Slides for public – contains no ACIC

NICE National Institute for Health and Care Excellence

Inotersen for treating hereditary transthyretin-related amyloidosis

Chair's presentation

2nd evaluation committee meeting

Highly Specialised Technologies committee

Lead team: Glenda Sobey, Mark Sheehan, Francis Pang

ERG: Aberdeen HTA Group

NICE technical team: Orsolya Balogh, Christian Griffiths, Sheela Upadhyaya

Company: Akcea

12 February 2019

Inotersen (Tegsedi)

Akcea Therapeutics

Marketing authorisation	Indicated for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis
Mechanism of action	Inotersen is a first-in-class antisense oligonucleotide (ASO) that inhibits production of the transthyretin protein
Administration & dose	• Subcutaneous injection • Recommended dose is 284 mg once every week (injection should be given on the same day every week) – plus daily vitamin A • Dose adjustments in case of reduction in platelet count: ○ confirmed platelet count ≥75 to <100 x109/L, dose frequency should be reduced to 284 mg every 2 weeks ○ confirmed platelet count <75 x109/L, dosing should be paused until 3 successive values > 100 x109/L are obtained. On re-initiation of treatment, dose frequency should be reduced to 284 mg every 2 weeks ○ confirmed platelet count <25 x109/L, treatment should be permanently discontinued, and corticosteroids administered
List price and PAS discount	• The list price for inotersen is £5,925 per weekly dose • Simple discount patient access scheme (PAS) approved*

[redacted]

**All results will incorporate PAS discount*

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: approximately [redacted]* people diagnosed in England eligible for inotersen
  Common UK genetic mutations include V30M (52%), THR60ALA (13%) and LEU58HIS (6%) – ***trial data***
- 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 cardiac features	Key neurological features

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

[redacted]

* Estimated by Akcea Therapeutics

Classification of hATTR amyloidosis

RECAP

- Diagnosis involves a comprehensive clinical assessment
  - Including neurological, cardiological, renal and ophthalmological assessments, complete family history
- Symptoms of hATTR-PN are frequently attributed to more common disorders
  - Average diagnostic delay of 4 years
- Symptoms can start between 10 years to beyond 80 years, with wide variations across different populations and mutations
- hATTR-PN most often can be staged using ambulatory status

Coutinho Stage*	Ambulatory Status
Stage 1	– Does not require assistance with ambulation (unimpaired ambulation) – Mostly mild sensory, motor, and autonomic neuropathy in the lower limbs (e.g., weakness of extensors in big toes)
Stage 2	– Requires assistance with ambulation – Disease progression in lower limbs – Symptoms develop in hands (weakness and wasting of muscles)
Stage 3	– Wheelchair bound or bedridden – Severe sensory, motor, and autonomic neuropathy of all limbs

Source: Table B1 Company submission

[redacted]

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

RECAP

Summary of evidence

Clinical evidence

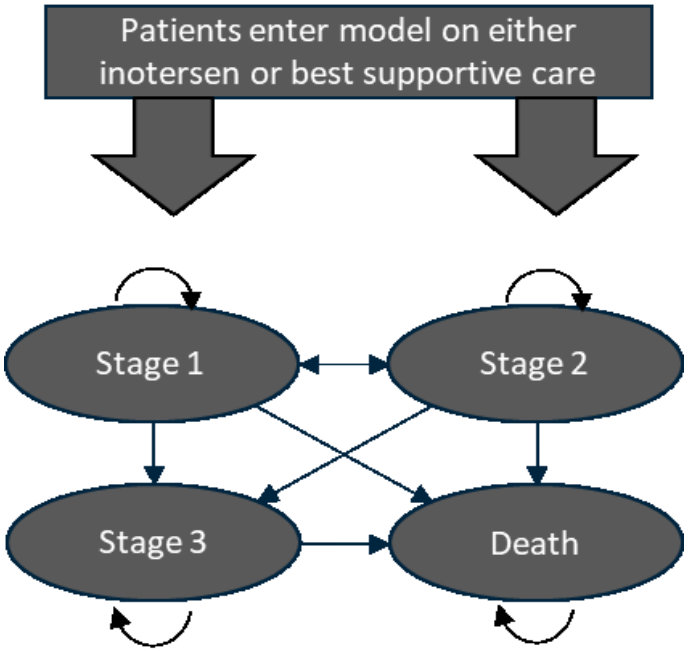
- Main clinical trial NEURO-TTR key outcomes
  - **mNIS+7 and Norfolk QoL-DN**: statistically significant improvement in neurological disease progression and quality of life with inotersen
  - **mean TTR reduction** over 15 months: ranging from 68% in week 13 to 74% in week 65
  - **cardiac outcomes**: better improvement with inotersen
  - **SF-36 health survey**: statistically significant difference in favour of inotersen treatment
- Norfolk-QoL, mNIS+7, and SF-36 all relate directly to patients' feeling and functioning
- Patient experts explained that benefit seen in trial translated into a marked effect on patients' lives (e.g., regaining of social life, return to work, improvement in mental health)
- Insufficient evidence on the long-term benefit of inotersen, but further data are being collected in the extension study

[redacted]

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

Summary of evidence

Economic evidence – model structure



Note: The cycle length is 4 weeks.

Source: Figure 11 of company submission

- Markov model compares inotersen vs. established clinical management without inotersen (best supportive care - BSC)
- 4 health states based on 3 Coutinho staging + death
- 1.5% discount rate; 4 weeks cycle; 41 years time horizon (lifetime); NHS/PSS perspective
- Cohort of hATTR amyloidosis patients (NEURO-TTR trial population)

- Transitions between Coutinho (FAP) disease stages modelled independently for each model arm
  - No improvement from Stage 3:
    - People cannot move back from Stage 3 to Stage 2 or Stage 1
    - Inotersen is not given in Stage 3

[redacted]

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

Issue	Committee's consideration
Clinical evidence of inotersen	• Considerable benefit in slowing disease progression • Long-term benefit uncertain
Stopping rules	• No clear commissioning criteria • People assumed to stop treatment on entering Stage 3 in model
Safety	• Manageable with increased monitoring
Model structure	• Reflects the course of the condition
Discontinuation	• Reasonable extrapolation curve is the one which allows for a persisting but decreasing rate of stopping treatment over time • **Log-logistic** curve best reflects the likely rate of stopping of inotersen in clinical practice over time
Number of carers	• As a reasonable estimate, 1 carer should be included in every stage in the model
Disutilities and costs of adverse events	• For clarity committee preferred disutilities and costs of adverse events (AEs) included in the model

[redacted]

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

Issue	Committee's consideration
Utility regression model*	• No algorithms to map Norfolk QoL-DN to the EQ-5D • Committee would like to see EQ-5D values estimated by applying the UK tariff to the raw EQ-5D response data from the THAOS registry, if not available prefer to use values from Faria et al (sourced by ERG)
Mortality*	• Company's approach uncertain, committee prefers lower hazard ratios (HR)
Compliance rate	• [redacted] should be used in the model
Healthcare resource use costs	• Company's approach is adequate
Discount rate	• 3.5% should be applied for both costs and health effects
ICERs	• The committee's preferred base case was associated with an ICER of £646,767 per QALY
QALY weighting	• Inotersen does not meet the criteria for applying a QALY weight
Managed access arrangement	• Inotersen provided some benefit in slowing disease progression • Estimates of costs and benefits provided by the model were uncertain → Further data collection, as proposed in a managed access arrangement would not be a possible route to resolving uncertainties

[redacted] EQ-5D: EuroQol 5-Dimensions, Five Level Questionnaire, ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year

***further clarification requested**

Summary of evidence

Cost-effectiveness results (PAS)

	Inotersen		BSC				
Description	Cost	QALY	Cost	QALY	Inc. Cost	Inc. QALY	Determin. ICER
Company preferred analysis	XXXXXX	XXXX	XXXXXX	XXXX	XXXXXX	XXXX	£369,569
ERG preferred analysis	XXXXXX	XXXX	XXXXXX	XXXX	XXXXXX	XXXX	£683,178
Committee preferred analysis	XXXXXX	XXXX	XXXXXX	XXXX	XXXXXX	XXXX	£646,767

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

Committee's preferred base-case before consultation

- Costs and QALYs are discounted at 3.5%
- Treatment discontinuation is modelled using a log logistic curve
- Compliance with treatment is set to XXX in the model
- Utilities are based on Faria, et al., linear calculation
- N=1 carer is assumed
- ERG amendments to the costs and disutility of AEs are applied
- Healthcare resource use (HRU) costs used as in the company's original analysis

XXXXXX

ECD preliminary recommendation + clarification requested by committee

*Inotersen is **not recommended**, within its marketing authorisation, for treating polyneuropathy in adults with hereditary transthyretin-related amyloidosis*

The following clarification were requested from the company in preparation for the 2nd committee meeting:

- Lower hazard ratios to predict mortality in the model
- EQ-5D values estimated by applying the UK tariff to the raw EQ-5D response data from the THAOS registry– if data are available

[redacted]

ECD consultation responses

- Consultee comments from:
  - Company (Akcea)
  - Clinical expert (C. Whelan endorsed by Royal College of Pathologist)

- Web comments from:
  - None

- No comment response from:
  - Department of Health and Social Care

[redacted]

ECD consultation responses

Company

During consultation Akcea have amended their model base case as well as submitted newly available information and provided clarification on points as requested

- Provided information clarifying areas of uncertainty raised in the ECD
  - Long-term benefits of inotersen – *new data up to 104 weeks from NEURO-TTR Extension*
  - Appropriateness of a treatment stopping rule
  - Preferred source of utility data
  - Preferred assumption regarding the number of carers in each stage

- Presented the following for consideration:
  - An updated model to address issues raised in the ECD
  - Included estimates of Coutinho (FAP) stage specific HRU costs, utilities and mortality hazard ratios associated with best supportive care (BSC), in an attempt to improve consistency with the ongoing NICE appraisal of patisiran*
  - Further amendments to align assumptions about the treatment pathway when 'on treatment' with the ongoing NICE appraisal of patisiran*

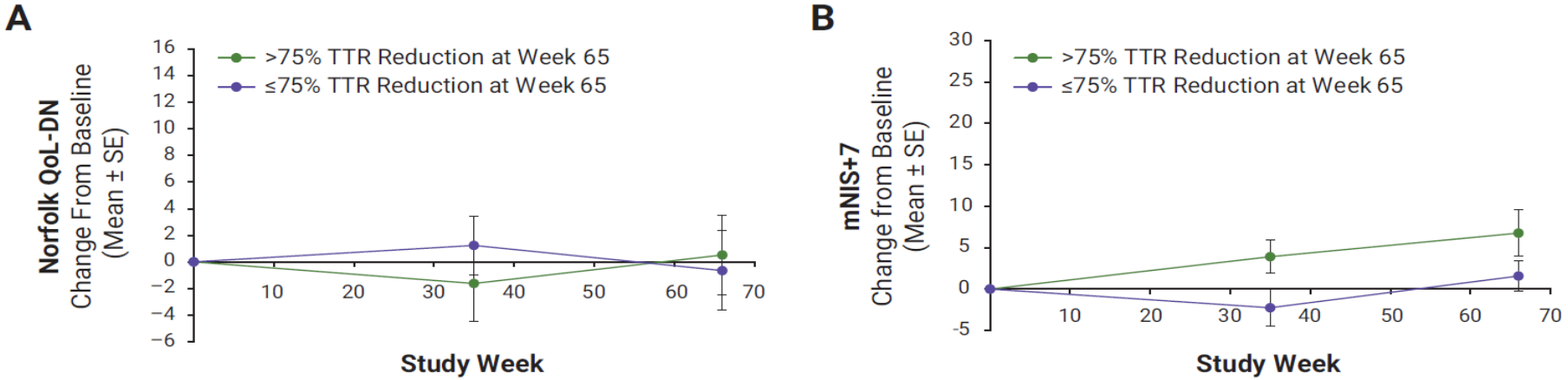
[redacted]

** Patisiran for treating hereditary transthyretin-related amyloidosis – under evaluation through NICE Highly Specialised Technologies Programme*

ECD consultation responses and ERG critique

New evidence - long-term benefits of inotersen (1/2)

- **ECD**: 'people whose TTR serum level decreased by 80% have a better prognosis …inotersen did not decrease the TTR serum level by 80%... with inotersen treatment there is disease progression and people progress into more severe stages'
- **Clinical expert**: Circulating TTR reduction has not been validated in TTR amyloidosis
  - But accept that higher 'knockdown' of TTR likely to give greater benefit in halting or reversing progression of disease
- Turnover and production of TTR varies from person to person → some may derive benefit from a knockdown lower than 80%
- **Company:** No evidence that supports the use of a binary 80% threshold as a criterion for long-term clinical benefits



- No statistically significant difference in mNIS+7 or Norfolk QoL-DN scores between patients with <75% TTR serum level reduction and >75% TTR reduction

[redacted] · TTR serum levels are an imprecise surrogate for clinically relevant outcomes

Source: Figure 1 of company ECD response

ECD consultation responses and ERG critique

New evidence - long-term benefits of inotersen (2/2)

- **ECD**: 'Long-term clearance of amyloid may not be achieved…further data are being collected…committee concluded… insufficient evidence on the long-term benefits of inotersen…uncertain whether the clinical benefit maintained long term'
- **Company**: New extension evidence available which shows the long-term benefit of inotersen is maintained for at least two years
  - Sustained improvement in Norfolk-QoL, mNIS+7, and SF-36 up to **104 weeks**:

	Difference between inotersen-inotersen group and placebo-inotersen group	Difference between placebo-inotersen group and projected continuation line
Norfolk QoL-DN (Change from baseline)	**-11.9**	**-10.3**
mNIS+7 (Change from baseline)	**-17.1**	**-23.8**
SF-36v2 PCS (Change from baseline)	**5.2**	**3.2**

Source: Table 1 of company ECD response

- **ERG comment**: Results show Total Norfolk QoL-DN (TQoL) benefits maintained on inotersen versus projected placebo continuation out to 104 weeks
  - [redacted] Long term benefits remain uncertain

ECD consultation responses and ERG critique

New evidence – treatment stopping rules

- **Company**: MA is for treating **stage 1 or stage 2 polyneuropathy in adults with hATTR**
- Stopping rule not explicitly reported in SmPC

- Evidence outside of inotersen's marketing authorisation is very limited
  - Should not be considered in NICE's decision making (***no change in company model***)
  - Company happy to provide materials to support conversations about starting and stopping inotersen according to its licence

- **ERG**: Considered the *impact of removing the stopping rule in an exploratory analysis* (*see impact on ERG base-case on slide 30*)

Stopping rule explained in ECD

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

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

Economic model: assume discontinuation of treatment in FAP 3

[redacted]

SmPC: Summary of Product Characteristics

ECD consultation responses and ERG critique

New evidence – preferred source of utility data (1/2)

- **ECD**: 'Company used utilities from Stewart et al., reports utilities according to Coutinho stages using a Brazilian value set … committee concluded utility values were highly uncertain… alternative utility sources used in ERG's analyses, Faria et al. (2012)… committee preferred to see the UK tariff applied to raw EQ-5D data, without these data, it preferred to use values from Faria'
- **Company**: in ***revised model generate stage specific utilities that are more applicable for use in the UK setting***
  - Utilities that would be close to the values that might be obtained if raw data available from the THAOS registry
    - Using one or two EQ-5D health states where the Brazilian tariff based value is closest to the mean disease stage values for patients in the THAOS registry (taken utility score from Stewart and found the EQ-5D profile with Brazilian valuation closest to these means)
    - UK tariffs then applied to selected EQ-5D profile to approximate mean UK utility by stage

FAP stage	Revised company submission	Original company submission	Committee's and ERG's preference
Stage 1	0.812	0.697	0.636
Stage 2	0.205	0.429	0.501
Stage 3	-0.094	0.084	0.375
Death	0.000	0.000	0.000

- *Using revised health state utilities in the model reduced the ECD preferred ICER* ***by 43.2%***

[redacted]

Source: Table 4 of ERG commentary on ECD

ECD consultation responses and ERG critique

New evidence - preferred source of utility data (2/2)

- **Company**: Acknowledge uncertainty around using Brazilian tariff → but considers approach to be highly conservative
- **ERG**: Approach is uncertain and has limited face validity
  - Assumes that single state profile can be used to approximate the expected difference in mean UK and Brazilian utility values by stage
  - Does not account for distribution of profiles or variability in preference patterns for different dimensions of the EQ-5D between the UK and Brazilian data
  - Approach not validated and generates counterintuitive health state classifications
    - FAP stage III utility is 31332, which specifies 'no problems' with self-care → lacks face validity and is unlikely to reflect the health status of someone with Stage 3 disease
  - Values between best and worst states with UK tariff is substantially wider than Brazilian tariff
- ERG not convinced the company provided a strong case to move away from the ECDs preferred utilities (used mapping from TQoL to EQ-5D using the linear function described in Faria et al)

Company provided additional comments on the appropriateness of utilising values from the tafamidis AGNSS appraisal (not distinguish between FAP stages) and using SF-36 data collected in the NEUR-TTR trial (committee concluded it is highly uncertain) → ***comments not presented here***

[redacted]

AGNSS: Advisory Group for National Specialised Services

ECD consultation responses and ERG critique

New evidence - number of carers in each stage

- **ECD**: 'appropriate to consider carer disutility in the model...patients spend most time in the Stage 1 and Stage 2 health states, assuming 2 full-time carers throughout the model period was inappropriate… committee concluded that…it would prefer 1 carer in every stage in the model'
- **Company**: People with Stage 3 are bedridden or confined to a wheelchair
  - Assistance is needed constantly, day and night
- Company conducted a Caregiver Impact Study of 36 carers of patients with hATTR-PN

Coutinho Stage	Hours of practical care per day	Hours of emotional support per day	Hours per week
Stage 1	2.64	3.56	43.4
Stage 2	6.88	4.74	81.4
Stage 3	10.67	1.76	87

Source: adapted from table 14 of company ECD response

- ***Revised company base case*** considers a more conservative approach: patients require one, one, and two full-time carers per patient in Stage 1, 2 and 3
  - *Reduced the ECD preferred ICER* ***by 13%***

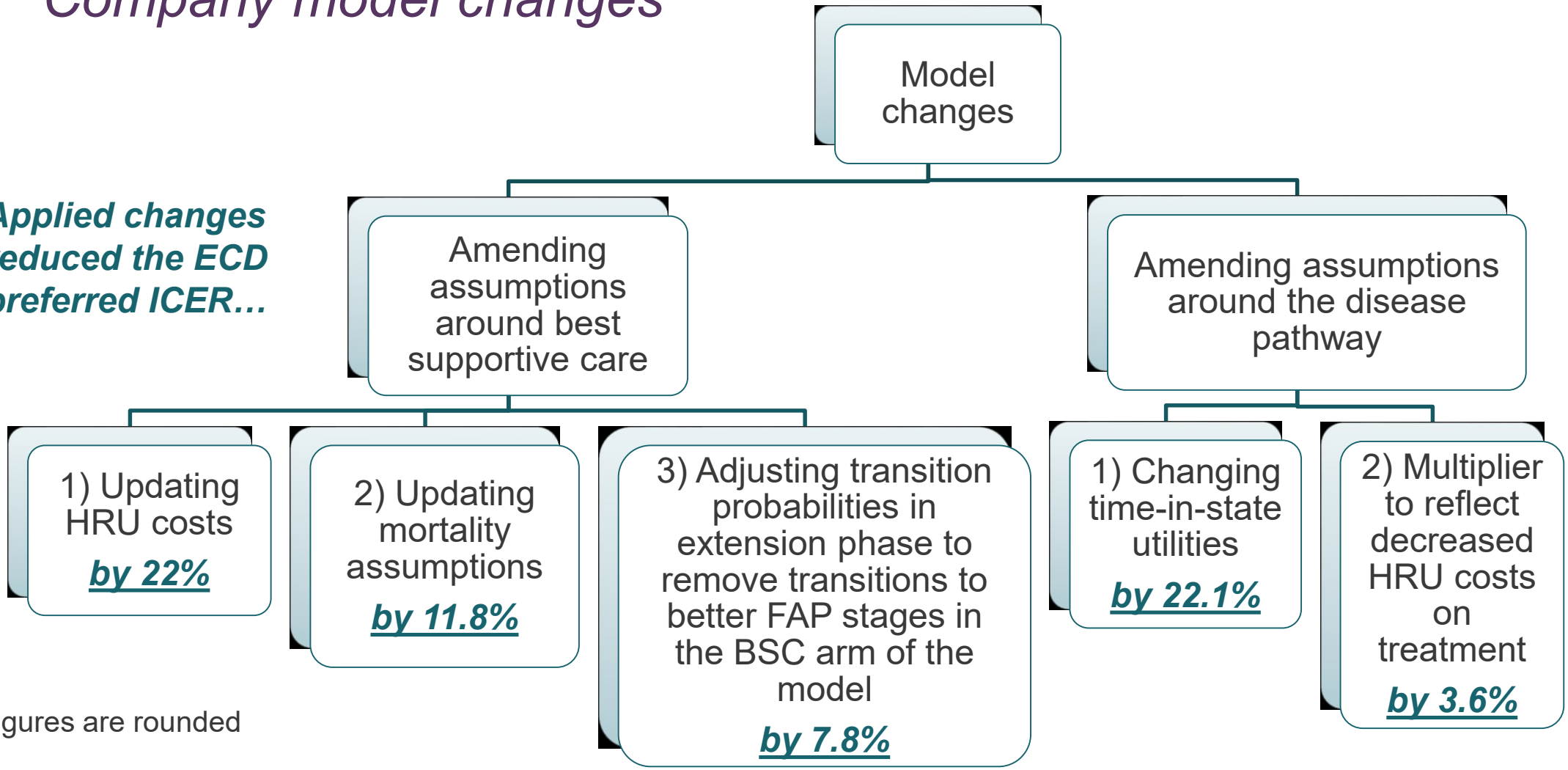
ERG comment: For consistency with the preferred assumptions of the ECD, the ***ERG's base-case apply the disutility for one carer across all FAP stages***

[redacted]

ECD consultation responses

Company model changes

Applied changes reduced the ECD preferred ICER…



figures are rounded

Company incorporated further model assumptions reflecting the committee's preferred analyses, as outlined in the ECD (discontinuation extrapolation curve – using log-logistic distribution, partially implemented cost and disutilities of AEs, adoption of 3.5% discount rate, adoption of desired compliance rate)

[redacted]

ECD consultation responses and ERG critique

BSC adjustment 1

Model changes – Updating HRU costs

- **Company**: replaced the healthcare resource use costs using publicly available data from the patisiran appraisal
  - Sourced from a Delphi panel (conducted by the MA holder of patisiran)
  - Costs were converted from six-monthly (as reported for patisiran) to four-weekly cycles
  - Applied costs in **revised model**: **£35** Stage 1; **£12,680** Stage 3; Stage 2 (interpolation using weightings) **£8,548**
- **ERG comments**: appropriate to use health state costs, sourced from the patisiran appraisal, mapped between PND* and FAP stages
- ERG identified *error* in the mapping approach
  - Costs applied to Stage 1 incorrectly mapped from costs for PND 0 from patisiran
    - Approach not consistent with mapping processes suggested by literature (Adams, 2013; Adams, et al., 2016) → ***ERG mapped PND 1 and 2 costs to FAP 1 in its base-case***
  - No need to interpolate to get Stage 2 costs → available for patisiran
    - Company's approach over-estimates the difference between Stage 1 and Stage 2 costs, but under-estimates the difference between Stages 2 and 3
      - *ERG corrected cost for Stage 2*: using PNDIIIA and PNDIIIB – converted from a 6 month to a 4 week cycle = £904.39 and ***used in its base-case***

[redacted]

*Discrete measure of disease evolution and severity of hATTR based on polyneuropathy disability → PND score

ECD consultation responses and ERG critique

BSC adjustment 2

Model changes – Updating mortality assumptions

- **ECD**: 'uncertainty around this parameter…based on expert opinion rather than published data…hazard ratios were highly uncertain and committee would like to see scenario analyses using lower hazard ratios in the model'
- **Company**: Updated the hazard ratios while excluding mortality caused by cardio-myopathy (Suhr et al, 1994)
  - PND stage I → FAP Stage 1; PND stage IV → FAP Stage 3; FAP Stage 2 contains elements of PND stages II, IIIa and IIIb
  - HRs used in the **revised model**: **2.01**, **2.42** and **9.53** for Stage 1, 2, 3 respectively
- **ERG**: more appropriate to map PND stages IIIa and IIIb to FAP Stage 2 (Adams, et al., 2016) → **ERG *mapped PND I and II to FAP 1 in its base-case***

- **Company**: Adopting the same BSC assumptions as other hATTR submissions, allows a fair and robust assessment of the product
  - HRs validated by UK clinicians at an advisory board
- **ERG**: Approach appears reasonable and consistent with the assumptions used for patisiran
  - Greater proportion of the cohort remain alive to benefit from inotersen treatment, generating greater life year and QALY gains

[redacted]

ECD consultation responses and ERG critique

BSC adjustment 3

Model changes – Adjusting transition probabilities in extension phase

- **Company**: **in revised model people on BSC cannot transition from Stage 2 to Stage 1 after week 66 of treatment**
- Transition probability over extrapolation phase changed
  - Placebo effect possible during the trial period leading to a slight increase in quality of life (QoL) → possible until end of the trial
  - Effect would not translate into routine clinical practice → implausible to imagine a BSC patient experiencing a significant uplift in QoL after 66 weeks of decline
- **ERG comment**: appears inconsistent to remove placebo effect from BSC arm, but not do the same for inotersen arm → anticipate improvement only in the inotersen arm
  - Creates a bias in favour of inotersen, placebo effect or random variation can happen in both arms
  - Observation of possible transition from Stage 2 to 1 in the BSC cohort more likely due to random variation in the subjective TQoL score and arbitrarily defined TQoL thresholds
- Company's argument was implemented in the patisiran evaluation and not challenged in the patisiran ECD
  - More methodologically sound to retain the effect as per the original company submission

[redacted]

ECD consultation responses

Summary of parameter changes in the updated company model

Parameter	Originally submitted	Revised model
BSC probability of transitioning from Stage 2 to Stage 1 after Week 66	XXXX	0.00%
HRU costs	Stage 1: £393 Stage 2: £1,307 Stage 3: £1,745	Stage 1: £36 Stage 2: £8,548 Stage 3: £12,681
Mortality hazard ratios	Stage 1: 5 Stage 2: 10 Stage 3: 19	Stage 1: 2.01 Stage 2: 2.42 Stage 3: 9.53

Source: Table 5 of company ECD response

[redacted]

ECD consultation responses and ERG critique

Pathway adjustment 1

Model changes – Changing time-in-state utilities (1/3)

- **Company**: ***implemented utility values in revised model that increase or decrease with time-in-state for inotersen and BSC patients***
- Patient-level analysis of NEURO-TTR showed that patient utility improved within each state while on inotersen and reduced while on BSC from baseline to Week 66

Patient population	Mean TQoL score at Week 66		Improvement on inotersen
	Inotersen	BSC	
Stage 1	XXXX	XXXX	-0.94
Stage 2	XXXX	XXXX	-4.35
Stage 3	XXXX	XXXX	-9.99

Source: Table 6 of company ECD response

  - Broad spectrum of disease severity within states → utility would linearly improve with inotersen and worsen with BSC to next stage over time → made model more clinically realistic
- Increase or decrease in utility per cycle was calculated by observing the difference in utility at baseline compared to the end of the NEURO-TTR study, at 66 weeks
  - Utility for people on inotersen increased by 0.0002 for each cycle they remain in same state
  - Utility for people on BSC reduced by -0.0038 for each cycle they remain in same health state
- Calculation of utility gains from incremental improvements in TQoL score using linear mapping function from Faria *et al.* (2012)

[redacted]

- Preferred source of utility values: *Brazilian THAOS values converted to UK utility tariffs* (*new evidence presented earlier*)

ECD consultation responses and ERG critique

Model changes – Changing time-in-state utilities (2/3)

Pathway adjustment 1

- **Company**: Utilities capped to never increase beyond the baseline utility of the next-best stage and decrease beyond the utility of the next-worst stage
  - Stage 1 utilities capped at 0.83 representing general population health (Ara and Brazier, 2010), Stage 3 capped at -0.093 (similar to average health state utility for Stage 3 disease)
  - After transition to another stage, utility was reset to the average for that stage. If a patient discontinued, utility would remain at the level it was prior to discontinuation

Health state	Patient EQ-5D-3L utility	Maximum utility in this stage	Minimum utility in this stage	Utility after ten cycles of INO*	Utility after ten cycles of BSC
Stage 1	0.812	0.835	0.205	0.814	0.780
Stage 2	0.205	0.812	-0.093	0.207	0.180
Stage 3	-0.093	0.205	-0.093	N/A	-0.093

Source: Table 7 of company ECD response

- **ERG comment**: accepts the rationale but notes that in the ECD for patisiran, committee questioned the reliability of the method used to generate the utilities
  - Assuming that inotersen utility increases linearly on treatment over the full duration of time - *claimed to slow the rate of progression rather than reverse it* - appears counter-intuitive
  - A more conservative approach might have been to assume that the rate of utility decline within stage is slower for inotersen than BSC
  - Assumption of linear changes in utility extrapolated beyond 66 weeks is still uncertain → *explore the impact of including and excluding time in state utility adjustments in its base case*

[redacted]

*INO: inotersen

ECD consultation responses and ERG critique

Pathway adjustment 1

Model changes – Changing time-in-state utilities (3/3)

- **Company**: analysis not restricted to people with no change in stage between baseline (BL) and week 66 → did not provide stage specific analysis in Stage 3 (given baseline population and stopping rule applied)
- **ERG:** Magnitude of bias small → would be mitigated if within state utility used based on trial participants stable between baseline and week 66
  - Agrees with company for not providing stage specific analysis in Stage 3

Table illustrates impact if '***stable in stage***' approach would have been used

Within state adjustment	TQOL BL	TQOL w66	4 weekly utility change	ICER: comp.	ICER: ERG
Company preferred 'within state' utility adjustment					
Inotersen	[redacted]	[redacted]	0.0002	£150,636	£281,571
BSC	[redacted]	[redacted]	-0.0038		
Apply Stage 1 stable only					
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]		
Apply Stage 2 stable only					
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]		
Remove within state adjustment completely					
	N/A	N/A	N/A	[redacted]	[redacted]

[redacted]

Source: Table 1 of ERG addendum

ECD consultation responses and ERG critique

Model changes – Applying a multiplier to reflect decreased HRU costs on inotersen treatment

- **Company**: **revised model applied a 43% reduction to the inotersen health state costs for FAP Stages 1 and 2 only**
  - For the full duration of health state occupancy in FAP Stages 1 and 2, and applied only to the proportion of the inotersen cohort that are on treatment (as in patisiran)
    - Reflects the expected significant reduction in HRU costs on inotersen treatment within stage (follows the same rationale as per the improvements in QoL)

- **ERG**: True percentage reduction is likely to be highly uncertain and has not been subjected to sensitivity analysis → *conducted further exploratory analysis demonstrating impact of removing discount*
  - 43% reduction was also applied to one-off poly-neuropathy costs in the patisiran appraisal (***not included in revised company base-case)***
    - Appropriate to apply reduction to one-off ploy-neuropathy costs for consistency → ***included in ERG's base-case*** using costs sourced from the patisiran appraisal

[redacted]

Updated company model

Company base-case includes:

- Preferred HRU assumptions:
  - Revised health state costs
  - 43% reduction of health state costs in the inotersen arm (inotersen arm FAP 1 and 2)
- Updated HRs from patisiran assessment *(Maps PND 1 to FAP 1)*
- Removal of BSC transitions from FAP 2 to FAP 1
- Applying 1 carer in Stage 1 and 2, and 2 carers in Stage 3
- Stop inotersen treatment in Stage 3
- Preferred utility assumptions:
  - Revised FAP stage utility mapping
    - Average of FAP Stage 3 mapped to EQ-5D state '33311' and FAP Stage 3 mapped to EQ-5D state '31332'
  - Treatment arm specific adjustment of utility by time in state
- Including other committee preferred assumptions
  - Discontinuation log-logistic extrapolation curve, partially implemented cost and disutilities of AEs, adoption of 3.5% discount rate, adoption of desired compliance rate

[redacted]

Cost-effectiveness estimates include confidential PAS discount

ERG changes to updated company model

ERG present several exploratory analyses and alternative base-cases:

- **ERG preferred base-case analysis**
  - ERG preferred cost revisions
    - Map PND 1 and 2 to FAP 1 + apply patisiran one off costs + apply 43% reduction to health state costs in the inotersen arm of the model
  - ERG updated HRs from patisiran assessment *(Maps PND I and II to FAP 1)*
  - Treatment arm specific adjustment of utility by time in state – *Faria et al. with time in state adjustment*
- **+ Additional utility adjustment**
  - ERG preferred analysis, without time in state utility adjustment
- **+ Additional HRU cost adjustment**
  - ERG preferred analysis, with HRU costs mapped from PND I to FAP 1

- Also present additional scenarios which explore the impact and sensitivity of allowing treatment continuation in Stage 3

[redacted]

Company and ERG base-cases and additional scenario analyses (including PAS price)

		Cost	QALY	LYG	Inc. Cost	Inc. QALY	Inc. LYG	Determin. ICER
ECD preferred assumptions (NICE, 2018)	BSC	[redacted]	[redacted]	7.541				
	Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£646,767
Revised company base case	BSC	[redacted]	[redacted]	10.510	[redacted]			
	Inotersen	[redacted]	[redacted]	12.502	[redacted]	[redacted]	1.991	**£150,636**
ERG preferred analysis	BSC	[redacted]	[redacted]	11.028	[redacted]			
	Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£281,571
ERG preferred analysis, without time in state utility adjustment	BSC	[redacted]	[redacted]	11.028	[redacted]			
	Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£367,993
ERG preferred analysis, with HRU costs mapped from PND I to FAP 1	BSC	[redacted]	[redacted]	11.028	[redacted]			
	Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£282,059
Allow treatment continuation in Stage 3 applied to ERG base-case	BSC	[redacted]	[redacted]	11.028	[redacted]			
	Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£407,952

[redacted]

ECD consultation responses

Additional company comments

- Progressive loss of independence and dignity experienced by hATTR-PN patients negatively affects every aspect of patients', family members' and carers' lives
- Carers have to stop their own social activities and employment in order to provide medical support, care and assist with activities of daily living
- Inotersen offers the potential to slow, arrest or reverse disease progression in patients with Stage 1 or 2 hATTR
  - Patients remain in earlier stages of the disease for longer → allow them to retain their independence longer through preservation of their ambulatory ability and key health domains
  - Opportunity to continue with employment, actively participate in family and social life for longer
- [redacted]
- [redacted]
  - [redacted]
- [redacted]

[redacted]

NAC: National Amyloidosis Centre

Key issues for consideration

- Has the company addressed all the committee's concerns outlined in the ECD?
  - What is the committee's view on the additional evidence provided?
    - Does the follow-up evidence generated from the NEURO-TTR Extension study indicate that inotersen could halt or reverse disease progression?
    - Should treatment with inotersen stop when people enter Stage 3?
    - Would the committee accept revised number of carers in the model (1 carer in Stage 1 and Stage 2; 2 carers in Stage 3)?
  - Is the committee satisfied with the company's revised model which aligns some assumptions with the patisiran appraisal?
    - Is the committee convinced that revised stage-specific utilities are more applicable to the UK setting?
    - Would the committee accept:
      - The company's updated healthcare resource use costs and mortality assumptions?
      - Adjustment of transition probabilities in extension phase to reflect transitions in Stage 2 for BSC group
      - Inclusion of utilities that vary according to time-in-state?
- Has the committee changed opinion on the recommendation of inotersen? What is the committee's preferred base case?

[redacted]