Slides for public – redacted

Lead team presentation

Inotersen for treating hereditary transthyretin amyloidosis

1st Evaluation Committee Meeting
Highly Specialised Technology, 14 November 2018
Clinical effectiveness

Lead team member: Glenda Sobey
Company: Akcea Therapeutics
Chair: Peter Jackson
Evidence review group: Aberdeen HTA Group
NICE team: Orsolya Balogh, Frances Nixon, Sheela Upadhyaya

[redacted]

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 in trial: V30M (52%), THR60ALA (13%) and LEU58HIS (6%)
  - 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 [redacted] wasting

* 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 Advisory Group for National Specialised Services (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, evaluation of existing and new therapies

[redacted]

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	• Subcutaneous 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*

RECAP

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; 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

[redacted]

RECAP

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]

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

NHSE comments

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

[redacted]

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

Clinical effectiveness evidence

[redacted]

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

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

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

mNIS+7

- A composite neurological impairment score with 2 composite scores (maximum of 304 points)
  - Neuropathy impairment score
  - Modified +7 score - large and small fibre sensory tests
  - mNIS+7 specifically modified 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
- ***Decrease*** in mNIS+7 score = ***improvement*** in neurological impairment
  - *Difference of 2 points is a clinically important difference*

Norfolk QoL-DN

- A patient-reported measure validated in patients with hATTR with polyneuropathy
- Designed to capture the impact of neuropathy on quality of life (scores range: -4 to 135)
  - 5 domains : physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy
- ***Decrease*** in Norfolk QoL-DN total score = ***improvement*** of quality of life
  - No minimal clinically important difference reported in the literature

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]

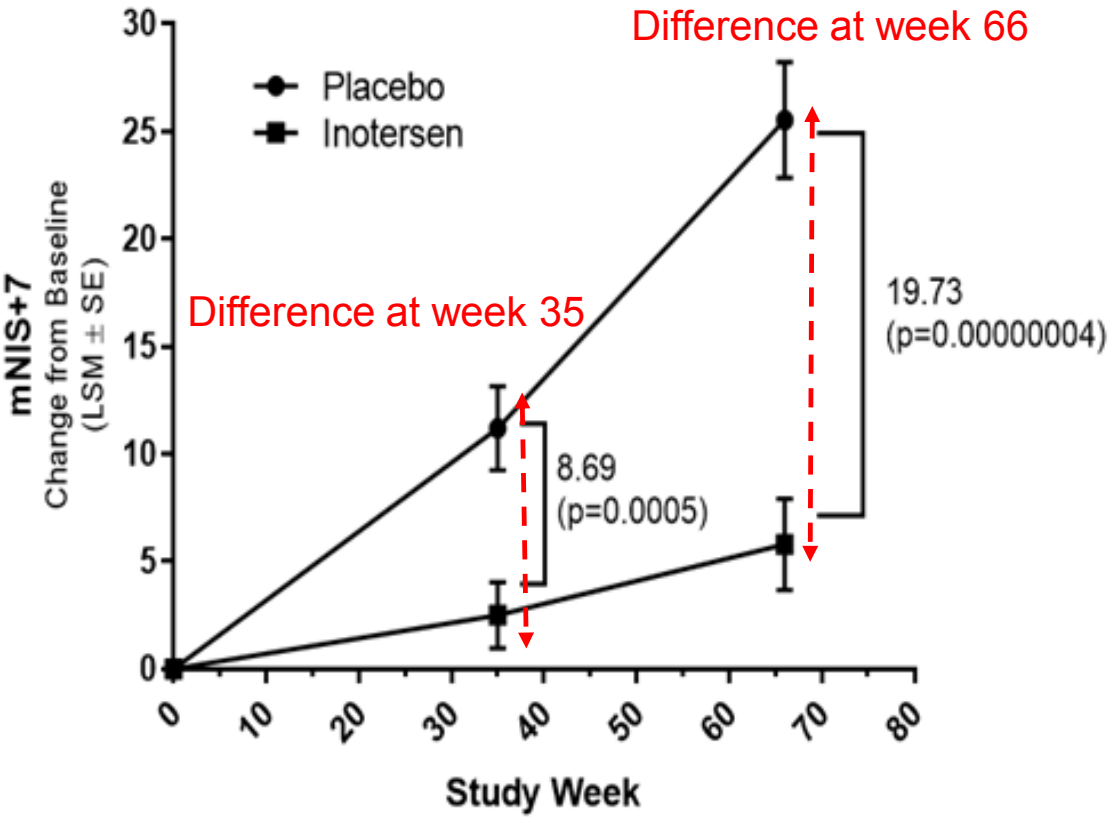
*NEURO-TTR Safety Set (SS) and Full Analysis Set (FAS) differed by seven patients; ‡NEURO-TTR [redacted] PND: polyneuropathy disability

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

Clinically important difference: 2 points



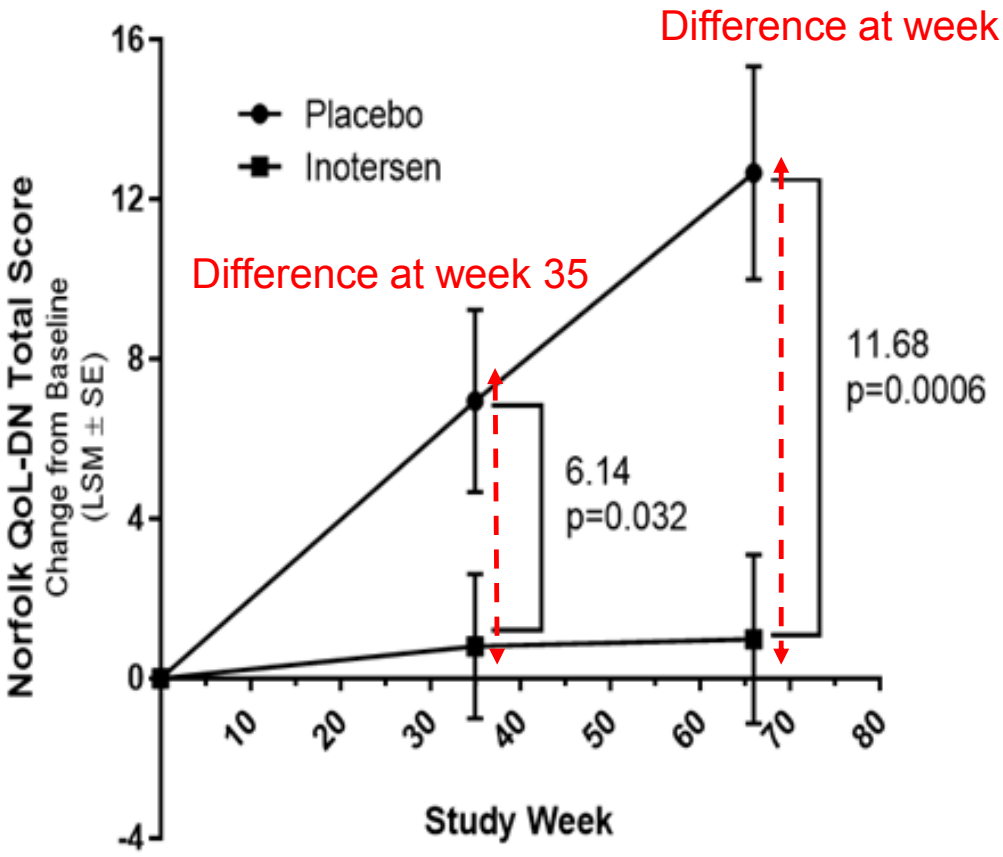
Source: Figure 6 of company submission

- ***Statistically significant improvement observed in neurological disease progression with inotersen***
- **mNIS+7:** mean composite score on placebo arm ***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 evident but was significantly less than on placebo treatment

[redacted]

Clinical results: NEURO-TTR 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 quality of life (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: post hoc analysis of subset of patients with severe cardiomyopathy (CM) at baseline

Decrease in cardiac thickness and mass suggest regression of cardiac amyloidosis

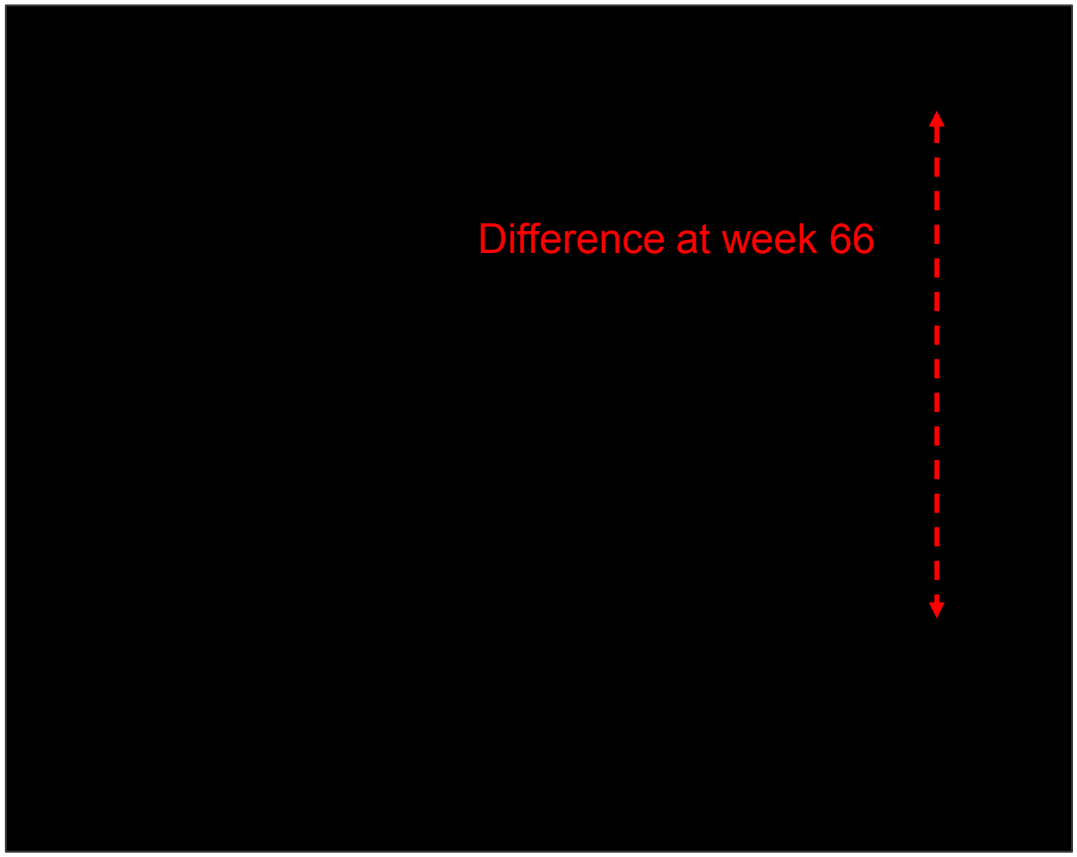
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[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

- Robust reduction in circulating transthyretin (TTR) levels observed
- Proportion of patients in inotersen arm with ≥ 60% decrease in TTR levels ***reached 80% by week 13 through to week 66***
- Placebo group mean serum TTR concentration decreased by 8.50% at week 3 and then ***remained constant*** throughout the study period
- Differences in LSMs between the arms from baseline were statistically significant ($p<0.001$) at all time points

[redacted]

Clinical results: SF-36 health survey

SF-36 physical component summary (PCS), mental component summary (MCS) and mental health domain scores reported

- ***Statistically significant difference in favour of inotersen treatment*** (LSM difference 3.59, p=0.006) was observed in the ***PCS score 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 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

[redacted]

Clinical results: Subgroup analysis

Inotersen appeared 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

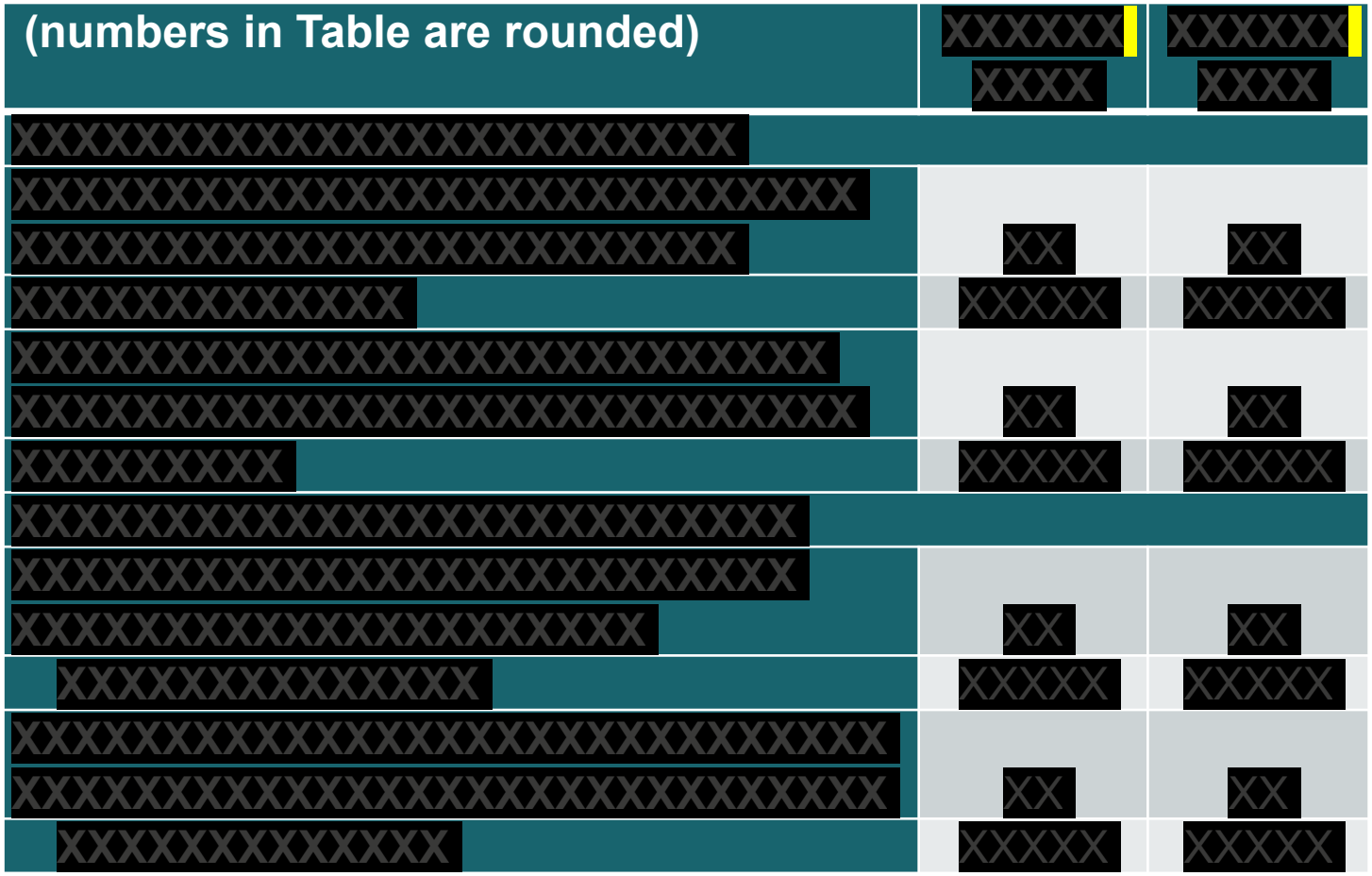
Subgroup	n, placebo, inotersen	mNIS+7		Norfolk QoL-DN	
		Difference	p-value	Difference	p-value
V30M mutation					
V30M	29, 39	-18.86	<0.001	-12.25	0.010
Non-V30M	23, 46	-21.27	<0.001	-11.12	0.025
Disease stage					
Stage 1	33, 56	-14.20	<0.001	-9.93	0.019
Stage 2	19, 29	-29.12	<0.001	-15.04	0.008
Previous 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

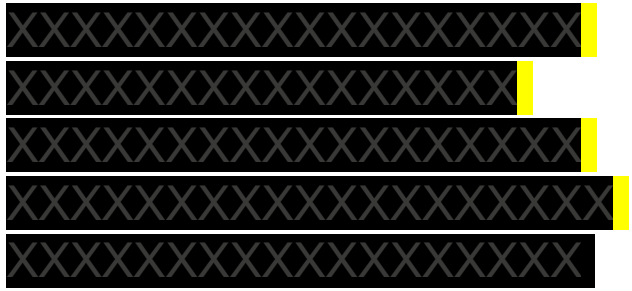
Source: Table C15 of company submission

[redacted]

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]

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

[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)

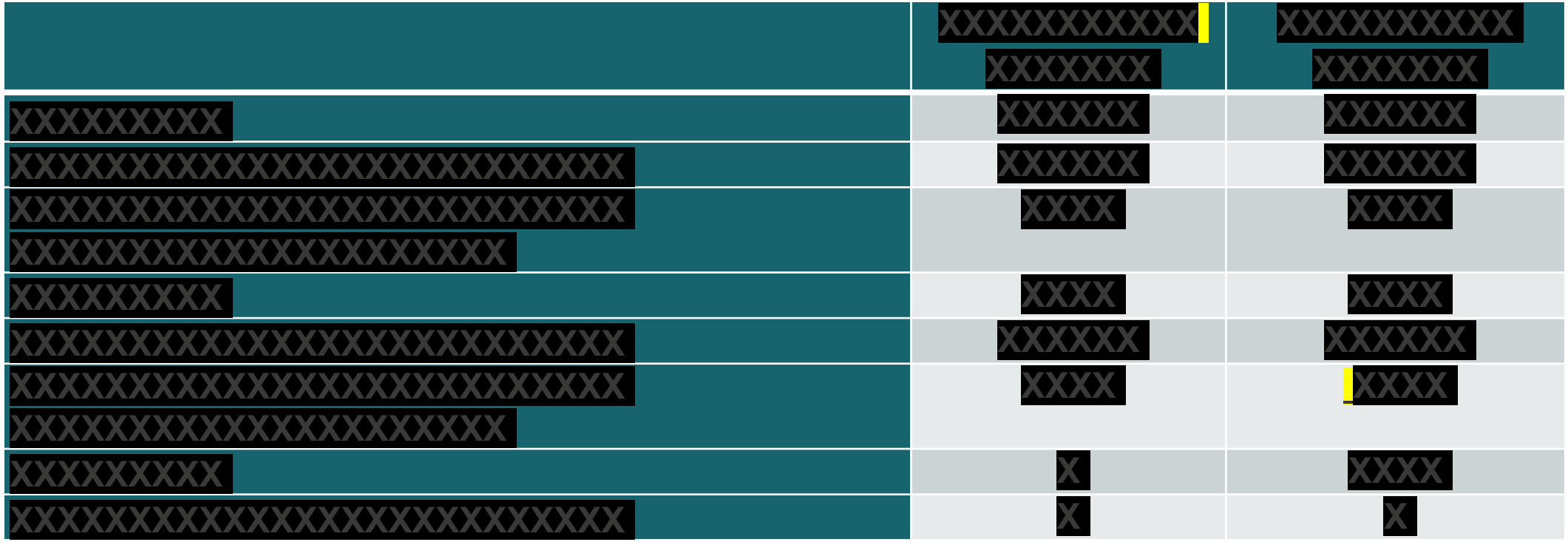
Source: Table C24 of company submission

- Most frequently reported study related treatment-emergent adverse events (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 (AEs) 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 5 deaths were consistent with progression or complication of the underlying disease

[redacted]

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
-
-
  -

How does the committee view the safety profile of inotersen?

ERG critique on clinical evidence I.

Theme	ERG comments
Literature review, data extraction	• Company's search strategies were appropriate • Unclear whether data extraction method was appropriate • Number of reviewers of the systematic review process and level of independence of researchers at each stage not reported
Quality of trials	• Company used an appropriate risk of bias tool • Process of quality assessment was not fully described • Generally well conducted trials • Evidence submitted reasonable, however coming from a single study only
Adverse events in NEURO-TTR	• Principal safety concerns identified: glomerulonephritis and thrombocytopenia • 1 death led to implementation of more frequent platelet monitoring • Safety risks associated with inotersen can be effectively monitored with routine testing in clinical practice → early detection and management of AEs
Adverse events in NEURO-TTR Extension	• No specific data on types of AE provided • In the inotersen-inotersen group [redacted], compared with the placebo-inotersen group ([redacted]
Clinical effectiveness	• Inotersen was shown to be effective in the studied population

ERG critique on clinical evidence II.

Theme	ERG comments
Discrepancy between number of participants reported in submission and Benson et al.	• Numbers reported in submission differ to those presented in the main trial ○ Previous treatment with tafamidis or diflunisal; disease stage 1 and 2; V30M TTR mutation • 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 not clear • [redacted] placebo and [redacted] inotersen patients entered the NEURO-TTR Extension study ←→ patient disposition indicates [redacted] • ERG not able to ascertain from information presented why there were differences between the numbers • Results for [redacted] • It is assumed that [redacted] in patient numbers relates to the definition of the FAS → not clearly presented

[redacted]

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]

Slides for public – redacted

Lead team presentation

Inotersen for treating hereditary transthyretin amyloidosis

1st Evaluation Committee Meeting
Highly Specialised Technology, 14 November 2018
Economic effectiveness

Lead team member: Francis Pang
Company: Akcea Therapeutics
Chair: Peter Jackson
Evidence review group: Aberdeen HTA Group
NICE team: Orsolya Balogh, Frances Nixon, Sheela Upadhyaya

[redacted]

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 inferred from the NEURO-TTR study based on defined Total Norfolk QoL-DN 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]

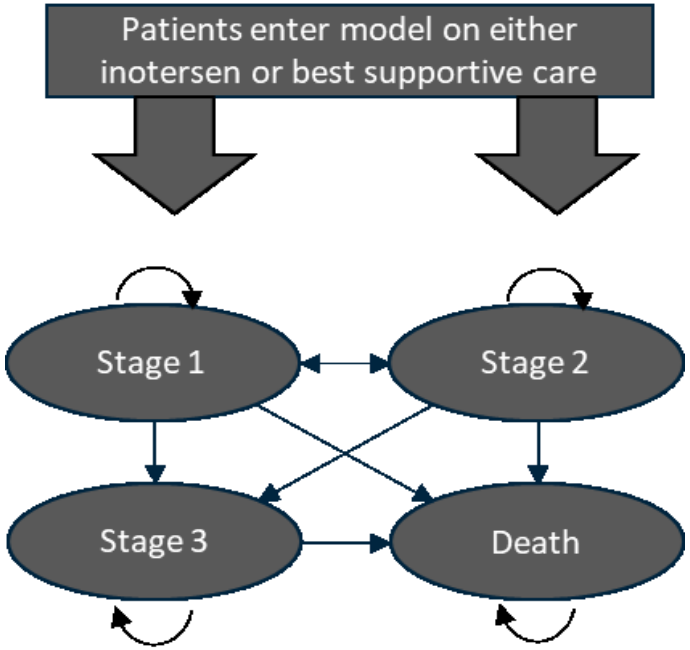
Key issues for consideration II.

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?

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 (best supportive care - BSC)
- 4 health states based on 3 Coutinho staging + death
- 1.5% discount rate; 4 weeks cycle; 41 years time horizon (lifetime); 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]

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]

Transitions in the model

- Transitions between Coutinho disease stages modelled independently for each model arm
  - No improvement from Stage 3:
    - 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]

ICER: Incremental cost-effectiveness ratio

Model structure – discontinuation rule

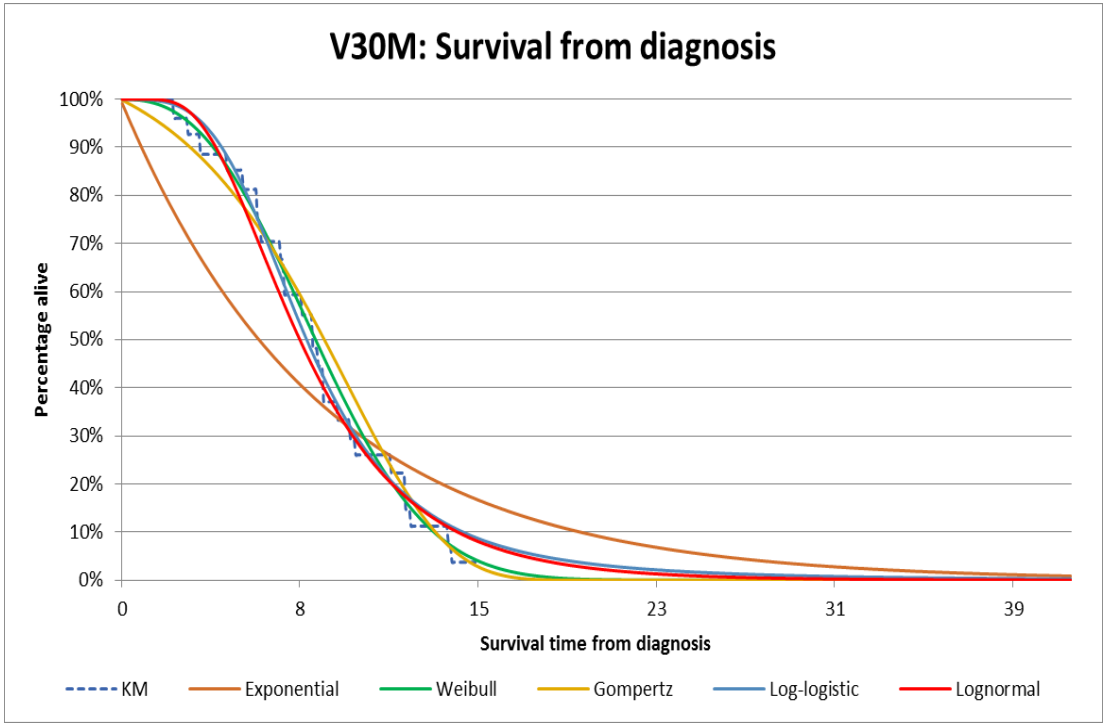
- Patients were assumed to discontinue treatment on entering Stage 3
  - Company explained this is in line with licence
- Discontinuation also based on discontinuation of treatment for other reasons which has been modelled using survival curves (see in later slide)

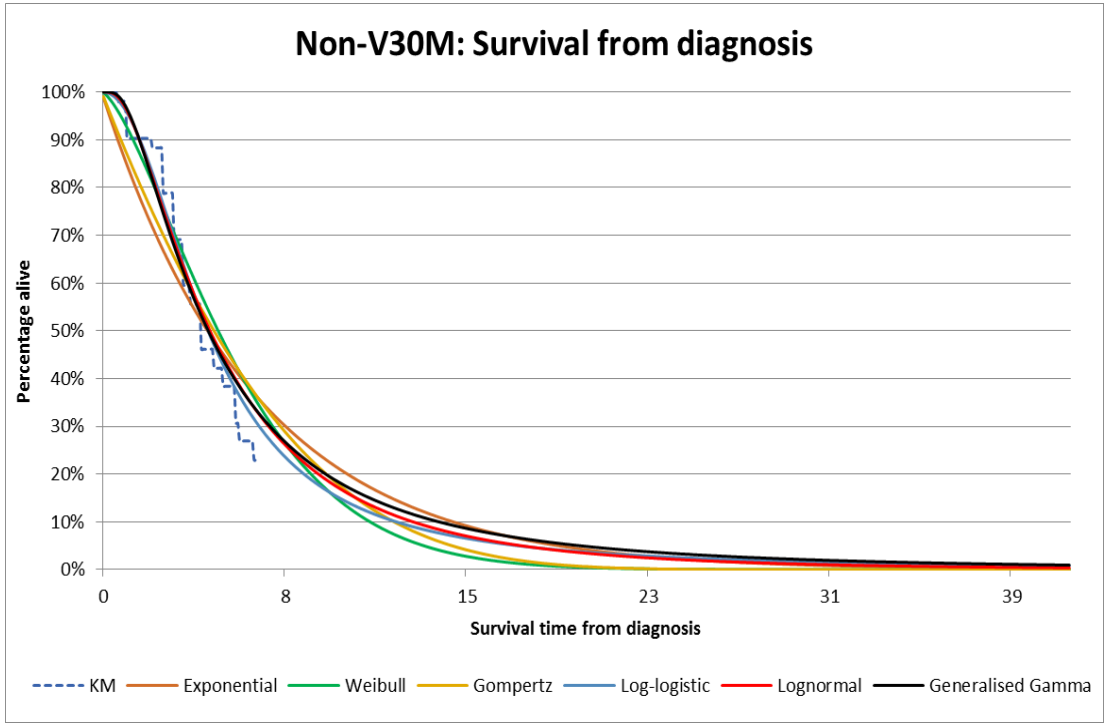
- ***ERG comment***:
- Unclear how consistent a decision to withdraw treatment would be with Coutinho staging (i.e. TQoL score) used in the model
- ERG's clinical expert notes: patients are bedridden or have severe autonomic neuropathy, reasonable to assume they would be withdrawn from treatment soon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

[redacted]

Modelling mortality I.

- There are no published data available to link Coutinho disease stage with mortality
  - Company submission used mortality data from time of disease onset by V30M mutation status, obtained from Kaplan Maier (KM) data published by Sattianayagam et. al, 2012
  - Used parametric survival analysis of the digitised KM 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





[redacted]

Source: Figure 12 and 13 of company submission

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 = X; Stage 2: HR = XX; Stage 3: HR = XX → 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
  - 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
  - Utility values in each stage combined for V30M and non-V30M cohort from the publication and applied in the model

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

[redacted]

Source: Table C29 of company submission

ERG critique of health state utilities I.

Limitations associated with company approach for utility data used in the model

- ***Transferability to a UK setting is unclear***
  - Use of EQ-5D values based on Brazilian general population preferences is questionable
- ***No work has been carried out to determine comparability of valuation sets***
  - Adequate sensitivity analyses around uncertain values not conducted
- ***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

[redacted]

ERG critique of health state utilities II.

Alternative sources to obtain utility values

ERG consider three plausible alternative sources of utility data that could be 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 → disease stage specific values using UK tariff → robust disease stage specific utilities for use in 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 exploration of utility impact for those who progress → 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 describing relationship between TQoL and EQ-5D → plausible alternative scenario analysis in the economic model
   - Different mapping functions generate a range of plausible health state utility values

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

[redacted]

What is the most appropriate source of utility for each health state?

Carer disutility

- Quality of life impact on carers in hATTR is significant and substantial
- No studies assessed impact on carer quality of life by health states described in model
  - Systematic literature review in similar disease areas → disutility can be 0.14 (e.g. stroke)
- As hATTR-PN patients progress through disease stages, burden on carers increases
- It was assumed in the model that each patient has two full-time carers

Health state	EQ-5D-3L disutility per carer	Total disutility applied in model (2 x carers)	Note
Stage 1	-0.0025	-0.0050	No impairment to walking
Stage 2	-0.0275	-0.0550	Walking assistance
Stage 3	-0.125	-0.2500	Wheelchair or bedridden

Source: Table C30 of company submission

- ***ERG comment***: it is appropriate to consider carer disutility in the model
- For tafamidis a quality-adjusted life year (QALY) loss of 0.01 applied for Stage 3 disease based on Alzheimer appraisal (one carer assumed in tafamidis assessment)
- It remains 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

[redacted] ***Additional ERG scenario analyses was conducted to explore the impact of carer disutility on the ICER***

Adverse event utilities and costs

- Originally cost and utility impact of treatment related AEs observed in NEURO-TTR study excluded from model
- Company provided justifications at clarification stage
  - Difference in number of AE between the treatment arms was not statistically significant
  - Most AEs mild (serious adverse events <5%), impact of including AE on ICER is minimal

- At clarification company provided partially-complete scenario analysis where utility decrements (of some serious AEs) and costs of most serious AEs are included in model
- Disutility associated with myelopathy, glomerulonephritis, tubulointerstitial nephritis and thrombocytopenia excluded from AE scenario analysis → incur no utility loss
- Monitoring cost updated with cost of phlebotomist time → negligible impact on ICER

- ***ERG comment***: excluding AEs creates a bias, in favour of inotersen and should be included in base case analysis
- Informed assumptions regarding the utility decrement would have been superior to assuming these serious adverse events have no utility decrement
  - ERG attempted to source utility data, or made alternative assumptions, verified by clinical expert opinion, where possible (*see next slide*)

[redacted]

Company and ERG adverse event disutilities used in the model

Inotersen ERG analysis includes disutilities for adverse events

Adverse event rates per cycle	Inotersen	BSC	Duration (days)		Disutility applied		Total disutility	
			CS	ERG	CS	ERG	CS	ERG
Glomerulonephritis	0.18%	0%	0	***30***	0	***-0.31 (de Wit 2001)***	0	***-0.025***
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

[redacted]

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
  - Original company submission extrapolation curve: Gompertz as believed the likelihood of discontinuing inotersen would decrease over time

- During clarification, survival curves were updated using data from both NEURO-TTR and NEURO-TTR Extension study → using exponential survival curves as tapering off of the KM curve was not observed within NEURO-TTR extension study as initially expected

- ***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)
  - 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

* List price

eGFR: estimated glomerular filtration rate; UPCR: urine protein to creatinine ratio

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

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 [redacted] (inotersen) and [redacted] (BSC), incremental LYG of [redacted] → 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 [redacted], 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

[redacted]

Should a 1.5% or 3.5% discount rate be used?

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 detail – 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	XXXXXXX	XXXX	0.00	£324,054
Revised base-case after clarification							
BSC	XXXXXX	XXXX	7.541				
Inotersen	XXXXXX	XXXX	8.559	XXXXXXX	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 %

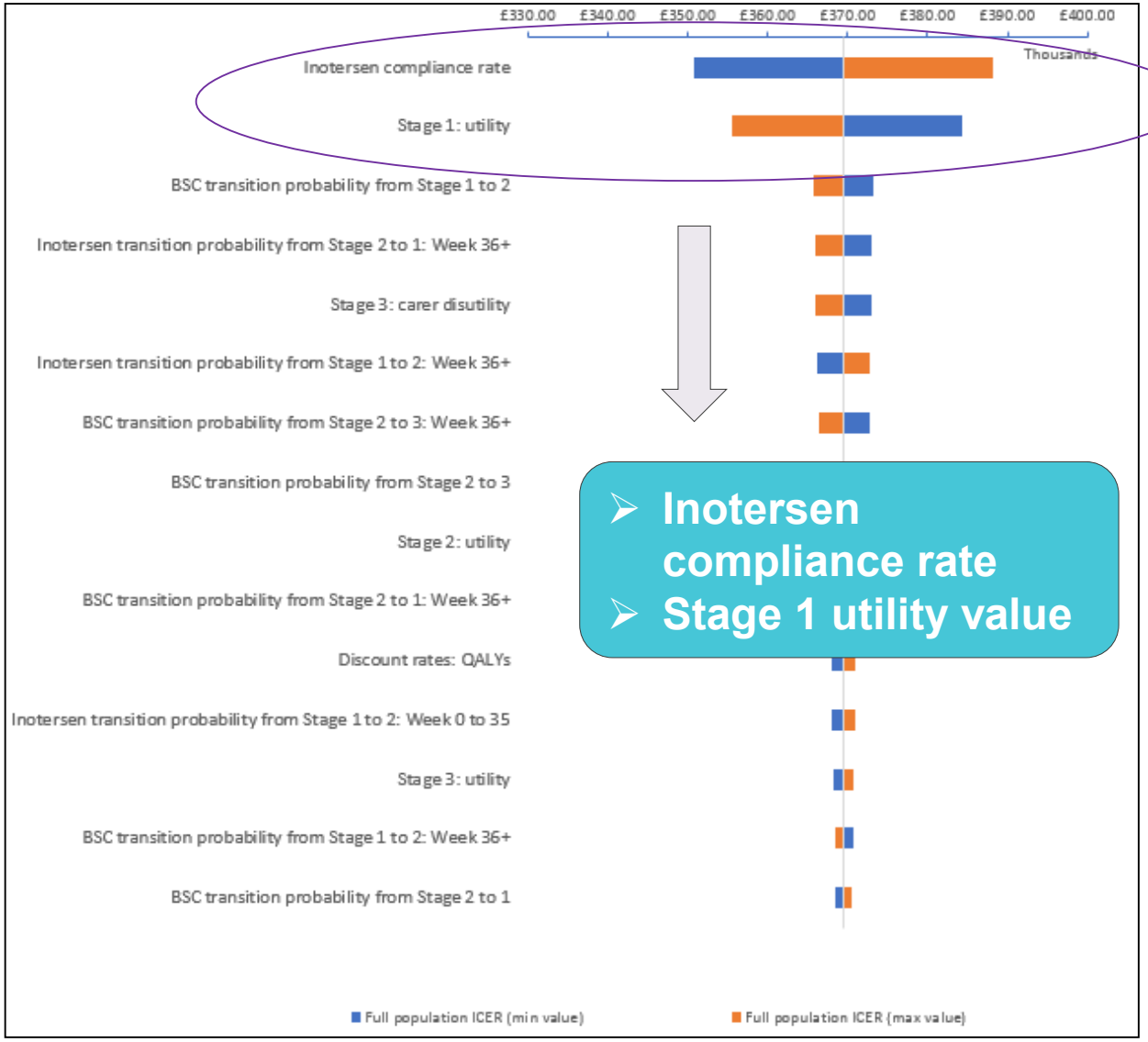
Company corrections to base-case

- 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
- ***ERG comment***: changes outlined implemented correctly
  - Amendments increased the ICER and all deterministic sensitivity analyses

XXXX

Results of the original company base-case won't be considered further

Company uni-variate deterministic sensitivity analyses



- Inotersen compliance rate
- Stage 1 utility value

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

- DSAs have ***minimal impact*** on ICER
  - None of the analyses reduced ICER below £350,000 per QALY gained
- ***ERG comment***:
- 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 (***ERG conducted additional multi-variate sensitivity analyses***)
  - Explore the impact of varying important model parameters

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

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***

[redacted]

What are the most plausible ICERs?

Additional work: Multi-variate sensitivity analyses

Using company's preferred base case model specification

Company's cost-effectiveness plane

Source: Figure A6 in clarification response (Appendix)

ERG comment:

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

Greater uncertainty in the ICER compared to company's PSA

[redacted]

ERG's cost-effectiveness plane

Source: Figure 13 of ERG report

Primary 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 utilities
  - Number of assumed carers

- ***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 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	XXXX	XXXX	£369,569
ERG	Base case A	XXXX	XXXX	£683,178
	Base case B	XXXX	XXXX	£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] What QALY weighting should be used in decision-making?

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]

Any additional considerations required?

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

What factors affecting the guidance need to be taken into account?

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 inferred from the NEURO-TTR study based on defined Total Norfolk QoL-DN 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?

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] What is the committee's view of the structure and assumptions in the economic model?

Authors

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with input from the Lead Team:

- **Francis Pang** (cost)
- **Glenda Sobey** (clinical)
- **Mark Sheehan** (lay)

Slides for committee, projector and public – noACIC

Lead team presentation

Inotersen for treating hereditary transthyretin amyloidosis

1st Evaluation Committee Meeting
Highly Specialised Technology, 14 November 2018
Lay slides

Lead team member: Mark Sheehan (patient's perspective)
Company: Akcea Therapeutics
Chair: Peter Jackson
Evidence review group: Aberdeen HTA Group
NICE team: Orsolya Balogh, Frances Nixon, Sheela Upadhyaya

[redacted]

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

- 25 survey participants (16%) and 5 (56%) of the focus group participants were resident in the 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

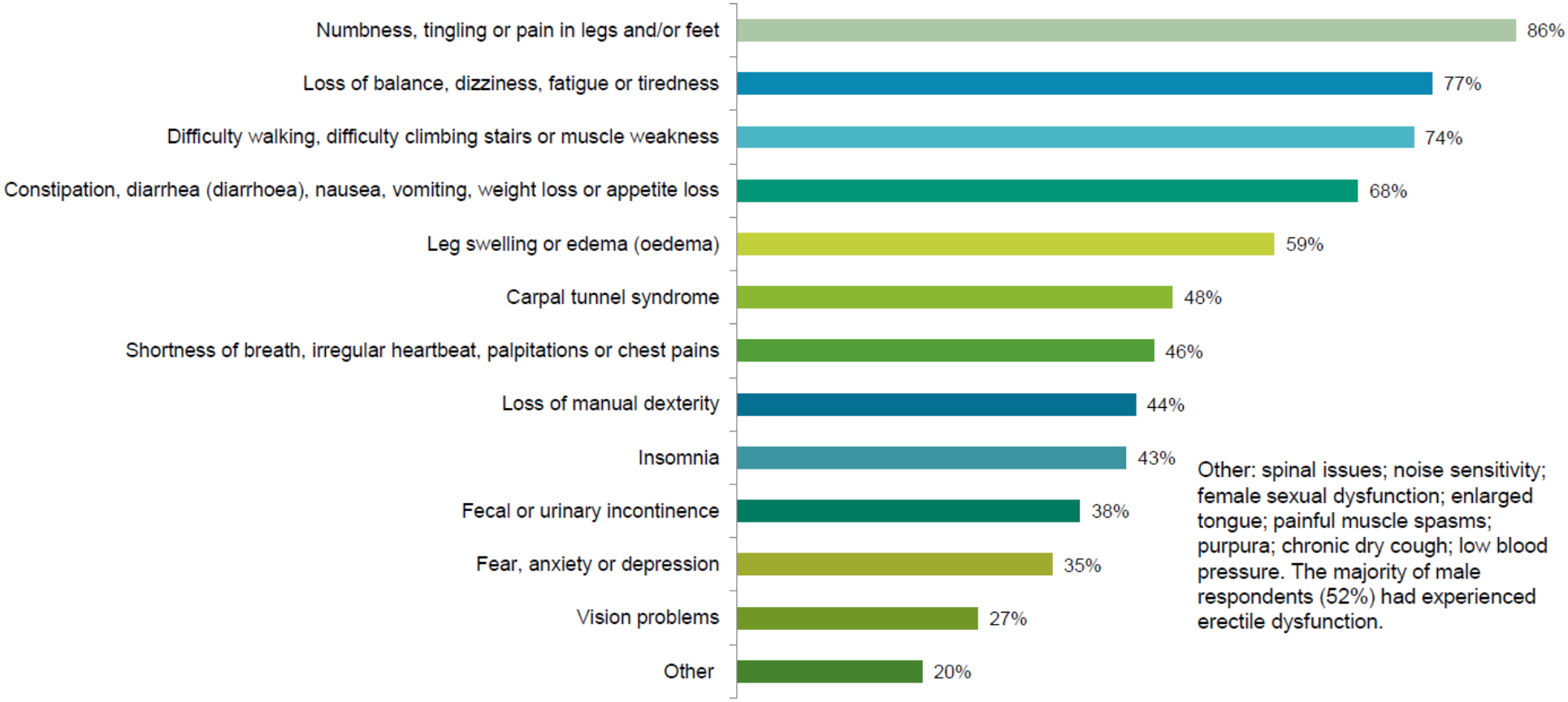
- The disease also has a considerable impact on patients work or professional lives
- Patients reported that one of the most challenging aspects of having the disease is losing independence and becoming dependent on other family members
- Many patients have been carers for loved ones and also live with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

Impact of hATTR amyloidosis on patients II.

Amyloidosis Research Consortium (ARC) UK survey 2018

Patients experience a high, multi-systemic symptom burden

Amyloidosis Research Consortium UK



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)

[redacted]

Source: Slide 7 – ARC summary report

Impact of hATTR amyloidosis on patients III.

Amyloidosis Research Consortium (ARC) UK survey 2018

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?

[redacted]

Source: Slide 8 – ARC summary report

Impact of hATTR amyloidosis on patients IV.

Patient expert submissions (1/2)

- **Lack of understanding of hATTR amyloidosis by GPs and hospitals** which can cause a lot of anxiety and a delay in treatment
- It has a **major impact on patient's and family's life**:
  - **Day-to-day general activities are harder and slower** (due to neuropathy and muscle wastage); partner has had to take on all the physical house chores and most of the running of the family
  - **Patient usually loses employment**, then hobbies, then social life, then the ability to self-care
  - **Effect on bowel movements is the worst:** very difficult to control diarrhoeas, can result in weight loss and incontinence, need to be careful on what to eat and have quick access to toilets, often lead to social isolation and travel restriction.
  - **Psychologically devastating:** some patients are aware of what to expect as they have seen their relatives with the disease progressed and died
  - **Profound concern about children:** possible and even likely, that they will develop the disease at some point in their lives. There are also situations where more than 1 patient is affected in one family, which makes the situation extremely difficult for the carers

Impact of hATTR amyloidosis on patients V.

Patient expert submissions (2/2)

- **Living with disease is painful, depressing and disabling**:
  - **Neurogenic pain** feels like suddenly being stabbed, with very short-duration intense pain and long-lasting aches. Can feel like burning, like being scalded
  - **Numbness** due to neuropathy starts in feet. It gets difficult to just stand up and balance.
  - **Eyes are often involved** with glaucoma, vitreous opacification and loss of sight as a result. Being blind and having numb hands is a devastating combination, completely disabling
  - **Autonomic dysfunction** include hypotension, feeling fainting, digestive, sexual (including impotence), and urinary (frequent urinary infections) symptoms
  - **Weakness and muscle atrophy** causes difficulty, first walking, then using the hands.
  - **Cardiac involvement** often start with tiredness and shortness of breath. Often palpitations and arrhythmias require a pacemaker
  - Advanced stages develop **central nervous degeneration**, with headaches and progressive dementia, patient is in pain, unable to walk or stand, unable to use his or her hands, unable to self-care, with diarrhoea, with pressure ulcers and blind, results in a situation worse than death

Impact of hATTR amyloidosis on patients VI.

Amyloidosis Research Consortium (ARC) UK survey 2018 and patient expert submissions

Significant unmet need

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

- “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.”

[redacted]

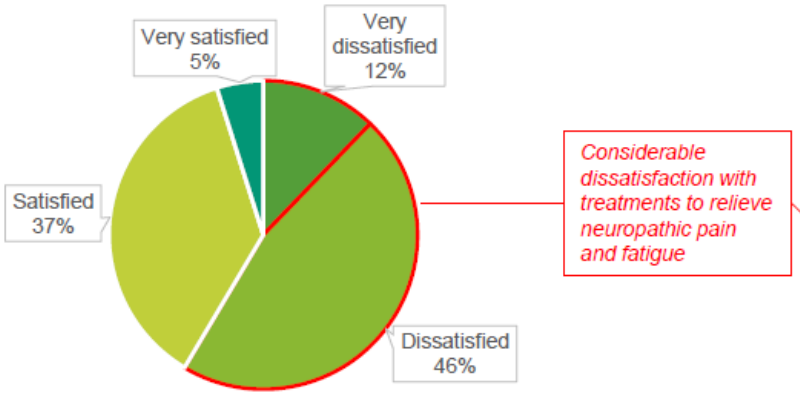
RECAP

Impact of hATTR amyloidosis on patients VII.

Amyloidosis Research Consortium (ARC) UK survey 2018

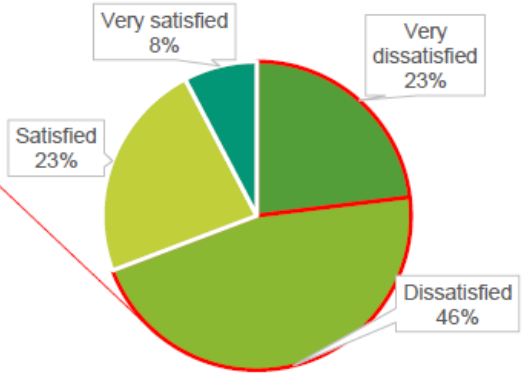
There is variable satisfaction with symptom-relief treatments and strategies

Amyloidosis Research Consortium UK

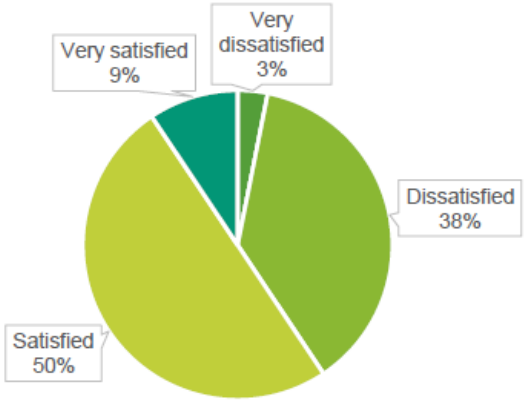


Treatments to reduce neuropathic pain (n=41)

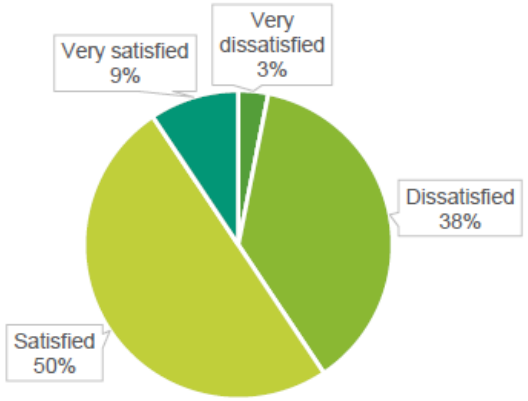
Considerable dissatisfaction with treatments to relieve neuropathic pain and fatigue



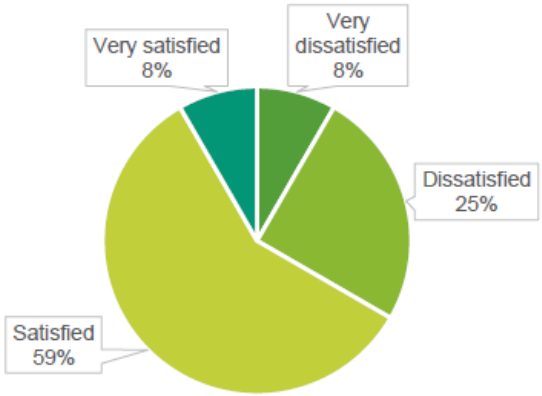
Treatments to relieve fatigue (n=13)



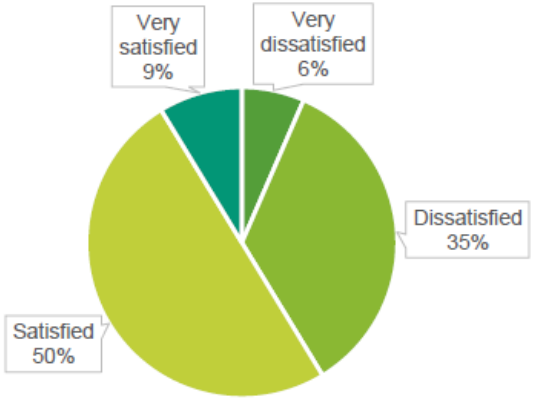
Treatments for managing cardiac function (n=32)



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?

Source: Slide 10 – 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

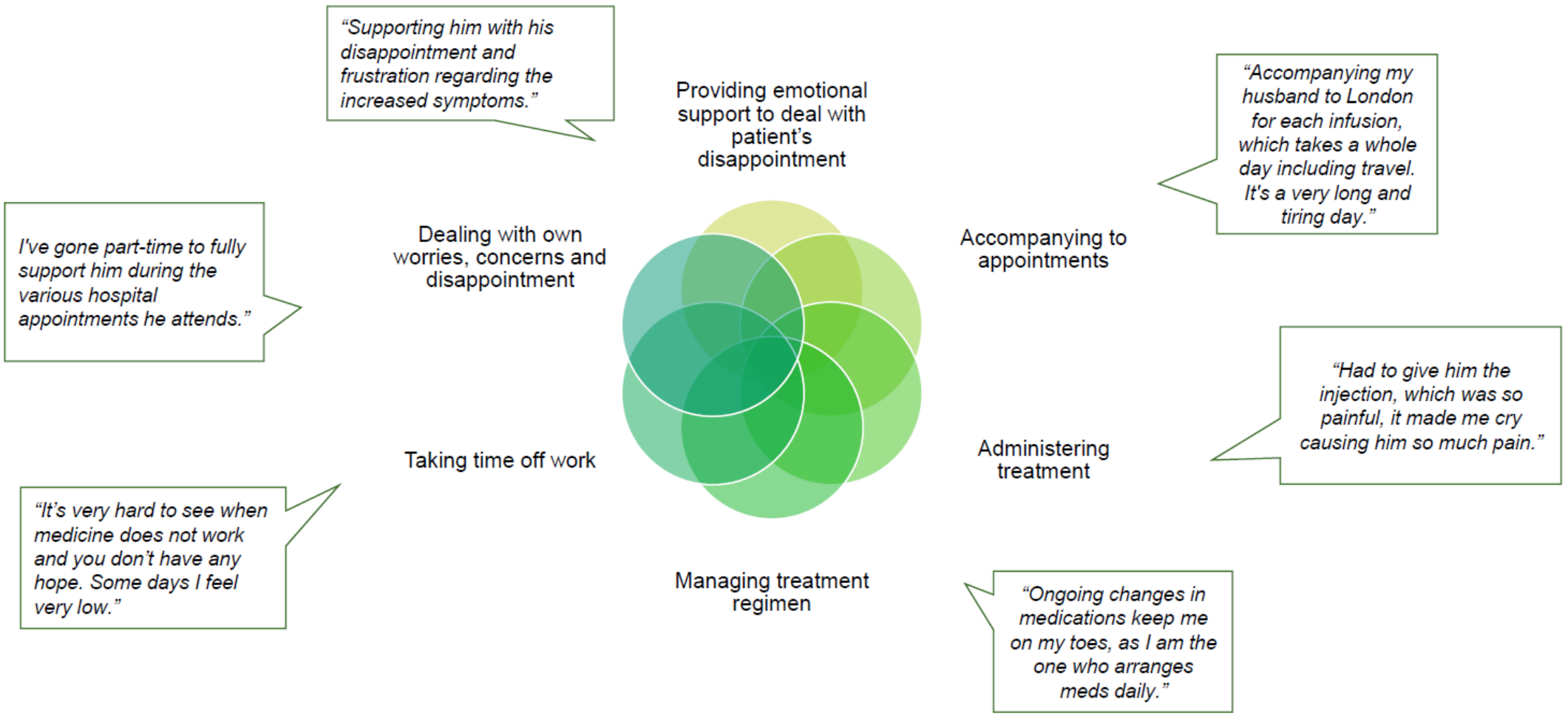
RECAP

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



Source: Slide 20 – ARC summary report

Impact of inotersen on patients I.

Amyloidosis Research Consortium (ARC) UK survey 2018

- 7 patients with experience of inotersen
- 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
- “The need for regular platelet monitoring could be perceived as a disadvantage. [A] 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.”
- “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.

Impact of inotersen on patients II.

Patient expert submissions

- 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.

- The advantages of this new treatment are that it seems to stop progression of the disease, with a low complication rate.
- Several patients on the trial for this drug (in USA, Portugal and Holland) “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.”
- They found taking the drug very easy and convenient. They have regular blood tests, but this does not seem to bother them too much.

[redacted]