Slides for committee, projector and public – noACIC

Lead team's presentation

Patisiran for treating hereditary transthyretin-related amyloidosis

1st Evaluation Committee meeting

Highly Specialised Technologies committee, 14 November 2018

Lead team (clinical): Paul Arundel

Company: Alnylam

Chair: Peter Jackson

Evidence review group: School of Health and Related Research (ScHARR)

NICE team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

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Key issues for consideration

Clinical evidence

- Is APOLLO generalisable to clinical practice in the England?

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

- Does the committee consider patisiran clinically effective?

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

Disease background

Hereditary transthyretin-related (hATTR) amyloidosis

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

* Data from the National Amyloidosis Centre (NAC)

Disease background

hATTR amyloidosis

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

Neurological features	Cardiac features

• **Peripheral neuropathy**:
  • Sensory abnormalities in extremities
  • Motor weakness
  • Cachexia
  • Loss of ambulation
• **Autonomic dysfunction**:
  • Low blood pressure when standing up
  • Impotence
  • Severe GI symptoms
  • Bladder dysfunction, recurrent infections
  • Cardiac arrhythmias
• Progress to death due to GI symptoms, malnutrition and wasting
	• Cardiomyopathy: Progressive thickening of the ventricular walls and interventricular septum
	  • Results in heart failure
	• Heart failure progresses rapidly
	  • Substantial worsening of cardiac function, loss of ability to walk
	• Progress to death

Staging of hATTR amyloidosis

No staging/ scoring system covers all disease aspects; several scoring systems available:

- familial amyloidotic polyneuropathy (FAP) system (Coutinho) *(used in licence for patisiran)*
- polyneuropathy disability (PND) score
- Gillmore *et al.* 2017 system for cardiomyopathy (based on NTpro-BNP* & eGFR**)

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

NICE *NT-proBNP is a cardiac biomarker which Gillmore used to define a staging system for cardiac transthyretin amyloidosis using a cut-off 3,000 pg/mL; high NT-proBNP indicates greater cardiac involvement ** estimated glomerular filtration rate

Current treatment options

- No available pharmacologic disease-modifying treatment options in the UK
- Available treatment options aim at symptom relief and supportive care
  - Pain management, surgery, mobility support to avoid hypotension
  - Restriction of salt intake, diuretics, pacemakers, and arrhythmia management
- 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 – contraindicated in heart failure, GI bleeding, and hepatic/renal failure
- Liver transplant rarely performed for hATTR amyloidosis in the UK – outcomes are poor in patients with cardiac involvement

Patisiran (Onpattro)

Alnylam

Marketing authorisation	Indicated for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy*
Mechanism of action	RNA interference agent: suppresses production of TTR (including abnormal TTR) to reduce the accumulation of amyloid deposits
Administration & dose	• Intravenous infusion • 0.3 mg/kg once every 3 weeks, for lifetime
List price and PAS discount	• List price: £7,676 per 10 mg (5 mL) vial; £[redacted] per patient per cycle** • Simple discount PAS approved; included in economic analyses

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

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*Using familial amyloidotic polyneuropathy (FAP) system
**cycle of 6-month
PAS: patient access scheme; SPC: summary of product characteristics

Decision problem

	NICE final scope	Company submission	ERG comments
Pop.	People with hATTR amyloidosis	• Adults with hATTR amyloidosis with PN • No evidence presented for patients with predominantly cardiac forms of hATTR in absence of PN	Population aligned with indication & APOLLO although 1 patient in placebo group had FAP 3 disease at baseline
Comp.	Established clinical management without patisiran	BSC	BSC undefined; potential variations across centres
Out.	• Neurological impairment • Symptoms of PN • Cardiac function • Autonomic function • Weight loss • Effects of amyloid deposits in other organs and tissues (including eye) • Serum transthyretin • Motor function • Mortality • AE of treatment • HRQoL (patients and carers)	Effects of amyloid deposits in other organs and tissues (including the eye), and HRQoL for carers not included	None

BSC: best supportive care; HRQoL: health-related quality of life; PN: polyneuropathy

Clinical experts (1/2)

- Condition
  - hATTR is a rare, progressive, devastating, dignity-removing disease; leads to death within 7-10 yr
  - Patients presenting with cardiac involvement have a worse prognosis (survival 4-5 years) than those presenting with a peripheral neuropathy
  - Autonomic nerve symptoms cause many of the most unpleasant, disabling and quality of life destroying symptoms in hATTR amyloidosis
- Epidemiology
  - About 30 new cases each year in the UK. Most patients are based in England
  - Mid estimated prevalence of hATTR (Schmidt *et al.,* 2018) is 97. More than 50% are expected to receive treatment
- New technologies
  - Inhibition of production of amyloid precursor proteins, transthyretin (TTR), seen as “giant leap”
  - Aim to slow or (ideally) stop progression, enable gradual improvement and recovery, and thereby improve mobility and prevent disability
  - Would be given in addition to current supportive care
  - Discontinuation considered when there is evidence of intolerance or lack of efficacy (e.g. over 12 months or more)
  - Patients are most likely to benefit if diagnosed early (stage 1); patients in stage 3 may benefit from treatment (although not possible to assess in trials)

Clinical experts (2/2)

- Outcomes
  - mNIS+7 (measuring neurology impairment) is a sophisticated outcome to assess motor strength, reflexes, sensation, nerve conduction and postural blood pressure
  - Clinically significant outcome is maintenance of ability to walk/without greater walking aids
  - Clinical benefits of patisiran are reflected in quality of life and clinical metrics; autonomic benefits are difficult to quantify and will be associated with reduction of disease progression
- Service delivery
  - UK patients are assessed (for overall clinical status, neuropathy progression and cardiac involvement) and followed up for 6 months at NAC
    - Additional neurological assessments at the National Hospital for Neurology, UCLH
  - Patisiran will be first administered to patients at NAC and then at home (Alnylam plan to provide a home infusion service)
- Current treatment options are limited:
  - Tafamidis is not available in the UK; diflunisal is often used off-license but has little impact on disease progression and can cause side effects; liver transplantation is very rarely used
- No guidelines exist to support clinical practice; no defined pathway of care

NHS England comments

- No 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
- Small requirement for staff training will be required

NAC: National Amyloidosis Centre

Clinical trial evidence

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

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

*Non-exhaustive list of outcomes

Endpoint definition: mNIS+7 and Norfolk QoL-DN

mNIS+7

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

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 (company)*

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

Patient baseline characteristics

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

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ERG critique on clinical trial designs

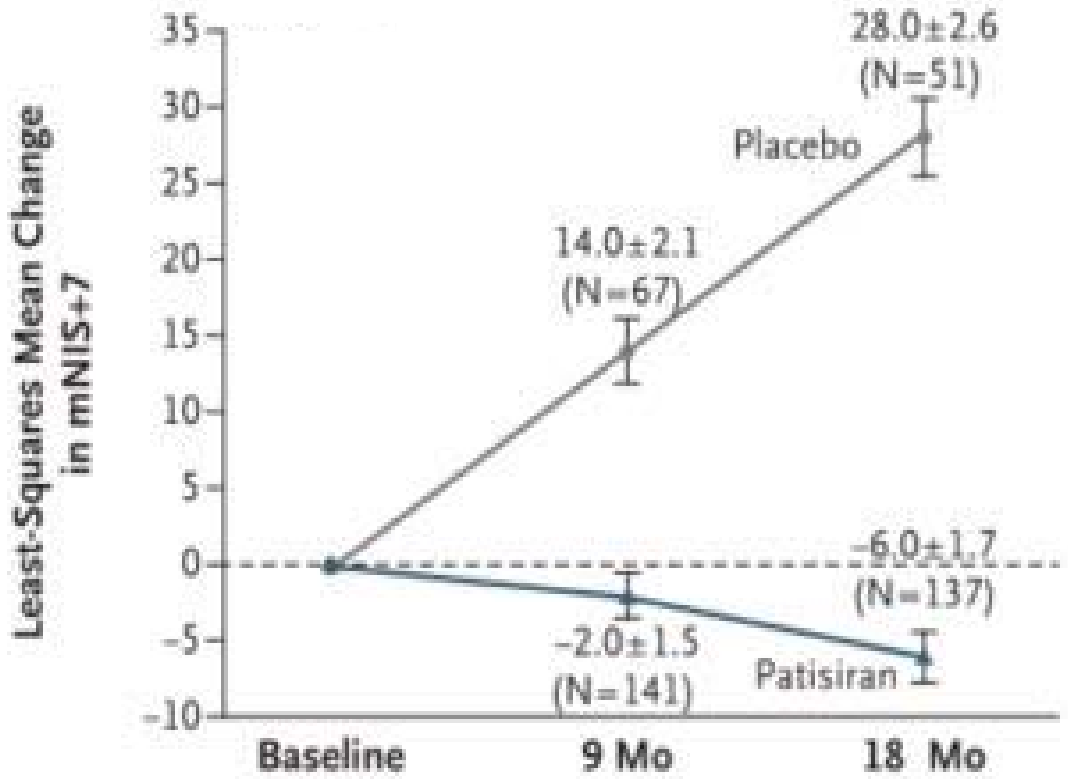
Theme	ERG comments
Phase 2 and Phase 2 OLE study quality	• Unclear impact of study quality on results because no formal overall assessment of risk of bias • Phase 2 and Phase 2 OLE are at a moderate risk of bias • Global OLE may be at high risk of bias

Uncertainty on reliability of APOLLO clinical evidence	• APOLLO patients are consistent with patients seen in clinical practice
	• Moderate risk of bias in APOLLO:
	  • More patients met cardiac involvement criteria in patisiran (61%) vs placebo (47%) arm; company interpret as patisiran-treated patients have a worse prognosis overall
	  • Unexpected imbalances in drop-outs between groups: more discontinuations and withdrawals in placebo (38%) vs. patisiran (7%) arm

Issues with primary outcome	Various issues are associated with measuring change from baseline: regression to mean may be strong, post-treatment value must be linearly related to pre-treatment value, result should not be baseline-dependent
Subgroup effects	Possible heterogeneous treatment effects could not be ruled out because company did not perform formal interaction test

Clinical results: mNIS + 7

APOLLO



Patisiran vs placebo

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

Clinically important difference: 2 points (company)

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

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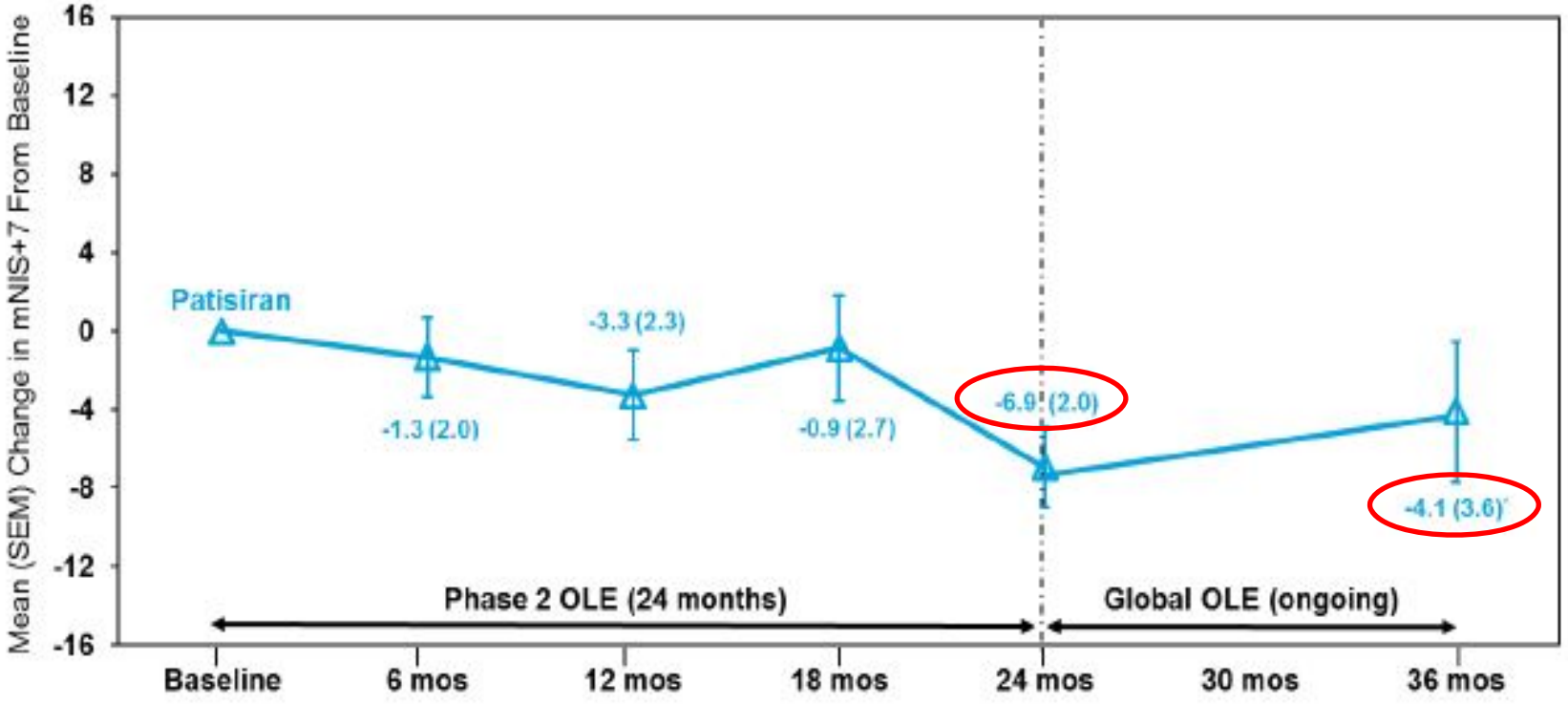
Clinical results: mNIS + 7

Phase 2 OLE and Global OLE (long-term efficacy)



- **Phase 2 OLE:** 74% of patients had no change or an improvement in mNIS+7 at 24 months relative to baseline

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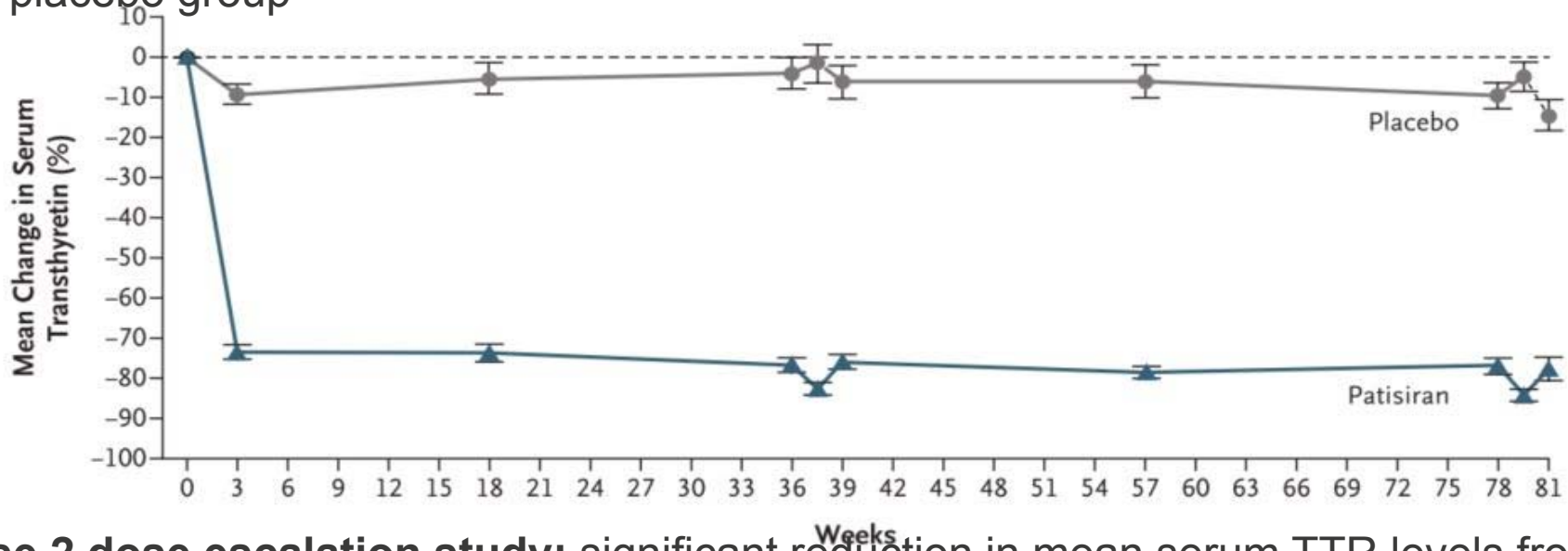
Source: Figure 17 p. 96 of company submission3

Clinical results: serum TTR

APOLLO, Phase 2 and Phase 2 OLE

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

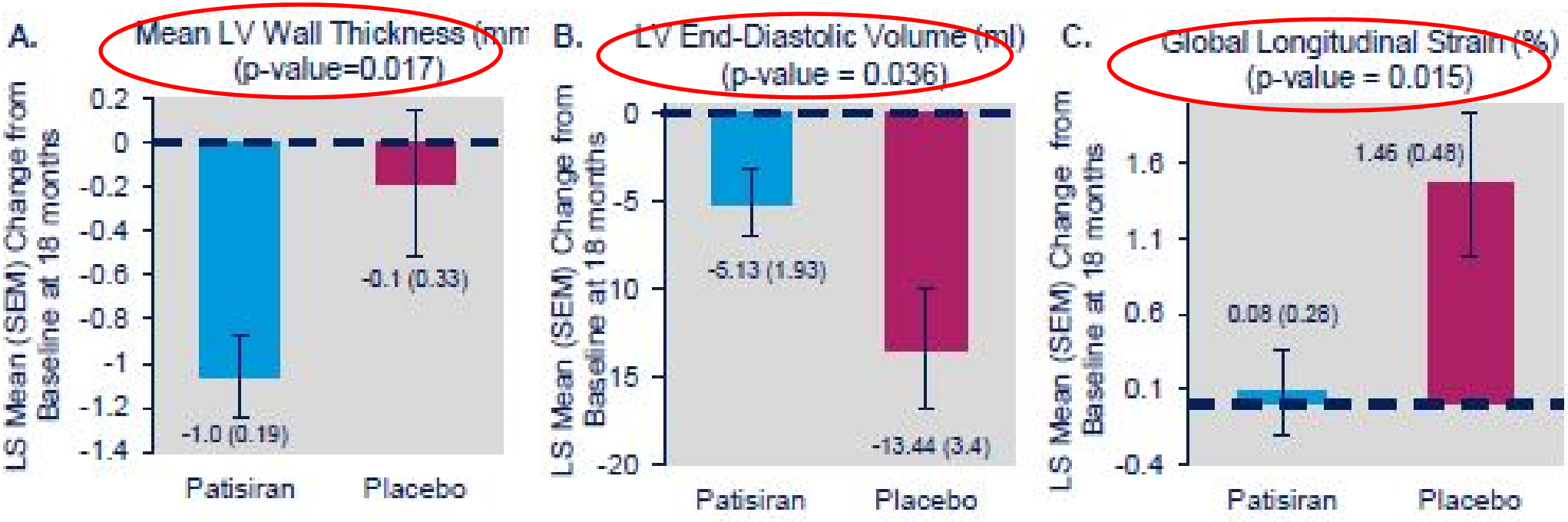


- **Phase 2 dose escalation study:** significant reduction in mean serum TTR levels from baseline at nadir after the first (83.8%) and second (86.7%) dose of patisiran
- **Phase 2 OLE (24 months):** mean serum TTR knockdown was 82%
- Clinically important difference (company): TTR reduction of ≥80% is predicted to halt or reverse neuropathy progression, as indicated by stabilisation or improvement in mNIS+7
- TTR knockdown correlates with change from baseline in mNIS+7: Pearson's r = 0.59 (95% CI, 0.49–0.68)

Clinical results: cardiac outcomes

APOLLO

- **Cardiac subpopulations** (61% patisiran; 47% BSC): cardiac outcomes improved in most measures in patisiran group vs placebo at 18 months:



- **Non-cardiac subpopulation & overall population**: results were broadly similar

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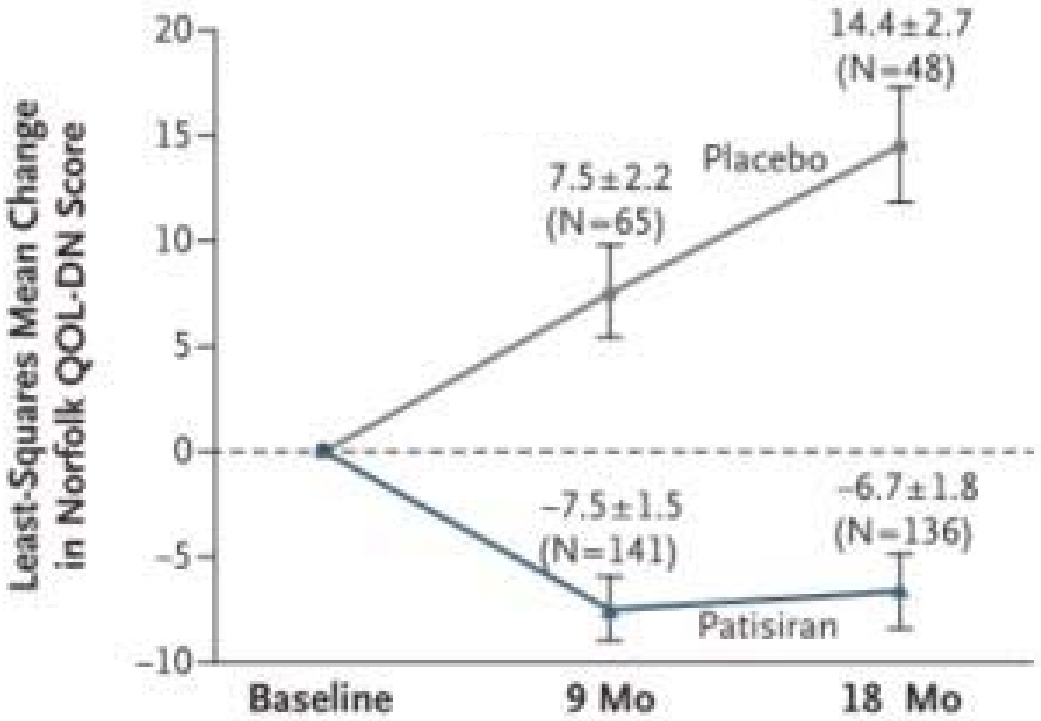
Clinical results: Norfolk QoL-DN

APOLLO



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

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

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

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

Clinical results: EQ-5D-5L

APOLLO and Phase 2

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

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

Adverse events (AEs)

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

Adverse events (AEs)

	Parent study			Global OLE
	APOLLO		Phase 2 OLE	
Treatment group	Placebo (n=49) n (%)	Patisiran (n=137) n (%)	Patisiran (n=25) n (%)	TOTAL (n=211) n (%)
Treatment duration	**Up to 48 months**			
Any AE	45 (92)	119 (87)	25 (100)	189 (90)
TRAE	22 (45)	30 (22)	7 (28)	59 (28)
Severe AE	16 (33)	19 (14)	3 (12)	38 (18)
Severe TRAE	1 (2)	1 (1)	0	2 (1)
Serious AE	19 (40)	30 (22)	6 (24)	55 (26)
Serious TRAE	2 (4)	0	0	2 (1)
AE leading to withdrawal	9 (18)	7 (5)	0	16 (8)
TRAE leading to withdrawal	1 (2)	0	0	1 (0.5)
Death	7 (14)	4 (3)	0	11 (5)

TRAE: treatment-related adverse events

Key issues for consideration

Clinical evidence

- Is APOLLO generalisable to clinical practice in the England?

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

- Does the committee consider patisiran clinically effective?

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

Slides for projector and public

Lead team's presentation

Patisiran for treating hereditary transthyretin-related amyloidosis

1st Evaluation Committee meeting

Highly Specialised Technologies committee, 14 November 2018

Lead team: Stuart Davies (cost-effectiveness)

Company: Alnylam

Chair: Peter Jackson

Evidence review group: School of Health and Related Research (ScHARR)

NICE team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

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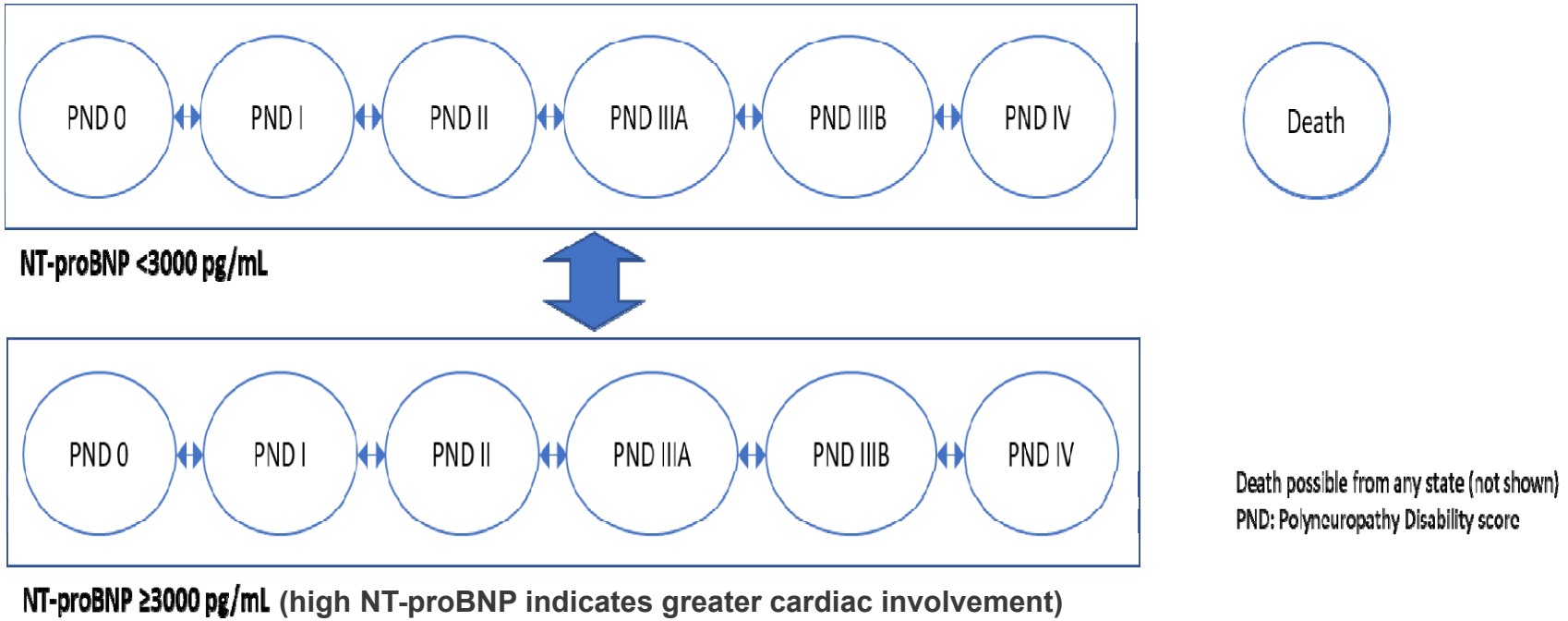
Key issues for consideration

Cost-effectiveness evidence

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

Company model structure - description



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

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Company model structure - overview and key assumptions

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

Model heath states based on PND score & NT-proBNP

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

ERG critique of model structure

Limitations	ERG justification

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

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

Starting and stopping rules

	Clinical practice (SPC)	Economic model
Start of treatment	Adult patients with hATTR amyloidosis with Stage 1 or 2 polyneuropathy (FAP stage I and II, equivalent to PND score I, II, IIIa, IIIb)	• All patients with hATTR amyloidosis with polyneuropathy are eligible to start patisiran, irrespective of NT-proBNP level or PND score (excluding PND 0) • APOLLO includes 1 placebo-treated patient with FAP Stage 3/PND IV
Stopping treatment	No explicit definition	No "response-based" stopping rules: patients continue treatment indefinitely in all health states; discontinuation curve applied to reflect some stopping over time

ERG comments:

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

Starting state distribution

- Patients can enter the model in any alive health state (except for PND 0) based on baseline distribution of PND scores (APOLLO) * probability of initial NT-proBNP is > 3,000pg/mL
- **ERG comments:** company applied an equal probability of initial NT-proBNP is > 3,000pg/mL ([redacted]) across PND states – unnecessary
- At clarification, the company submitted the probabilities of high NT-proBNP by PND state

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

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

Transition probabilities

Company's approach used 2 transitions matrices

	OBSERVED period (baseline to 18 months)	EXTRAPOLATED period (beyond 18 months)
Patisiran	• Transition matrices calculated using APOLLO data (18-month data, converted to 6-month cycles) • Inclusion of "non-informative prior distribution" - equal probability of transitioning between health states of 0.083	Same transition matrix as observed period applied
BSC		Patients can either stay in current state or progress to next worst state. Transition matrices calculated from: 1. PND score: probability of PND decline at 18 months, adjusted to 6-month cycles 2. NT-proBNP level: probability of transition from low to high NT-proBNP over 18 months *n.b. no prior distribution included, so patients could not move by >1 state*

ERG critique on transition probabilities

Limitations	ERG justification
"Non-informative" prior (used in observed period) can be unrealistic	Parameter estimates based on "non-informative" priors are unlikely to represent reasonable beliefs when the sample data are limited
BSC transition matrices (used in extrapolated period)	• Model assumes BSC-treated patients cannot transition to an improved or worsened by more than 1 state • This is a strong assumption, but likely to be uncertain
Matrix adjustment method produces bias in favour of BSC	• Method used to convert 18-month data to 6-month cycles is inappropriate when there are more than 2 heath states • produces a small bias in favour of BSC; however other methods are also imperfect • If the model was defined by FAP stage (rather than PND), the issue would still remain, although lessened
Unsure about gamma parametric curve (NT-proBNP for BSC in extrapolated period)	All surviving patients develop cardiac involvement (NT-proBNP>3,000 pg/ml) after ~5 years; ERG is unsure whether this was intended or how it should be interpreted

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Mortality risk

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

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

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

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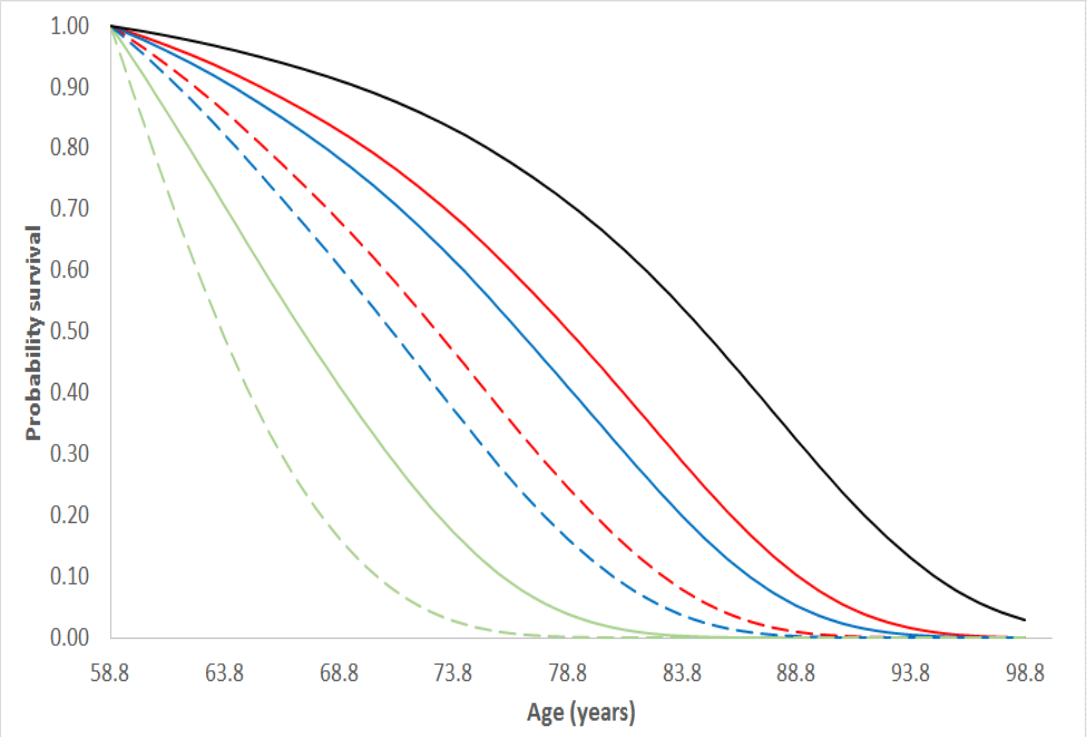
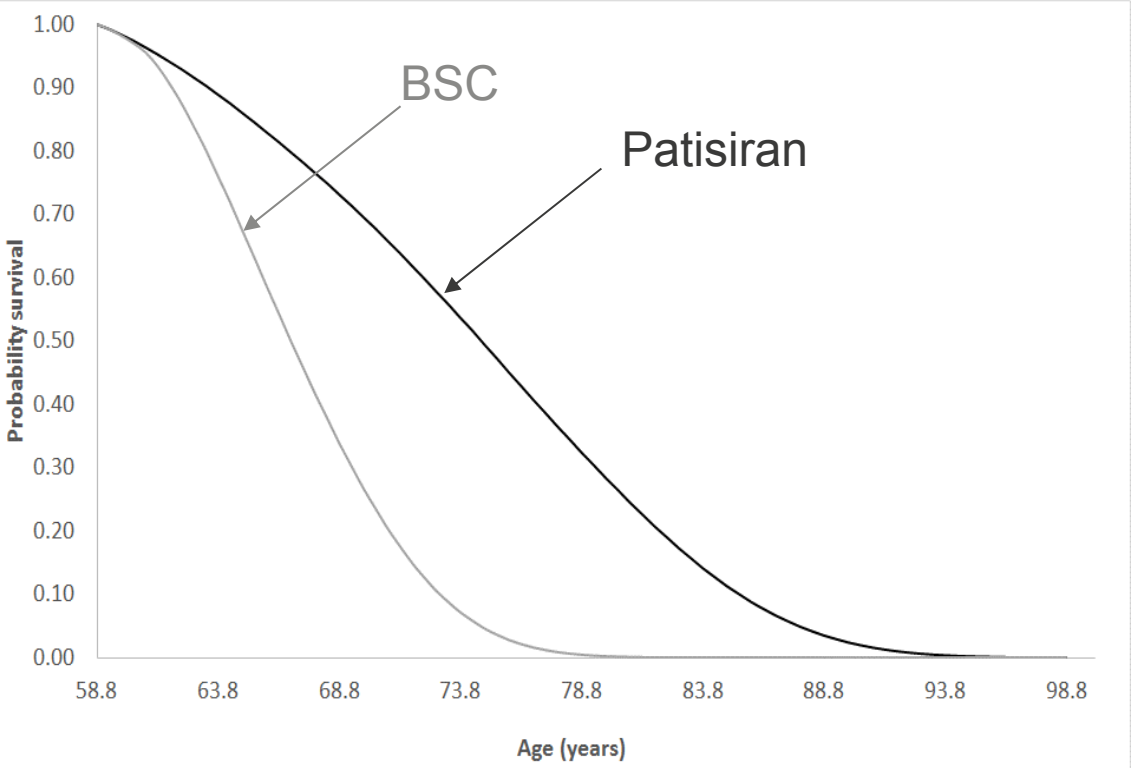
Mortality risk – overall survival prediction

Overall survival by PND and NT-proBNP scores



PND 0-II - Low NT-proBNP
PND IIIA-IIIB - Low NT-proBNP
PND IV - Low NT-proBNP
PND 0-II - High NT-proBNP
PND IIIA-IIIB - High NT-proBNP
PND IV - High NT-proBNP
General population

Overall survival prediction for patisiran and BSC



ERG critique on mortality risk

Limitations	ERG justification
General method	• Largely based on external data; no consideration given to plausible underlying hazard functions or to supplementing the observed data with experts' beliefs

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

Health-related quality of life (HRQoL)

Company 's approach

Each health state starts with a given utility (same for BSC and patisiran arm)

Utilities from APOLLO (EQ-5D-5L mapped to EQ-5D-3L)

Utilities can either increases (patisiran) or decreases (BSC) over time; monthly changes were taken from a regression analysis

Regression includes parameters for PND state, per-month change with patisiran and per-month change with BSC

Utilities capped so they cannot exceed a minimum (BSC) or maximum (patisiran) in each health state from by the 25th or 75th percentiles of utilities in APOLLO trial

Additional cap applied to ensure utilities do not exceed general population (Kind *et al.,* 1999)

A caregiver disutility of 0.01 was applied in PND IV health state (Alzheimer's, AGNSS tafamidis report)

HRQoL

ERG critique on company's approach

ERG comments:

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

[redacted]

HRQoL

Company base case and ERG scenario utilities

ERG identified other sources of utilities that they explore in their scenario analyses:

- Stewart *et al*., 2013: utilities by FAP stage and Val30Met mutations
- Ara and Brazier, 2010: general population cap

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

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

Resource use

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

**Per 6 months; function of cost per vial, body weight distribution, number of administrations and RDI (effective compliance; estimated at 0.97 [APOLLO])*
CM: cardiomyopathy; PN: polyneuropathy

- **ERG comments**
  - Limitation of Delphi: unlikely to reflect the true expected cost and uncertainty
  - AEs assumed to occur at a constant rate; but would reduce over time
  - Homecare costs not included
  - Errors in cost calculations: repeated application of 'one-off' costs, double-counting of 'one-off' costs, and administration and premedication costs not adjusted by compliance

Discount rate

- Company applied differential discount rates of 1.5% for outcomes and 3.5% for costs based on:
  - NICE criteria for 1.5% discount rate for outcomes met because patisiran has shown a high level of safety and effectiveness over the long term and has demonstrated ability to halt or reverse disease progression and improve HRQoL
  - Criterion of health benefits sustained over 30 years would unfairly penalise patients with hATTR amyloidosis as they are often older and therefore would have had an additional life expectancy less than 30 years even in the absence of this disease

- **ERG note** this approach is inappropriate because:
  - NICE Reference Case (and non-reference case) does not support use of differential discount rates
  - Only some patients are close to death and not all have severely impaired HRQoL (as shown by modelled overall survival and utilities)
  - Lack of evidence to show that patisiran can improve patients' HRQoL or survival beyond 18 months
  - The expected survival for a matched cohort in UK general population is less than 30 years
  - Proposed arguments for differential discounting could be made for any appraisal

Company's base case

PAS price

	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Probabilistic**					
Patisiran	[redacted]	8.42	[redacted]	8.11	[redacted]
BSC	[redacted]	0.31	-		-
Deterministic					
Patisiran	[redacted]	8.52	[redacted]	8.30	[redacted]
BSC	[redacted]	0.22	-		-

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

*based on discount rates of 1.5% for health outcomes and 3.5% for costs
** probabilistic results based on a re-run of the company's model by the ERG

Undiscounted QALY gain (deterministic): 9.86 vs 0.13 = 9.73

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Deterministic sensitivity analysis

PAS price

Company scenario analyses (PAS price)

Scenario	Inc. QALYs	Inc. costs	ICER (£/QALY)	Δ ICER
Company base case	*8.30*	[redacted]	[redacted]	
Scenario 1A – assumed all patients with missing data progress to next worst state	7.36	[redacted]	[redacted]	↑
Scenario 1B – assume all patients with missing data regress to next best state	8.46**	[redacted]	[redacted]	↑
Scenario 2 – no utility max/min cap	10.61	[redacted]	[redacted]	↓
Scenario 3 – exponential time on treatment function (decrease proportion of patients that continue to receive patisiran)	8.30	[redacted]	[redacted]	↓
Scenario 4 – mortality caused by only cardiomyopathy	11.17	[redacted]	[redacted]	↓↓

*based on discount rates of 1.5% for health outcomes and 3.5% for costs
** *The results for this scenario appear to be incorrect in the CS*

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↓↓ *shows larger decrease than* ↓

ERG exploratory analyses

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

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

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

ERG preferred analysis (PAS price)

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Company's base case					[redacted]
(1) Correction of minor errors (applied in subsequent analyses)					
Patisiran	8.52	[redacted]	8.30	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(2) Equal 3.5% discount rates applied					
Patisiran	7.14	[redacted]	6.82	[redacted]	[redacted]
BSC	0.32	[redacted]	-	-	-
(3) Recalculation of starting state distribution and removal of patient with FAP 3					
Patisiran	8.53	[redacted]	8.31	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(4) Use of general population cap from Ara and Brazier					
Patisiran	8.54	[redacted]	8.32	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(5) Mortality effect from Gillmore *et al* removed for low NT-proBNP states					
Patisiran	8.52	[redacted]	8.30	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(6) ERG-preferred analysis (deterministic, analyses 1-5 combined)					
Patisiran	7.17	[redacted]	6.85	[redacted]	[redacted]
BSC	0.32	[redacted]	-	-	-

ERG exploratory analysis (PAS price)

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER	Δ ICER
(6) ERG-preferred analysis					[redacted]	
(7) Change of utility over time is removed						
Patisiran	5.58	[redacted]	3.87	[redacted]	[redacted]	↑↑
BSC	1.71	[redacted]	-	-	-	
(8a) Utility values from Stewart et al - Val30Met mutation						
Patisiran	5.75	[redacted]	3.51	[redacted]	[redacted]	↑↑↑
BSC	2.25	[redacted]	-	-	-	
(8b) Utility values from Stewart et al - other mutations						
Patisiran	5.36	[redacted]	3.41	[redacted]	[redacted]	↑↑↑
BSC	1.95	[redacted]	-	-	-	
(9) Utilities: lower utility assumed for high NT-proBNP states						
Patisiran	7.08	[redacted]	6.73	[redacted]	[redacted]	↑
BSC	0.35	[redacted]	-	-	-	

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↑↑↑ *shows larger increase than* ↑

ERG's exploratory analysis (PAS price)

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

↓↓ *shows larger decrease than* ↓

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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 increments)
Greater than or equal to 30	3

QALY gain undiscounted

Deterministic analyses			QALY gain undiscounted	QALY gain discounted	ICER (£/QALY)
Company	Base case		8.30	9.73	[redacted]
	Scenarios with QALY gain >10	2	12.58	10.61	[redacted]
		4	13.35	11.17	[redacted]
ERG	Base case		9.76	6.85	[redacted]
	Scenario (11) with highest QALY gain		13.70	8.99	[redacted]

Budget impact
PAS price

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

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

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

* From the company submission, numbers based on prevalent patients registered at NAC

Equality

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

Innovation

The company considers patisiran is an innovative treatment because:

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

Factors affecting the guidance

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

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

Key issues for consideration

Cost-effectiveness evidence

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

Slides for committee, projector and public – noACIC

Lead team presentation

Patisiran for treating hereditary transthyretin-related amyloidosis

1st Evaluation Committee meeting
Highly Specialised Technologies committee, 14 November 2018

Lead team: Mark Sheehan (patient's perspective)
Company: Alnylam
Chair: Peter Jackson
Evidence review group: School of Health and Related Research (ScHARR)
NICE team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

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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

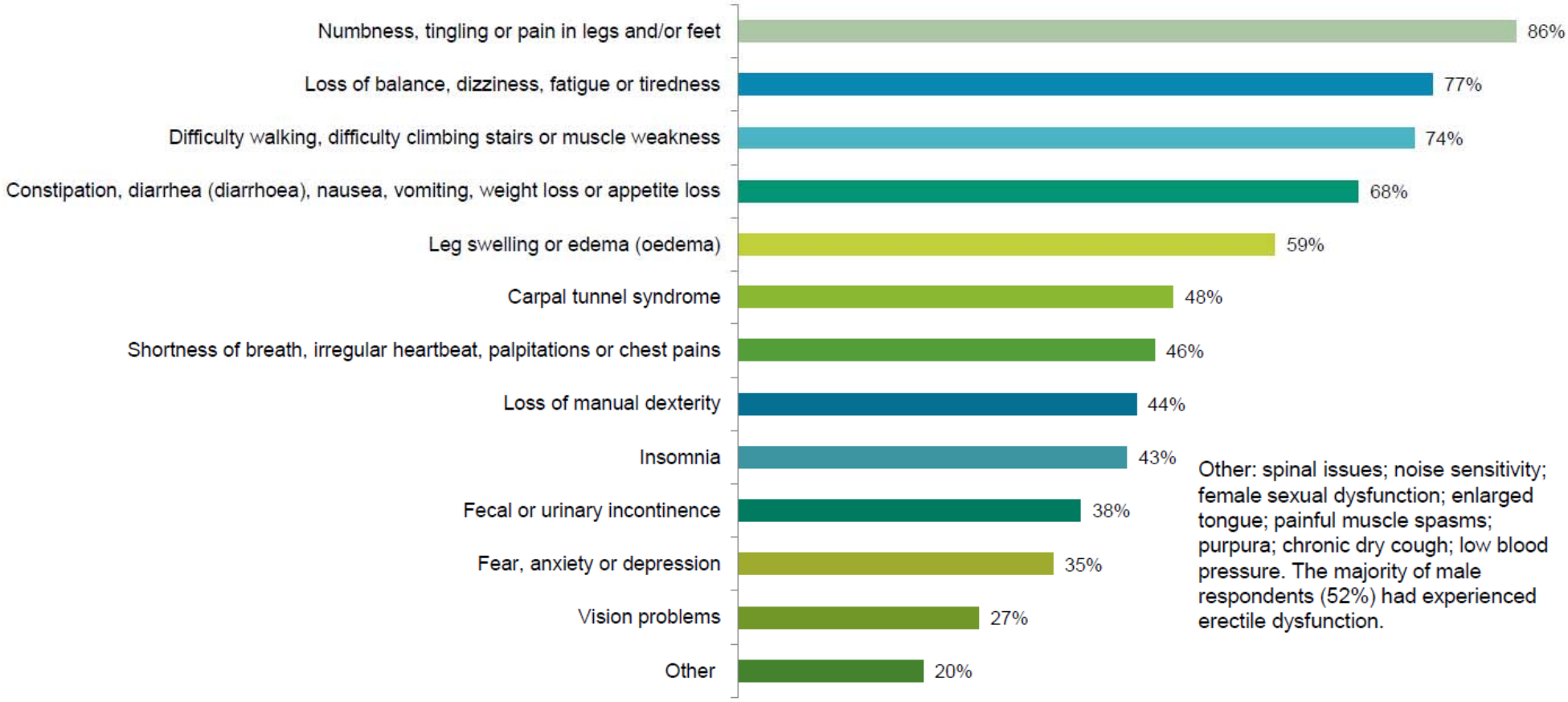
- The disease also has a considerable impact on patients work or professional lives
- Patients reported that one of the most challenging aspects of having the disease is losing independence and becoming dependent on other family members
- Many patients have been carers for loved ones and also live with 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)

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?

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: it is possible and even likely, that they will develop the disease at some point in their lives. There are also situations where more than one patient is affected in one family, which makes the situation extremely difficult for the carers

Impact of hATTR amyloidosis 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

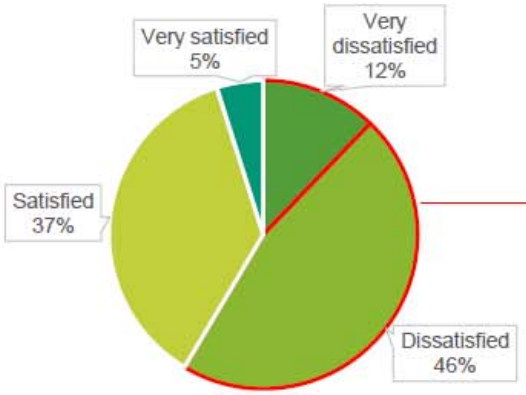
- "The unmet need is substantial. The hATTR amyloidosis is debilitating and progressive. Marginal improvements in slowing or stopping progression could have transformational improvements in the quality of life for patients and their families."

Impact of hATTR amyloidosis on patients VII.

Amyloidosis Research Consortium (ARC) UK survey 2018

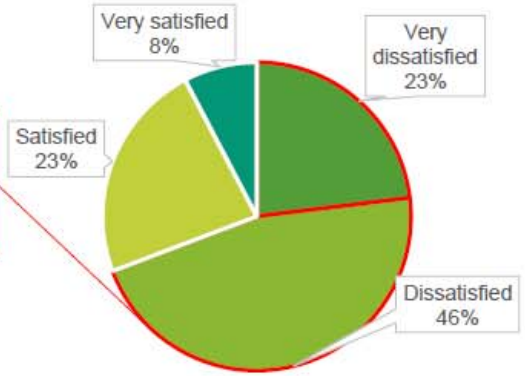
There is variable satisfaction with symptom-relief treatments and strategies

Amyloidosis Research Consortium UK

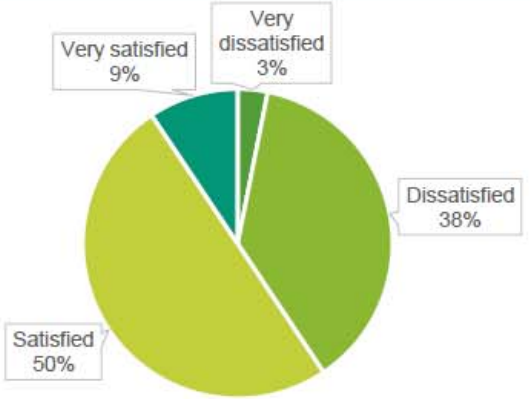


Treatments to reduce neuropathic pain (n=41)

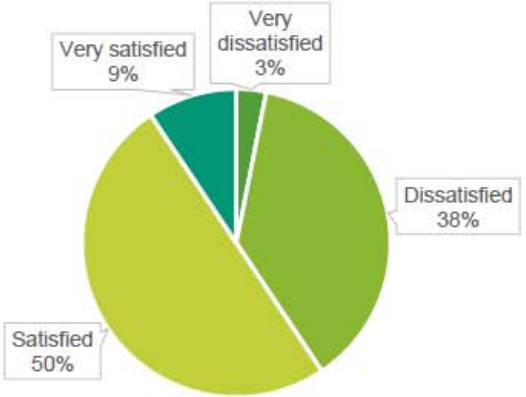
Considerable dissatisfaction with treatments to relieve neuropathic pain and fatigue



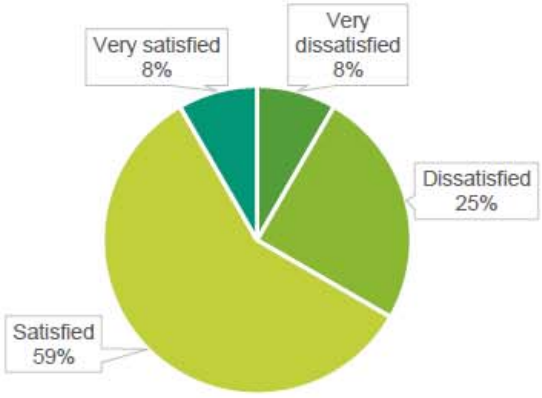
Treatments to relieve fatigue (n=13)



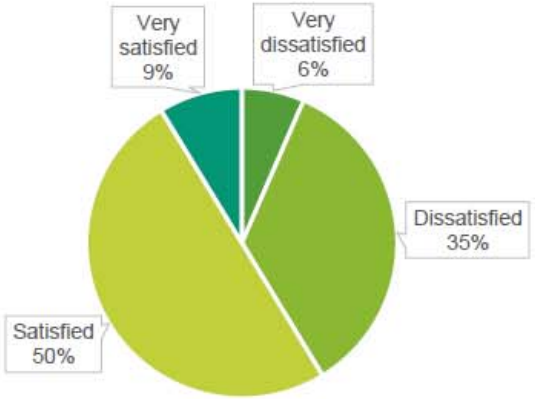
Treatments for managing cardiac function (n=32)



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?

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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."

Impact of patisiran on patients I.

Patient expert submissions (1/2)

- 20 patients with experience of patisiran
- Patients indicated that they considered patisiran to have had a positive effect on managing their disease and minimising their symptoms
- Patients “found the travelling for treatment to be inconvenient, although they felt it ‘was worth it’ due to the positive effects they were experiencing. When discussing this issue patients told us they would like to have the option for the treatment to be available locally.”
- “The desire to have [a] range of options to meet individual preferences [about treatment delivery] and other personal and disease considerations is evidenced in our research with patients and carers”.

Impact of patisiran on patients II.

Patient expert submissions (2/2)

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

NICE

* NAC: National Amyloidosis Centre