Public slides

NICE National Institute for Health and Care Excellence

Patisiran for treating hereditary transthyretin-related amyloidosis

Chair's presentation

2nd evaluation committee meeting

Highly Specialised Technologies committee

Lead team: Paul Arundel, Stuart Davis and Mark Sheelan

ERG: School of Health and Related Research (ScHARR)

NICE technical team: Aminata Thiam, Eleanor Donegan, Sheela Upadhyaya

Company: Alnylam

12 February 2019

Key issues

- Mortality has been modelled by combining both the effect of polyneuropathy (PND) and cardiac involvement. Does the committee believe that removing the PND mortality is realistic?
- Which utility trajectory does the committee consider to be most appropriate:
  - one that uses min/max caps ?
  - one whereby the duration of treatment benefit is limited by time ?
- What is the committee's preferred base case?
- Has the committee changed opinion on the recommendation of patisiran?
- Should treatment with patisiran stop when people enter FAP stage 3?

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

*cycle of 6-month

FAP: familial amyloidotic polyneuropathy; PAS: patient access scheme; SPC: summary of product characteristics

Recap: 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 genetic 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 GI symptoms
  • Bladder dysfunction, recurrent infections
  • Cardiac arrhythmias
• Progress to death
	• Cardiomyopathy results in heart failure
	• Heart failure progresses rapidly
	  • Substantial worsening of cardiac function, loss of ability to walk
	• Progress to death

* Data from the National Amyloidosis Centre (NAC)

Recap: Staging of hATTR amyloidosis

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

- familial amyloidotic polyneuropathy (FAP) stage (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

Recap: Summary of evidence

Clinical evidence

- APOLLO key outcomes
  - **mNIS+7** and **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 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

Recap: Summary of evidence

Starting and stopping patisiran

- MA is for treating **hATTR amyloidosis at FAP stages 1 and 2**
- Stopping rule not explicitly reported in SPC

Starting rule

Clinical expert: people with no symptom (FAP 0) would not be treated

Stopping rule

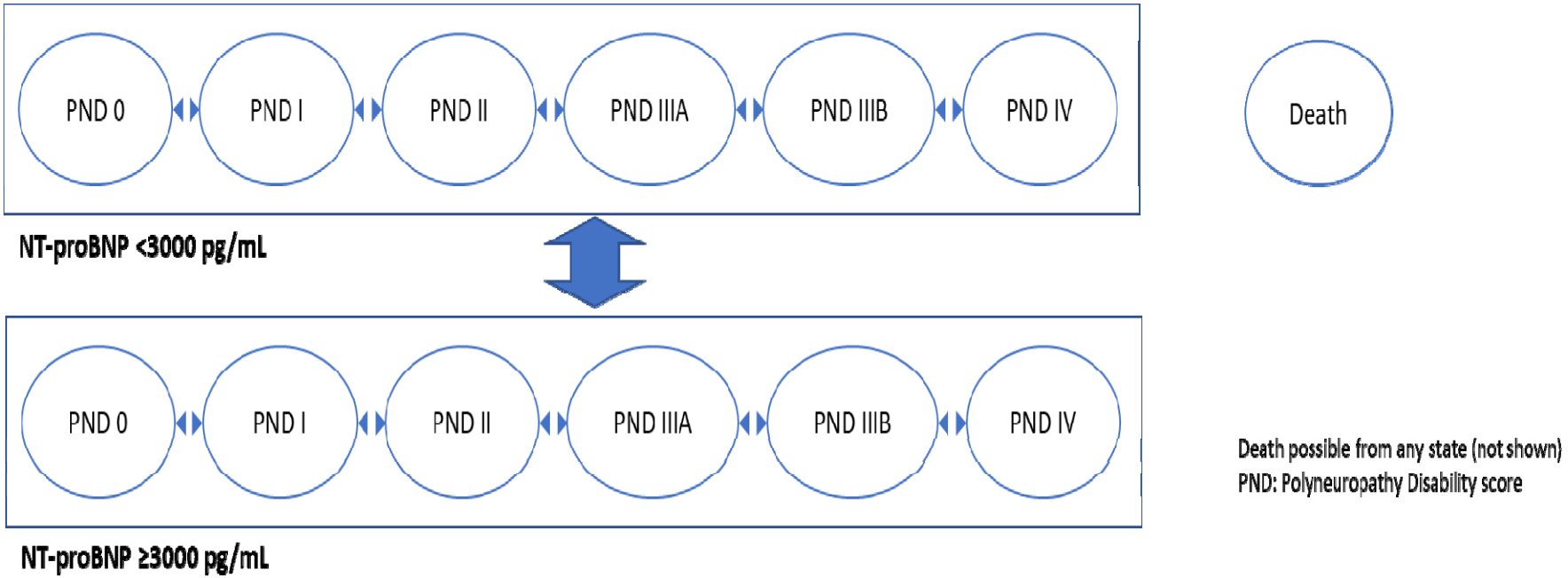
Clinical expert: very few would stop patisiran when progress to FAP 3, only if no more benefit

NHS England: patisiran should be stopped when progress to FAP 3

Economic model: assume continuation treatment in FAP 3 & applied a discontinuation curve to reflect some patients stopping over time

Recap: Summary of evidence

Economic evidence – model structure



- Markov model compares patisiran + BSC vs. BSC
- 12 alive health states defined by a **combination of the severity of polyneuropathy (PND score) 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**

Recap: Summary of evidence

Economic evidence - utilities

Each health state starts with a given utility, which then either increases or decreases each month for the patisiran/BSC arm, up to or down to a cap

- Model includes utilities from APOLLO (EQ-5D-5L mapped to EQ-5D-3L)
- A Maximum and minimum utility cap was applied to avoid “ceiling effects”
- Additional cap to ensure utilities do not exceed general population (Kind et al. 1999)

Monthly utility changes were taken from a regression analysis

- Company’s regression analysis assumed PND score & treatment by time as significant covariates
- A utility can vary within the same PND health state depending on treatment group

Applied a caregiver disutility of 0.01 in PND IV health state (Alzheimer’s, AGNSS tafamidis report)

Recap: 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 to general population mortality risk, for each health state
  - Assumed that increasing mortality risk associated with increasing polyneuropathy (PND) and cardiac involvement (NT-proBNP)

Recap: Summary of evidence

Cost-effectiveness results - company's base case (PAS price)

	Total costs (£)	Total QALYs		Inc. costs (£)	Inc. QALYs		Cost per QALY gained (£/QALY)
		undisc.	disc*.		undisc.	disc*.	
Probabilistic							
Patisiran	[redacted]	NR	8.42	[redacted]	NR	8.11	[redacted]
BSC	[redacted]	NR	0.31	-	-		-
Deterministic							
Patisiran	[redacted]	9.86	8.52	[redacted]	9.73	8.30	[redacted]
BSC	[redacted]	0.13	0.22	-	-		-

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

*based on differential discount rates of 1.5% for health outcomes and 3.5% for costs which were not accepted by committee

Recap: Summary of evidence

Cost-effectiveness results – ERG preferred (PAS price)

Option	QALYs (disc.)	Costs	Inc. QALYs (disc.)	Inc. costs	ICER (per QALY gained)
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 for cost and heath benefits 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 et Brazier (rather than Kind et al.)					
Patisiran	8.54	[redacted]	8.32	[redacted]	[redacted]
BSC	0.22	[redacted]	-	-	-
(5) Mortality effect from Gillmore et al was 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]	-	-	-

Recap: Summary of evidence

Cost-effectiveness results – ERG exploratory analysis (PAS price)

Option	QALYs (disc.)	Costs	Inc. QALYs (disc.)	Inc. costs	ICER (per QALY gained)
(6) ERG-preferred analysis					[redacted]
(7) Change of utility over time is removed (removal of [redacted] for patisiran and [redacted] for BSC, per month)					
Patisiran	5.58	[redacted]	3.87	[redacted]	[redacted]
BSC	1.71	[redacted]	-	-	-
(8a) Utility values from Stewart et al - Val30Met mutation (rather than APOLLO)					
Patisiran	5.75	[redacted]	3.51	[redacted]	[redacted]
BSC	2.25	[redacted]	-	-	-
(8b) Utility values from Stewart et al - other mutations (rather than APOLLO)					
Patisiran	5.36	[redacted]	3.41	[redacted]	[redacted]
BSC	1.95	[redacted]	-	-	-
(9) Utilities: lower utility assumed for high NT-proBNP states (rather than similar irrespective of high or low NT-proBNP states)					
Patisiran	7.08	[redacted]	6.73	[redacted]	[redacted]
BSC	0.35	[redacted]	-	-	-

NICE

Recap: Summary of evidence

Cost-effectiveness results – ERG exploratory analysis (PAS price)

Option	QALYs	Costs	Inc. QALYs	Inc. costs	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 PND-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]	-	-	-

NICE

Committee's key considerations - ECM1 (1/2)

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	• Absence of clear commissioning criteria thus clinicians are likely to continue treatment in FAP 3 • No formal rule included in model; application of discontinuation curve to reflect some discontinuation
Safety	Manageable
Model structure	• Broadly reasonable but does not capture all aspects of disease because model is based on combination of PND and NT-proBNP which only capture mobility impairment (rather than FAP which would have captured autonomic symptoms too) • Unlikely to reflect true expected cost effectiveness
Disease progression in extrapolated period (>18 months)	• Uncertainty because method converting 18-month data to 6-month data cycles is inappropriate • Use of 9-month data would have been informative

Committee's key considerations - ECM1 (2/2)

Issue	Committee's consideration

Utility regression model	• Alternative model with greater face-validity is welcomed
	• Regression model is unreliable because
	  • incorrect terms were included
	  • max/min cap arbitrarily chosen

Mortality	Although company's approach is convoluted, circular and uncertain, the committee accepted it because of the lack of other evidence
Discount rate	3.5% should be applied for both costs and health effects
ICERs	Most plausible ICER likely to lie between ERG's preferred analysis ([redacted]) and scenario in which the change in utility over time was removed [redacted])
QALY weighting	Patisiran does not meet the criteria for applying a QALY weight
Managed access arrangement	Committee was convinced of the patisiran's clinical benefit; uncertainties lie with how the clinical benefit is translated in economic data (e.g., model structure, utilities), therefore further clinical data collection is unlikely to resolve the uncertainties

ECD consultation responses

- Web comments from:
  - Comparator company (Akcea, inotersen)

- Consultee comments from:
  - Clinical experts (P. Hawkins; C. Whelan endorsed by Royal College of Pathologist)
  - Company (Alnylam)

Stopping rules

ECD consultation responses

- **Web comment**: NICE to review treatments within their license (no stopping rule for stage 3 which is outside of the MA); Committee to resolve ambiguity on stopping rule
  - No formal stopping rule applied in model so patients could continue treatment indefinitely; a treatment discontinuation curve was applied– best reflection of hATTR clinical context?
  - Significant uncertainty into model: ICERs reflecting stages 1 to 3 disease estimate costs and benefits of stages 1 and 2 disease only

Burden of continuous infusion

ECD consultation responses

- **Web comment:** patient and carer burden on patisiran's mode of administration (intravenous infusion once every 3 weeks) is not clearly captured in the ECD
  - ARC (Amyloidosis Research Consortium) patient survey: 50% of patients rated 'mode of administration' as important /very important, and 59% rated 'place of administration' as important or very important
  - Additional cost such as transport and opportunity cost of paid employment
  - This justifies difference (of cost) between BSC in patisiran vs BSC other hATTR therapies

Mean TTR reduction and amyloid regression

ECD consultation responses

- **Web comment**: no direct peer-reviewed evidence of amyloid regression (clearance of amyloid deposits) with patisiran. No validation of clinical meaningful reduction in TTR amyloidosis. Turnover and production of TTR varies therefore benefit of knockdown varies between individuals
- **Clinical expert:** mean TTR reduction > 80% lead to sustained benefit and likely to further improve function of organs and tissues affected by ATTR:
  - 5,000 patients with amyloid light-chain amyloidosis (NAC)
  - Analogous with knock-down treatments of all other types of amyloidosis
  - Patisiran's long term studies suggest benefit of patisiran is maintained and prolonged
  - Positive experience of compassionate access programme and EAMS: 10 patients treated for over a year;

[redacted]

[redacted]

Mean TTR reduction measurements and long-term effect

ECD consultation responses

- **Web comment**: most appropriate measurement of TTR reduction is pre-dose mean (rather than post-dose mean max) and median of whole sample at month 3, 6, 9, 12, 15 and 18
  - Mean TTR of 87.8% as the “mean maximal reduction”
    - Lack of statistical definition; interpreted as the highest individual data point per patient out of many possible data points, without consistency in timeframe of measurement
    - Statistical experts: not a valid way to report data and therefore unsure if ECD interpretation is correct
  - TTR reduction measurements collected post dose in APOLLO (rather than pre dose)
    - Not a valid methodology for determining reduction over time
    - May lead to a larger decrease due to immediate impacts of patisiran dosing
- **Web comment**: persistent reduction in TTR should not be observed after 18 months once use of treatment has stabilised; anecdotal observations of single patients are not representative of mean treatment effect
- **Web comment**: appropriateness of 80% threshold?

Model structure based on PND score

ECD consultation responses and ERG critique

- **ECD** 'PND is not the best overall descriptor of the condition because it only captures mobility impairment…, a FAP model would have also captured the autonomic symptoms'.
- **Company:** PND Score has better discrimination in measuring changes in disease severity (has 6 levels of change vs. FAP stage only has 4 levels)
- **ERG comments:**
  - Model is defined on PND and NT-proBNP score and exclude states/events associated with other key impacts of the disease (i.e. autonomic dysfunction). This is a limitation which introduces uncertainty around expected cost-effectiveness
  - A model defined on FAP stage:
    - Would have required fewer health states
    - Would have required APOLLO data to "stretched" less but may have resulted in a model less sensitive to changes
    - Would not have fully addressed issues relating to definition of model health states
  - Previous FAP-based model include tafamidis model submitted to AGNSS, inotersen model submitted by Akcea, evaluation report of patisiran and inotersen submitted by Institute for Clinical and Economic Review (ICER)

Disease progression and transition matrices

ECD consultation responses and ERG critique

- **Company:**
  - 6-month cycle is consistent with assessment and follow-up times in clinical practice
  - Conversion from 18 to 6 months is mathematically challenging; introduces small bias in favour of BSC
  - 9-month is not a pre-specified final endpoint and is less reliable than using 18-month data
- **ERG comments:**
  - Issues in applying conversion are partly a consequence of sparsely populated transition matrices (for patisiran, 29 of 144 cells have events; for BSC, 19 of 144 cells have events)
  - Matrices would not have required any adjustment if longer cycle duration had been selected
  - 9-month data is an additional information and, if included in model, may have produced different extrapolation across PND health states
  - Transition matrices have less impact on ICER than utility assumptions

Utilities – regression model (1/2)

ECD consultation responses and ERG critique

- **Company** submitted (at clarification) an expanded regression model which was not taken into account in ERG's preferred analyses; expanded model included treatment group; time; PND score; NT-ProBNP, and a treatment-by-time interaction term
- **ERG** explained that model relied on assumption of constant rate of improvement/worsening and applied minimum/maximum caps; this reduces the ICER for by around [redacted].

[redacted]

[redacted]

Utilities – regression model (2/2)

ECD consultation responses and ERG critique

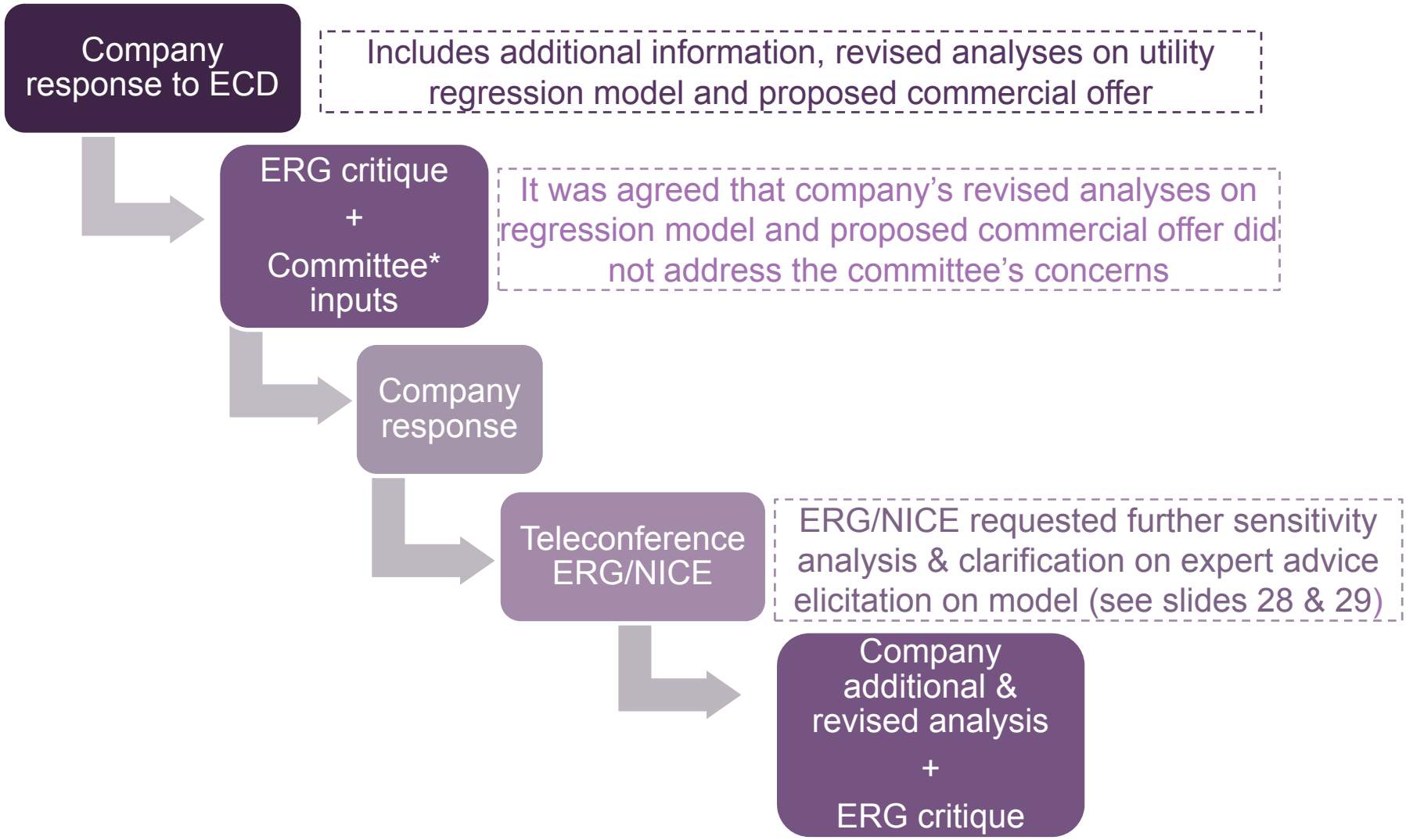
- **Company** consider min/max caps have not been arbitrarily chosen:
  - selection of caps driven by evidence on basis of 25th/75th percentiles of observed EQ-5D data from APOLLO
  - caps represent the "mean best achievable EQ-5D for a given PND state with an undefined level of improvement in other symptoms …(possibly… autonomic and/or cardiac-related symptoms)"
  - **ERG** still believes that the selection of min/max cap values is arbitrary; caps are particularly important as these can override predictions of regression equations after 5-6 years; unclear how caps should be interpreted

- **Company** consider regression analyses do not generate unrealistic values:
  - "unrealistic" values for PND 0 apply to small percentage of patients (most are PND I-IV)
  - PND alone does not drive quality of life
  - Committee's critique is inconsistent with previous NICE TA in multiple sclerosis (TA 533 Ocrevus): committee accepted a patient could change utility without changing EDSS score
  - **ERG** note the 2 approaches are not comparable – Ocrevus model does not include assumption that utility, in a given EDSS health state, can improve over time as consequence of treatment effects on other disease-related factors beyond the EDSS

EDSS: Expanded Disability Status Scale

Company/NICE/ERG interactions prior to ECM2

Purpose of interactions



NICE

*The committee was represented by the committee chair and committee member who is a health economist

Company/NICE/ERG interactions prior to ECM2

Revised analyses

- **Company's revised analyses** in response to ECD:
  - Revised regression model which included all the terms (treatment group; time; PND score; NT-ProBNP, and a treatment-by-time interaction term)
  - Baseline to 18 months: post hoc mixed-model of repeated measures show utility can improve/decrease (patisiran/BSC) within same PND score

  - After 18 months: because *"neither of [patisiran/BSC] curves was approaching a plateau by trial end"*, utilities were extrapolated based on a time-dependent effect

Company/NICE/ERG interactions prior to ECM2

Revised analyses

- **ERG/committee critique:**
  - Max/min utility caps are a consequence of inappropriately extrapolating results from the repeated measures mixed-model. **Company should consider alternative models** that better represent the data (e.g., Tobit model)
  - ERG queried the rationale for the extrapolation of utility benefit post 18 months
  - Unclear what the experts were asked when asked to validate the approach to the extrapolation of utility (e.g. interpretation of definition/values of utility caps or whether these met their expectations regarding additional mean health gains/losses over and above PND)
  - Previous FAP-based models* do not assume continuously improving/worsening utility in each FAP state
  - Reasonable to explore impact of using alternative utilities from the literature

- The **company disagreed with ERG/committee critique**:
  - Tobit model would not solve the capping issue
  - Regression model allows estimation of utility at any given time (rather than 9 and 18 months); the curve presents actual observed data from APOLLO; consequently the sentence *"neither of these curves was approaching a plateau by trial end"* was not an interpretation of model result, but the observed clinical data from the study.

NICE

*Previous FAP-based model include tafamidis model submitted to AGNSS, inotersen model submitted by Akcea, evaluation report of patisiran and inotersen submitted by Institute for Clinical and Economic Review (ICER)

Company/NICE/ERG interactions prior to ECM2

Revised analyses

- Following a teleconference with NICE and ERG it was agreed that a Tobit model was not required as it would not address the primary concern of utility capping, **company provided a revised based case based on 2 alternative scenarios which explores assumptions whereby the duration of treatment benefit is limited by time**
  - Regression model does not rely on capping system
  - Incorporation of attenuation of benefit for patisiran based on the arbitrary periods of time to:
    - 7 years
    - 5 years (based on ERG stating that constraints on min/max values override regression equation outputs in 5-6 years)
    - 4 years
  - Company consider the above analysis to be conservative (utility in BSC does not worsen) which is clinically implausible and in conflict with expert clinical opinion received from NAC*.
  - Company could not pursue alternative modelling in further detail due to limited time; but note that if an approach were taken to follow the NAC opinion, it would lower the ICERS
  - Further information of how clinical advice on utility values was elicited was also provided
- ERG believes that it may be appropriate to consider a broader range of timepoints; this is explored in additional analyses by the ERG

NICE

NAC: National Amyloidosis Centre

Company/NICE/ERG interactions prior to ECM2

Clinical expert validation of utility values in model

- **Query:** Was clinical advice requested on suitability of utility caps or were experts asked to validate the clinically plausibility of the modelled utility profile within the PND health states?
- **Response: meetings with clinical experts at NAC**
  - September 2017 – concept validation of model structure based on PND with inclusion of cardiac health states (NT-pro BNP) and projection of patisiran benefits post 18 months (patisiran improve and BSC decline as per natural history of the disease)
  - June 2018 – external validation of the model:
    - Total QOL changing over time within PND health state and between treatment arms (clinical experts noted that QOL is driven mainly by autonomic symptoms)
    - Validation of capping approach to avoid implausible results post 18 month (clinical experts considered it was conservative to limit decline with BSC)
  - December 2018 (post ECD) – meeting to consider committee concerns with model
    - 0-18 months: utilities varying by treatment and time within PND score (observed EQ-5D data)
    - Post 18 months: capping is reasonable approach, patisiran treatment effect expected to last long-term whereas BSC patients expected to get worse with time

NICE

NAC: National Amyloidosis Centre

Company new analyses

Scenarios A1, A2, B1 and B2 - definition

ERG preferred analysis (accepted by committee):

- Correction or errors
- Equal discount rates: 3.5%
- Recalculated starting state distribution:
- Ara and Brazier general population
- Adjusted mortality calculation: mortality effect of cardiac involvement was removed for low NT-proBNP states

SCENARIO A1

1. Utility regression model include all terms
+
2. Inclusion of PND-related caregiver (1 per patient in each health state; as per inotersen submission)*

SCENARIO A2

SCENARIO A1 (with no min/max caps)
+
Loss of effect (7, 5 or 4 years)

SCENARIO B1

SCENARIO A
+
3. Removal of mortality associated with PND

SCENARIO B2

SCENARIO B1 (with no min/max caps)
+
Loss of effect (7, 5 or 4 years)

- New company base case = scenario B

NICE

*In original base case, company included a caregiver disutility of 0.001 for patients with PND IV

Company and ERG's analysis on scenario A

The company explored arbitrary timepoints (4, 5 and 7 years); ERG explored additional broader range of timepoints (2, 3, and 6 years) on scenario A

	QALYs	Costs	Inc. QALYs	Inc. costs	ICER	Δ ICER
Company scenario A1 (utility regression all terms + 1 carer)						
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BSC	[redacted]	[redacted]	-	-	-	
Company scenario A2 (A1 + "Loss of effect" at 2 years)						↑↑
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	-	-	-	
Company scenario A2 (A1 + "Loss of effect" at 3 years)						↑
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	-	-	-	
Company scenario A2 (A1 + "Loss of effect" at 4 years)						↑
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	-	-	-	
Company scenario A2 (A1 + "Loss of effect" at 5 years)						↓
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	-	-	-	
Company scenario A2 (A1 + "Loss of effect" at 6 years)						↓
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	-	-	-	
Company scenario A2 (A1 + "Loss of effect" at 7 years)						↓
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	↑↑

ERG additional timepoint

ERG additional timepoint

ERG additional timepoint

shows larger increase than ↑

Company and ERG analysis on scenario B

	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company scenario B1 (utility regression all terms + 1 carer + no PND mortality)					
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			
Company scenario B2 (A1 + "Loss of effect" at 4 years)					
Patisiran	NA	NA	NA	NA	[redacted]
BSC	NA	NA	NA	NA	-
Company scenario B2 (A1 + "Loss of effect" at 5 years)					
Patisiran	NA	NA	NA	NA	[redacted]
BSC	NA	NA	NA	NA	-
Company scenario B2 (A1 + "Loss of effect" at 7 years)					
Patisiran	NA	NA	NA	NA	[redacted]
BSC	NA	NA	NA	NA	-

NA: the company did not provide information QALYs and costs

ERG comments:

- Scenario B: ICERs are more than [redacted] per QALY lower than ICERs for Scenario A
- **Scenario B does not reflect ERG's preferred scenario**; whilst there is uncertainty surrounding the relationship between PND score and mortality risk, the ERG's clinical advisors believed that increased PND is likely to be associated with increased mortality risk. Hence the ERG has not considered this scenario further

Company and ERG analyses

ERG comments:

- Able to replicate company's results; analyses implemented without error
- Inclusion of PND-related caregiver burden may be reasonable
- Scenario A2 and B2 (loss of effect after time period): there is considerable uncertainty on duration of improvement/worsening in HRQoL associated with non-PND-specific symptoms in both patisiran and BSC groups:
  - <4 years: marked increase of ICER compared base case scenario A1
  - at 4 or 5 years: ICERs similar to scenario A1 (utility caps defined according to 25th/75th percentiles of EQ-5D scores). This is because caps take effect around these timepoints for most of model health states therefore there is a minimal impact on ICER.
  - at 7 years: ICER [redacted]; this is because patisiran group is assumed to accrue more QALYs, and BSC group is assumed to generate fewer QALYs, relative to scenario A1

Additional company comments

ECD consultation responses

- Managed access arrangement: additional data, especially long-term data, are going to be extremely important in defining the true value of patisiran therefore a managed access arrangement should be considered
- Application of QALY weighing should be reviewed: QALY-gain in base-case analysis and ERG's analysis are close to 10 and are also conservative. Therefore 'true' QALY value probably meets or exceeds 10
- Potential inequality issues:
  - Application of same QALY weighing for all age groups raises equality issues because it gives preference to therapies for younger patients
  - Disproportionate harm in communities with higher prevalence of specific mutations (e.g., Afro-Caribbean and Irish) if access to patisiran is not provided
- The company acknowledged model limitations in following areas: mortality, resource use, discount rate and other assumptions. In the updated model submitted during consultation, the company used the ERG assumptions for the listed parameters.

Key issues

- Mortality has been modelled by combining both the effect of polyneuropathy (PND) and cardiac involvement. Does the committee believe that removing the PND mortality is realistic?
- Which utility trajectory does the committee consider to be most appropriate:
  - one that uses min/max caps ?
  - one whereby the duration of treatment benefit is limited by time ?
- What is the committee's preferred base case?
- Has the committee changed opinion on the recommendation of patisiran?
- Should treatment with patisiran stop when people enter FAP stage 3?