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NICE National Institute for Health and Care Excellence

Patisiran for treating hereditary transthyretin-related amyloidosis

Chair's presentation

3rd evaluation committee meeting

Highly Specialised Technologies, 21 May 2019

Lead team: Paul Arundel, Stuart Davis and Mark Sheehan

ERG: School of Health and Related Research (ScHARR)

NICE technical team: Orsolya Balogh, Richard Diaz, Sheela Upadhyaya

Company: Alnylam

Patisiran (Onpattro)

Alnylam

Marketing authorisation	• Indicated for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy *(using FAP stage)*
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

[redacted]

*cycle of 6-month

FAP: familial amyloidotic polyneuropathy; PAS: patient access scheme; TTR: transthyretin

Nature of the condition

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
- Common UK mutations include Val122Ile (39%), Thr60Ala (25%) and Val30Met (17%)
- Reduced life expectancy: 3–15 years from onset of symptoms
- A spectrum of clinical manifestations of hATTR amyloidosis: including polyneuropathy and cardiomyopathy (most people have both)

Key neurological features	Key cardiac features

• **Peripheral neuropathy**:
  • Sensory abnormalities in extremities
  • Loss of ambulation
• **Autonomic dysfunction**:
  • Low blood pressure when standing up
  • Severe gastrointestinal (GI) symptoms
  • Bladder dysfunction, recurrent infections
  • Cardiac arrhythmias
  • Progress to death
	• Cardiomyopathy (CM) results in heart failure
	• Heart failure progresses rapidly
	  • Substantial worsening of cardiac function, loss of ability to walk
	• Progress to death

[redacted]

* Data from the National Amyloidosis Centre (NAC)

Staging of hATTR amyloidosis

- No staging/ scoring system covers all disease aspects; several scoring systems available:
- Familial amyloidotic polyneuropathy (FAP) stage (also known as 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
0	No impairment
I	Sensory disturbances, preserved walking capability
II	Impaired walking capability but ability to walk without a stick or crutches
IIIA	Walking only with the help of one stick or crutch
IIIB	Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

FAP	FAP stage description
0	No symptoms
I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II	Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
III	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

*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

Summary of evidence

Clinical evidence

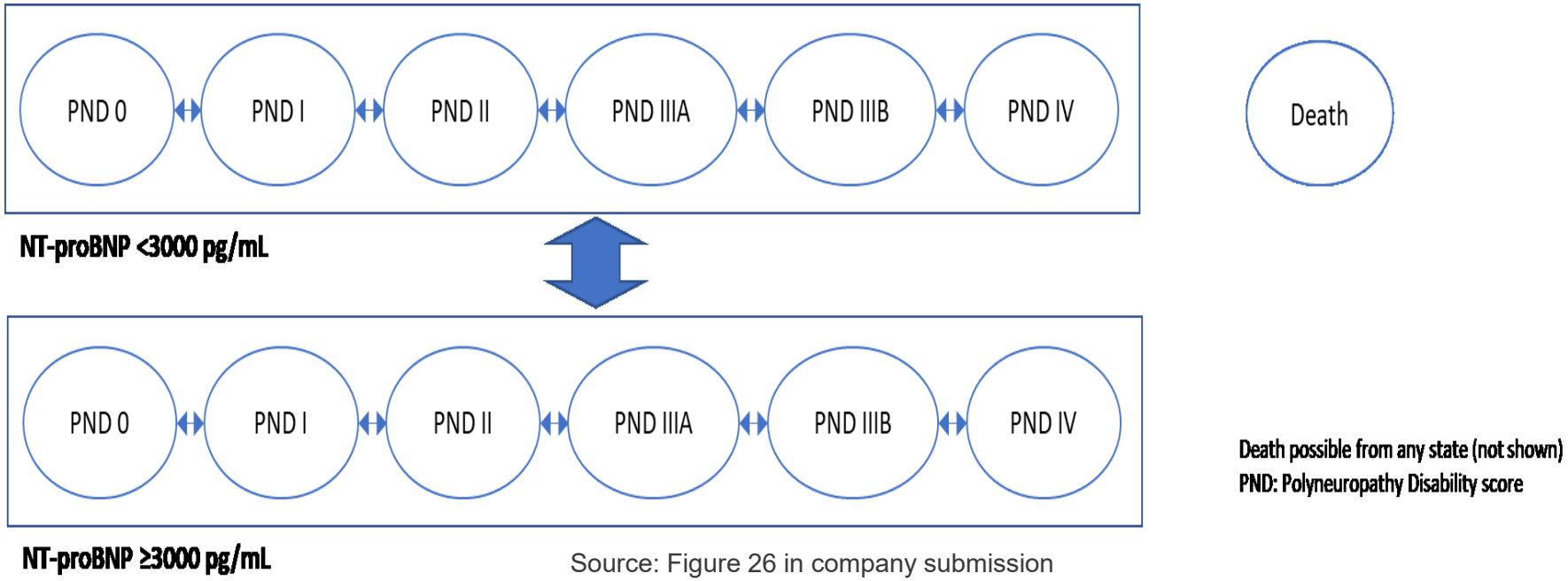
- APOLLO key outcomes
  - Effect on neurologic impairment using mNIS+7 and quality of life using Norfolk QoL-DN: statistically significant difference in favour of patisiran
  - Mean TTR reduction over 18 months: 87.8% patisiran
  - Cardiac outcomes: better improvement in patisiran
  - EQ-5D-5L: patients' utilities improved on patisiran and worsened on best supportive care (BSC)
  - Clinical experts observed reduction of amyloid deposits in all organs in medical imaging
  - Patient experts explained that benefit seen in trial translated into a marked effect on patients' lives (e.g., regain of social life, back at work full time)
  - No long-term clinical evidence available, but further data are accumulated

[redacted]

mNIS+7: Modified Neuropathy Impairment Score +7, Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy

Summary of evidence

Economic evidence – model structure



Source: Figure 26 in company submission

- Markov model compares patisiran + BSC vs. BSC
- 12 alive health states defined by a combination of the severity of polyneuropathy and cardiac involvement (NT-proBNP):
  - Company argued PND provides more granular assessment of condition than FAP (because has more stages for symptomatic patients)
- 40 years cycle length (lifetime), 6 month cycle
- 3.5% discount for costs; 1.5% discount for outcomes

[redacted]

Summary of evidence

Economic evidence - disease progression and mortality

- 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)
  - 18-month APOLLO data converted in 6-month cycle

- Mortality calculated by applying hazard ratios (HRs) to general population mortality risk, for each health state
  - Assumed that increasing mortality risk associated with increasing polyneuropathy and cardiac involvement
  - Largely based on external data, with hazard ratios for PND score and NT-proBNP extracted from Gillmore et al. (2017) and Suhr et al. (1994) respectively, and assumed to act independently

[redacted]

Committee's key considerations during 1st and 2nd meeting

ECD preliminary recommendation:
Patisiran is not recommended, within its marketing authorisation, for treating hereditary transthyretin-related amyloidosis in adults.

Issue	Committee's consideration
Clinical evidence of patisiran	• Showed considerable short-term benefit • Long-term benefit not available
Stopping rules	• If recommended, patisiran would be started in people with FAP stages I and II, and would be stopped when patients progress to FAP stage III (PND IV) • A discontinuation curve based on a log-normal parametric function applied to reflect some patients stopping over time, but still included treatment during FAP stage III
Safety	• Manageable
Model structure	• Broadly reasonable but does not capture all aspects of disease • Based on combination of PND and NT-proBNP, but excludes states or events associated with other key impacts (autonomic dysfunction) • Unlikely to reflect true expected cost effectiveness

[redacted]

Committee's key considerations during 1st and 2nd meeting

Issue	Committee's consideration
Utility regression model	• Model includes following regression terms: treatment group, time, PND score, NT-ProBNP, treatment-by-time interaction term • Minimum and maximum utility caps arbitrarily chosen - removed • Improvement in quality of life within a given PND stage is limited by time (5 years) to reflect clinical practice • Utility cap used for general population based on Ara and Brazier (2010)
Mortality	• Removing mortality effect for lower NT-proBNP states is feasible, but removing mortality effect associated with PND score in all patients considered to be unrealistic • Combining both the effect of PND and cardiac involvement is reasonable • Although approach is convoluted, circular and uncertain, the committee accepted it because of lack of other evidence
Discount rate	• 3.5% applied for both costs and health effects
Caregiver disutility	• 1 caregiver in FAP stages I and II, and 2 caregivers in FAP stage III • PND-related disutilities applied in model
ICERs	• Most plausible ICER XXXXXXX (February 2019 - with no access proposal or PAS)

[redacted]

Evaluation history

- **November 2018**: **1st Evaluation Committee meeting**
  - *Patisiran was **not recommended***
  - *ECD released*

- **February 2019**: **2nd Evaluation Committee meeting**

Committee considered comments received during consultation and a new commercial offer proposed by the company

  - *Patisiran was **not recommended***
  - *No guidance was published*

  - *After ECM2: NICE and ERG provided feedback on modelling assumptions*
  - *Company submitted additional evidence (new model) – and a new PAS was provided*

- **May 2019**: **3rd Evaluation Committee meeting**

[redacted]

Suggestions by the committee after 2nd evaluation meeting

- Consider a stopping rule in accordance with the marketing authorisation: patisiran to be stopped if patients enter FAP stage III (PND IV)
- Consider adding caregiver disutilities to achieve consistency with the inotersen* model
  - 1 caregiver in FAP stages I and II, and 2 caregivers in FAP stage III
- Consider revising offer to a simple PAS

[redacted]

*Inotersen for treating hereditary transthyretin-related amyloidosis: under publication evaluated through Highly Specialised Technologies process

Additional evidence submitted by Alnylam

The company has presented the following additional *evidence/model changes* for consideration:

Changes in response to committee suggestions:

- Inclusion of caregiver disutilities based on the inotersen model (1 caregiver in FAP stages I and II, and *2 caregivers in* FAP stage III)
- Incorporated a stopping rule in which patients discontinue patisiran on progression to PND IV (FAP stage III)
- Incorporation of a revised simple PAS discount *(commercial in confidence)*

Further changes:

- Incorporated a stopping rule (*as described above*) and re-introduced the log-normal time-to-treatment discontinuation function to all other model health states

- Additional disutilities applied to the BSC group which are intended to reflect the additional impact of GI-related autonomic dysfunction
  - ***Amended model*** *(based on ERG feedback before 3rd meeting) autonomic-related disutility applied to patients who receive BSC after they discontinue patisiran*
  - ***Amended model*** *(based on ERG feedback before 3rd meeting) a 5-year cap on within-state disutility was implemented among patients who receive BSC after they discontinue patisiran*
- An assumption that mortality is driven by NTpro-BNP alone and is independent of PND score

[redacted]

Changes in response to committee suggestion

New evidence: Inclusion of caregiver disutilities

Company comment:

- ***Revised caregiver disutilities*** based on an assumption of one full-time caregiver for each patient with a PND Score of I, II, IIIA, and IIIB; and two caregivers for patients with PND Score IV ***applied*** (as accepted in inotersen* evaluation)

ERG comment:

- ERG believes that for the sake of consistency, it is reasonable to include these additional caregiver disutilities in the patisiran model

**Inotersen model uses a conservative approach by applying caregiver disutilities for 1 full-time caregiver in FAP stages I and II, and 2 full-time caregivers in FAP stage III*

Is the committee satisfied with the implementation of caregiver disutilities in the updated company model?

[redacted]

Changes in response to committee suggestion

New evidence: Modelling discontinuation of patisiran treatment on progression to PND IV

Company comment:

Stopping rule implemented in model to simulate impact of discontinuing patisiran treatment when progressing to PND IV – *(company also re-introduced time-to-treatment discontinuation (TTD) function; see slide 16)*

In the updated company model:

- Patients can discontinue patisiran in any health states, with per-cycle probabilities determined by log normal time-to-treatment discontinuation function fitted to data from APOLLO
- Patients who discontinue patisiran will subsequently receive BSC - prognosis governed by BSC transition probabilities
- HRQoL for patisiran discontinuers assumed to decrease according to the slope of the time-dependent HRQoL functions for BSC, starting from patient's last "on treatment" utility value
  - Applied using weighted average method: cohort already off-treatment in previous cycle and cohort discontinuing in current cycle
- Transition matrices were adjusted to avoid the possibility that patients could improve to a lower PND Score after reaching PND Score IV

[redacted]

HRQol: Health related quality of life

Changes in response to committee suggestion

New evidence: Modelling discontinuation of patisiran treatment on progression to PND IV (continued)

ERG comment:

Identified issues around estimation of HRQoL in patisiran discontinuers

- Problematic given the assumptions regarding time- and state-dependent utilities (usually governed by health states and not time)
- A more appropriate approach would use tunnel states to account for subsequent HRQoL trajectory of patients in a given health state who discontinue patisiran at each timepoint – semi-Markov or patient-level simulation (states would explicitly account for changes in HRQoL e.g. incident and prevalent discontinuers)
- It would not be possible to appropriately implement the intended assumptions using the existing Markov model structure

- ERG asked the company to clarify the assumptions underpinning implementation of post-discontinuation utility in the model
  - Company stated these were the same as those used in the inotersen* model - ***ERG is unable to confirm this and due to the complexity of the formulae in the model is unable to check its implementation and effect***

**The inotersen company have attempted to account for time in state, using a simulation study in VB (informed by the transition probabilities for the model)*
Separate utility data are generated from the simulation study accounting for time in stage for each model cohort (inotersen on treatment, inotersen off treatment and BSC) by stage

[redacted]

Is the committee satisfied with the implementation of discontinuation of patisiran in the updated model?

New evidence: re-introduction of log-normal time-to-treatment discontinuation function

Company comment:

- Time-on-treatment was included in original submission (log-normal fitted to data in APOLLO), but was removed from the model in the ERG-preferred analysis
- In parallel with other discontinuation rules, ***TTD was re-introduced into the model***
  - Discontinued patients receive BSC and utility decreases in line with BSC
- Using log-normal function impact is two-fold:
  - It helps estimate how patients perform on BSC whether they are discontinuing treatment for any reason or progressing to PND Score IV
  - It improves consistency of other assumptions that being implemented (e.g. stopping rule)
- Log-normal function to extrapolate discontinuation data for patisiran is reasonable – measured by goodness of fit and plausibility of long-term extrapolation
  - Which allows for a persisting, but decreasing rate of stopping treatment over time

Treatment discontinuation is modelled using a log logistic-curve in the inotersen model

ERG comment:

- The simultaneous application of TTD function from APOLLO and company's PND IV stopping rule may overestimate the joint discontinuation risk
- Inappropriate to use inotersen TTD function as this relates to a different technology - ***ERG believes these analyses should be disregarded***

[redacted]

Does the committee consider appropriate to apply the time-to-treatment discontinuation function in the model?

New evidence: additional GI-related disutilities applied to the BSC group

Company comment:

- Autonomic neuropathy is present in 56% to 65% of patients with hATTR
- Impact of autonomic dysfunction is significant (most common symptoms are GI effects), but difficult to comprehensively incorporate aspects of autonomic dysfunction in the model
- ***Company sought to further capture the GI aspects of autonomic dysfunction in the model by adding additional disutility***
- Adding disutility mirror the characteristics of prevalent genotype-phenotype of UK population
  - 75% of UK patients suffer from autonomic dysfunction (presentation with T60A mutation)
  - In APOLLO presence of T60A mutation was relatively small
- EQ5D utilities in the overall APOLLO study cohort may underestimate the amount of dysautonomia present in the UK hATTR population
  - Therefore in the BSC group applied UK disutility values related to functional digestive disorders and 'other' intestinal disorders identified by ICD diagnosis code
    - Patients with PND>I incur further time-independent GI-related disutilities, based on values from a UK catalogue of utility values for chronic conditions in the UK (Sullivan et al)
    - Patients in PND II incur a disutility of ***-0.0727*** during each model cycle
    - Patients in PND IIIA to IV incur a disutility of ***-0.1243*** during each model cycle

[redacted]

Does the committee consider appropriate to apply additional GI-related disutilities to the BSC group?

EQ-5D: EuroQol 5-Dimensions; ICD: International Statistical Classification of Diseases and Related Health Problems

New evidence: additional GI-related disutilities applied to the BSC group (continued)

ERG comment:

- Concerns about new assumption:
  - If inclusion of further GI-related disutilities is intended to quantify other factors which are not reflected in the definition of PND- and NT-proBNP-related health states → it means it is unclear what the time-dependent utilities are intended to reflect
  - Inclusion of both effects on HRQoL ***may represent double-counting*** and, ***may overestimate the negative health impact*** of the disease on patients treated with BSC

- GI-related disutilities to BSC patients with PND>1 at all timepoints implies:
  - Patients will experience symptoms indefinitely
  - Impact of GI-related symptoms not reflected in the time- and state-dependent EQ-5D estimates
    - hATTR amyloidosis is a progressive disease in which symptoms accumulate over time → this assumption is unlikely to be reasonable

- No information provided whether health states valued in Sullivan reflect specific health impacts that are not captured in the existing time- and state-dependent utilities

- Application of constant disutilities to all patients with PND>I together with the time- and state-dependent EQ-5D estimates is inconsistent with the predictions of the regression model fitted to EQ-5D data from APOLLO

[redacted]

ERG: Inclusion of additional disutilities for BSC increases the magnitude of the QALY losses in the BSC group and reduces the ICER for patisiran versus BSC by around [redacted]

New evidence: GI-related related disutilities applied in the updated model *after discontinuation*

Company comment:

- Patisiran discontinuers do not incur full GI-related disutilities
  - Amended version after engagement with ERG: discontinuers incur 10% of the full GI-related disutilities only; which increases by 10% in each cycle until the 5 year cap is reached

ERG comment:

- If patisiran discontinuers do not incur any of the additional GI-related disutilities
  - Even after discontinuation, patisiran provides a lifetime protective effect against GI-related autonomic dysfunction → not appropriate, should be applied to all patients who are receiving BSC (regardless of previous treatment)
- After engagement: *an amended version of the updated model provided*
  - *ERG believes the company applied a fixed 10% disutility in every cycle*
  - Still assumes some degree of protective effect of the drug after discontinuation
- ***ERG presented additional analyses to implement GI-related disutilities for discontinuers***
  - GI-related disutilities applied immediately for discontinuers and BSC
  - GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)

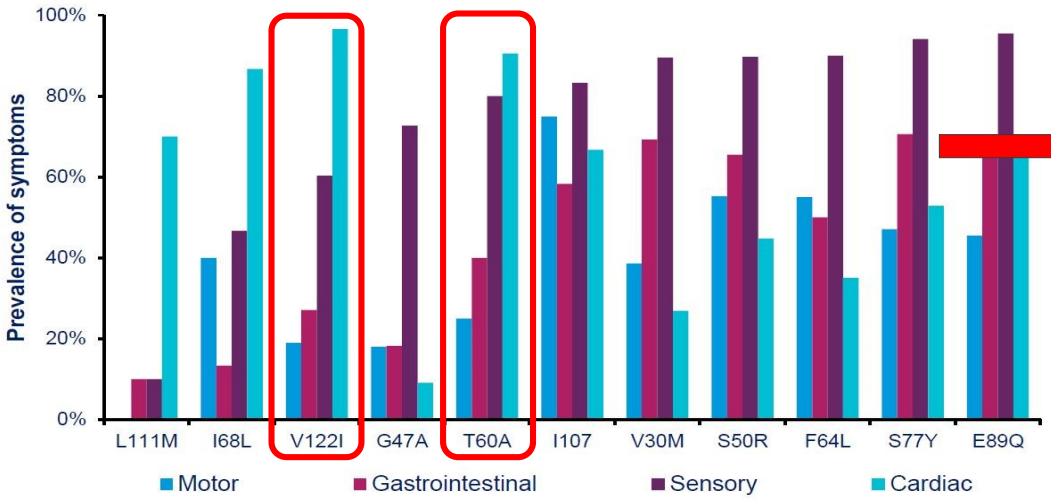
[redacted]

If accepting application of additional GI-related disutilities, which disutility direction does the committee consider to be appropriate?

New evidence: hATTR amyloidosis mortality risk does not increase with increasing PND score

Company comment:

Leading cause of death in hATTR amyloidosis in the UK is cardiomyopathy



Source: Figure 1 in company additional evidence document

THAOS registry data presented to articulate existence of mixed phenotypes

V122I and T60A amyloidosis present with a mixed phenotype

- V122I presents with cardiac complications (96.6%); 60.3% sensory neuropathy, 19.0% motor neuropathy, and 27.1% GI (autonomic) symptoms

- V122I mutation (previously thought to be the most cardiomyopathy-specific pathogenic variant) should be recognized for its potential to cause a wide range of symptoms

- *Cardiac mortality data source included in submission (Gillmore) largely comprised V122I and T60A mutations – 2 mutations not significantly represented in APOLLO study*

Company: Population described in Gillmore broadly applicable to the patient population enrolled in the patisiran APOLLO study

[redacted]

- Since both groups of patients present with a ***mixed phenotype*** comprising ***both polyneuropathy and cardiomyopathy features***

New evidence: hATTR amyloidosis mortality risk does not increase with increasing PND score (continued)

Company comment:

- Choice to use either NT-proBNP mortality (Gillmore 2017) or PND-Score mortality (Suhr 1994) yield similar life years gained (LYG) in the BSC arm (point raised by ERG during engagement)
- Estimated LYGs in the BSC arm is numerically similar to the estimated LYG in the BSC arm of the inotersen model (with and without PND score)

LYG in BSC arm	Patisiran NT-proBNP only	Patisiran PND score only	Inotersen ERG preferred analysis	Inotersen revised company base case (PND only*)
Discounted	10.97	8.92	9.2	8.47
Undiscounted	14.53	11.05	11.03	10.51

Source: Table 1 in company additional evidence document

- Estimation of mortality by PND only in patisiran model was criticised by ERG – Suhr: small cohort study, 1/3 of patients had CM – included in original patisiran model for completeness

Company: recognised committee's previous decision* but emphasised that *most appropriate approach for modelling mortality is to exclusively use cardiomyopathy* - ***model the effects of patisiran and BSC on mortality through NT-proBNP alone***

**Cardiomyopathy on mortality excluded (accepted by evaluation committee) from the inotersen model - applying 2.01, 2.42 and 9.53 by FAP stages (based on Suhr 1994)*

[redacted]

ERG comment: Disagrees with company that LYG estimates for inotersen are similar

New evidence: hATTR amyloidosis mortality risk does not increase with increasing PND score (continued)

HRs applied in company models

Health states	Mortality HR applied in health states	
	Company's original model (PND and NT-proBNP mortality risks)*	Company's updated model (NT-proBNP risks only)
PND 0-II, NT-proBNP<3,000pg/mL	2.01	2.01
PND IIIa and IIIb, NT-proBNP<3,000pg/mL	2.62	2.01
PND IV, NT-proBNP<3,000pg/mL	9.53	2.01
PND 0-II, NT-proBNP≥3,000pg/mL	4.12	4.12
PND IIIa and IIIb, NT-proBNP≥3,000pg/mL	5.35	4.12
PND IV, NT-proBNP≥3,000pg/mL	19.49	4.12

Source: Table 1 in ERG addendum

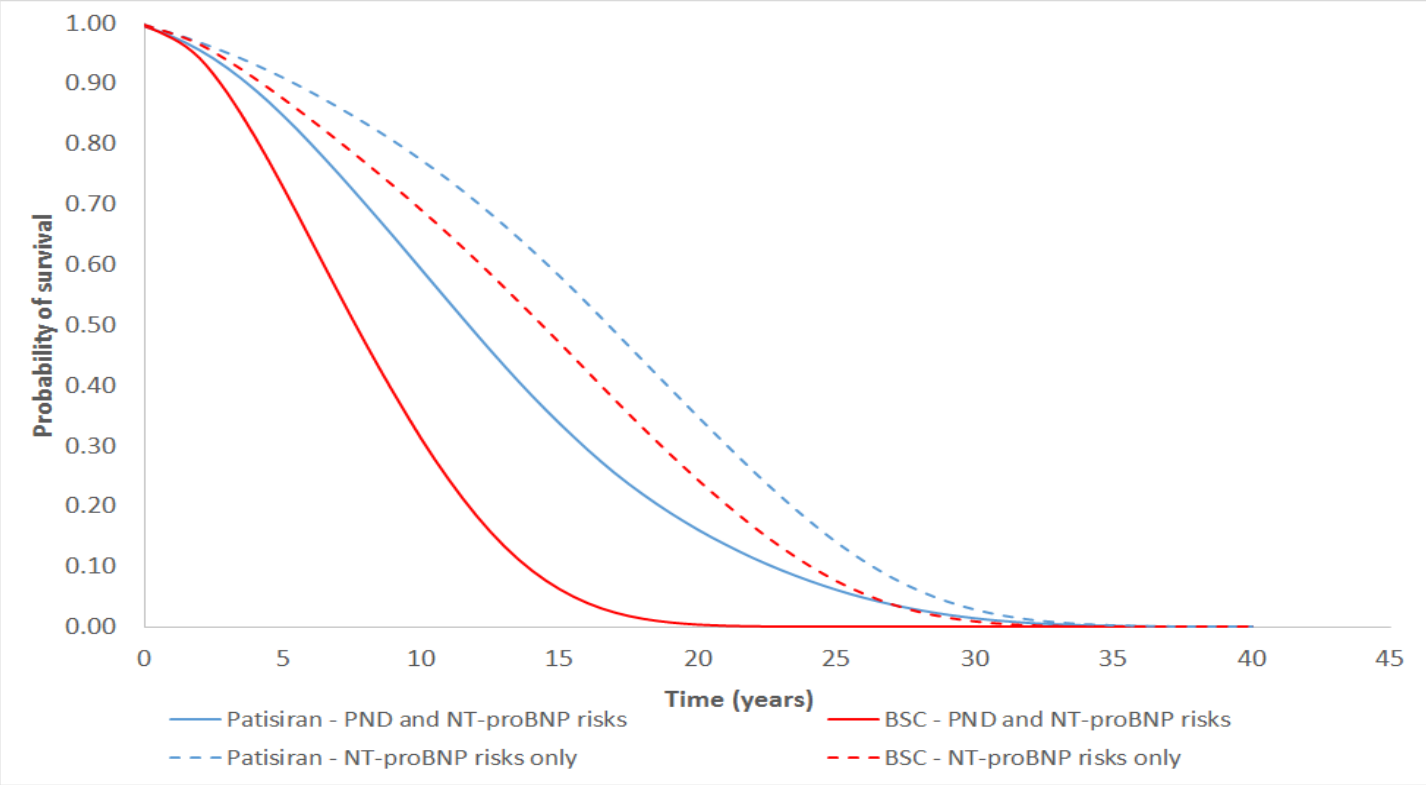
Company comment: ERG considered a scenario in which PND-related mortality was removed from the model → reasonable, since most patients with hATTR amyloidosis die from cardiac complications or wasting, rather than from polyneuropathy

ERG comment: this analysis was originally presented to highlight the significant impact of the assumption of time- and state-dependent improvements in HRQoL for patisiran and time- and state-dependent worsening in HRQoL for BSC on the ICER for patisiran

[redacted]

ERG comment: new survival assumptions have a substantial impact upon the expected survival, QALYs, costs and cost-effectiveness estimates

New evidence: hATTR amyloidosis mortality risk does not increase with increasing PND score (continued)



Source: Figure 1 in ERG Addendum

Figure presents the modelled survival trajectories for the patisiran and BSC groups:

a) Including both PND and NT-proBNP risks (as per the company's original model)
b) Including NT-proBNP risks only (as per the company's updated model)

Do clinical experts believe that increasing PND score has no impact on mortality?

[redacted]

New evidence: hATTR amyloidosis mortality risk does not increase with increasing PND score (continued)

ERG comment: Removal of the PND-related mortality HRs leads to:

- Lower modelled risk of death for patients in all health states, except for PND0-II, NT-proBNP<3,000pg/mL
- Marked increase in expected survival durations for patients in both patisiran and BSC groups

- **Issues with new model assumption:**
  - Mean undiscounted survival for BSC group **8.27** (original model); **14.53** years (company's new model) → increase of **6.27** years
  - Incremental QALYs gained for patisiran group are increased (per cycle QALY gains in the BSC group become negative after 2 years and remain negative for subsequent cycles)
  - Mean cost of BSC are more than doubled as a consequence of extended survival and the fact that all extended survival time for BSC patients spent in PND IV
- Committee previously accepted company's original approach: modelling mortality risks by combining **both** polyneuropathy and cardiac involvement → new approach inconsistent
- Company's original submission included validation of original model by clinical experts
  - ERG does not consider the company's updated mortality assumptions to be reasonable and questions whether updated modelled survival estimates would remain plausible to experts

[redacted]

- However, for consistency with assumption accepted for inotersen appraisal: ***ERG provided additional analyses in which only PND-related mortality risks are used***

QALY: Quality-adjusted life year

New evidence: Company's updated base-case and scenario analyses provided by ERG (including revised PAS)

	Absolute			Incremental			
	LYGs	QALYs	Cost	LYGs	QALYs	Cost	ICER (per QALY gained)
Company's new base-case							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	£80,730
BSC	14.53	-4.67	[redacted]	-	-	-	-
Scenario 1 – model including PND and NT-proBNP risks							
Patisiran	12.79	4.58	[redacted]	4.52	6.21	[redacted]	[redacted]
BSC	8.27	-1.63	[redacted]	-	-	-	-
Scenario 2 – time-dependent utilities capped at 5-years, no GI-related disutilities							
Patisiran	16.62	4.04	[redacted]	2.09	7.47	[redacted]	[redacted]
BSC	14.53	-3.43	[redacted]	-	-	-	-
Scenario 3 – no caregiver disutilities							
Patisiran	16.62	4.31	[redacted]	2.09	7.14	[redacted]	[redacted]
BSC	14.53	-2.83	[redacted]	-	-	-	-
Scenario 4 – PND IV stopping rule only							
Patisiran	16.74	4.33	[redacted]	2.21	9.00	[redacted]	[redacted]
BSC	14.53	-4.67	[redacted]	-	-	-	-
Scenario 5 – time to treatment discontinuation curve only							
Patisiran	17.94	6.95	[redacted]	3.41	11.45	[redacted]	[redacted]
BSC	14.53	-4.50	[redacted]	-	-	-	-

[redacted] ICER: Incremental cost-effectiveness ratio

The company's updated model applies a simple price discount (commercial in confidence)

New evidence: ERG exploratory analyses

The ERG has undertaken additional exploratory analyses using the amended version of the company's updated model (including changes in amended model)

All of the ERG's exploratory analyses have the following features:

i. Carer disutilities are included in all analyses. These are applied outside of the minimum/maximum utility caps

ii. All analyses include the PND IV stopping rule and the APOLLO time-to-treatment discontinuation function

iii. All analyses include the current PAS discount for patisiran

iv. GI-related disutility is applied equally to patients receiving BSC and to patients who have discontinued patisiran (*3 scenarios – 100%, 50% and 0%*). This is applied outside of the minimum/maximum utility caps

[redacted]

ERG exploratory analyses including PAS discount

Option	LYGs	QALYs	Cost	LYGs diff.	QALYs diff.	Cost diff.	ICER
Company's updated model base case							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	£80,730
BSC	14.53	-4.67	[redacted]	-	-	-	-
Analysis 1. Updated model, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	16.62	3.55	[redacted]	2.09	8.23	[redacted]	[redacted]
BSC	14.53	-4.67	[redacted]	-	-	-	-
Analysis 2a. Updated model, PND and NT-proBNP mortality HRs, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	12.79	4.37	[redacted]	4.52	6.00	[redacted]	[redacted]
BSC	8.27	-1.63	[redacted]	- -	-	-	
Analysis 2b. Updated model, PND and NT-proBNP mortality HRs, GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)							
Patisiran	12.79	4.47	[redacted]	4.52	5.73	[redacted]	[redacted]
BSC	8.27	-1.25	[redacted]	- -	-	-	
Analysis 2c. Updated model, PND and NT-proBNP mortality HRs, no GI-related disutilities applied							
Patisiran	12.79	4.58	[redacted]	4.52	5.46	[redacted]	[redacted]
BSC	8.27	-0.88	[redacted]	- -	-		-

[redacted]

ERG exploratory analyses including PAS discount (continued)

Option	LYGs	QALYs	Cost	LYGs diff.	QALYs diff.	Cost diff.	ICER
Company's updated model base case							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	£80,730
BSC	14.53	-4.67	[redacted]	-	-	-	-
Analysis 3a. Updated model, PND mortality HRs only, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	14.25	4.09	[redacted]	3.21	7.09	[redacted]	[redacted]
BSC	11.05	-3.00	[redacted]	- -	-		-
Analysis 3b. Updated model, PND mortality HRs only, GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)							
Patisiran	14.25	4.25	[redacted]	3.21	6.75	[redacted]	£125,256
BSC	11.05	-2.50	[redacted]	- -	-		-
Analysis 3c. Updated model, PND mortality HRs only, no GI-related disutilities applied							
Patisiran	14.25	4.41	[redacted]	3.21	6.42	[redacted]	[redacted]
BSC	11.05	-2.01	[redacted]	-	-		

[redacted]

What is the committee's preferred base case?

Key issues for consideration

- ***Is the committee satisfied with the implementation of caregiver disutilities in the updated company model?***
- A stopping rule was implemented in the model to simulate impact of discontinuing patisiran treatment when progressing to PND IV. ***Is the committee satisfied with the implementation of discontinuation of patisiran in the updated model?***
- The company used log-normal function to extrapolate discontinuation data for patisiran. ***Does the committee consider appropriate to apply time-to-treatment discontinuation function in the model?***
- The company incorporated disutility for functional digestive disorders and 'other' intestinal disorders identified by ICD codes. ***Does the committee consider appropriate to apply additional GI-related disutilities to the BSC group?***
- Patisiran discontinuers incur 10% of the full GI-related disutilities only. The ERG presented exploratory analyses to model uncertainty around GI-related disutilities. ***If accepting application of additional GI-related disutilities, which disutility direction does the committee consider to be appropriate?***
- Mortality has been modelled by using the effect of cardiac involvement only. ***Does the committee believe that removing the PND mortality is realistic?***
- ***What is the committee's preferred base case?***
- ***Has the committee changed opinion on the recommendation of patisiran?***

[redacted]