options for hATTR are limited. The TTR stabilising drug diflusinal is often used but has little impact on the natural history of the disease. Liver transplantation is currently used to treat hATTR, however, only a small subset of patients are eligible for this treatment, the costs are high and the treatment is also limited by the availability of donor organs.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There are significant differences in age of disease onset dependent on the type of mutation and ethnic background. As a general rule, patients presenting with cardiac involvement have a worse prognosis than those presenting with a peripheral neuropathy.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

It is possible that patients receiving new genetic therapies will require closer neurological surveillance than is currently undertaken.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The current available treatment for hATTR is liver transplantation. The proposed technology is likely to be safer, cheaper and with comparable or reduced clinical follow up costs. The drug related side effect of thrombocytopenia will mean that patients will require regular blood monitoring.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: British Society of Heart Failure/ Royal College of Physicians
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? √
- On the board of the BSH and Fellow of RCP. Employee of National Amyloidosis Centre in London as Consultant Cardiologist.
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

none

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Hereditary transthyretin (TTR) amyloidosis is a devastating, debilitating disease with a heavy burden of symptoms including peripheral neuropathy with progressive disabling sensory and motor neuropathy; autonomic neuropathy with postural hypotension, alternating diarrhoea and constipation, erectile dysfunction and in some patients, cardiomyopathy with progressive heart failure symptoms. In those with neuropathy, estimated survival is 8-10 years over which time, patients become progressively immobile and ultimately are wheelchair bound. Once there is cardiac involvement, the survival is around 4-5 years. As this is hereditary, often patients have witnessed a parent or other relative's demise and have been the main carer during that time. It is inherited in an autosomal dominant fashion with variable penetrance. There are over 100 TTR mutations which have been found to be amyloidogenic.
At the National Amyloidosis Centre, over the last 5 years around 200 patients have been diagnosed with either neuropathy or neuropathy and cardiomyopathy. We see around 30 new cases each year. The majority of these patients are based in England but around 5-10 patients are from Scotland, Northern Ireland or Ireland. We would anticipate that the majority of these patients would be eligible for treatment.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients are referred to the National Amyloidosis Centre (NAC) in London from all over the UK and also from Ireland. This is a highly specialised service or the diagnosis of this condition. Patients are reviewed on a 6 monthly basis at the NAC. More patients are referred to the NAC from the South of England than from the North as patients may find it too challenging to travel long distances. There is no difference in opinion as current practice is largely supportive in the management of symptoms. Currently there is no approved treatment available to patients in the UK. Some patients may receive diflunisal off licence, an old fashioned NSAID, which may stabilise the transthyretin protein in the liver. This drug has been increasingly difficult to source over the last 2-3 years (it is not manufactured in the UK). It can cause renal dysfunction, peripheral oedema and stomach ulceration. The trial data which demonstrated slowing down of neuropathy was seen in a population that is uncommon in the UK (ATTR V30M) and therefore may be less relevant for the English population. We have not experienced halting of progression with this drug. Tafamidis, another TTR stabiliser, which is available in the rest of Europe, is not available in the UK (or America).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The majority of patients seen at the NAC have both neuropathy and cardiomyopathy and therefore the median survival is reduced to 4-5 years from diagnosis. Patients are most likely to benefit if they are diagnosed early (stage 1). Patients with a known bleeding disorder may be at risk if thrombocytopenia is severe. Around half subjects in the trial developed thrombocytopenia but this was mild to moderate in the majority of cases. Patients with significant mobility problems may benefit from the home based care with subcutaneous injections rather than travelling to a centre for an intravenous infusion. Provision would need to be in place for home blood sampling fortnightly to monitor platelet count and renal function.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals).

There will be an increase in referrals to the specialised service. Relatives may wish to be actively screened for the TTR mutation and monitored for the development of the disease. Home care provision will need to increase, as mentioned, to allow monitoring of platelet count and renal function. Provision by the company for a central monitoring board to act on these blood results, must be considered.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not applicable

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Since there are no treatments available at present in the UK, there are no relevant clinical guidelines for the treatment of this condition at present. With the possibility of 2 new treatments, guidelines for their use should be developed.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There is no current alternative used in the UK. However, Inotersen can be given at home by injection whereas patisiran is given by intravenous infusion in a centre. Patisiran however does not require regular blood tests.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

In my experience as PI for the Inotersen trial in the UK, patients have been happy to have weekly blood tests in order to receive Inotersen in the open label extension.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Starting criteria will be led by how Inotersen is licensed. The company should collect robust outcome data for those patients receiving Inotersen in terms of neuropathy progression and quality of life.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The NeuroTTR study met the primary endpoints of slowing neuropathy progression demonstrated by a neuropathy score and improving quality of life compared with placebo. Some patients reported improvement in neuropathy symptoms. Inotersen was given once weekly by subcutaneous injection. There were 5 deaths in the Inotersen arm, one of which was felt to be related to Inotersen as a result of severe thrombocytopenia. There were no deaths in the placebo arm. Since mortality was not an endpoint, no conclusion can be drawn from this.
Most patients were able to self administer but carers or homecare nurses could also administer the drug. As a result of clinically significant thrombocytopenia and renal dysfunction, blood tests were increased to weekly and continue to be the case. From my experience, patients have accepted these weekly blood tests in order to continue on Inotersen (now in the open label extension).
There needs to be a robust system for monitoring of platelets and renal function in the real world setting. I understand that Akcea/Ionis have offered to provide homecare for the blood tests and will provide personnel to act upon the results. This is imperative from a safety aspect.
The most important outcomes are halting progression of the neuropathy and improving quality of life.
The UK took part in this study so it is relevant for UK patients.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

From my experience with trial patients, low platelet counts have been subclinical. They are prepared for regular blood tests and this does not seem to impact poorly on their quality of life.
No other adverse events have come to light in my experience.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

We would advocate that patients have the diagnosis confirmed at the NAC and if eligible for Inotersen, would be prescribed Inotersen from the NAC with follow up in the TTR clinic. They would also have local follow up with their neurologist and cardiologist. Their clinical condition would be monitored at the NAC.
Inotersen can be self administered at home. Staff are required to take weekly blood tests. Staff are required to act upon the results of these blood tests.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Since Inotersen can be administered at home, people with disabilities would not be discriminated against.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Edmund Jessop**
2. Name of organisation	**NHS England**

3. Job title or position	**Public health adviser**
4. Are you (please tick all that apply):	Commissioning services for NHS England for the condition for which NICE is considering this technology?
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion per annum in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England has not published any guidelines for this condition.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The National Amyloid Centre (NAC) at the Royal Free hospital in London is the recognised centre for diagnostic evaluation of patients suspected of amyloid-forming conditions. The pathway for ongoing care and treatment of patients with an established diagnosis is less well defined and although most patients will be under the care of the NAC, some patients may be under the care of local neurologists or other specialists.
8. What impact would the technology have on the current pathway of care?	The availability of disease modifying treatment is likely to improve the definition and clarity of pathways for ongoing care and treatment of patients with the condition.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Not in use

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The main extra resource use will be in monitoring the effects of treatments – increased outpatient attendance and costs of investigations or imaging.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment should be initiated and monitored by the NAC but with arrangements for local shared care where appropriate.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will a small requirement for staff training.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	To be decided.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	None to date
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement – condition

Inotersen for treating hereditary transthyretin-related amyloidosis [ID1242]

Thank you for agreeing to give us your views for these highly specialised technologies evaluations.

You can provide a unique perspective on the condition in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Because of the nature of these two evaluations, we would be grateful if we could ask you to comment on the condition and current treatments only, and not on the individual technologies. Where the questionnaire refers to the new technologies, you are welcome to comment on new disease-modifying treatments for hATTR amyloidosis in general, but we ask you not to comment on the relative merits of patisiran and inotersen specifically.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Philip Hawkins**
2. Name of organisation	
3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not	☐ yes

have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technologies in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would new disease-modifying	

therapies have on the current pathway of care?	
11. Will the technologies be used (or are they already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technologies and current care?	
• In what clinical setting should the technologies be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technologies? (For example, for facilities, equipment, or training.)	

12. Are there any groups of people for whom the technologies would be more or less effective (or appropriate) than the general population?	
The use of the technologies	
13. Will the technologies be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for their use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technologies? Do these include any additional testing?	
15. Do you consider that the use of the technologies will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits and how might they	

improve the way that current need is met?	
• Are the technologies a 'step-change' in the management of the condition?	
• Does the use of the technologies address any particular unmet need of the patient population?	
Sources of evidence	
17. Do clinical trials in this condition reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes for people with this condition?	

• If surrogate outcome measures are used, do they adequately predict long-term clinical outcomes?	
18. Are you aware of any relevant evidence that might not be found by a systematic review of published evidence?	
19. How do data on real-world experience in this condition compare with clinical trial data?	
Equality	
20a. Are there any potential equality issues that should be taken into account when considering this treatment?	

20b. Consider whether these issues are different from issues with current care and why.	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Alexander Martin Rossor**
2. Name of organisation	**Association of British Neurologists and British Peripheral Nerve Society**

3. Job title or position	**Honorary Consultant Neurologist and Wellcome Trust Post-Doctoral Clinical Fellow at the UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	**x** yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow disease progression and reduce disability.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A stable neuropathy rating scale over a period of one year Stabilisation or absence of autonomic dysfunction
9. In your view, is there an unmet need for patients and	HTTR is a progressive condition with significant morbidity arising from the cardiomyopathy and peripheral and autonomic neuropathies. The lack of effective therapies means there is an unmet need for patients and healthcare professionals

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients with hTTR currently receive supportive care from a variety of specialists including cardiologists, neurologists and gastroenterologists. This includes medical heart failure management, pain management and management of autonomic failure and diarrhoea. In addition, patients require walking aids including orthotics, walking sticks and wheelchairs and adaptations to their home environment. Diflusinal, an oral medication is frequently commenced in patients with hTTR.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Not that I am aware of.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined in the UK. All patients diagnosed with hTTR are initially referred to the National Amyloid Centre. Neurological assessment and monitoring is undertaken every 6 months at the National Hospital for Neurology and Neurosurgery.

• What impact would the technology have on the current pathway of care?	Patients will require training in administering the treatment in their local area. There will need to be a new system in place for local blood monitoring whilst on therapy.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will require new systems to facilitate delivery and monitoring of the medication (that are not currently employed for patients with hTTR).
• How does healthcare resource use differ between the technology and current care?	The proposed treatment will require patient or carer training to administer the subcutaneous injections and also regular blood monitoring.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In my opinion the technology should be initiated by the National amyloid centre, however administration of the medication and blood monitoring should be undertaken locally in secondary or primary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	A specialist nurse would be required to undertake training of patients and carers in the administration of the medication and to undertake regular blood monitoring.
12. Do you expect the technology to provide clinically	Yes

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Unable to comment
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	The technology will require patients or carers to administer subcutaneous injections and for regular blood monitoring. This should not require hospital admission and should result in little change to current models

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	of care. Some patients with hTTR, however, have significant hand weakness from their neuropathy and will require a carer or district nurse to administer the medication.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I am not aware of any rules
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	I do not know enough about how a QALY is calculated to be able to comment.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	There are currently no disease modifying treatments available for hTTR. One of the most troubling symptoms for patients with hTTR is the severe autonomic neuropathy that results in intractable diarrhoea and incontinence, impotence and syncope. Any technology that can slow down the rate of progression of the disease and delay these symptoms will have significant health-related benefits.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, it is one of the first disease modifying therapies for hTTR.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The technology will require regular blood monitoring which is unlikely to have a significant impact on a patient's quality of life. The regular blood monitoring will be similar to that required for patients on regular immunosuppression.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes form a neurological perspective are progression of the peripheral and autonomic neuropathy. The primary outcome measure is designed for monitoring peripheral neuropathy.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	The treatment regime in the trial would be relatively easily adopted in normal NHS clinical practice.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

- The aim of treatment should be to slow disease progression
- The proposed treatment is a significant advance in the management of patients with TTR amyloidosis
- The clinical trial is applicable to current UK practice
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Mr Vincent Nicholas**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Amyloidosis Research Consortium UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	As my mother died of Amyloidosis in 1991 I was automatically tested for the gene by the NAC. At that time there was very little known about the disease and treatment was limited. It had a major impact on my life and my family. My wife and I went away and wrote our bucket lists!

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Since getting symptoms of Amyloidosis in 2009 it has had a major impact on my life and the family's life. In 2010 I had a liver transplant which had a huge affect on me and the family with regards to stress and emotional anxiety. My wife and I spent a lot of time having counselling. I believe that by having the liver transplant it has slowed down the progression of the disease. It has affected my life and the family's life in many ways: - I can no longer do too many physical activities. Day to day general activities is harder and slower. - My wife has had to take on all the physical house chores and DIY. - Do to the neuropathy and muscle wastage very day to day activities are harder and slower to do. - The worst thing is the affect it has on my bowl movements. I have to be careful what I eat and have quick access to toilet facilities. This restricts where we travel and holiday types. - I have become emotional about things and get frustrated by the simplest problem. - My wife who is my carer has had to take on most of the running of the family. I'm still able to help with cooking and running the girls to school at the moment. - I get very tired and am unable to do more than 2/3 jobs a day. I had to retire 2 years ago due to ill health. - Luckily on the financial side I am ok due to having a good pension.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Currently there are no drug treatments available. Also the majority of the NHS apart from the NAC has knowledge or training about Amyloidosis.
11. Is there an unmet need for patients with this condition?	Lack of understanding by GP's and hospitals about Amyloidosis.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also	This new drug will have a major impact on our lives. It will ease the disabilities that come with this disease and holt its progression. Amyloidosis then is longer a terminal illness!

include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	The current treatment is easy but takes about 3 hours. The main problem is the time and cost needed to get to the NAC in London. This takes place every 3 weeks. Also someone has to travel with me just in case I need support after the treatment.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they	As the side effects with this drug is very minimal the only disadvantages is where the treatment is taken and the time and cost to get there.

long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Not qualified or have the knowledge to answer this.
Equality	
16. Are there any potential equality issues that should be taken into account when	**No**

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	No
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • This drug treatment is life changing. • It will hopefully stop and reverse some of the symptoms that we have. • Quality of life will be improved for the patient and their families. • No longer will liver transplants be needed. • The next generation will no longer have to suffer with this debilitating disease.	

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Carlos Heras-Palou**
2. Are you (please tick all that apply):	**X** a patient with the condition? ☐ a carer of a patient with the condition? X a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Nominated by Akcea I am the chair of UK TTR Amyloidosis Patient Association www.ttramyloidosis.uk
4. Did your nominating organisation submit a submission?	X yes, they did no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	X yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	The difficulty is that most doctors are not aware of the disease, and only very specialist centres have the knowledge and facilities to investigate and diagnose ttr amyloidosis. This can cause a lot of anxiety to the patient and family and a delay in treatment.

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Living with disease is painful, depressing and disabling. Main problems are: -Very difficult to control diarrhoeas. This results is weight loss, can cause incontinence that often leads to social isolation and not being able to hold a job or even go out of the house. Treatments like codeine may help on the day but they can have a rebound effect the following day when symptoms are even worse. -Diarrhoea and pain at night is very common and seriously disturbs rest. This is a big problem when it happens every night. -Neurogenic pain feels like suddenly being stabbed, out of the blue, with vey intense pain that is short in duration, and aches that last a long time. The pains usually start affecting the feet, and then progress proximally aa the neuropathy advances. Then it affects the hands. Sometimes the pain feels like burning, like being scalded, but there is nothing to show for it. This type of pain does not respond well to usual painkillers, and even gabapentin and pregabalin do not seem very effective. -Autonomic nerve symptoms include those related to hypotension, including feeling light headed and fainting, digestive (vomiting, problems swallowing and abdominal pain as well as the mentioned diarrhoea), sexual (including impotence), urinary (difficulty voiding can result in frequent urinary infections) -Cardiac involvement often starts with tiredness and shortness of breath. This affects walking distance and later ability to self care. Often palpitations and arrythmias require a pacemaker. -Deposition of amyloid in the kidneys can develop into renal failure. This complicates the whole management of the disease. -The numbness due to neuropathy starts in the feet. This causes problems with shoes with ulcers like in the diabetic foot situation. Also, a sensory ataxia due to loss of proprioception. For example, it is difficult to stand up since the balance is affected. This results in movements that makes the patient look like he or she is drunk. -Weakness and muscle atrophy causes difficulty, first walking, then using the hands. The weakness progresses proximally and in advanced stages, even breathing is difficult. The first thing to be lost is usually employment, then hobbies, then social life, then the ability to self care. -The fact that this is a familial disease means that the patients often have seen relatives with the disease degenerate and die, so they are well aware of what is waiting for them. Psychologically this is devastating.

	-There is often a profound concern about children, since it is possible, even likely, that they will develop the disease at some point. There are also situations where more than one patient is affected in the family, which makes the situation extremely difficult for the carers. -The eyes are involved in the disease with glaucoma, vitreous opacification and loss of sight as a result. Being blind and having numb hands is a devastating combination, completely disabling. -Advanced cases develop central nervous degeneration, with headaches and progressive dementia. -Advanced stages of the disease, with a patient in pain, unable to walk or stand, unable to use his or her hands, unable to selfcare, with diarrhoea, with pressure ulcers and blind, results in a situation worse than death.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	The only treatment licenced and recommended in the UK has been liver transplant. Many patients are not suitable for this. The results (I have known more than 20 patients who underwent liver transplant) are not very good. It seems to slow the disease for a while, but then it comes back perhaps after 7 or 8 years. Having a liver transplant does not seem to protect the eyes or the brain. The incidence of cancer in these patients -anecdotally- seems to be high, and the complication rate is very significant. My mother and my godmother (aunty) had a liver transplants and they survived for about 8 or 9 years with a poor quality of life. One of my cousins have had a liver transplant and now has breast cancer, which presents a very difficult problem. Another cousin developed liver cirrhosis following transplant.
11. Is there an unmet need for patients with this condition?	There is no available good treatment at present for the patients in the UK.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment?	The advantages of this new treatment are that it seems to stop progression of the disease, with a low

Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	complication rate. I have spoken to several patients that have been on the trial for this drug (in USA, Portugal and Holland) and they seem very positive about the effectiveness of the treatment. It has changed their life completely. It has also given them hope for the future, and importantly they know that in the future, there will be a treatment for their children if that is required.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	They found taking the drug very easy and convenient. They have regular blood tests, but this does not seem to bother them too much.

Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	Having regular blood tests is a slight inconvenient. Patients know this is necessary because there have been some complications reported in the trial. The patients I have spoken to, don't report any significant side effects.
Patient population	
15. Are there any groups of patients who might benefit more or less from the	Perhaps some genotypes will respond better to treatment than others.

treatment than others? If so, please describe them and explain why.	
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**Not that I can see**
Other issues	
17. Are there any other issues that you would like the committee to consider?	Patients with advanced disease were not included in the trial. However they could benefit significantly from this treatment.
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • This is a devastating and lethal disease • There is no treatment at present • This new drug has proven to be effective	

- The safety profile seems good from the point of view of the patient
-
-

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About you	
1.Your name	**Eric Low**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Amyloidosis Research Consortium UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	n/a

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	n/a

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	There are no other licensed disease-modifying treatments available on the NHS, although patients may be offered off-label treatments, including diflunisal and doxycycline. A very small number of patients have liver transplants. Beyond this, treatment is primarily aimed at managing the symptoms of the disease.
11. Is there an unmet need for patients with this condition?	The unmet need is substantial. The hTTR amyloidosis is debilitating and progressive. Marginal improvements in slowing or stopping progression could have transformational improvements in the quality of life for patients and their families. Patients usually experience multiple symptoms, including sensory, motor and autonomic deficits and, for some patients, cardiac involvement. These translate into numerous effects on daily living, including mobility issues, insomnia, pain, intermittent diarrhoea, sexual dysfunction, vision and motility problems, imbalance and instability and an effect on patients' abilities to undertake daily activities.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to	Inotersen appears to work in the majority of patients and the side-effects and potential inconvenience of treatment administrations are outweighed by the benefits. Inotersen has the ability to improve the symptoms associated with hTTR amyloidosis, providing much needed hope for the future, improved physical and emotional performance, meaning patients can be more socially and economically active.

work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	n/a
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is	There are few disadvantages. It is important to have choice regarding where patients can receive treatment. For some, travelling to hospital regularly may be inconvenient and costly and therefore a home care option is a must. Conversely, some patients prefer not to receive treatment at home and therefore should be able to continue to receive treatment at a specialist centre. Doctors and nurses should conduct a patient/family holist needs assessment before treatment starts, and at appropriate time points during

taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	treatment so see if anything has changed in the situation of the patient or the family requiring a potential change in treatment arrangements. The need for regular platelet monitoring could be perceived as a disadvantage. We understand, however, that the proposed inotersen service design aims to minimise the possible burden this could have on patients by ensuring that blood tests for monitoring platelet levels are done at the patient's home. To the extent that it is possible, we urge NICE to ensure that the company has a comprehensive service delivery model in place that is not just practical from a feasibility perspective but is built around the specific needs of patients. Further, we would expect the company to carry out patient/ carer experience/satisfaction surveys throughout the duration of treatment and for this data to be provided (where permissible) to the patient's clinical team to inform ongoing needs assessment.
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Patients should be treated within the licensed indication and following an appropriate discussion and holistic needs assessment with their doctor and nurse about the potential benefits and risks of the treatment including how and where it is administered. These are the patients most likely to benefit.

Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	No
Other issues	
17. Are there any other issues that you would like the committee to consider?	No

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

- This condition is debilitating and progressive and has a significant impact emotionally, socially, economically and physically on patients and their families
- There are currently no licensed or any other effective treatments and therefore the unmet need is significant.
- Inotersen offers a significant step change in the management of this disease: the fact that it offers a convenient method of administration is especially positive
- This is a situation where there are clearly additional benefits (e.g. on carers, productivity, convenience, independence etc) that may not be captured in either the clinical evidence or modelling; and these need to be factored in

Thank you for your time.

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Inotersen for treating hereditary transthyretin-related amyloidosis

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to declare.

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[redacted]

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.

This report should be referenced as follows:

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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] 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], 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		
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)		

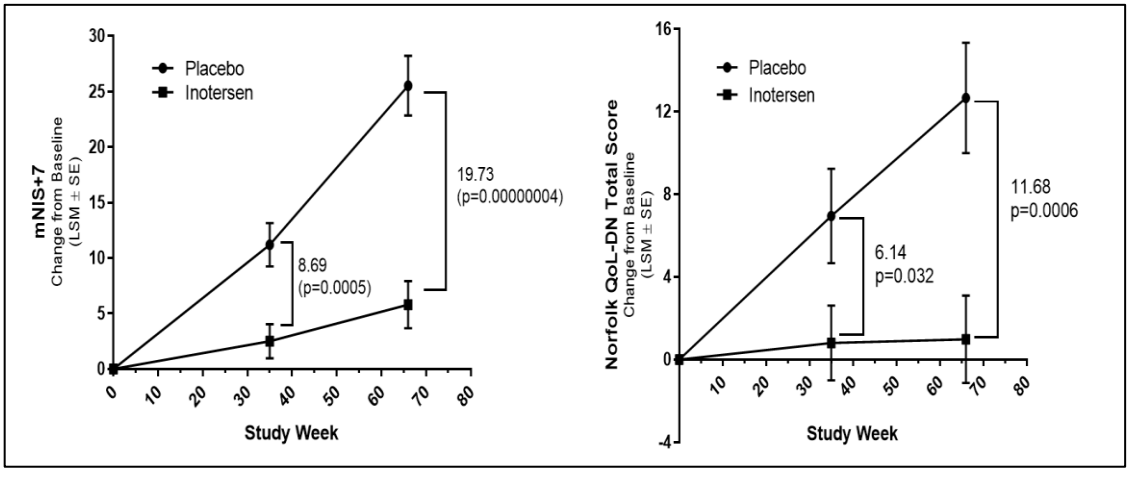
Abbreviations: BMI, body mass index; CM, cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; kg/m^2, kilograms per square metre; mNIS+7, modified neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; NT-proBNP, N terminal prohormone 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]

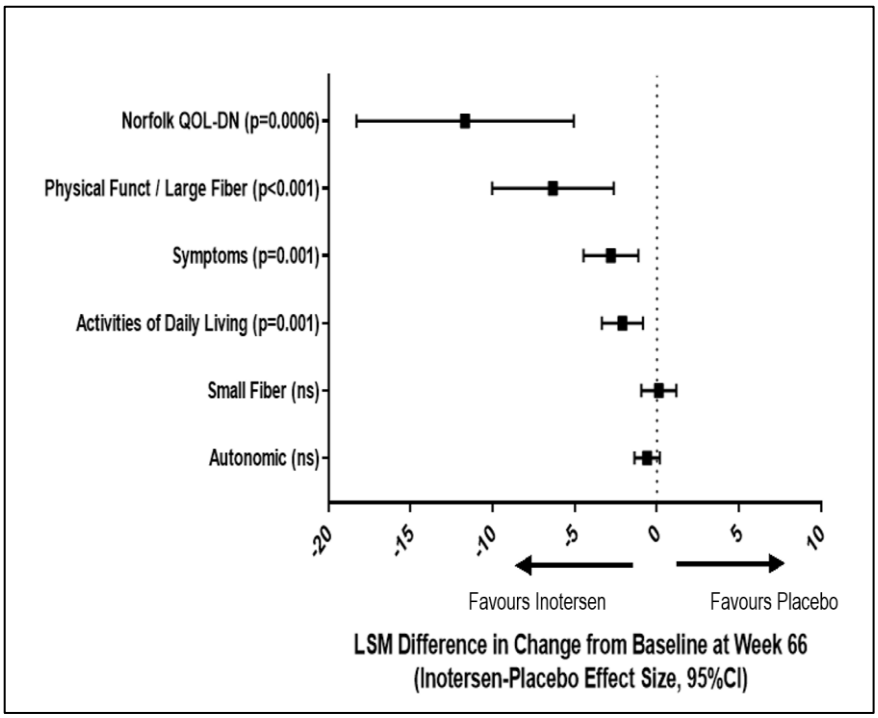
† Analysis based on data collected up to 52 days after last dose of study drug; *Reported on page 72 of company's submission; **Reported in Table C16 of company's submission
Abbreviations: BMI, body mass index; CM, cardiomyopathy; CS, company submission; ECHO, echocardiogram; FAS, full analysis set; 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.

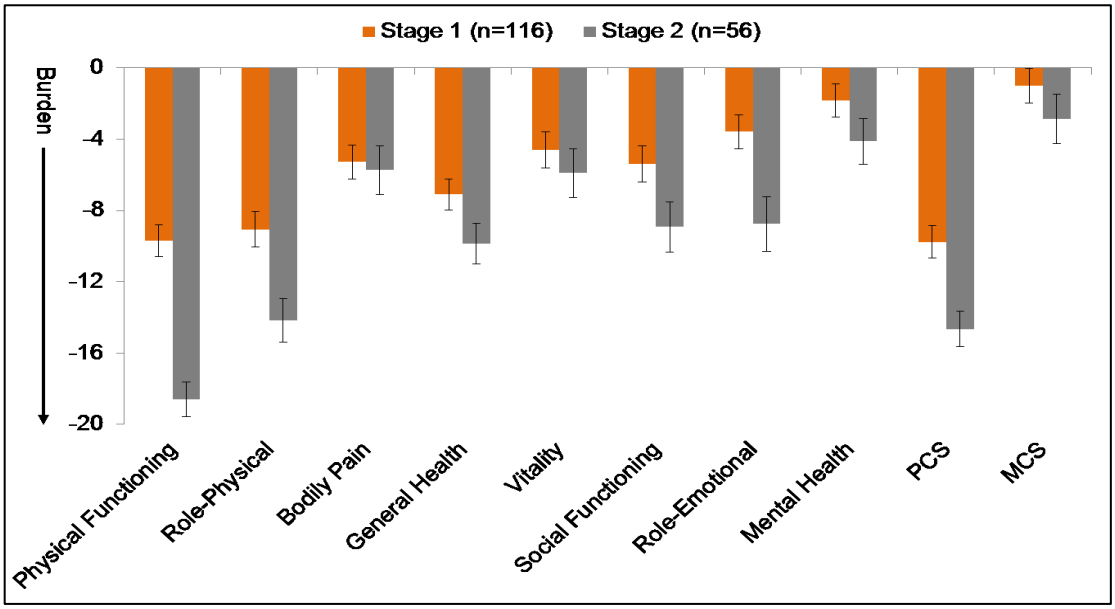
Patient experience

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]. [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

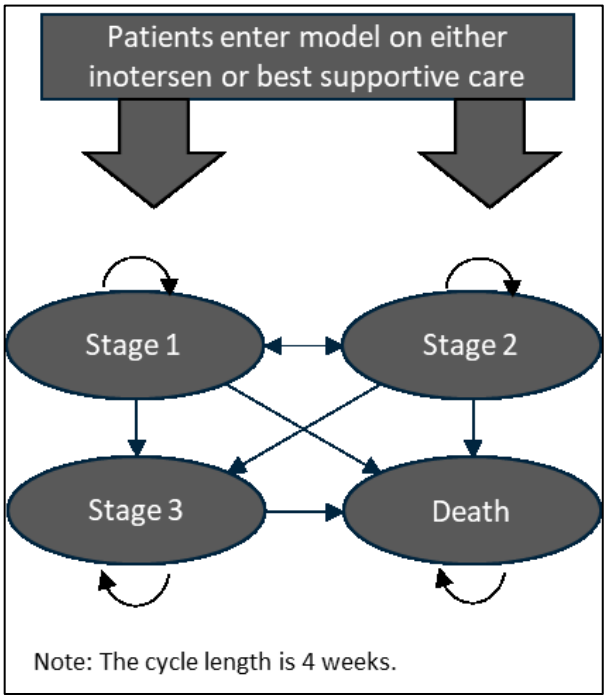
changes in HRQL		accurately reflect those of the UK general population.[32] The Brazilian value set generates substantially different utility scores to the UK value set, particularly for poorer health states (such as those experienced by people with hATTR).
Discount rate	An annual rate of 3.5% on both 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)

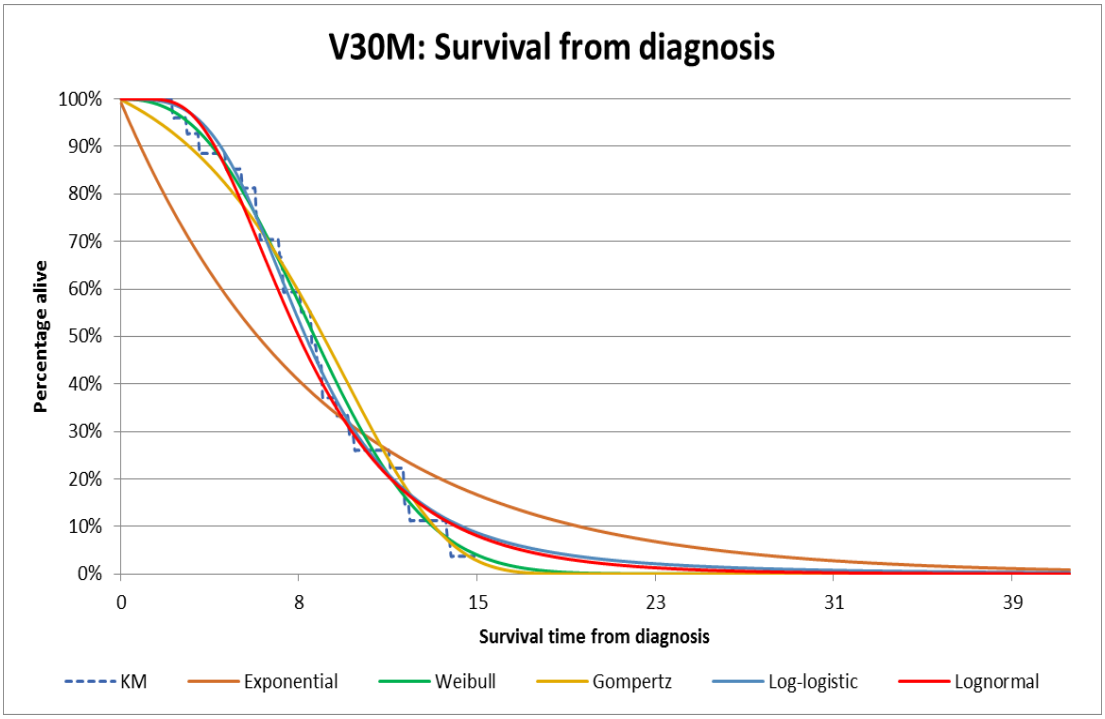
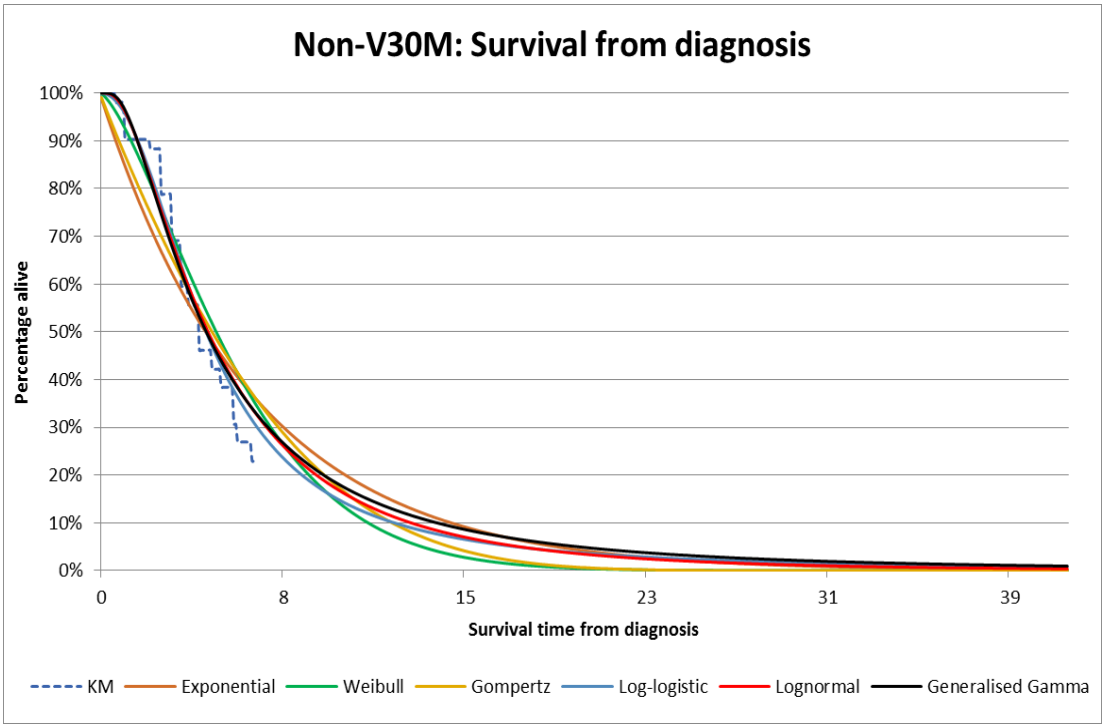


Figure 7 Kaplan Meier and parametric distributions for the non-V30M population (Re-produced from Figure 13 of the CS)



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.

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

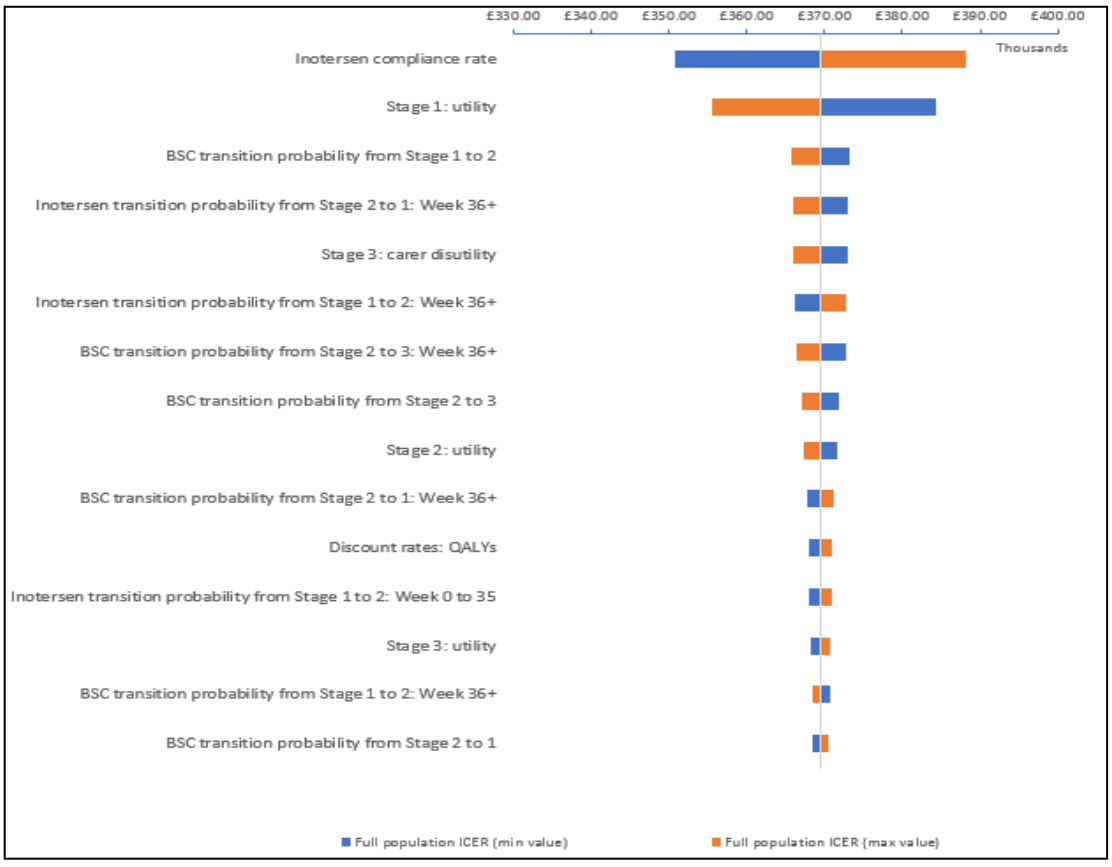
healthcare resource utilisation costs in the BSC arm. The greatest proportion of BSC costs are incurred in Stage 3, reflecting the higher progression rate and higher health state costs incurred with progressively more debilitating disease.

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=[redacted] patients (Year 1) to N=[redacted] (Year 5). The BIA estimates that the net impact of introducing inotersen on the NHS will be [redacted] in year 1 increasing to [redacted] 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen market share (estimate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population receiving inotersen (estimate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget (inotersen not introduced)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget (inotersen introduced)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 29 October 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Executive summary

Executive summary
Akcea appreciates the opportunity to review and outline any factual inaccuracies in the ERG Report on inotersen for treating hereditary transthyretin amyloidosis [ID1242]. We appreciate the Aberdeen HTA Group's review of the revised model submitted after the ERG's initial review, as we believe this helps demonstrate the more robust and consistent modelling approach implemented. There are some factual inaccuracies in their review, and we have outlined these below using the standard pro-forma response template. We look forward to working with you to advance this appraisal and support the appropriate access of this innovative medicine to appropriate patients.

Issue 2 Utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response / comment
The ERG criticises the use of disease progression cut-offs taken from a previous NICE submission. Page 68, Line 13: "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"	We would propose clarifying that the justification is a precedent from NICE: "the cut-offs used to define disease progression **have previously been accepted by NICE from the** tafamidis assessment**"**	In the original company submission, the justification for the use of the cut-offs to define disease progression were outlined in Table D1. As explained in the submission, this was to align with the approach previously accepted by NICE in the tafamidis appraisal. The text should be updated to reflect on the justification provided by the manufacturer.	This statement is not a factual inaccuracy. The cut-offs used are indeed arbitrary, and this was also noted in the critique of Tafamidis as provided by Faria et al. The ERG report makes it clear that they are sourced from, and consistent with the Tafamidis assessment.
The ERG criticises the source of EQ-5D data, and recommends a different source in various places. For example; Page 82, Line 7: "First, the company could have attempted to obtain raw EQ-5D response data sourced directly from the THAOS study." Page 126, Line 18: "With regards to utility data, the ERG consider it inappropriate	While we agree that the THAOS study is a valuable data source for quality of life data, the text should be updated to reflect that the THAOS data owners have not been willing to share the relevant data from this registry. For example: "The company has **attempted** to obtain raw EQ-5D response data sourced directly from the THAOS study **but they have not been provided access by the registry owners**." "With regards to utility data, the ERG consider it **unfortunate** that the company use Brazilian	The THAOS registry an independent registry run by another pharmaceutical company. Akcea has requested access to this database repeatedly but has so far been unsuccessful. Akcea agrees that the THAOS data valued with the UK EQ-5D value set would be the preferred data source, and are continuing their attempts to access the registry. The likely impact of switching QoL valuation is difficult to predict in the absence of the THAOS registry data, although there are some	*Page 82, line 7:* This is not a factual inaccuracy as the company did not make us aware that they were unable to gain access to the data. However, in light of the new information provided here, the ERG acknowledge that the company state they have attempted to do this but were unable. *Page 126, line 18:* This is not a factual inaccuracy, the ERG consider it inappropriate to use Brazilian valuations. The information provided here was

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." Page 132, Line 20: "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."	valuations, **though accept it was not** 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." "**Access to the** THAOS registry data, **would be** a valuable resource that could be used to generate better utility data for use in the model, **but it is accepted this is an infeasible source for use in the submission**."	publications attempting to quantify the difference that could be expected. For example, Takemoto et al. (2015) find that EQ-5D scores are generally much lower for the UK population when the utility is below 0.5 compared to the Brazilian population. In this case it is likely that the ICER would be improved by using the ERG's preferred data source, since time spent in Stage 3 would be even less desirable and inotersen prevents and delays entry into Stage 3. Takemoto, M. L. S., da Silva, N. L., Ribeiro-Pereira, A. C. P., Schilithz, A. O. C., & Suzuki, C. (2015). Differences in utility scores obtained through Brazilian and UK value sets: a cross-sectional study. Health and quality of life outcomes, 13(1), 119.	not available to the ERG at the time of writing the report. *Page 132, Line 20:* This is not a factual inaccuracy (see response above).

Issue 3 Compliance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response / comment
The ERG have provided a critique of the implementation of compliance rates amongst the modelled patient population. Page 93, Line 9: "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."	The ERG appears to have slightly misunderstood the implementation of this parameter, and so we propose amending the text to remove the confusion. For example: "The ERG 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."	The ERG appears to have misunderstood how compliance was calculated. This is explained in Table D1 (Page 103) of the original submission and again in response to ERG clarification question B5 (Page 21) Compliance was calculated by taking the number of doses actually taken as the numerator and the number of doses expected up to the point of discontinuation as the denominator. Therefore, a patient who discontinued in week 8 but who had 8 doses up to that point would be treated as being 100% compliant (from week 8 onwards they would be treated as a 'discontinuer' – discontinuers also do not take the drug, but this is not a compliance issue and is handled by different parameters in the model). Patients who discontinue are likely to have a different compliance profile to those who do not. Therefore, to exclude them will bias the overall compliance rate, and the miscounting	The ERG have not mis-understood how compliance is calculated, and do not contest the description provided opposite. However, we are unclear as to why the compliance parameter value changed from [redacted] to [redacted] in response to the clarification letter. The company explained, in their response to clarification that: *"Previously the model incorrectly counted the compliance of discontinuers, who will likely have a different compliance profile to those who are stable on drug".* This gave the ERG the impression that the compliance rate was changed to exclude the compliance of discontinuers, which the ERG deem inappropriate. The ERG remain unclear as to what the initial error was, and how the calculation has been revised to address it. However, the ERG acknowledge that we may have mis-understood the company's approach, and suggest a minor re-wording of the text to reflect the lack of clarity regarding the initial change of the parameter value from ~[redacted] to [redacted]% in response to the clarification letter.

		of the compliance profile of discontinuers had a moderate impact on the overall compliance rate of the trial – from around [redacted] to around [redacted]. We agree with the ERG that it is inappropriate to exclude the compliance of discontinuers, but it is factually inaccurate to say that we have done so.	The text on page 93 is amended as follows: *The ERG are unclear 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. The ERG's understanding, based on the response to the clarification letter, was that the company's revised calculation may have excluded the compliance of discontinuers and the ERG considers this inappropriate as it would under cost doses observed up to the end of the NEURO-TTR trial.*
Page 93, Line 20: "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."	The ERG is correct that there is no explicit modelling of wastage in the economic model, but the treatment pathway would make such a calculation inappropriate. Consequently, we propose rewording the ERG's comment to capture that there is no explicit modelling of wastage but that this should not affect accuracy:	Owing to the method of distribution in the manufacturer's model (4 syringes delivered per 28 days each containing a once-weekly dose of inotersen), drug wastage due to missed doses is already accounted for. Any missed dose would be taken in the next week, and the next packet of four syringes delivered a week later than planned. The ERG's proposed calculation could possibly be included to account for doses permanently missed, which would result in a slight improvement in the ICER. If a patient who dies or discontinues midway through a four-week cycle (for example, after taking the second syringe in a packet but	The ERG do not believe that this is a factual inaccuracy, though acknowledge that the 4-weekly distribution cycle is unlikely to allow significant wastage. However, even if one vial was wasted, this would have a substantial cost implication. The ERG note this issue is unlikely to have any meaningful impact on the ICER.

	"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, **however this has** been captured in the economic model."	before the third syringe), the NHS would incur charges for all four doses but only have used a portion. As the full cost of all four syringes are charged at the beginning of each cycle, there is no mechanical way to account for this in the model. Were such a calculation to be included, this would marginally improve the ICER, since the final four-week pack taken in the final cycle for a particular patient should not be charged at full price, lowering overall cost. This, however, would be not be appropriate and aligned with what happens in clinical practice, since once the four-week pack is delivered then supply chain integrity is lost, and consequently the NHS has effectively 'consumed' all four syringes, even if the patient does not use them.	

Issue 4 PSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response / comment
Page 108, Line 2 "The company submission provides little information regarding how the PSA was conducted, why certain	Akcea proposes rewording this sentence to ensure that critique of the parameters chosen is not confused with a critique of the transparency of the submission. For example:	Akcea has used standard methods to conduct the PSA and for the selection of distributions, while the distribution parameters are clearly explained in the text. The parameters are most explicitly described in Table D10 (Page 115) of the original submission,	This is not a factual inaccuracy. The company have provided inadequate information about how the PSA was conducted. This may be a difference of

distributions were chosen, or how distribution parameters were obtained for sampling."	"The company submission provides ~~little~~ information regarding how the PSA was conducted, why certain distributions were chosen, **and** how distribution parameters were obtained for sampling."	and all nonstandard features of the methods are described in Section 12.4 (Page 126). The characterisation of the PSA approach as giving 'little information' is misleading – the approach to investigating uncertainty is clearly described.	opinion between the company and the ERG, but is not factually inaccurate.
The ERG describe a change they make to the PSA implementation. Page 108, Line 8: "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"	We believe the ERG may have correctly identified an error, but do not agree with their proposed solution. Consequently, we propose a change to the text explaining this. For example: **"The ERG identified an error in the assignation of the utility value of carers, which was subsequently corrected by the manufacturer"**	We agree this is a minor error, but upon consideration we do not agree with the ERG's proposed change. Since the absolute values of the disutilities are on the scale 0-1, the appropriate way is to sample the absolute value of the disutility in the PSA and then to subtract this value from total utilities. This has been updated in the model, and the PSA rerun. This appropriateness of this approach is demonstrated by the outputs of the three proposed models (see table below). All three approaches produce incremental costs similar to the deterministic base case, but the proposed ERG amendment gives incremental QALYs significantly further away from the deterministic base case than either manufacturer proposed PSA specifications. The PSA should converge to the deterministic ICER unless there is significant nonlinearity in the model, which is not the case in this submission.	The ERG disagree that this is factually inaccurate. The error identified, and acknowledged here by the company (impacted on stage 3 disutility only). To maintain consistency, the ERG implemented a correction consistent with the disutility applied to carers in stage 1 and 2 disease. However, there may have been an additional inconsistency in other model formulae that means the proposed solution from the ERG over-rides other formulae. As the company have not provided the model used to calculate the additional ICERs provided in this factual accuracy check, it has not been

<table>
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<td>
<table>
<tr><th></th><th>Base case (deterministic)</th><th>Base case (PSA)</th><th>ERG proposed PSA</th><th>Corrected PSA</th></tr>
<tr><td>Inc. cost</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc. QALY</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ICER</td><td>£369,470</td><td>£368,592</td><td>£392,667</td><td>£370,656</td></tr>
</table>

This has a very minimal impact on the submission, except that it alters the CEAC (see below), which partially addresses ERG concerns about uncertainty.
</td>
<td>possible for the ERG to re-check the calculation.

The ERG do however accept that it is appropriate for the probabilistic PSA results to converge to the deterministic value.

The ERG disagrees that the solution implemented by the company adequately addresses the concerns about uncertainty raised elsewhere in the ERG report.</td>
</tr>
<tr>
<td>Page 109, Line 19

“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 ([redacted]), £300k ([redacted]), £400k ([redacted]), £500k ([redacted]).”</td>
<td>In light of the above, we propose the CEAC should be updated:

“For the company’s submitted PSA, with correction of the carer disutility parameters, the probability that inotersen is cost effectiveness at increasing thresholds of WTP per QALY gained is as follows: £200k ([redacted]), £300k ([redacted]), £400k ([redacted]), £500k ([redacted]).”</td>
<td>As above.</td>
<td>This is not a factual inaccuracy, and it is not appropriate for the ERG to report probabilities of cost-effectiveness it has not been able to verify against the company’s source model.</td>
</tr>
</table>

Issue 5 Treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment / response
Page 70, Line 10 "It is unclear whether this assumption [that treatment would be discontinued in Stage 3] is externally valid and transferable to real-world practice"	This is factually inaccurate and inconsistent with the SPC, therefore we propose a change of wording to the following: "This assumption [that treatment would be discontinued in Stage 3] is consistent with the SPC for inotersen"	The ERG's position is not consistent with the licence for inotersen, which is for use at Stage 1 and 2 only; as such, it is not aligned with the SPC to continue treatment to patients with Stage 3 disease. For details, please see section 4.1 of the SPC. The ERG may not have been aware of this aspect of the license, as they describe the non-prescription of inotersen in Stage 3 as an 'assumption'. However, they conclude that this 'assumption' is appropriate, and so the slight ERG inaccuracy on this point does not have any impact on the base-case ICER. However, it may contribute to their conclusions on the uncertainty of the result, since they were not aware there was no uncertainty on this point.	The ERG acknowledge that our statement may be misleading and have amended as suggested by the company to: *"This assumption [that treatment would be discontinued in Stage 3] is consistent with the SPC for inotersen"* The ERG would like to confirm however that the amendment to this particular statement does not influence our conclusions on

			uncertainty in the model.
The ERG highlights a number of discrepancies between the company submission and the Benson publication with regards to the number of participants (and %) with previous treatment with tafamidis or diflunisal; disease stage 1 and 2; V30M TTR mutation. Page 3, Line 19: "The ERG questioned some discrepancies between the baseline characteristics reported in the company's submission and those reported in the Benson publication".	We believe these discrepancies have already been explained, and it would be helpful to include this explanation in order to demonstrate it is not just a simple submission error. For example: "Discrepancies between the company submission and publication with regards to the number of participants (and %) with previous treatment with tafamidis or diflunisal; disease stage 1 and 2; V30M TTR mutation **is explained with reference to the randomisation strategy employed by the company."**	Benson et al (2018) presented data for randomisation stratum by CRF only, in the publication. This is separated into randomisation stratum by IXRS and CRF within the CSR and is the source of the data in the company submission. [redacted] Benson, M. D., Waddington-Cruz, M., Berk, J. L., Polydefkis, M., Dyck, P. J., Wang, A. K., ... & Scheinberg, M. (2018). Inotersen treatment for patients with hereditary transthyretin amyloidosis. New England Journal of Medicine, 379(1), 22-31.	The ERG do not believe this is a factual inaccuracy. In the response to clarification queries, the company explain the apparent discrepancy with reference to the different randomisation strategies employed between the two documents. How ever the ERG did not understand this explanation

Page 75, Line 14: "It is unclear from the CS why these time period cut-offs were chosen, or what impact this decision has on the ICER."	We propose highlighting that there is a very good justification for the time periods chosen. For example: "It is unclear from the CS ~~**why these time period cut-offs were chosen, or**~~ what impact this decision has on the ICER."	The time periods are chosen as they relate to the time periods in the study when data were captured; they are therefore the only reasonable time periods which could be used in the model. These time periods are clearly described in the clinical section of the submission, most explicitly in Table C3 on Page 41. As such, the approach presented by the manufacturer are the most appropriate values.	The ERG acknowledge that this statement is factually inaccurate and have amended as suggested by the company to: *"It is unclear from the CS what impact this decision has on the ICER"*

Issue 6 PSS costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response / comment
Table 17 (Page 63): "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"	We broadly agree with the ERG on this point, only diverging on whether including PSS costs is possible (see justification). We would therefore recommend a more accurate wording that highlights the state of PSS costs in the model. For example: "**Not all** relevant PSS costs **have been** included. For example, costs of residential care have not been explicitly considered in the cost-effectiveness model."	Akcea agrees that there are additional PSS cost which have not been included in the model. No source was identified containing details of these costs for the target population, but the manufacturer considered a number of possible proxies for PSS costs in related populations to test the impact on the ICER. As a result of this uncertainty, the submission took the conservative approach of including only those PSS costs which could be explicitly justified. The likely impact of including PSS costs will be to lower the ICER. This is because preventing progression of hATTR-PN will maintain productivity in patients and their carers, as well as reduce the burden on residential care. For example, a proxy for PSS costs associated with each Stage of hATTR could be PSS costs for differing severities of multiple sclerosis (with EDSS 0–3 mapped to Stage 1, EDSS 4–6.5 mapped to Stage 2 and EDSS 7–9 mapped to Stage 3). With this assumption,	The ERG statement referenced is not factually inaccurate. The ERG are in agreement with the company regarding this point, and agree that the likely impact of including PSS costs would be to reduce the ICER.

		sources such as Brundin et al. (2017) could be used as proxies for PSS costs, which would have the effect of lowering the base-case ICER to £333,769 (down from £369,470) Based on the significant decrease in the ICER that including PSS costs can generate, we believe it is more factually accurate to make it clear that relevant PSS costs are an uncertainty likely to favour inotersen. Brundin, L., Kobelt, G., Berg, J., Capsa, D., Eriksson, J., & European Multiple Sclerosis Platform. (2017). New insights into the burden and costs of multiple sclerosis in Europe: Results for Sweden. Multiple Sclerosis Journal, 23(2_suppl), 179-191.	

Issue 7 Carers

Description of problem	Description of proposed amendment	Justification for amendment	ERG response / comment
Page 84, Line 13: "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".	We believe this is a misunderstanding of the source of the claim, and so propose the following re-wording: "The CS identified an independent systematic review of carer's disutility in similar disease areas."	This appears to be an error of interpretation - the SLR was not performed as a part of this appraisal, but instead performed by Wittenberg et al. (2013) and identified as a reference. This study is referenced in the usual way, and therefore details of the search can be identified as for any other reference. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. PharmacoEconomics. 2013;31(6):489-500.	The ERG acknowledge that this statement is factually inaccurate and have amended as suggested by the company to: *"The CS identified an independent systematic review of carer's disutility in similar disease areas."*
The ERG state that the inclusion of two carers is an area of uncertainty. This appears to be based on a belief that the claim is supported using paediatric rather than adult evidence. For example; Page 5, Line 31:	As above, we believe this is a misunderstanding of the source of the claim, and so propose the statements are revised as follows: "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	We believe some confusion has arisen over the source that was used in the revised model submitted. The ERG correctly describes that the original submission references a prior NICE submission for Duchenne muscular dystrophy as its justification for assuming two carers. This was criticised as being more relevant to a paediatric population, as described.	These statements are not factually incorrect, are based on the company's original submission and as noted by the company here, the ERG report makes reference to the company's response to clarification queries on page 84 of the ERG report.

"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." Page 84, Line 28: "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. However, that evaluation considered a paediatric 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:.."	argue that all patients would have two carers, and this assumption is based on **an assessment of the number of hours of care that is required by ATTR patients, which is directly relevant to the patient population**." "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. 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 **identified an alternative source describing the care burden for adult ATTR patients** clarified that:…"	However, the ERG have not highlighted that the clarification provided was sourced from a different source, the Stewart et al. (2018) publication, which is a study of adult ATTR-PN and ATTR-CM patients and therefore directly relevant to the submission. However, Stewart et al. (2018) does not directly give the average number of carers; the clarification which follows are the assumptions made by the manufacturer to generate a 'number of carers' figure from a 'median hours caring' figure. (NICE). NIfHaCE. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene, HST3. Stewart, M., Shaffer, S., Murphy, B., Loftus, J., Alvir, J., Cicchetti, M., & Lenderking, W. R. (2018). Characterizing the High Disease Burden of Transthyretin Amyloidosis for Patients and Caregivers. Neurology and therapy, 1-16.	

Issue 8 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment / response
Page 61, Line 26 "Inclusion and exclusion criteria for the global systematic review are discussed in **Section 4.1.1**."	"Inclusion and exclusion criteria for the global systematic review are discussed in **Section 4.1.2**."	Typographical error.	The ERG agree with the proposed amendment
Table 26 (Page 87) 0.639 – **(average 0.575+0.55) = -0.076**	0.639 – **average(0.575,0.55) = -0.077**	Typographical error.	The ERG agree with the proposed amendment
Page 88, Line 26 [redacted] over the lifetime of the modelled cohort in the company base case."	[redacted] over the lifetime of the modelled cohort in the company base case."	Typographical error.	This reflects a typo in the company's response to clarification letter that has been addressed elsewhere in the ERG report. The correction is now made here also.
Page 101, Line 5 cycle **84 (6.92** years)	cycle **85 (7.00** years)	Typographical error.	The ERG agree with the proposed amendment
Page 104, Line 6 "Overall, inotersen generated an incremental cost of [redacted]	Overall, inotersen generated an incremental cost of [redacted]	Typographical error.	The ERG agree with the proposed amendment
Page 104, Line 19 with [redacted] and [redacted] of the total cost incurred in disease stages 2 and 3 respectively	with [redacted] and [redacted] of the total cost incurred in disease stages 2 and 3 respectively	Typographical error.	The ERG agree with the proposed amendment

Table 34 (Page 107) Incremental costs reported as [redacted]	Incremental costs should have been reported as [redacted]	Typographical error.	This is not a typographical error, and produces the exact number given by the economic model. It is also consistent with the mean costs by model arm reported in Table 34, scenario 6. There is however a typographical error in Table 12 of the response to clarification letter.

Aberdeen HTA Group

Inotersen for treating hereditary transthyretin-related amyloidosis

Erratum to the ERG report

Date completed 05 November, 2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number HST 17/40/02.

Contains CIC / AIC

[redacted]

This document is intended to replace pages 61, 70, 75, 84, 87, 88, 93, 101 & 104, of the original ERG assessment report for *Inotersen for treating hereditary transthyretin-related amyloidosis* which contained a few inaccuracies. In addition, we amended a number of further minor (typographical) errors identified in the report. The amended pages follow in order of page number below.

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 4.1.2.

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.

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. This assumption is consistent with the SPC for inotersen. 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

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 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

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 identified an independent systematic review of carer's disutility in similar disease areas. However, no further information is provided in the CS regarding the search strategy, inclusion / exclusion criteria, or study selection / data extraction methods used 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:

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) = -0.077	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.

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 are unclear 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. The ERG's understanding, based on the response to the clarification letter, was that the company's revised calculation may have excluded the compliance of discontinuers and the ERG considers this inappropriate as it would under cost 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 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 85 (7 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 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

Aberdeen HTA Group

Inotersen for treating hereditary transthyretin-related amyloidosis

Post appraisal committee meeting analyses requested by NICE

Date completed 15 November, 2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number HST 17/40/02.

Contains CIC

[redacted]

Table 1 below reports the results of additional analyses requested by NICE on November 15th, 2018, post the first appraisal committee meeting for Inotersen. The analysis applies an amended version of the ERG's preferred base case A (See Table 40, analysis number 23 of the ERG report). The amendment changes the compliance parameter from [redacted] to [redacted]. This amendment reflects clarification provided by the company at the appraisal committee meeting regarding the correct compliance parameter for use in the model. The analysis below describes the results of a scenario where:

- Costs and QALYs are discounted at 3.5% per annum
- Treatment discontinuation is modelled using a log logistic curve
- Compliance is set to [redacted] in the model.
- Utilities are based on Faria, et al., linear calculation
- N=1 carer is assumed
- ERG amendments to the costs and disutility of adverse events are applied.

Table 1

ERG analysis	£	Q	LYG	diff £	diff QALY	diff LYG	ICER	% change from company preferred base case
BSC	[redacted]	[redacted]	7.541					
Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£646,767	+75.05%