NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Inotersen for treating hereditary transthyretin amyloidosis [ID1242]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - Akcea Therapeutics

3. **Comments on the Evaluation Consultation Document from experts:**
   - Dr C Whelan– clinical expert, nominated by Akcea Therapeutics (endorsed by British Society of Heart Failure and Royal College of Physicians)

     A 'no comment response' was submitted by NHS England

4. **Evidence Review Group critique company ECD response**

5. **Company ECD response - additional clarification questions**
   - NICE request to the company for additional clarification on their ECD response
   - Company response to NICE request for additional clarification

6. **Evidence Review Group critique company ECD response - addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Inotersen for treating hereditary transthyretin-related amyloidosis

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Akcea</td><td>
Executive summary

Akcea would like to thank the committee for the detailed Evaluation Consultation Document (ECD), and the opportunity to respond to it. We are glad that the committee has recognised inotersen to be an innovative treatment for hATTR. We note also that the committee recognised the significant health burden of this disease for patients and those caring for them.

As a result of recommendations and judgements made in the ECD, Akcea have amended their model base case as well as submitting newly available information and providing clarification on points as required (see below for more details). This significantly improves the base case incremental cost-effectiveness ratio (ICER) to £131,260-£150,636 (see Error! Reference source not found.), which supports Akcea's case that their original model submission was conservative.
Table 1: Revised company base case ICER following amends post ECD
<table>
<tr><th></th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr>
<tr><td>Revised company base case</td><td>£150,636</td><td>£131,260</td></tr>
</table>

The model changes fall into three broad groups:

Amending assumptions around best supportive care to conform with the best supportive care assumptions accepted by NICE as part of the ongoing assessments of other hATTR products, confirmed with expert clinicians, and as agreed with members of the NICE committee on a clarification call (section 4)
Amending assumptions around the disease pathway in order to consistently reflect judgements made in the ECD reports for both inotersen and other hATTR products (section 5)
Amending the model to conform with NICE's preferred inputs as described in the ECD report for inotersen:

</td><td>Thank you for your comment. The evaluation committee considered evidence submitted by the company. The committee also noted that the company revised its commercial offer for inotersen, and although there were outstanding uncertainties the committee recommended inotersen as an option for treating hATTR amyloidosis. Please see sections 4.26,4.27 and 4.33 of the final evaluation document (FED).</td></tr>
</table>

Consultee	Comment	Response
	o Discontinuation extrapolation curve (section 8) o Inclusion of adverse events (section 9) o Adoption of 3.5% discount rate (section 10) These are described in more detail below: In addition to model amendments, Akcea presents new evidence and argumentation on a number of points where the committee expressed uncertainty. These points include: • The long-term benefits of inotersen (section 2) • The appropriateness of a treatment stopping rule (section 3) • The preferred source of time-in-state utility data (section 6) • The preferred assumption regarding the number of carers in each Stage (section 7) The model amends and additional information provided to mitigate key uncertainties significantly improve the cost-effectiveness case for Inotersen. Given these changes, we would like to request that NICE now supports commercial discussions with NHS England to enable inotersen to be made available to patients living with hATTR; a devastating disease with no therapeutic treatment options.	
Akcea	**Long term benefits of inotersen** Akcea has published new evidence (not available at the time of the committee meeting) to further support its case that the benefits of inotersen will be preserved long-term. Akcea challenges the committee's conclusion that there was insufficient evidence on the long-term benefits of inotersen and that there is uncertainty about whether clinical benefits would be maintained in the long term, and is confident that the new evidence presented will help resolve committee uncertainty. Additionally, the ECD concludes that reductions in TTR serum levels are insufficient to conclude that the benefit to patients will be maintained in the long-term. Akcea challenges this interpretation of the evidence for four reasons: • New extension evidence is available which shows the long-term benefit of inotersen is maintained for at least two years • Reduction in TTR is a surrogate outcome and, on its own, is not currently established as a reliable prognostic indicator of long-term benefit • The NEURO-TTR trial was not designed or powered to demonstrate a specific TTR serum level reduction.	Thank you for your comment. Please see response to the comments in the sections below.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>

To use a non-validated surrogate marker like reduction in TTR levels, which is not systematically correlated to functional outcomes, as a prognostic indicator instead of patient-related outcome measures would contradict NICE's own methods guidance.
There is no defined consensus on level of optimal TTR reduction

<u>New extension evidence is available which shows the long-term benefit of inotersen is maintained for at least two years</u>

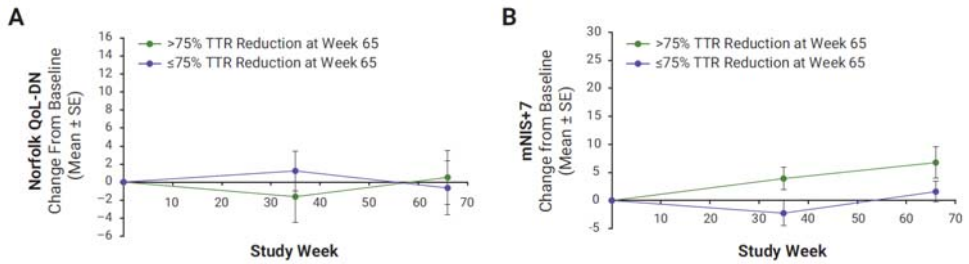
Since the committee meeting, further follow-up data on long-term outcomes has become available from the OLE study. These data were presented to the American Society of Hematology's annual conference in December 2018 (Brannagan et al., 2018), and demonstrates sustained improvement in Norfolk-QoL, mNIS+7, and SF-36 up to 104 weeks in both the inotersen-inotersen group versus the inotersen-placebo group, and in the inotersen-placebo group versus the projected continuation line from the placebo group before their switching onto inotersen (Error! Reference source not found.).

Table 1: Long-term clinical data from NEURO-TTR open-label extension study at 104 weeks
<table>
<tr><td></td><td>Difference between inotersen-inotersen group and placebo-inotersen group</td><td>Difference between placebo-inotersen group and projected continuation line</td></tr>
<tr><td>Norfolk QoL-DN (Change from baseline)</td><td>-11.9</td><td>-10.3</td></tr>
<tr><td>mNIS+7 (Change from baseline)</td><td>-17.1</td><td>-23.8</td></tr>
<tr><td>SF-36v2 PCS (Change from baseline)</td><td>5.2</td><td>3.2</td></tr>
</table>
<u>Reduction in TTR is a surrogate outcome</u>

There is general agreement among experts in the amyloidosis community that TTR reduction is closely associated with clinical benefits in ATTR amyloidosis. Given that the mechanism of action of inotersen is mediated through TTR, it is unsurprising that there will be an association between TTR levels and patient outcomes. However, there is no evidence to suggest that there is a threshold after which patients will have a clinically important improvement in prognosis. A TTR serum level reduction threshold may be established over time based on data from large sample sizes, but the heterogeneity of the patient population makes this challenging. There is no evidence that supports the use of a binary 80% threshold in TTR serum reduction
</td><td>Thank you for your comment. The committee acknowledged the new evidence provided by the company and concluded that the evidence showed that inotersen had considerable benefit in slowing disease progression, but it did not stop progression. Please see section 4.8 of the FED.

Thank you for your comment. The committee concluded that although inotersen did not decrease serum TTR level by 80%, it provided clinical benefit. It also noted that further data collected in the extension</td></tr>
</table>

Consultee	Comment	Response
	as a criterion for long-term clinical benefits, as put forward by the committee without providing a reference. We do remain optimistic that we can work with the community to establish this over time. Factors that are critical to the accurate measurement and interpretation of TTR include, for example: • The timepoint at which TTR is assessed after initiation of treatment; for example, at 3 versus 6 versus 9 months. • Whether the threshold criteria is established on first-line patients or all patients • Whether and how to take into account the pre-dose mean TTR • Whether and how to correct for specific mutations identified in hATTR ("Mutations in Hereditary Amyloidosis," n.d.) • Whether and how to correct for important patient-specific factors, such as range of organ involvement, age at diagnosis, time from diagnosis to treatment and so on In addition to the difficulties highlighted above, one key reason why TTR serum levels have not been systematically correlated to functional outcomes is that there are different ways of measuring TTR levels. For example, Figure 2A of Adams et al. (2018) combines pre-dose and post-dose measurements of serum TTR levels in the same graph. Later in this paper a claim of an 81% median reduction is made which is hard to directly compare with other literature as it is unclear if this reduction was derived from measurements taken pre-dose, post-dose, or a mixture of pre- and post-dose. In a different source, the 'mean max' reduction is reported, which is not an accepted statistical methodology and again makes it difficult to compare literature on TTR serum levels (Alnylam Pharmaceuticals, 2018). Treatment with inotersen led to a 79% reduction in median TTR serum levels (Benson et al., 2018). An analysis completed by Akcea and presented at the Peripheral Nerve Society congress showed that there was no statistically significant difference in the clinically relevant mNIS+7 or Norfolk QoL-DN scores between patients with <75% TTR serum level reduction and >75% TTR reduction (see Figure 1), which supports the case that marginal changes in TTR levels do not lead to significant differences in clinically relevant outcomes. The analysis also showed that the mNIS+7 or Norfolk QoL-DN scores of some patients who achieved a 90% reduction in TTR serum levels did not show improved quality of life, whereas some patients who achieved a 50% TTR serum reduction did improve, which also supports the case that TTR serum levels are an imprecise surrogate for clinically relevant outcomes. **Figure 1. No differences were seen in (A) Norfolk QoL-DN and (B) mNIS+7 between inotersen-treated patients with >75% versus ≤75% reduction of week 65 TTR levels.**	study showed that there was still insufficient evidence on the long-term benefits of inotersen. It therefore remained uncertain whether the clinical benefit would be maintained in the long term. Please see section 4.10 of the FED.

Consultee	Comment	Response
	 We support the concept that high levels of TTR reduction leads to better outcomes, but evidence for a particular threshold does not yet exist for ATTR amyloidosis. We hope to work with the leading clinicians in the amyloidosis research community, including those in the National Amyloidosis Centre, to help gather such evidence over time. We believe this will require a rigorous and consistent method of measuring TTR reduction at a specific timepoint across treatments. We are encouraged that there are multiple treatments that can help to establish this in a consistent and transparent fashion. We look forward to taking part in efforts to establish response criteria in patients with ATTR amyloidosis. However, at this point, the default assumption must be that the significant improvements in clinical and PRO outcomes take precedence over a threshold with limited clinical consensus and applicability. The assumption such a threshold exists is unscientific and unjustified in the absence of significant new evidence. <u>The NEURO-TTR trial was not designed or powered to demonstrate a specific TTR serum level reduction.</u> Akcea would like to remind the committee that the NEURO-TTR trial was not designed or powered to demonstrate a specific TTR serum level reduction. The primary efficacy outcomes of the trial were the change from baseline in Norfolk QoL-DN and mNIS+7 scores, while the change from baseline in TTR serum levels was an additional secondary pharmacodynamic outcome. It is Akcea's opinion that it is inappropriate for the committee to draw conclusions on the long-term clinical efficacy of inotersen based on an outcome intended only to demonstrate the pharmacodynamic properties of inotersen on the body and not its clinical efficacy. <u>To use a surrogate marker would contradict NICE's own methods guidance.</u> Finally, NICE is explicit in its methods guidance that surrogate outcomes like biomarkers are inappropriate to use when patient-reported outcomes are available: "Clinical end points that reflect how a patient feels, functions, or how long a patient survives are regarded as more informative than surrogate end points (such as laboratory tests and imaging findings) (NICE, 2013)." The purpose of this judgement by NICE is to prevent arbitrary clinical thresholds from preventing access to treatment which patients themselves report is	Thank you for your comment. The evaluation committee has taken into account all factors that may affect its decision. Thank you for your comment. The evaluation committee has taken into account all factors that may affect its decision. During

Consultee	Comment	Response
	working for them, and to focus public spending on areas where patients are most likely to benefit. Norfolk-QoL, mNIS+7, and SF-36 all relate directly to patients' feeling and functioning, while TTR is – at best – a heterogenous indicator lacking "strong evidence that it predicts health-related quality of life". It therefore contradicts NICE's own methods guidance to conclude, based on TTR reduction, that it is uncertain whether inotersen has long term clinical benefit without substantial and compelling evidence that the 80% TTR reduction threshold mentioned in the ECD is anything more than arbitrary, particularly given that the clinical and patient reported outcome measures available from the NEURO-TTR and OLE studies clearly demonstrate significant and sustained benefit of inotersen.	consultation, clinicians explained that a greater decrease in serum TTR level is likely to give greater benefit in halting or reversing progression of the disease. Please see section 4.9 of the FED.
Akcea	**Treatment stopping rules** The ECD makes reference to the fact that the stopping rule applied in the model was a source of uncertainty, since it is possible that a patient benefitting from inotersen and their clinician would not want to stop treatment when that patient enters Stage 3. The Summary of Product Characteristics is explicit about the license of the product: *"Tegsedi is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)." (SPC, 2018)* NHS England confirms that their interpretation of this licence indication is the same as Akcea's; "NHS England stated that it interpreted the wording of the marketing authorisation to mean that treatment should stop when the condition progresses to stage 3" (ECD, Page 14) Akcea appreciate the concerns raised by NICE. However, evidence outside of inotersen's marketing authorisation is very limited, and will inevitably be assumption-based. As such, Akcea firmly believe this should not be considered in NICE's decision making. However, in appreciation of the difficulty that the application of the marketing authorisation may create for clinicians, Akcea are happy to provide materials to support conversations about starting and stopping inotersen according to its licence. Finally, we are mindful that it is NICE's remit to assess inotersen within its marketing authorisation as per the NICE scope and Akcea have found no precedent where NICE have extended their remit to assess a treatment outside of its marketing authorisation. We have therefore provided estimates of clinical and cost-effectiveness for the marketing authorisation of inotersen only.	Thank you for your comment. The committee acknowledged that the stopping rule applied in the model may not reflect how clinicians would prefer to use the treatment. It agreed with the approach in the updated company model that inotersen would be started when the disease is in stage 1 or 2 and would be stopped when the condition progresses to stage 3. Please see sections 4.13 and 4.14 of the FED.
Akcea	**Best supportive care alignment assumptions** As discussed on a teleconference with members of the NICE committee on 6th December 2018 and then confirmed on a subsequent teleconference on 17th December 2018, Akcea have made amendments to	Thank you for your comment. Please see response to the comments in the sections below.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
their model in order to ensure that their assumptions on the costs, utilities and mortality associated with the best supportive care (BSC) group in their model align with NICE's evaluation in other hATTR submissions. This will ensure that NICE's decision making will be consistent for all hATTR therapies, with particular respect to assumptions accepted about the behaviour of the control group of patients (i.e. those on BSC) which, in turn, allows a fair assessment of the treatment effect of inotersen.
Changes have only been made where there is a clear indication from NICE that the change will be viewed as appropriate, most commonly because the same assumption was adopted in the submission for another hATTR treatment and either accepted or not criticised by NICE. In addition, changes were only implemented once they had been validated by UK clinicians at an advisory board held in November 2018. It is essential that NICE's approach to the appraisal of all hATTR technologies are aligned to ensure that assumptions made on BSC are consistent in order to ensure a fair appraisal of these technologies.

The changes to the inotersen model that have been implemented to align with the BSC group described in other hATTR submissions and accepted by NICE are:
• Updating HRU costs
• Updating mortality assumptions

Adjusting transition probabilities in extension phase to reflect transitions in Stage 2 for BSC group

<u>Updating HRU costs</u>

The first model amendment was to replace the health resource utilisation (HRU) costs in the model with those made publicly available in the documents produced for consideration of the NICE appraisal of patisiran. The costs themselves were sourced from a Delphi panel conducted by the manufacturer, which Akcea recognises as a potential source of uncertainty, however the figures have been validated by a UK advisory board, which found that these costs were reflective of costs incurred by the NHS in the UK. These costs were given as a range; therefore, the low cost end of the range was assumed to correspond to Coutinho Stage 1 whilst the high cost end of the range is equivalent to Stage 3. A weighted average of costs was applied to Stage 2.

Table 1 shows the impact of this amend on the results.

Table 1: ICER when using alternative HRU costs
<table>
<tr><th></th><th>ICER – Log-logistic distribution for discontinuation (ERG</th><th>ICER – Exponential distribution for discontinuation</th></tr>
</table>
</td><td>Thank you for your comment. The committee reviewed the changes introduced by the company after consultation and concluded that there were some uncertainties in the company's resource use assumptions but accepted the updated model for decision making. Please see section 4.24 of the FED.</td></tr>
</table>

Consultee	Comment	Response

	preferred case)	
HRU costs from patisiran committee papers (base case)	£150,636	£131,260
HRU costs presented at 1st inotersen committee meeting	£257,578	£252,300

Updating mortality assumptions

The second change made to align the inotersen BSC group with the BSC group in other hATTR submissions is to update mortality assumptions.

As this was an area of uncertainty for the committee, Akcea has conducted various scenario analyses to allay the committee's concerns regarding this.

The committee was especially interested in testing lower mortality ratios than those modelled in the base case. In general, lower mortality ratios favour inotersen as they emphasise that inotersen patients spend less time in the expensive and low quality of life Stage 3.

Our base case is designed to conform to the ERG's preferred scenario, as described in the patisiran ECD report, which is to test "the impact of removing the mortality effect in patients with no cardiac involvement". Therefore, our base case adopts the mortality ratios presented in this submission for the non-cardiac group, which are 2.01 for PND stage 0-II, 2.62 for PND stage III and 9.53 for PND stage IV. These values are sourced from Suhr et al (1994). Coutinho Stage 1 is considered equivalent to PND stage I, Coutinho Stage 3 is considered equivalent to PND stage IV and Coutinho Stage 2 contains elements of PND stages II, IIIa and IIIb. Consequently, a weighted average of mortality was used to populate Coutinho Stage 2. Therefore, the final hazard ratios (HRs) used in the model were 2.01, 2.42 and 9.53 for Stage 1, Stage 2, and Stage 3 respectively. As the committee expressed concern over uncertainty in both ECD reports, eight scenarios were modelled, and are described in **Error! Reference source not found.**.

Table 3: ICER when different mortality assumptions are made

Scenario	Stage 1 HR	Stage 2 HR	Stage 3 HR	Log-logistic ICER	Exponential ICER
Base case	2.01	2.42	9.53	£150,636	£131,260
50% of	1.01	1.21	4.77	£123,390	£101,562

Thank you for your comment. The committee concluded that the updated hazard ratios for mortality better reflected the risk associated with having the condition and it was satisfied with the revised approach. Please see section 4.16 of the FED.

Consultee	Comment	Response

base case values					
2 x base case values	4.02	4.83	19.06	£182,375	£166,705
General pop mortality	1.00	1.00	1.00	£57,189	£42,629
50% of general pop	0.50	0.50	0.50	£53,852	£39,422
2 x general pop	2.00	2.00	2.00	£63,099	£48,743
Original submission	5.00	10.00	19.00	£174,415	£160,337
Cardiac involvement group from patisiran submission only	4.12	5.35	19.49	£183,008	£167,566

Akcea accepts that there is uncertainty about mortality ratios, but contends that the revised base case is appropriate as:

- It is the approach requested by the ERG and is therefore consistent with Akcea's approach of adopting the same BSC assumptions as other hATTR submissions, to allow a fair and robust assessment of the product
- It is validated by UK clinicians at an advisory board
- It generates an ICER which is positioned approximately midway between the ICERs generated by other plausible approaches (i.e. it appears to not over or underestimate mortality based on other sources)

<u>Adjusting transition probabilities in extension phase to reflect assumptions accepted by NICE on improvements in Stage 2 for BSC group</u>

The third model amendment was the addition of the assumption that BSC patients cannot transition from Stage 2 to Stage 1 after week 66 of treatment, i.e. after the end of the trial period. The assumption was

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>validated by UK clinicians at an advisory board who noted that it may be possible for BSC patients to experience a placebo effect during the trial period leading to a slight increase in QoL, which may be sufficient for a small proportion of stage 2 patients to transition back to Stage 1. The clinicians however stressed that any such placebo effect would be very unlikely and, should it exist, would end after the completion of the trial. Therefore, any placebo effect would not translate into routine clinical practice, as it would be implausible to imagine a BSC patient experiencing a significant uplift in their quality of life after 66 weeks of decline.

Table 2: ICER when different BSC transition assumptions are made
<table><tr><th></th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr><tr><td>Limits on BSC transitions (base case)</td><td>£150,636</td><td>£131,260</td></tr><tr><td>No limits on BSC transitions</td><td>£198,641</td><td>£179,607</td></tr></table>
Conclusions

Three model amends have been implemented which significantly strengthen both the clinical and economic case for the reimbursement of inotersen. Moreover, these amends allow a robust and consistent approach to be taken by NICE for the modelling of the BSC state for hATTR-PN, which should be consistent between all technology appraisals for the same indication and population. The amended BSC transitions give more realistic estimates of the large increase in QoL that patients on inotersen experience compared to BSC patients and highlights the huge difference that inotersen could make to patients' lives if it was available on the NHS. The amends regarding new HRU costs represent a more accurate representation of the economic impact that reimbursement of inotersen would have and the savings that would be made in health resource utilisation.

Table 3 lists the changes that have been made to the inotersen model to ensure that BSC has the same assumptions in both models:

Table 3: Parameter changes in the inotersen model
<table><tr><th>Parameter</th><th>Originally submitted</th><th>Currently in model</th></tr><tr><td>BSC probability of transitioning from Stage 2 to Stage 1 after Week</td><td>[redacted]</td><td>0.00%</td></tr></table></td><td>Thank you for your comment. The committee concluded that it was satisfied with the company's revised approach to modelling disease progression. Please see section 4.15 of the FED.

Thank you for your comment. The evaluation committee has taken into account all factors that affect its decision.</td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><td>66</td><td></td><td></td></tr>
<tr><td>HRU costs</td><td>Stage 1: £393
Stage 2: £1,307
Stage 3: £1,745</td><td>Stage 1: £36
Stage 2: £8,548
Stage 3: £12,681</td></tr>
<tr><td>Mortality HRs</td><td>Stage 1: 5
Stage 2: 10
Stage 3: 19</td><td>Stage 1: 2.01
Stage 2: 2.42
Stage 3: 9.53</td></tr>
</table>

All of these assumptions have either been taken directly or calculated from publicly available data in the documents produced for consideration by NICE as part of the assessment of another hATTR submission. Matching these assumptions will ensure that there is a fair comparison made between inotersen and other hATTR submissions by the committee.</td><td></td></tr>
<tr><td>Akcea</td><td>Benefits of inotersen alignment assumptions

In addition to changes made purely to align the best supportive care groups, Akcea has made two further model amends intended to align assumptions about the treatment pathway when on treatment. These are:

• Including utilities that vary according to time-in-state

• A multiplier to reflect decreased HRU costs on treatment

<u>Changing time-in-state utilities</u>

The first change to the treatment pathway was to implement utility values that increase or decrease with time-in-state for inotersen and BSC patients, respectively. In order to capture the effect of treatment on QoL whilst patients remain within a health-state, a patient-level analysis of the NEURO-TTR trial was undertaken which demonstrated that patient utility improved within each state whilst on inotersen and reduced within each state whilst on BSC from baseline to Week 66, as demonstrated in Table 4.

Table 4: Comparison of the TQoL scores of inotersen and BSC patients at Week 66
<table>
<tr><th rowspan="2">Patient population</th><th colspan="2">Mean TQoL score at Week 66</th><th rowspan="2">Improvement on inotersen</th></tr>
<tr><th>Inotersen</th><th>BSC</th></tr>
<tr><td>Stage 1</td><td>[redacted]</td><td>[redacted]</td><td>-0.94</td></tr>
<tr><td>Stage 2</td><td>[redacted]</td><td>[redacted]</td><td>-4.35</td></tr>
<tr><td>Stage 3</td><td>[redacted]</td><td>[redacted]</td><td>-9.99</td></tr>
</table>

The assumption of improving utility within state with inotersen over time and worsening utility within each</td><td>Thank you for your comment. Please see response to the comments in the sections below.

Thank you for your comment. The committee concluded that introducing time-dependent utilities in the company's base case was acceptable. Please see section 4.23 of the FED.</td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
state with BSC over time was ratified with clinicians during an advisory board. Clinicians found that the patient-level analysis was not a chance finding and reflects that there is a broad spectrum of disease severity within each state; there was consensus that utility would linearly improve with inotersen and worsen with BSC to the next stage over time (as opposed to sheer jumps for example from Stage 2 [0.429] to Stage 3 [0.084]). Therefore, the implementation of this change has made the model more clinically realistic.

The relative 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. The model implements a ‘time-in-state’ adjustment to reflect the change in utility observed in the NEURO-TTR study. The utility for patients on inotersen is increased by 0.0002 for each cycle that they remain in the same health state. Similarly, the utility for patients on BSC is reduced by 0.0038 for each cycle that they remain in the same health state. The calculation of these utility gain from these incremental improvements in TQoL score is based on the mapping from Faria et al. (2012) to show how utility generally changes with time on treatment, which gives the formula for converting TQoL scores to EQ-5D scores as 0.913991-0.005682*TQoL. Over the 66 weeks of the trial, those patients stable on inotersen improved their average TQoL score by 0.66 (from 48.22 to 47.56) which corresponds to a utility improvement of 0.0038 or a four-weekly improvement of 0.0002. Those on BSC declined by 10.96 TQoL points (from 48.67 to 59.63), corresponding to a 66-week utility decline of 0.0622, or a four-weekly decline of 0.0038. Given the limited evidence on converting marginal TQoL changes into EQ-5D and in the absence of EQ-5D data direct from the NEURO-TTR study, Akcea found the only reasonable approach to quantify the changes in utilities with time-in-state was to utilise the mapping from Faria et al. The limitations of this approach are described in section 6 below.

Utilities were capped to never increase beyond the baseline utility of the next-best stage. In Stage 1, utilities were capped so that they could not improve beyond 0.83, representing general population health taken from Ara and Brazier (2010), which was the ERG’s preferred source for general population utility. Utilities were also prevented from decreasing beyond the utility of the next-worst stage (or -0.093 in stage 3 in absence of data to inform a lower bound), as this lower-bound capping was requested by NICE. After a transition to another stage, utility was reset to the average utility in that stage. If a patient discontinued, their utility would remain at whatever level it was prior to discontinuation but otherwise begin to increment downwards as per any patient on BSC. Table 5 details this information and gives the example of expected utility after 10 cycles stably in this stage. Base case utilities are described further in section 6.

Table 5 Detail of patient quality of life caps and increments in each stage
<table>
<tr><td>Health state</td><td>Patient EQ-5D-3L utility</td><td>Maximum utility in this stage</td><td>Minimum utility in this stage</td><td>Utility after ten cycles of inotersen in this stage</td><td>Utility after ten cycles of BSC in this stage</td></tr>
</table>
</td><td></td></tr>
</table>

Consultee	Comment	Response

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

The implementation of patient-tracking in the manner described is impossible in a Markov Chain model. Consequently, the utility scores in each cycle are pre-generated using VBA patient-level tracking, and then applied as appropriate to the Markov Trace. **Table 6** shows the impact of this amend on the results.

Table 6: ICER with and without increasing/decreasing utilities

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	ICER – Exponential distribution for discontinuation
Increasing/decreasing utilities (base case)	£150,636	£131,260
Static utilities	£157,668	£135,833

Multiplier to reflect decreased HRU costs on treatment

The second model amendment to align the hATTR submissions' treatment pathway was the addition of a multiplier which reduces HRU costs when the patient is receiving inotersen treatment. This is to reflect the expected significant reduction in HRU costs when the patient is on inotersen treatment within stage, which follows the same rationale as per the improvements in QoL discussed above. This is because patients on inotersen have – on average - less progressed disease even within the same stage as an equivalent BSC patient, as shown in **Table 7**.

Table 7: Comparison of the TQoL scores of inotersen and BSC patients at Week 66

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

This therefore indicates that the level of care they will require is less than an equivalent BSC patient, as it is

Thank you for your comment. The committee concluded that there were some uncertainties in the company's resource use assumptions but accepted the updated model for decision making. Please see section 4.24 of the FED.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>known that care requirements and associated morbidity are strongly dependent on disease progression. Additionally, the increased QoL and improved health demonstrated in the NEURO-TTR trial are likely to cause psychological benefits; patients on treatment believe that they are doing better so would not pursue the same level of care as patients on BSC. These arguments were validated at an UK advisory board in November 2018 in which clinicians agreed that HRU would be lower in patients receiving inotersen compared to BSC.

The level of this adjustment is set at 43% for Stage 1 and Stage 2 patients and 0% for Stage 3 patients (since these patients will discontinue inotersen treatment once they enter Stage 3). This figure is based on publicly available documents produced for the NICE appraisal of another hATTR therapy. The parameter value itself is sourced from a Delphi panel conducted by the manufacturer of patisiran. The exact value is given in the NICE documents, and so this value has been applied to the inotersen submission to ensure consistency between the reduction in costs from treatment across the two models. Table 8 details the costs implemented in the revised base case and Table 9 shows the impact of this amend on the results.

Table 8. List of disease stages and associated costs in the cost-effectiveness model
<table>
<tr><th>Disease stage</th><th>Value (inotersen)</th><th>Value (BSC)</th><th>Reference</th></tr>
<tr><td>Stage 1 per cycle (4-week)</td><td>£21</td><td>£36</td><td rowspan="3">Patisiran ECD</td></tr>
<tr><td>Stage 2 per cycle (4-week)</td><td>£4,873</td><td>£8,548</td></tr>
<tr><td>Stage 3 per cycle (4-week)</td><td>£12,681</td><td>£12,681</td></tr>
</table>

Table 9: ICER with and without 43% reduction in HRU costs
<table>
<tr><th></th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr>
<tr><td>75% reduction in inotersen HRU costs for Stage 1 and 2</td><td>£117,396</td><td>£87,329</td></tr>
<tr><td>43% reduction in inotersen HRU costs for Stage 1 and 2 (base case)</td><td>£150,636</td><td>£131,260</td></tr>
<tr><td>25% reduction in inotersen HRU costs for Stage 1 and 2</td><td>£169,334</td><td>£155,971</td></tr>
<tr><td>0% reduction in inotersen HRU costs for Stage 1 and 2</td><td>£195,302</td><td>£190,292</td></tr>
</table></td><td></td></tr>
<tr><td>Akcea</td><td>Utility value data source</td><td>Thank you for your</td></tr>
</table>

Consultee	Comment	Response
	Akcea agrees with the committee that the THAOS data valued with the UK EQ-5D value set would be the preferred data source, however the THAOS registry is independently run by another pharmaceutical company. Akcea has requested access to this database repeatedly but has so far been unsuccessful. We understand that efforts are being made by ARC UK and NICE to access this data but as yet this is not available. In the absence of the relevant data from the THAOS registry, there are three proposed utility sources which could be used: • Brazilian THAOS values converted to UK utility tariffs • Utility values taken from the tafamidis appraisal (Faria et al, 2012 • SF-36 data from NEURO-TTR (Stage 1 and Stage 2 only) <u>Brazilian THAOS values converted to UK utility tariffs</u> We believe that applying UK utilities to the Brazilian THAOS scores is closest to what the committee has requested, and so have adopted this as part of our revised base case and discuss our reasoning for this decision below. Akcea discussed at the committee meeting that applying the Brazilian tariff to EQ-5D data from the THAOS registry provides a conservative estimate of cost-effectiveness for inotersen. Whilst we agree that the utility values are uncertain in the absence of data to apply the UK tariff, the values presented to the committee are conservative with regard to what the 'true' ICER would be were the UK tariff applied. The reason for this is described by the ERG – "a standard decrement for any level 3 response was not applied in the Brazilian value set, but was used in the UK value set, meaning that poorer health states are valued substantially lower in the UK tariffs compared to the Brazilian tariffs". This in turn means that the worst health state in the model (Stage 3) is significantly worse using UK tariffs than Brazilian tariffs, which improves the ICER as inotersen slows or halts progression into Stage 3. In order to investigate this fully, Akcea have calculated the utilities of every health-state as defined using EQ-5D-3L using both the UK and Brazilian valuation tariffs – please see **Error! Reference source not found.**. It was noted that for every EQ-5D response which could plausibly map to Stage 3 health states (any Brazilian utility lower than 0.404), performing a conversion to the UK tariff reduced the ICER, often dramatically. For Stages 1 and 2, the effect was less pronounced; for EQ-5D responses eliciting Brazilian utilities close to Stage 1 and Stage 2, conversion to the UK tariff increased the ICER by a small amount in Stage 1, and reduced the ICER by a moderate amount in Stage 2. Taking the utility values that most closely matched those applied in the model (11212 for Stage 1, valued at	comment. The committee acknowledged the company's comments. It understood that there were advantages and disadvantages with each source of utility data and recognised the uncertainties around the utility values used in the updated company model. Because the preferred raw EQ-5D data were not available, the committee concluded that the company's revised approach to modelling health-related quality of life, although not optimal, was acceptable for decision making. Please see sections 4.19 – 4.22 of the FED.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
0.704 in Brazil and 0.812 in the UK; 22213 for Stage 2, valued at 0.427 in Brazil and 0.205 in the UK; and an average of 33311 and 31332 for Stage 3, valued at 0.086 for both in Brazil, and 0.028 and -0.215 respectively in the UK), the Brazilian valuation of EQ-5D was underestimated for patients in good health, and overestimated for those in the poorest health states compared to the values that would be calculated in the UK (Table 10).

Table 10: Method of estimating THAOS registry results from existing Brazilian data
<table>
<tr><th>Stage</th><th>Utility for this stage, taken from Stewart et al 2017, which are themselves sourced from the THAOS registry</th><th>EQ-5D input which gives closest result when Brazilian weighting applied (corresponding utility) (Santos et al., 2016)</th><th>Utility output when this EQ-5D input is weighted using UK tariff (Dolan, 1997)</th></tr>
<tr><td>Stage 1</td><td>0.697</td><td>11212 (0.704)</td><td>0.812</td></tr>
<tr><td>Stage 2</td><td>0.429</td><td>22213 (0.427)</td><td>0.205</td></tr>
<tr><td>Stage 3</td><td>0.084</td><td>33311 and 31332 (0.086)</td><td>-0.094
(average of 0.028 and -0.215)</td></tr>
<tr><td>Death</td><td>0</td><td>N/A</td><td>0</td></tr>
</table>

These findings are consistent with published literature describing conversions between Brazilian and UK utilities; see for example,Takemoto et al (2015).

Therefore, whilst we acknowledge there is uncertainty in applying Brazilian tariffs to a model from a UK perspective, we have demonstrated that using the Brazilian tariffs for this decision problem is a highly conservative approach. As the committee have expressed concern about the use of Brazilian tariffs and in the absence of data from the THAOS registry, Akcea have applied UK converted numbers outlined in Table 10 to the revised base case, the impact of which is demonstrated in Table 11.

<u>Utility values taken from the tafamidis Advisory Group for National Specialised Services (AGNSS) appraisal (Faria et al, 2012)</u>

The second approach is to use utility values from the tafamidis AGNSS appraisal <u>(Faria et al, 2012)</u>. This approach is not aligned with the committee's goals of distinguishing between the three Coutinho stages, and is therefore not appropriate for the submission.

Akcea does not agree with the committee's assessment that it would be more appropriate to use the
</td><td>Thank you for your comment. The committee understood that utilities from Faria et al. were based on mapping total quality of</td></tr>
</table>

Consultee	Comment	Response
	mapping of TQoL to EQ-5D from the tafamidis NICE appraisal, as reported by Faria et al. 2012, due to the uncertainty surrounding the calculation of health-state utility values by mapping TQoL to EQ-5D. Whilst the mapping is sufficient to observe trends between TQoL and EQ-5D (as we have used to implement improvements in quality of life), Akcea do not believe it to be sufficient to assume a causal relationship between the two measures as there are domains within the TQoL that are not included within the EQ-5D and vice versa, so one cannot simply map between them. For instance, the TQoL questionnaire asks about symptoms, diagnosis, activities of daily living and generic health status whereas EQ-5D-3L includes questions about anxiety and depression addressing the emotional impact of the condition. Indeed, the ERG from the tafamidis appraisal requested alternative mappings be provided between the TQoL score and EQ-5D, indicating that the assumption of a linear relationship between the two measures is weak and inappropriate. Additionally, the mapping function used to transform TQoL scores to EQ-5D scores was created by the manufacturer of tafamidis for the tafamidis Advisory Group for National Specialised Services (AGNSS) submission. No evidence was provided on the validity of this mapping function and it has no basis in literature, meaning that there is a great deal of uncertainty surrounding this mapping. This point was made by the ERG reviewing the tafamidis submission, and so adopting this approach which was criticised by the ERG of a previous submission should not now be encouraged, especially in the face of more compelling evidence which more closely matches the approach that all parties agree would be 'gold standard'. Furthermore, as noted by the committee in the ECD, the lowest possible EQ-5D utility based on this mapping is 0.147 instead of 0 – far above the limits that can be reached from the EQ-5D and not realistically corresponding to a true description of a typical Stage 3 health state where – by definition – mobility, self-care and usual activities are severely impaired (as mobility is the diagnostic criteria separating Stage 3 from Stage 2). As well as being a testament to the poor quality of the mapping function, this means that utility gains may be underestimated if the mapping is used, especially for Stage 3 patients with the lowest utilities and therefore contradicts direct patient reported outcome measures as seen in the Stewart et al 2017 paper. Finally, it is well documented that mapping equations do not perform well when data are non-linear. When considering observed utility data from Stewart et al., non-linearity is clear, particularly when considering utility differences between Stage 1 and 2 (0.268), versus Stage 2 and 3 (0.345), and a minimally important difference in EQ-5D being 0.05. Therefore, attempting to put EQ-5D scores on a linear scale will clearly overestimate poorer health and underestimate good health in patients, a common issue with mapping equations. This significantly biases against inotersen given that treatment prevents patients transitioning to poorer health states and keeps patients in better-off health states. <u>SF-36 data from NEURO-TTR (Stage 1 and Stage 2 only)</u> The third proposed approach is to use the SF-36 data collected in the NEURO-TTR trial. This approach was	life data (based on defined total quality of life score cut-offs on the Norfolk QoL-DN questionnaire) to the EQ-5D. It understood based on an ERG comment that the lowest possible EQ-5D based utility was above 0, and therefore utility gains might be underestimated with this method. Please see section 4.21 of the FED.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>agreed in the committee meeting to be severely lacking compared to the other two possibilities; no SF-36 data was collected on patients in Stage 3 as these patients were not on treatment, and as Stage 3 utilities are critical for driving cost-effectiveness results, this approach adds significant uncertainty without providing any obvious benefits.

Conclusion

For the reasons discussed above, there is a much greater degree of uncertainty surrounding mapping TQoL to EQ-5D utility values using the mapping function by Faria et al than that proposed in the revised base case. Considering the continued unavailability of the THAOS registry data, we maintain that the converted utility values from the Stewart et al. 2017 study are the only appropriate values that are available and relevant to hATTR patients. Table 11 shows how the ICER changes when the source of utility data is changed.

Table 11: ICER when different utility values are used
<table>
<tr><th>Source of utility values</th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr>
<tr><td>THAOS registry</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Stewart (2017) paper converted to UK tariff (base case)</td><td>£150,636</td><td>£131,260</td></tr>
<tr><td>Stewart (2017) paper not converted to UK tariff (i.e. Brazil tariff, as per original submission)</td><td>£173,562</td><td>£150,470</td></tr>
<tr><td>Faria. et al (2012) assuming stages represent difference-in-kind from each other (separate regression for each stage, 4th column of Table 28, so Stage 2 represent a step-change from Stage 1)</td><td>£171,157</td><td>£147,280</td></tr>
<tr><td>Faria et al. 2012 assuming stages represent difference-of-</td><td>£203,781</td><td>£175,420</td></tr>
</table></td><td>Thank you for your comment. The committee considered all options as possible source of utility data in the model, however it understood that SF-36 data from NEURO-TTR study would only provide utility values for stages 1 and 2. Please see section 4.21 of the FED.</td></tr>
</table>

Consultee	Comment	Response
	degree from each other (one regression model every stage, 3rd column of Table 27, so Stage 2 represents only an arbitrary distinction between a bad Stage 1 and a good Stage 2)	
Akcea	**Carers** Akcea acknowledges the committee's concerns regarding the number of carers assumed at each stage of the disease in the model, however we do not agree with the ERG's recommendation to assume one carer in every stage in the model. In particular, we do not agree that a Stage 3 hATTR-PN patient would only require one carer. During a call with NICE on 6th December 2018, it was confirmed that the interpretation of the NICE committee was that one carer in Stages 1 and 2, and two carers in Stage 3 was an appropriate base case. In Stage 3 of the disease, patients are bedridden or confined to a wheelchair and usually have other severe symptoms such as diarrhoea, peripheral neuropathy and cardiomyopathy. In this state, patients need assistance from a carer for even the most basic of tasks, and this assistance is needed constantly, day and night. Indeed, the ECD states: "In the advanced stage of the condition 24-hour care is essential because of immobility and possible loss of eyesight, combined with other symptoms such as incontinence" (ECD, Page 15) It is therefore unrealistic to assume that this care could be delivered by one individual. Furthermore, being a carer for a person with that level of challenge is burdensome – fatigue, depression and anxiety are all reported by carers of people with advanced hATTR (Gertz, 2017). Since the committee meeting, Akcea has conducted a Caregiver Impact Study of 36 carers of patients with hATTR-PN, six of whom were recruited via ARC UK and 30 via a specialist panel agency. Of the 36 carers, eight were from the UK, 23 from the US and five from Canada, Australia, and New Zealand. This survey also included 36 members of the general population matched on carer demographics (age, gender, living status, employment status) who were recruited via a specialist panel agency. The study concluded that carers spend a significant amount of time caring for patients, with the total number of hours of practical care (e.g. performing physical tasks such as getting in/out of bed, dressing, general ambulation, cooking, and eating, maintaining personal hygiene and administering treatment) given by a single carer calculated as 2.64, 6.88 and 10.67 hours per day for Stage 1, Stage 2 and Stage 3, respectively (**Table 12**). There is a sharp increase in the total number of hours spent caring as the patient progresses through hATTR, with a	Thank you for your comment. The committee reviewed the carer testimonies and accepted the company's revised approach. It concluded that it was appropriate to assume 1 carer in stages 1 and 2, and 2 carers in stage 3 of the model. Please see section 4.17 of the FED.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
single carer providing four times as much care per day for a Stage 3 patients compared to a Stage 1 patient. Over a seven-day week, this gives the total number of hours of practical care given per carer as 18.50, 48.19, and 74.67 hours per week for Stages 1, Stage 2, and Stage 3 patients, respectively. Assuming a standard 37.5 hour working week for full-time employees (Office for National Statistics, 2018), the hours spent giving practical care corresponds to 0.49, 1.29, and 1.99 full-time jobs per carer of a hATTR patient in Stage 1, Stage 2, and Stage 3, respectively.

As well as practical care, the hATTR Caregiver Impact Study also asked how many hours per day carers spent giving emotional support to patients, and this was reported as 3.56, 4.74, and 1.76 hours per day for Stage 1, Stage 2 and Stage 3, respectively (Table 12). When combined with practical care this gives the total number of hours of care given per carer as 43.42, 81.39, and 87.00 hours per week, which corresponds to 1.16, 2.17, and 2.32 full-time jobs per carer of a hATTR patient in Stage 1, Stage 2, and Stage 3, respectively. It is known that the burden of care such as increased anxiety, depression and fatigue increases significantly as later Stages are entered by the patient (Gertz, 2017).

However, as Akcea cannot prove that practical care and emotional support are exclusive, the revised base case considers a more conservative approach whereby patients require one, one, and two full-time carers per patient in Stage 1, Stage 2 and Stage 3, respectively.

Table 12: Hours of care and emotional support per day by disease stage
<table>
<tr><th>Coutinho Stage</th><th>Hours of practical care per day</th><th>Hours of emotional support per day</th></tr>
<tr><td>Stage 1</td><td>2.64</td><td>3.56</td></tr>
<tr><td>Stage 2</td><td>6.88</td><td>4.74</td></tr>
<tr><td>Stage 3</td><td>10.67</td><td>1.76</td></tr>
</table>

This is therefore consistent with the NICE committee’s preference for assuming one carer per patient in all but Stage 3, where two carers are required. The number of carers and hours of care were validated by five clinical experts and one patient representative at an advisory board meeting in November 2018 , who estimated that a Stage 3 patient may need as many as three full time carers. This is further validated by the literature reviewed and cited in the original submission, which estimates the average hATTR patient received a median of 144 hours of care per week (Gertz, 2017). Assuming a median full-time week over 7-days of 52.5 hours (aligned with a median 37.5 hour work-week as reported by the Office of National Statistics), this equates to almost three full time carers per patient.

Table 13 shows the effect on the ICER when various numbers of carers are assumed at each disease stage.
</td><td></td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>Table 13: ICER when different numbers of carers are assumed for each disease stage
<table>
<tr><th>Number of carers used in Stages 1, 2 and 3 respectively</th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr>
<tr><td>1, 1, 2 (revised base case and NICE preferred case)</td><td>£150,636</td><td>£131,260</td></tr>
<tr><td>1, 1, 3</td><td>£139,769</td><td>£121,230</td></tr>
<tr><td>1, 1, 1</td><td>£163,335</td><td>£143,098</td></tr>
<tr><td>1, 2, 2</td><td>£151,537</td><td>£132,173</td></tr>
<tr><td>2, 2, 2</td><td>£151,870</td><td>£132,460</td></tr>
</table></td><td></td></tr>
<tr><td>Akcea</td><td>Treatment discontinuation

Akcea appreciates the concerns of the committee regarding the rate of inotersen treatment discontinuation. While we maintain that the exponential distribution is the best statistical fit for the discontinuation data available, as confirmed by AIC and BIC testing, we realise that, at present, there is no longer-term data available for inotersen discontinuation. As such, we have complied with NICE’s request to present exponential (manufacturer preferred curve) and log-logistic (ERG preferred curve) discontinuation assumptions side-by-side throughout the ECD response. We have presented log-logistic as our base case as this was stated as NICE’s preferred approach.

Table 14 shows the effect on the ICER when the exponential and log-logistic distributions are used to model treatment discontinuation.

Table 14: ICER when using exponential and log-logistic distributions for treatment discontinuation
<table>
<tr><th>Distribution</th><th>ICER</th></tr>
<tr><td>Log-logistic (base case)</td><td>£150,636</td></tr>
<tr><td>Exponential</td><td>£131,260</td></tr>
</table></td><td>Thank you for your comment. The committee was satisfied that the preferred assumption was implemented correctly.</td></tr>
<tr><td>Akcea</td><td>Adverse events

Akcea accepts that NICE would prefer to see scenarios including adverse events, and therefore have included them in all scenarios in this response document. We agree with NICE that the impact of including such scenarios is negligible.

Table 15 shows how the ICER changes when adverse events are not included.

Table 15: ICER with and without adverse events included</td><td>Thank you for your comment. The committee was satisfied that the preferred assumptions were implemented correctly.</td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr>
<tr><td>Adverse events included (base case)</td><td>£150,636</td><td>£131,260</td></tr>
<tr><td>Adverse events not included</td><td>£150,162</td><td>£130,828</td></tr>
</table>
</td><td></td></tr>
<tr><td>Akcea</td><td>
Discount rate

Akcea is pleased that NICE accepts two of the three criteria for non-reference case discount rate of providing long-term clinical benefits to patients (see key issue 1) and not committing the NHS to significant irrecoverable costs. Given inotersen’s ability to reverse hATTR-PN in some cases it is disappointing that NICE does not accept that the final criterion, that of returning to perfect or near-perfect health, can be met. However as NICE have clearly signalled that they do not wish to see a 1.5% discount rate for costs and QALYs, a 3.5% rate is used throughout the resubmission.

Table 16 shows the effect on the ICER when the reference and non-reference case discount rates for costs and QALYs are used.

Table 16: ICER when different discount rates are used
<table>
<tr><th>Discount rate</th><th>ICER – Log-logistic distribution for discontinuation (ERG preferred case)</th><th>ICER – Exponential distribution for discontinuation</th></tr>
<tr><td>3.5% costs and QALYs (base case)</td><td>£150,636</td><td>£131,260</td></tr>
<tr><td>1.5% costs and QALYs</td><td>£151,548</td><td>£129,300</td></tr>
</table>
</td><td>Thank you for your comment. The committee was satisfied that the preferred assumption was implemented correctly.</td></tr>
<tr><td>Akcea</td><td>
Impact of inotersen beyond direct health benefits

Akcea acknowledges the committee’s concerns regarding the wider impact of inotersen and how to balance this with their concerns about its cost-effectiveness, however, amends have been made to our model to align assumptions on BSC and treatment effect with other ongoing technology appraisals in the same disease, and have sought to address the committee’s concerns. When considered together, these changes show inotersen to be significantly more cost-effective than that presented in the original submission and at the first NICE committee meeting. Akcea hopes that the committee will take this into consideration when
</td><td>Thank you for your comment. The evaluation committee considered the impact of the technology beyond direct health benefits. Please see section 4.29 of the FED.</td></tr>
</table>

Consultee	Comment	Response
	assessing the wider benefits of inotersen in future. Akcea would also like to reiterate that the progressive loss of independence and dignity experienced by hATTR-PN patients negatively affects every aspect of patients', family members' and carers' lives. Particularly, the symptoms of hATTR-PN have been demonstrated to detrimentally impact multiple aspects of patients' daily life, emotional wellbeing, relationships with family and friends, work and financial status, as well as physical health (Lovley, Guthrie and Pollock, 2018). For example, 27% of Stage 1 hATTR-PN patients and 30% of patients with Stage 2 hATTR-PN report some difficulty with reading a newspaper or book, and eating (Berk, Lin and Agarwal, 2018), and in a recent patient and carer study conducted in the UK (Richard, Lousada and Low, 2018 (unpublished)), 50% of patients with hATTR-PN stated that their condition has an extreme impact on their emotional well-being, with 35% stating that they had experienced fear, anxiety and depression in the last 12 months. A US survey (Ionis, 2017) found more than half (55%) of patients with hATTR-PN reported their mental health/outlook on life is impacted by the disease, with patients suffering from anxiety (71%), stress (62%) and depression (43%). In addition, disease burden increases with disease progression. The impact of hATTR-PN on carers is considerable in terms of the emotional burden of 'knowing what's to come', the practical caring burden (causing fatigue and anxiety) and the effect on their own ability to work and participate in social activities. Among carers (who do not have hATTR-PN themselves), the mean number of hours spent per day giving practical care to patients is reported at 2.6, 6.9 and 10.7 hours for Stage 1, Stage 2 and Stage 3, respectively. This significant amount of time spent caring for patients means that carers will have to relinquish their own social activities and employment in order to provide medical support, care and assist with activities of daily living, including household chores such as cleaning, shopping and cooking. At advanced stages of the disease, carers also provide daily personal care. Consequently, the disease has a significant knock-on impact on carers' own productivity at work as well as their ability to undertake paid work. In a recent hATTR Caregiver Impact Study, over half (56%) of carers stated that they had changed their employment as a result of hATTR, and Berk et al. reported that 12% of carers limited employed work to part-time whilst 15% were unable to continue employment altogether, with the ability to hold employment falling from 22% to 6% for those caring for a patient with Stage 1 and Stage 2 hATTR-PN, respectively. In the hATTR Patient and Caregiver Impact Study, over 70% of carers reported a detrimental impact of the disease on their own work and professional life, with 31% reporting a severe impact. As well as the impact on their employment, there is also a massive toll on the emotional and psychological wellbeing of carers, with a recent hATTR Caregiver Impact Study showing that carers have significantly higher anxiety levels, as measured by the Hospital Anxiety and Depression Scale (HADS), than controls; reporting 2.5 times higher levels of probable clinical anxiety than the matched controls. A recent survey revealed that 54% of carers of hATTR-PN patients described their emotional wellbeing as being severely affected by the disease, with 55% identifying social/family relationships as being 'extremely impacted' by the disease. Carers even reported a higher impact on their emotional wellbeing and social/family relationships than patients themselves.	

Consultee	Comment	Response
	If recommended by NICE, inotersen will offer the potential to slow, arrest or reverse disease progression in patients with Stage 1 or 2 hATTR by targeting the underlying cause of the disease. This will mean that patients remain in the earlier stages of the disease for longer, which in turn will allow them to retain their independence for longer through the preservation of their ambulatory ability and key health domains. [redacted] Therefore, as well as the direct health benefits that inotersen treatment will bestow, it will provide patients the opportunity to continue with employment, as well as actively participate in family life and social activities for longer. Furthermore, inotersen has the potential to reduce the burden borne by carers of patients with hATTR in terms of their work productivity and participation in family and social activities. Consequently, this will also lessen the impact on patients' and carers' emotional wellbeing.	
Akcea	[redacted]	Thank you for your comment. The evaluation committee considered the impact of the technology on the delivery of the specialised service. Please see section 4.30 of the FED.
Akcea	**Managed access agreement** Akcea would like to take this opportunity to highlight the changes that have been made to our model on the committee's recommendation, which include adopting the log-logistic curve to model discontinuation, including the costs and disutilities associated with serious adverse events, and changing the discount rate for costs and QALYs to the reference case of 3.5%. Where possible, scenario analyses have been conducted around these parameters, as well as other such as mortality hazard ratios, reducing any	Thank you for your comment. The committee noted that the company revised its commercial offer for inotersen, and although there were outstanding uncertainties the committee

Consultee	Comment	Response
	uncertainty around these inputs. We hope that the committee will take these parameter changes and additional analyses into account when considering options for managed access or commercial agreements.	recommended inotersen as an option for treating hATTR amyloidosis. Please see sections 4.26,4.27, and 4.33 of the FED. Please see section 4.27 of the FED.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical expert nominated by British Society of Heart Failure and Royal College of Physicians	Within this evaluation document, the committee has accurately described the condition, hereditary transthyretin-related amyloidosis, its burden on patients and their carers and the unmet need of this disease. The increasing burden as the disease progresses on patients and importantly, their family members who provide care, in terms of independence, dignity, ability to work and carry out daily activities is described. There is no treatment at present. With best supportive care, the disease progresses with the patient ultimately bedbound. The committee concludes that clinical trial evidence demonstrates that inotersen slows progression of the disease considerably. It is uncertain whether this is maintained long-term. It also concludes that there are uncertainties in the economic modelling particularly around utility values, numbers of carers, mortality and stopping treatment. The cost effectiveness estimates are much higher than what NICE considers acceptable for highly specialised technologies. Inotersen is innovative but does not appear to provide value for money and therefore is not recommended for routine funding in the NHS. • Has all of the relevant evidence been taken into account? The committee discussed and took into account relevant evidence with respect to inotersen, namely NEURO-TTR comparing inotersen with placebo, and the NEURO-TTR extension study. These studies are relevant to a UK population. The clinical effectiveness of inotersen is demonstrated in the NEURO-TTR study. Long term data are being accumulated in the extension study. • Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG.

Nominating organisation	Comment	Response
	These summaries are reasonable interpretations. A mean TTR reduction of 74% was seen with inotersen. A threshold for TTR knockdown at 80% for clinical effectiveness is discussed. It should be noted that this percentage has not been validated in TTR amyloidosis, although it is accepted that the higher the knockdown in all types of amyloidosis, the higher the percentage of patients whom are likely to benefit in terms of halting or reversing progression of disease. The turnover and production of TTR varies from patient to patient so some may derive benefit from a knockdown lower than 80% while other patients may require a much higher level of knockdown to gain the same benefit. The company's base case as well as the ERG's analysis, are described. In both scenarios, inotersen was associated with an ICER well above £100,000 per QALY gained (which NICE considers acceptable). • Are the provisional recommendations sound and a suitable basis for guidance to NHS England? I agree that these recommendations are sound and a suitable basis for guidance to NHS England at present.	Thank you for your comment. The committee noted comments from consultation that using a binary 80% value as a criterion for long-term clinical benefits has not been validated and the effect of reducing serum TTR levels would vary among patients because of differences in turnover and production of amyloid in the body. The committee concluded that although inotersen did not decrease serum TTR level by 80%, it provided clinical benefit. Please see section 4.9 of the FED.

Comments received from commentators

Commentator	Comment	Response
NA	NA	NA

Comments received from members of the public

Role*	Section	Comment	Response
NA	NA	NA	NA

Summary of comments received from members of the public

Theme	Response
NA	NA

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

NICE National Institute for Health and Care Excellence

Inotersen for treating hereditary transthyretin-related amyloidosis [ID1242]

Consultation on the evaluation consultation document – deadline for comments 5pm on 9/1/2019 **email:** TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent	**Akcea Therapeutics**
Disclosure	**None**
Name of commentator person completing form:	Luke Robinson, General Manager, UK, ROI & Nordics
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** Akcea would like to thank the committee for the detailed Evaluation Consultation Document (ECD), and the opportunity to respond to it. We are glad that the

committee has recognised inotersen to be an innovative treatment for hATTR. We note also that the committee recognised the significant health burden of this disease for patients and those caring for them.

As a result of recommendations and judgements made in the ECD, Akcea have amended their model base case as well as submitting newly available information and providing clarification on points as required (see below for more details). This significantly improves the base case incremental cost-effectiveness ratio (ICER) to £131,260-£150,636 (see Table 1), which supports Akcea's case that their original model submission was conservative.

Table 1: Revised company base case ICER following amends post ECD

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	**ICER – Exponential distribution for discontinuation**
Revised company base case	£150,636	£131,260

The model changes fall into three broad groups:

- Amending assumptions around best supportive care to conform with the best supportive care assumptions accepted by NICE as part of the ongoing assessments of other hATTR products, confirmed with expert clinicians, and as agreed with members of the NICE committee on a clarification call (section 4)
- Amending assumptions around the disease pathway in order to consistently reflect judgements made in the ECD reports for both inotersen and other hATTR products (section 5)
- Amending the model to conform with NICE's preferred inputs as described in the ECD report for inotersen:
    - Discontinuation extrapolation curve (section 8)
    - Inclusion of adverse events (section 9)
    - Adoption of 3.5% discount rate (section 10)

These are described in more detail below.

In addition to model amendments, Akcea presents new evidence and argumentation on a number of points where the committee expressed uncertainty. These points include:

- The long-term benefits of inotersen (section 2)
- The appropriateness of a treatment stopping rule (section 3)
- The preferred source of time-in-state utility data (section 6)
- The preferred assumption regarding the number of carers in each Stage (section 7)

The model amends and additional information provided to mitigate key uncertainties significantly improve the cost-effectiveness case for Inotersen. Given these changes, we would like to request that NICE now supports commercial discussions with NHS England to enable inotersen to be made available to patients living with hATTR; a devastating disease with no therapeutic treatment options.

Inotersen for treating hereditary transthyretin-related amyloidosis [ID1242]

Consultation on the evaluation consultation document – deadline for comments 5pm on 9/1/2019 **email:** TACommB@nice.org.uk/NICE DOCS

2	**Long term benefits of inotersen** Akcea has published new evidence (not available at the time of the committee meeting) to further support its case that the benefits of inotersen will be preserved long-term. Akcea challenges the committee's conclusion that there was insufficient evidence on the long-term benefits of inotersen and that there is uncertainty about whether clinical benefits would be maintained in the long term, and is confident that the new evidence presented will help resolve committee uncertainty. Additionally, the ECD concludes that reductions in TTR serum levels are insufficient to conclude that the benefit to patients will be maintained in the long-term. Akcea challenges this interpretation of the evidence for four reasons: • New extension evidence is available which shows the long-term benefit of inotersen is maintained for at least two years • Reduction in TTR is a surrogate outcome and, on its own, is not currently established as a reliable prognostic indicator of long-term benefit • The NEURO-TTR trial was not designed or powered to demonstrate a specific TTR serum level reduction. • To use a non-validated surrogate marker like reduction in TTR levels, which is not systematically correlated to functional outcomes, as a prognostic indicator instead of patient-related outcome measures would contradict NICE's own methods guidance. • There is no defined consensus on level of optimal TTR reduction <u>New extension evidence is available which shows the long-term benefit of inotersen is maintained for at least two years</u> Since the committee meeting, further follow-up data on long-term outcomes has become available from the OLE study. These data were presented to the American Society of Hematology's annual conference in December 2018 (Brannagan et al., 2018), and demonstrates sustained improvement in Norfolk-QoL, mNIS+7, and SF-36 up to 104 weeks in both the inotersen-inotersen group versus the inotersen-placebo group, and in the inotersen-placebo group versus the projected continuation line from the placebo group before their switching onto inotersen (Table 1). **Table 1: Long-term clinical data from NEURO-TTR open-label extension study at 104 weeks** See table below.

	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

Reduction in TTR is a surrogate outcome

There is general agreement among experts in the amyloidosis community that TTR reduction is closely associated with clinical benefits in ATTR amyloidosis. Given that the mechanism of action of inotersen is mediated through TTR, it is unsurprising that there will be an association between TTR levels and patient outcomes. However, there is no evidence to suggest that there is a threshold after which patients will have a clinically important improvement in prognosis. A TTR serum level reduction threshold may be established over time based on data from large sample sizes, but the heterogeneity of the patient population makes this challenging. There is no evidence that supports the use of a binary 80% threshold in TTR serum reduction as a criterion for long-term clinical benefits, as put forward by the committee without providing a reference. We do remain optimistic that we can work with the community to establish this over time. Factors that are critical to the accurate measurement and interpretation of TTR include, for example:

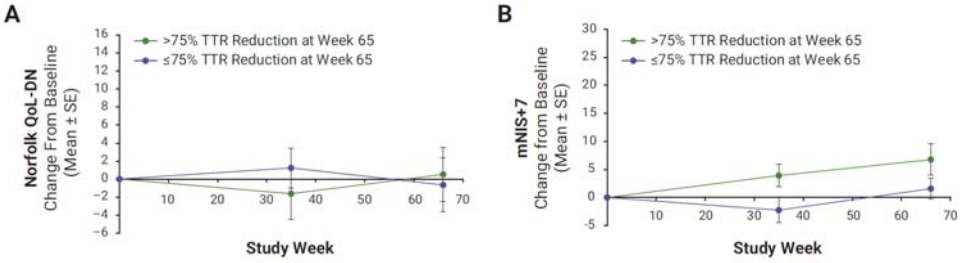
- The timepoint at which TTR is assessed after initiation of treatment; for example, at 3 versus 6 versus 9 months.
- Whether the threshold criteria is established on first-line patients or all patients
- Whether and how to take into account the pre-dose mean TTR
- Whether and how to correct for specific mutations identified in hATTR ("Mutations in Hereditary Amyloidosis," n.d.)
- Whether and how to correct for important patient-specific factors, such as range of organ involvement, age at diagnosis, time from diagnosis to treatment and so on

In addition to the difficulties highlighted above, one key reason why TTR serum levels have not been systematically correlated to functional outcomes is that there are different ways of measuring TTR levels. For example, Figure 2A of Adams et al. (2018) combines pre-dose and post-dose measurements of serum TTR levels in the same graph. Later in this paper a claim of an 81% median reduction is made which is hard to directly compare with other literature as it is unclear if this reduction was derived from measurements taken pre-dose, post-dose, or a mixture of pre- and post-dose. In a different source, the 'mean max' reduction is reported, which is not an accepted statistical methodology and again makes it difficult to compare literature on TTR serum levels (Alnylam Pharmaceuticals, 2018).

Treatment with inotersen led to a 79% reduction in median TTR serum levels (Benson et al., 2018). An analysis completed by Akcea and presented at the Peripheral Nerve Society congress showed that there was no statistically significant difference in the clinically relevant mNIS+7 or Norfolk QoL-DN scores between patients with <75% TTR serum level reduction and >75% TTR reduction (see Figure 1), which supports the case that marginal changes in TTR levels do not lead to significant differences in clinically relevant outcomes. The analysis also showed that the mNIS+7 or Norfolk QoL-DN scores of some patients who achieved a 90% reduction in TTR serum levels did not show improved quality of

life, whereas some patients who achieved a 50% TTR serum reduction did improve, which also supports the case that TTR serum levels are an imprecise surrogate for clinically relevant outcomes.

Figure 1. No differences were seen in (A) Norfolk QoL-DN and (B) mNIS+7 between inotersen-treated patients with >75% versus ≤75% reduction of week 65 TTR levels.



We support the concept that high levels of TTR reduction leads to better outcomes, but evidence for a particular threshold does not yet exist for ATTR amyloidosis. We hope to work with the leading clinicians in the amyloidosis research community, including those in the National Amyloidosis Centre, to help gather such evidence over time. We believe this will require a rigorous and consistent method of measuring TTR reduction at a specific timepoint across treatments. We are encouraged that there are multiple treatments that can help to establish this in a consistent and transparent fashion. We look forward to taking part in efforts to establish response criteria in patients with ATTR amyloidosis. However, at this point, the default assumption must be that the significant improvements in clinical and PRO outcomes take precedence over a threshold with limited clinical consensus and applicability. The assumption such a threshold exists is unscientific and unjustified in the absence of significant new evidence.

<u>The NEURO-TTR trial was not designed or powered to demonstrate a specific TTR serum level reduction.</u>

Akcea would like to remind the committee that the NEURO-TTR trial was not designed or powered to demonstrate a specific TTR serum level reduction. The primary efficacy outcomes of the trial were the change from baseline in Norfolk QoL-DN and mNIS+7 scores, while the change from baseline in TTR serum levels was an additional secondary pharmacodynamic outcome. It is Akcea's opinion that it is inappropriate for the committee to draw conclusions on the long-term clinical efficacy of inotersen based on an outcome intended only to demonstrate the pharmacodynamic properties of inotersen on the body and not its clinical efficacy.

<u>To use a surrogate marker would contradict NICE's own methods guidance.</u>

Finally, NICE is explicit in its methods guidance that surrogate outcomes like biomarkers are inappropriate to use when patient-reported outcomes are available: "Clinical end points that reflect how a patient feels, functions, or how long a patient survives are regarded as more informative than surrogate end points (such as laboratory tests and imaging findings) (NICE, 2013)." The

	purpose of this judgement by NICE is to prevent arbitrary clinical thresholds from preventing access to treatment which patients themselves report is working for them, and to focus public spending on areas where patients are most likely to benefit. Norfolk-QoL, mNIS+7, and SF-36 all relate directly to patients' feeling and functioning, while TTR is – at best – a heterogenous indicator lacking "strong evidence that it predicts health-related quality of life". It therefore contradicts NICE's own methods guidance to conclude, based on TTR reduction, that it is uncertain whether inotersen has long term clinical benefit without substantial and compelling evidence that the 80% TTR reduction threshold mentioned in the ECD is anything more than arbitrary, particularly given that the clinical and patient reported outcome measures available from the NEURO-TTR and OLE studies clearly demonstrate significant and sustained benefit of inotersen.
3	**Treatment stopping rules** The ECD makes reference to the fact that the stopping rule applied in the model was a source of uncertainty, since it is possible that a patient benefitting from inotersen and their clinician would not want to stop treatment when that patient enters Stage 3. The Summary of Product Characteristics is explicit about the license of the product: *"Tegsedi is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)." (SPC, 2018)* NHS England confirms that their interpretation of this licence indication is the same as Akcea's; "NHS England stated that it interpreted the wording of the marketing authorisation to mean that treatment should stop when the condition progresses to stage 3" (ECD, Page 14) Akcea appreciate the concerns raised by NICE. However, evidence outside of inotersen's marketing authorisation is very limited, and will inevitably be assumption-based. As such, Akcea firmly believe this should not be considered in NICE's decision making. However, in appreciation of the difficulty that the application of the marketing authorisation may create for clinicians, Akcea are happy to provide materials to support conversations about starting and stopping inotersen according to its licence. Finally, we are mindful that it is NICE's remit to assess inotersen within its marketing authorisation as per the NICE scope and Akcea have found no precedent where NICE have extended their remit to assess a treatment outside of its marketing authorisation. We have therefore provided estimates of clinical and cost-effectiveness for the marketing authorisation of inotersen only.
4	**Best supportive care alignment assumptions** As discussed on a teleconference with members of the NICE committee on 6th December 2018 and then confirmed on a subsequent teleconference on 17th December 2018, Akcea have made amendments to their model in order to ensure that their assumptions on the costs, utilities and mortality associated with

the best supportive care (BSC) group in their model align with NICE's evaluation in other hATTR submissions. This will ensure that NICE's decision making will be consistent for all hATTR therapies, with particular respect to assumptions accepted about the behaviour of the control group of patients (i.e. those on BSC) which, in turn, allows a fair assessment of the treatment effect of inotersen.

Changes have only been made where there is a clear indication from NICE that the change will be viewed as appropriate, most commonly because the same assumption was adopted in the submission for another hATTR treatment and either accepted or not criticised by NICE. In addition, changes were only implemented once they had been validated by UK clinicians at an advisory board held in November 2018. It is essential that NICE's approach to the appraisal of all hATTR technologies are aligned to ensure that assumptions made on BSC are consistent in order to ensure a fair appraisal of these technologies.

The changes to the inotersen model that have been implemented to align with the BSC group described in other hATTR submissions and accepted by NICE are:

- Updating HRU costs
- Updating mortality assumptions
- Adjusting transition probabilities in extension phase to reflect transitions in Stage 2 for BSC group

Updating HRU costs

The first model amendment was to replace the health resource utilisation (HRU) costs in the model with those made publicly available in the documents produced for consideration of the NICE appraisal of patisiran. The costs themselves were sourced from a Delphi panel conducted by the manufacturer, which Akcea recognises as a potential source of uncertainty, however the figures have been validated by a UK advisory board, which found that these costs were reflective of costs incurred by the NHS in the UK. These costs were given as a range; therefore, the low cost end of the range was assumed to correspond to Coutinho Stage 1 whilst the high cost end of the range is equivalent to Stage 3. A weighted average of costs was applied to Stage 2. Table 2 shows the impact of this amend on the results.

Table 2: ICER when using alternative HRU costs

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	**ICER – Exponential distribution for discontinuation**
HRU costs from patisiran committee papers (base case)	£150,636	£131,260
HRU costs presented at 1st inotersen committee meeting	£257,578	£252,300

Updating mortality assumptions

The second change made to align the inotersen BSC group with the BSC group in other hATTR submissions is to update mortality assumptions.

As this was an area of uncertainty for the committee, Akcea has conducted various scenario analyses to allay the committee's concerns regarding this.

The committee was especially interested in testing lower mortality ratios than those modelled in the base case. In general, lower mortality ratios favour inotersen as they emphasise that inotersen patients spend less time in the expensive and low quality of life Stage 3.

Our base case is designed to conform to the ERG's preferred scenario, as described in the patisiran ECD report, which is to test "the impact of removing the mortality effect in patients with no cardiac involvement". Therefore, our base case adopts the mortality ratios presented in this submission for the non-cardiac group, which are 2.01 for PND stage 0-II, 2.62 for PND stage III and 9.53 for PND stage IV. These values are sourced from Suhr et al (1994). Coutinho Stage 1 is considered equivalent to PND stage I, Coutinho Stage 3 is considered equivalent to PND stage IV and Coutinho Stage 2 contains elements of PND stages II, IIIa and IIIb. Consequently, a weighted average of mortality was used to populate Coutinho Stage 2. Therefore, the final hazard ratios (HRs) used in the model were 2.01, 2.42 and 9.53 for Stage 1, Stage 2, and Stage 3 respectively. As the committee expressed concern over uncertainty in both ECD reports, eight scenarios were modelled, and are described in Table 3.

Table 3: ICER when different mortality assumptions are made

Scenario	Stage 1 HR	Stage 2 HR	Stage 3 HR	Log-logistic ICER	Exponential ICER
Base case	2.01	2.42	9.53	£150,636	£131,260
50% of base case values	1.01	1.21	4.77	£123,390	£101,562
2 x base case values	4.02	4.83	19.06	£182,375	£166,705
General pop mortality	1.00	1.00	1.00	£57,189	£42,629
50% of general pop	0.50	0.50	0.50	£53,852	£39,422
2 x general pop	2.00	2.00	2.00	£63,099	£48,743
Original submission	5.00	10.00	19.00	£174,415	£160,337
Cardiac involvement group from patisiran submission only	4.12	5.35	19.49	£183,008	£167,566

Akcea accepts that there is uncertainty about mortality ratios, but contends that the revised base case is appropriate as:

- It is the approach requested by the ERG and is therefore consistent with Akcea's approach of adopting the same BSC assumptions as other hATTR submissions, to allow a fair and robust assessment of the product
- It is validated by UK clinicians at an advisory board
- It generates an ICER which is positioned approximately midway between the ICERs generated by other plausible approaches (i.e. it appears to not over or underestimate mortality based on other sources)

Adjusting transition probabilities in extension phase to reflect assumptions accepted by NICE on improvements in Stage 2 for BSC group

The third model amendment was the addition of the assumption that BSC patients cannot transition from Stage 2 to Stage 1 after week 66 of treatment, i.e. after the end of the trial period. The assumption was validated by UK clinicians at an advisory board who noted that it may be possible for BSC patients to experience a placebo effect during the trial period leading to a slight increase in QoL, which may be sufficient for a small proportion of stage 2 patients to transition back to Stage 1. The clinicians however stressed that any such placebo effect would be very unlikely and, should it exist, would end after the completion of the trial. Therefore, any placebo effect would not translate into routine clinical practice, as it would be implausible to imagine a BSC patient experiencing a significant uplift in their quality of life after 66 weeks of decline.

Table 4: ICER when different BSC transition assumptions are made

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	**ICER – Exponential distribution for discontinuation**
Limits on BSC transitions (base case)	£150,636	£131,260
No limits on BSC transitions	£198,641	£179,607

Conclusions

Three model amends have been implemented which significantly strengthen both the clinical and economic case for the reimbursement of inotersen. Moreover, these amends allow a robust and consistent approach to be taken by NICE for the modelling of the BSC state for hATTR-PN, which should be consistent between all technology appraisals for the same indication and population. The amended BSC transitions give more realistic estimates of the large increase in QoL that patients on inotersen experience compared to BSC patients and highlights the huge difference that inotersen could make to patients' lives if it was available on the NHS. The amends regarding new HRU costs represent a more accurate representation of the economic impact that reimbursement of inotersen would have and the savings that would be made in health resource utilisation.

Table 5 lists the changes that have been made to the inotersen model to ensure that BSC has the same assumptions in both models:

Table 5: Parameter changes in the inotersen model

Parameter	Originally submitted	Currently in model
BSC probability of transitioning from Stage 2 to Stage 1 after Week 66	[redacted]	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 HRs	Stage 1: 5 Stage 2: 10 Stage 3: 19	Stage 1: 2.01 Stage 2: 2.42 Stage 3: 9.53

All of these assumptions have either been taken directly or calculated from publicly available data in the documents produced for consideration by NICE as part of the assessment of another hATTR submission. Matching these assumptions will ensure that there is a fair comparison made between inotersen and other hATTR submissions by the committee.

5

Benefits of inotersen alignment assumptions

In addition to changes made purely to align the best supportive care groups, Akcea has made two further model amends intended to align assumptions about the treatment pathway when on treatment. These are:

- Including utilities that vary according to time-in-state
- A multiplier to reflect decreased HRU costs on treatment

Changing time-in-state utilities

The first change to the treatment pathway was to implement utility values that increase or decrease with time-in-state for inotersen and BSC patients, respectively. In order to capture the effect of treatment on QoL whilst patients remain within a health-state, a patient-level analysis of the NEURO-TTR trial was undertaken which demonstrated that patient utility improved within each state whilst on inotersen and reduced within each state whilst on BSC from baseline to Week 66, as demonstrated in Table 6.

Table 6: Comparison of the TQoL scores of inotersen and BSC patients at Week 66

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

The assumption of improving utility within state with inotersen over time and worsening utility within each state with BSC over time was ratified with clinicians during an advisory board. Clinicians found that the patient-level analysis was not a chance finding and reflects that there is a broad spectrum of disease severity within each state; there was consensus that utility would linearly improve with inotersen and worsen with BSC to the next stage over time (as opposed to sheer jumps for example from Stage 2 [0.429] to Stage 3 [0.084]). Therefore, the implementation of this change has made the model more clinically realistic.

The relative 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. The model implements a 'time-in-state' adjustment to reflect the change in utility observed in the NEURO-TTR study. The utility for patients on inotersen is increased by 0.0002 for each cycle that they remain in the same health state. Similarly, the utility for patients on BSC is reduced by 0.0038 for each cycle that they remain in the same health state. The calculation of these utility gain from these incremental improvements in TQoL score is based on the mapping from Faria *et al.* (2012) to show how utility generally changes with time on treatment, which gives the formula for converting TQoL scores to EQ-5D scores as 0.913991-0.005682*TQoL. Over the 66 weeks of the trial, those patients stable on inotersen improved their average TQoL score by 0.66 (from 48.22 to 47.56) which corresponds to a utility improvement of 0.0038 or a four-weekly improvement of 0.0002. Those on BSC declined by 10.96 TQoL points (from 48.67 to 59.63), corresponding to a 66-week utility decline of 0.0622, or a four-weekly decline of 0.0038. Given the limited evidence on converting marginal TQoL changes into EQ-5D and in the absence of EQ-5D data direct from the NEURO-TTR study, Akcea found the only reasonable approach to quantify the changes in utilities with time-in-state was to utilise the mapping from Faria et al. The limitations of this approach are described in section 6 below.

Utilities were capped to never increase beyond the baseline utility of the next-best stage. In Stage 1, utilities were capped so that they could not improve beyond 0.83, representing general population health taken from Ara and Brazier (2010), which was the ERG's preferred source for general population utility. Utilities were also prevented from decreasing beyond the utility of the next-worst stage (or -0.093 in stage 3 in absence of data to inform a lower bound), as this lower-bound capping was requested by NICE. After a transition to another stage, utility was reset to the average utility in that stage. If a patient discontinued, their utility would remain at whatever level it was prior to discontinuation but otherwise begin to increment downwards as per any patient on BSC. Table 7 details this information and gives the example of expected utility after 10 cycles stably in this stage. Base case utilities are described further in section 6.

Table 7 Detail of patient quality of life caps and increments in each stage

Health state	Patient EQ-5D-3L utility	Maximum utility in this stage	Minimum utility in this stage	Utility after ten cycles of inotersen in this stage	Utility after ten cycles of BSC in this stage

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

The implementation of patient-tracking in the manner described is impossible in a Markov Chain model. Consequently, the utility scores in each cycle are pre-generated using VBA patient-level tracking, and then applied as appropriate to the Markov Trace. Table 8 shows the impact of this amend on the results.

Table 8: ICER with and without increasing/decreasing utilities

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	**ICER – Exponential distribution for discontinuation**
Increasing/decreasing utilities (base case)	£150,636	£131,260
Static utilities	£157,668	£135,833

Multiplier to reflect decreased HRU costs on treatment

The second model amendment to align the hATTR submissions' treatment pathway was the addition of a multiplier which reduces HRU costs when the patient is receiving inotersen treatment. This is to reflect the expected significant reduction in HRU costs when the patient is on inotersen treatment within stage, which follows the same rationale as per the improvements in QoL discussed above. This is because patients on inotersen have – on average - less progressed disease even within the same stage as an equivalent BSC patient, as shown in Table 9.

Table 9: Comparison of the TQoL scores of inotersen and BSC patients at Week 66

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

This therefore indicates that the level of care they will require is less than an equivalent BSC patient, as it is known that care requirements and associated morbidity are strongly dependent on disease progression. Additionally, the increased QoL and improved health demonstrated in the NEURO-TTR trial are likely to cause psychological benefits; patients on treatment believe that they are doing better so would not pursue the same level of care as patients on BSC. These arguments were validated at an UK advisory board in November 2018 in which clinicians agreed that HRU would be lower in patients receiving inotersen compared to BSC.

The level of this adjustment is set at 43% for Stage 1 and Stage 2 patients and 0% for Stage 3 patients (since these patients will discontinue inotersen treatment

once they enter Stage 3). This figure is based on publicly available documents produced for the NICE appraisal of another hATTR therapy. The parameter value itself is sourced from a Delphi panel conducted by the manufacturer of patisiran. The exact value is given in the NICE documents, and so this value has been applied to the inotersen submission to ensure consistency between the reduction in costs from treatment across the two models. Table 10 details the costs implemented in the revised base case and Table 11 shows the impact of this amend on the results.

Table 10. List of disease stages and associated costs in the cost-effectiveness model

Disease stage	Value (inotersen)	Value (BSC)	Reference
Stage 1 per cycle (4-week)	£21	£36	Patisiran ECD
Stage 2 per cycle (4-week)	£4,873	£8,548	
Stage 3 per cycle (4-week)	£12,681	£12,681	

Table 11: ICER with and without 43% reduction in HRU costs

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	ICER – Exponential distribution for discontinuation
75% reduction in inotersen HRU costs for Stage 1 and 2	£117,396	£87,329
43% reduction in inotersen HRU costs for Stage 1 and 2 (base case)	£150,636	£131,260
25% reduction in inotersen HRU costs for Stage 1 and 2	£169,334	£155,971
0% reduction in inotersen HRU costs for Stage 1 and 2	£195,302	£190,292

6	**Utility value data source**

	Akcea agrees with the committee that the THAOS data valued with the UK EQ-5D value set would be the preferred data source, however the THAOS registry is independently run by another pharmaceutical company. Akcea has requested access to this database repeatedly but has so far been unsuccessful. We understand that efforts are being made by ARC UK and NICE to access this data but as yet this is not available. In the absence of the relevant data from the THAOS registry, there are three proposed utility sources which could be used: • Brazilian THAOS values converted to UK utility tariffs • Utility values taken from the tafamidis appraisal (Faria et al, 2012 • SF-36 data from NEURO-TTR (Stage 1 and Stage 2 only) <u>Brazilian THAOS values converted to UK utility tariffs</u> We believe that applying UK utilities to the Brazilian THAOS scores is closest to what the committee has requested, and so have adopted this as part of our revised base case and discuss our reasoning for this decision below. Akcea discussed at the committee meeting that applying the Brazilian tariff to EQ-5D data from the THAOS registry provides a conservative estimate of cost-effectiveness for inotersen. Whilst we agree that the utility values are uncertain in the absence of data to apply the UK tariff, the values presented to the committee are conservative with regard to what the 'true' ICER would be were the UK tariff applied. The reason for this is described by the ERG – "a standard decrement for any level 3 response was not applied in the Brazilian value set, but was used in the UK value set, meaning that poorer health states are valued substantially lower in the UK tariffs compared to the Brazilian tariffs". This in turn means that the worst health state in the model (Stage 3) is significantly worse using UK tariffs than Brazilian tariffs, which improves the ICER as inotersen slows or halts progression into Stage 3. In order to investigate this fully, Akcea have calculated the utilities of every health-state as defined using EQ-5D-3L using both the UK and Brazilian valuation tariffs – please see Appendix A: Utility values using UK and Brazilian tariffs. It was noted that for every EQ-5D response which could plausibly map to Stage 3 health states (any Brazilian utility lower than 0.404), performing a conversion to the UK tariff reduced the ICER, often dramatically. For Stages 1 and 2, the effect was less pronounced; for EQ-5D responses eliciting Brazilian utilities close to Stage 1 and Stage 2, conversion to the UK tariff increased the ICER by a small amount in Stage 1, and reduced the ICER by a moderate amount in Stage 2. Taking the utility values that most closely matched those applied in the model (11212 for Stage 1, valued at 0.704 in Brazil and 0.812 in the UK; 22213 for Stage 2, valued at 0.427 in Brazil and 0.205 in the UK; and an average of 33311 and 31332 for Stage 3, valued at 0.086 for both in Brazil, and 0.028 and -0.215 respectively in the UK), the Brazilian valuation of EQ-5D was underestimated for

patients in good health, and overestimated for those in the poorest health states compared to the values that would be calculated in the UK (Table 12).

Table 12: Method of estimating THAOS registry results from existing Brazilian data

Stage	Utility for this stage, taken from Stewart et al 2017, which are themselves sourced from the THAOS registry	EQ-5D input which gives closest result when Brazilian weighting applied (corresponding utility) (Santos et al., 2016)	Utility output when this EQ-5D input is weighted using UK tariff (Dolan, 1997)
Stage 1	0.697	11212 (0.704)	0.812
Stage 2	0.429	22213 (0.427)	0.205
Stage 3	0.084	33311 and 31332 (0.086)	-0.094 (average of 0.028 and -0.215)
Death	0	N/A	0

These findings are consistent with published literature describing conversions between Brazilian and UK utilities; see for example,Takemoto et al (2015).

Therefore, whilst we acknowledge there is uncertainty in applying Brazilian tariffs to a model from a UK perspective, we have demonstrated that using the Brazilian tariffs for this decision problem is a highly conservative approach. As the committee have expressed concern about the use of Brazilian tariffs and in the absence of data from the THAOS registry, Akcea have applied UK converted numbers outlined in Table 12 to the revised base case, the impact of which is demonstrated in Table 13.

Utility values taken from the tafamidis Advisory Group for National Specialised Services (AGNSS) appraisal (Faria et al, 2012)

The second approach is to use utility values from the tafamidis AGNSS appraisal (Faria et al, 2012). This approach is not aligned with the committee's goals of distinguishing between the three Coutinho stages, and is therefore not appropriate for the submission.

Akcea does not agree with the committee's assessment that it would be more appropriate to use the mapping of TQoL to EQ-5D from the tafamidis NICE appraisal, as reported by Faria et al. 2012, due to the uncertainty surrounding the calculation of health-state utility values by mapping TQoL to EQ-5D. Whilst the mapping is sufficient to observe trends between TQoL and EQ-5D (as we have used to implement improvements in quality of life), Akcea do not believe it to be sufficient to assume a causal relationship between the two measures as there are domains within the TQoL that are not included within the EQ-5D and vice versa, so one cannot simply map between them. For instance, the TQoL questionnaire asks about symptoms, diagnosis, activities of daily living and generic health status whereas EQ-5D-3L includes questions about anxiety and

	depression addressing the emotional impact of the condition. Indeed, the ERG from the tafamidis appraisal requested alternative mappings be provided between the TQoL score and EQ-5D, indicating that the assumption of a linear relationship between the two measures is weak and inappropriate. Additionally, the mapping function used to transform TQoL scores to EQ-5D scores was created by the manufacturer of tafamidis for the tafamidis Advisory Group for National Specialised Services (AGNSS) submission. No evidence was provided on the validity of this mapping function and it has no basis in literature, meaning that there is a great deal of uncertainty surrounding this mapping. This point was made by the ERG reviewing the tafamidis submission, and so adopting this approach which was criticised by the ERG of a previous submission should not now be encouraged, especially in the face of more compelling evidence which more closely matches the approach that all parties agree would be 'gold standard'. Furthermore, as noted by the committee in the ECD, the lowest possible EQ-5D utility based on this mapping is 0.147 instead of 0 – far above the limits that can be reached from the EQ-5D and not realistically corresponding to a true description of a typical Stage 3 health state where – by definition – mobility, self-care and usual activities are severely impaired (as mobility is the diagnostic criteria separating Stage 3 from Stage 2). As well as being a testament to the poor quality of the mapping function, this means that utility gains may be underestimated if the mapping is used, especially for Stage 3 patients with the lowest utilities and therefore contradicts direct patient reported outcome measures as seen in the Stewart et al 2017 paper. Finally, it is well documented that mapping equations do not perform well when data are non-linear. When considering observed utility data from Stewart et al., non-linearity is clear, particularly when considering utility differences between Stage 1 and 2 (0.268), versus Stage 2 and 3 (0.345), and a minimally important difference in EQ-5D being 0.05. Therefore, attempting to put EQ-5D scores on a linear scale will clearly overestimate poorer health and underestimate good health in patients, a common issue with mapping equations. This significantly biases against inotersen given that treatment prevents patients transitioning to poorer health states and keeps patients in better-off health states. <u>SF-36 data from NEURO-TTR (Stage 1 and Stage 2 only)</u> The third proposed approach is to use the SF-36 data collected in the NEURO-TTR trial. This approach was agreed in the committee meeting to be severely lacking compared to the other two possibilities; no SF-36 data was collected on patients in Stage 3 as these patients were not on treatment, and as Stage 3 utilities are critical for driving cost-effectiveness results, this approach adds significant uncertainty without providing any obvious benefits. <u>Conclusion</u> For the reasons discussed above, there is a much greater degree of uncertainty surrounding mapping TQoL to EQ-5D utility values using the mapping function by Faria et al than that proposed in the revised base case. Considering the continued unavailability of the THAOS registry data, we maintain that the

converted utility values from the Stewart et al. 2017 study are the only appropriate values that are available and relevant to hATTR patients. Table 13 shows how the ICER changes when the source of utility data is changed.

Table 13: ICER when different utility values are used

Source of utility values	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	ICER – Exponential distribution for discontinuation
THAOS registry	N/A	N/A
Stewart (2017) paper converted to UK tariff (base case)	£150,636	£131,260
Stewart (2017) paper not converted to UK tariff (i.e. Brazil tariff, as per original submission)	£173,562	£150,470
Faria. et al (2012) assuming stages represent difference-in-kind from each other (separate regression for each stage, 4th column of Table 28, so Stage 2 represent a step-change from Stage 1)	£171,157	£147,280
Faria et al. 2012 assuming stages represent difference-of-degree from each other (one regression model every stage, 3rd column of Table 27, so Stage 2 represents only an arbitrary distinction between a bad Stage 1 and a good Stage 2)	£203,781	£175,420

7

Carers

Akcea acknowledges the committee's concerns regarding the number of carers assumed at each stage of the disease in the model, however we do not agree with the ERG's recommendation to assume one carer in every stage in the model. In particular, we do not agree that a Stage 3 hATTR-PN patient would only require one carer. During a call with NICE on 6th December 2018, it was confirmed that the interpretation of the NICE committee was that one carer in Stages 1 and 2, and two carers in Stage 3 was an appropriate base case.

In Stage 3 of the disease, patients are bedridden or confined to a wheelchair and usually have other severe symptoms such as diarrhoea, peripheral neuropathy and cardiomyopathy. In this state, patients need assistance from a carer for even

the most basic of tasks, and this assistance is needed constantly, day and night. Indeed, the ECD states:

"In the advanced stage of the condition 24-hour care is essential because of immobility and possible loss of eyesight, combined with other symptoms such as incontinence" (ECD, Page 15)

It is therefore unrealistic to assume that this care could be delivered by one individual. Furthermore, being a carer for a person with that level of challenge is burdensome – fatigue, depression and anxiety are all reported by carers of people with advanced hATTR (Gertz, 2017).

Since the committee meeting, Akcea has conducted a Caregiver Impact Study of 36 carers of patients with hATTR-PN, six of whom were recruited via ARC UK and 30 via a specialist panel agency. Of the 36 carers, eight were from the UK, 23 from the US and five from Canada, Australia, and New Zealand. This survey also included 36 members of the general population matched on carer demographics (age, gender, living status, employment status) who were recruited via a specialist panel agency. The study concluded that carers spend a significant amount of time caring for patients, with the total number of hours of practical care (e.g. performing physical tasks such as getting in/out of bed, dressing, general ambulation, cooking, and eating, maintaining personal hygiene and administering treatment) given by a single carer calculated as 2.64, 6.88 and 10.67 hours per day for Stage 1, Stage 2 and Stage 3, respectively (Table 14). There is a sharp increase in the total number of hours spent caring as the patient progresses through hATTR, with a single carer providing four times as much care per day for a Stage 3 patients compared to a Stage 1 patient. Over a seven-day week, this gives the total number of hours of practical care given per carer as 18.50, 48.19, and 74.67 hours per week for Stages 1, Stage 2, and Stage 3 patients, respectively. Assuming a standard 37.5 hour working week for full-time employees (Office for National Statistics, 2018), the hours spent giving practical care corresponds to 0.49, 1.29, and 1.99 full-time jobs per carer of a hATTR patient in Stage 1, Stage 2, and Stage 3, respectively.

As well as practical care, the hATTR Caregiver Impact Study also asked how many hours per day carers spent giving emotional support to patients, and this was reported as 3.56, 4.74, and 1.76 hours per day for Stage 1, Stage 2 and Stage 3, respectively (Table 14). When combined with practical care this gives the total number of hours of care given per carer as 43.42, 81.39, and 87.00 hours per week, which corresponds to 1.16, 2.17, and 2.32 full-time jobs per carer of a hATTR patient in Stage 1, Stage 2, and Stage 3, respectively. It is known that the burden of care such as increased anxiety, depression and fatigue increases significantly as later Stages are entered by the patient (Gertz, 2017).

However, as Akcea cannot prove that practical care and emotional support are exclusive, the revised base case considers a more conservative approach whereby patients require one, one, and two full-time carers per patient in Stage 1, Stage 2 and Stage 3, respectively.

Table 14: Hours of care and emotional support per day by disease stage

Coutinho Stage	Hours of practical care per day	Hours of emotional support per day

Stage 1	2.64	3.56
Stage 2	6.88	4.74
Stage 3	10.67	1.76

This is therefore consistent with the NICE committee's preference for assuming one carer per patient in all but Stage 3, where two carers are required. The number of carers and hours of care were validated by five clinical experts and one patient representative at an advisory board meeting in November 2018 , who estimated that a Stage 3 patient may need as many as three full time carers. This is further validated by the literature reviewed and cited in the original submission, which estimates the average hATTR patient received a median of 144 hours of care per week (Gertz, 2017). Assuming a median full-time week over 7-days of 52.5 hours (aligned with a median 37.5 hour work-week as reported by the Office of National Statistics), this equates to almost three full time carers per patient.

Table 15 shows the effect on the ICER when various numbers of carers are assumed at each disease stage.

Table 15: ICER when different numbers of carers are assumed for each disease stage

Number of carers used in Stages 1, 2 and 3 respectively	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	ICER – Exponential distribution for discontinuation
1, 1, 2 (revised base case and NICE preferred case)	£150,636	£131,260
1, 1, 3	£139,769	£121,230
1, 1, 1	£163,335	£143,098
1, 2, 2	£151,537	£132,173
2, 2, 2	£151,870	£132,460

8 **Treatment discontinuation**

Akcea appreciates the concerns of the committee regarding the rate of inotersen treatment discontinuation. While we maintain that the exponential distribution is the best statistical fit for the discontinuation data available, as confirmed by AIC and BIC testing, we realise that, at present, there is no longer-term data available for inotersen discontinuation. As such, we have complied with NICE's request to present exponential (manufacturer preferred curve) and log-logistic (ERG preferred curve) discontinuation assumptions side-by-side throughout the ECD response. We have presented log-logistic as our base case as this was stated as NICE's preferred approach.

Table 16 shows the effect on the ICER when the exponential and log-logistic distributions are used to model treatment discontinuation.

Table 16: ICER when using exponential and log-logistic distributions for treatment discontinuation

Distribution	ICER
Log-logistic (base case)	£150,636
Exponential	£131,260

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Adverse events

Akcea accepts that NICE would prefer to see scenarios including adverse events, and therefore have included them in all scenarios in this response document. We agree with NICE that the impact of including such scenarios is negligible.

Table 17 shows how the ICER changes when adverse events are not included.

Table 17: ICER with and without adverse events included

	ICER – Log-logistic distribution for discontinuation (ERG preferred case)	**ICER – Exponential distribution for discontinuation**
Adverse events included (base case)	£150,636	£131,260
Adverse events not included	£150,162	£130,828

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Discount rate

Akcea is pleased that NICE accepts two of the three criteria for non-reference case discount rate of providing long-term clinical benefits to patients (see key issue 1) and not committing the NHS to significant irrecoverable costs. Given inotersen's ability to reverse hATTR-PN in some cases it is disappointing that NICE does not accept that the final criterion, that of returning to perfect or near-perfect health, can be met. However as NICE have clearly signalled that they do not wish to see a 1.5% discount rate for costs and QALYs, a 3.5% rate is used throughout the resubmission.

Table 18 shows the effect on the ICER when the reference and non-reference case discount rates for costs and QALYs are used.

Table 18: ICER when different discount rates are used

Discount rate	**ICER – Log-logistic distribution for discontinuation (ERG preferred case)**	**ICER – Exponential distribution for discontinuation**
3.5% costs and QALYs (base case)	£150,636	£131,260
1.5% costs and QALYs	£151,548	£129,300

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Impact of inotersen beyond direct health benefits

Akcea acknowledges the committee's concerns regarding the wider impact of inotersen and how to balance this with their concerns about its cost-effectiveness, however, amends have been made to our model to align assumptions on BSC and treatment effect with other ongoing technology appraisals in the same disease, and have sought to address the committee's concerns. When considered together, these changes show inotersen to be significantly more cost-effective than that presented in the original submission and at the first NICE committee meeting. Akcea hopes that the committee will

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	take this into consideration when assessing the wider benefits of inotersen in future. Akcea would also like to reiterate that the progressive loss of independence and dignity experienced by hATTR-PN patients negatively affects every aspect of patients', family members' and carers' lives. Particularly, the symptoms of hATTR-PN have been demonstrated to detrimentally impact multiple aspects of patients' daily life, emotional wellbeing, relationships with family and friends, work and financial status, as well as physical health (Lovley, Guthrie and Pollock, 2018). For example, 27% of Stage 1 hATTR-PN patients and 30% of patients with Stage 2 hATTR-PN report some difficulty with reading a newspaper or book, and eating (Berk, Lin and Agarwal, 2018), and in a recent patient and carer study conducted in the UK (Richard, Lousada and Low, 2018 (unpublished)), 50% of patients with hATTR-PN stated that their condition has an extreme impact on their emotional well-being, with 35% stating that they had experienced fear, anxiety and depression in the last 12 months. A US survey (Ionis, 2017) found more than half (55%) of patients with hATTR-PN reported their mental health/outlook on life is impacted by the disease, with patients suffering from anxiety (71%), stress (62%) and depression (43%). In addition, disease burden increases with disease progression. The impact of hATTR-PN on carers is considerable in terms of the emotional burden of 'knowing what's to come', the practical caring burden (causing fatigue and anxiety) and the effect on their own ability to work and participate in social activities. Among carers (who do not have hATTR-PN themselves), the mean number of hours spent per day giving practical care to patients is reported at 2.6, 6.9 and 10.7 hours for Stage 1, Stage 2 and Stage 3, respectively. This significant amount of time spent caring for patients means that carers will have to relinquish their own social activities and employment in order to provide medical support, care and assist with activities of daily living, including household chores such as cleaning, shopping and cooking. At advanced stages of the disease, carers also provide daily personal care. Consequently, the disease has a significant knock-on impact on carers' own productivity at work as well as their ability to undertake paid work. In a recent hATTR Caregiver Impact Study, over half (56%) of carers stated that they had changed their employment as a result of hATTR, and *Berk et al.* reported that 12% of carers limited employed work to part-time whilst 15% were unable to continue employment altogether, with the ability to hold employment falling from 22% to 6% for those caring for a patient with Stage 1 and Stage 2 hATTR-PN, respectively. In the hATTR Patient and Caregiver Impact Study, over 70% of carers reported a detrimental impact of the disease on their own work and professional life, with 31% reporting a severe impact. As well as the impact on their employment, there is also a massive toll on the emotional and psychological wellbeing of carers, with a recent hATTR Caregiver Impact Study showing that carers have significantly higher anxiety levels, as measured by the Hospital Anxiety and Depression Scale (HADS), than controls; reporting 2.5 times higher levels of probable clinical anxiety than the matched controls. A recent survey revealed that 54% of carers of hATTR-PN patients described their emotional wellbeing as being severely affected by the disease, with 55% identifying social/family relationships as being 'extremely

	impacted' by the disease. Carers even reported a higher impact on their emotional wellbeing and social/family relationships than patients themselves. If recommended by NICE, inotersen will offer the potential to slow, arrest or reverse disease progression in patients with Stage 1 or 2 hATTR by targeting the underlying cause of the disease. This will mean that patients remain in the earlier stages of the disease for longer, which in turn will allow them to retain their independence for longer through the preservation of their ambulatory ability and key health domains. [redacted] Therefore, as well as the direct health benefits that inotersen treatment will bestow, it will provide patients the opportunity to continue with employment, as well as actively participate in family life and social activities for longer. Furthermore, inotersen has the potential to reduce the burden borne by carers of patients with hATTR in terms of their work productivity and participation in family and social activities. Consequently, this will also lessen the impact on patients' and carers' emotional wellbeing.
12	[redacted]
13	**Managed access agreement**

Inotersen for treating hereditary transthyretin-related amyloidosis [ID1242]

Consultation on the evaluation consultation document – deadline for comments 5pm on 9/1/2019 **email:** TACommB@nice.org.uk/NICE DOCS

	Akcea would like to take this opportunity to highlight the changes that have been made to our model on the committee's recommendation, which include adopting the log-logistic curve to model discontinuation, including the costs and disutilities associated with serious adverse events, and changing the discount rate for costs and QALYs to the reference case of 3.5%. Where possible, scenario analyses have been conducted around these parameters, as well as other such as mortality hazard ratios, reducing any uncertainty around these inputs. We hope that the committee will take these parameter changes and additional analyses into account when considering options for managed access or commercial agreements.

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2 Appendix A: Utility values using UK and Brazilian tariffs

EQ-5D score	Utility value (UK tariff)	Utility value (Brazil tariff)
11111	1	1
11112	0.848	0.801
11121	0.796	0.787
11113	0.414	0.756
11211	0.883	0.754
12111	0.815	0.739
11122	0.725	0.737
21111	0.85	0.731
11212	0.812	0.704
11123	0.291	0.692
11221	0.76	0.69
12112	0.744	0.689
11131	0.264	0.683
21112	0.779	0.681
12121	0.692	0.675
11311	0.556	0.667
21121	0.727	0.667
11213	0.378	0.659
12113	0.31	0.644
12211	0.779	0.642
11222	0.689	0.64
21113	0.345	0.636
21211	0.814	0.634
13111	0.436	0.633
11132	0.193	0.633
12122	0.621	0.625
22111	0.746	0.619
11312	0.485	0.617
21122	0.656	0.617
11321	0.433	0.603
11223	0.255	0.595
12212	0.708	0.592
11133	0.028	0.588
11231	0.228	0.586
21212	0.743	0.584
13112	0.365	0.583
12123	0.187	0.58
12221	0.656	0.578
11313	0.32	0.572
21123	0.222	0.572
12131	0.16	0.571
21221	0.691	0.57
13121	0.313	0.569
22112	0.675	0.569
21131	0.195	0.563
12311	0.452	0.555
22121	0.623	0.555
11322	0.362	0.553
12213	0.274	0.547
21311	0.487	0.547
21213	0.309	0.539
13113	0.2	0.538
13211	0.4	0.536
11232	0.157	0.536

12222	0.585	0.528
22113	0.241	0.524
22211	0.71	0.522
12132	0.089	0.521
21222	0.62	0.52
13122	0.242	0.519
23111	0.367	0.513
21132	0.124	0.513
11323	0.197	0.508
12312	0.381	0.505
22122	0.552	0.505
11331	0.17	0.499
21312	0.416	0.497
11233	-0.008	0.491
12321	0.329	0.491
31111	0.336	0.488
13212	0.329	0.486
12223	0.151	0.483
21321	0.364	0.483
12133	-0.076	0.476
21223	0.186	0.475
12231	0.124	0.474
13123	0.077	0.474
13221	0.277	0.472
22212	0.639	0.472
21133	-0.041	0.468
21231	0.159	0.466
13131	0.05	0.465
23112	0.296	0.463
12313	0.216	0.46
22123	0.118	0.46
22221	0.587	0.458
21313	0.251	0.452
22131	0.091	0.451
11332	0.099	0.449
13311	0.342	0.449
23121	0.244	0.449
13213	0.164	0.441
12322	0.258	0.441
31112	0.265	0.438
22311	0.383	0.435
21322	0.293	0.433
22213	0.205	0.427
12232	0.053	0.424
31121	0.213	0.424
13222	0.206	0.422
23113	0.131	0.418
23211	0.331	0.416
21232	0.088	0.416
13132	-0.021	0.415
22222	0.516	0.408
11333	-0.066	0.404
22132	0.02	0.401
13312	0.271	0.399
23122	0.173	0.399
12323	0.093	0.396
31113	0.1	0.393

31211	0.3	0.391
21323	0.128	0.388
12331	0.066	0.387
13321	0.219	0.385
22312	0.312	0.385
12233	-0.112	0.379
21331	0.101	0.379
13223	0.041	0.377
32111	0.232	0.376
31122	0.142	0.374
21233	-0.077	0.371
22321	0.26	0.371
13133	-0.186	0.37
13231	0.014	0.368
23212	0.26	0.366
22223	0.082	0.363
22133	-0.145	0.356
13313	0.106	0.354
22231	0.055	0.354
23123	0.008	0.354
23221	0.208	0.352
23131	-0.019	0.345
31212	0.229	0.341
22313	0.147	0.34
12332	-0.005	0.337
13322	0.148	0.335
23311	0.273	0.329
31123	-0.023	0.329
21332	0.03	0.329
31221	0.177	0.327
32112	0.161	0.326
23213	0.095	0.321
22322	0.189	0.321
31131	-0.05	0.32
13232	-0.057	0.318
32121	0.109	0.312
22232	-0.016	0.304
31311	0.242	0.304
23222	0.137	0.302
31213	0.064	0.296
23132	-0.09	0.295
12333	-0.17	0.292
13323	-0.017	0.29
21333	-0.135	0.284
13331	-0.044	0.281
32113	-0.004	0.281
23312	0.202	0.279
32211	0.196	0.279
31222	0.106	0.277
22323	0.024	0.276
13233	-0.222	0.273
33111	0.122	0.27
31132	-0.121	0.27
22331	-0.003	0.267
23321	0.15	0.265
32122	0.038	0.262
22233	-0.181	0.259

23223	-0.028	0.257
31312	0.171	0.254
23133	-0.255	0.25
23231	-0.055	0.248
31321	0.119	0.24
23313	0.037	0.234
31223	-0.059	0.232
13332	-0.115	0.231
32212	0.125	0.229
31133	-0.286	0.225
31231	-0.086	0.223
33112	0.051	0.22
22332	-0.074	0.217
32123	-0.127	0.217
23322	0.079	0.215
32221	0.073	0.215
31313	0.006	0.209
32131	-0.154	0.208
33121	-0.001	0.206
23232	-0.126	0.198
32311	0.138	0.192
31322	0.048	0.19
13333	-0.28	0.186
32213	-0.04	0.184
33113	-0.114	0.175
33211	0.086	0.173
31232	-0.157	0.173
22333	-0.239	0.172
23323	-0.086	0.17
32222	0.002	0.165
23331	-0.113	0.161
32132	-0.225	0.158
33122	-0.072	0.156
23233	-0.291	0.153
31323	-0.117	0.145
32312	0.067	0.142
31331	-0.144	0.136
31233	-0.322	0.128
32321	0.015	0.128
33212	0.015	0.123
32223	-0.163	0.12
32133	-0.39	0.113
32231	-0.19	0.111
33123	-0.237	0.111
23332	-0.184	0.111
33221	-0.037	0.109
33131	-0.264	0.102
32313	-0.098	0.097
33311	0.028	0.086
31332	-0.215	0.086
33213	-0.15	0.078
32322	-0.056	0.078
23333	-0.349	0.066
32232	-0.261	0.061
33222	-0.108	0.059
33132	-0.335	0.052
31333	-0.38	0.041

33312	-0.043	0.036
32323	-0.221	0.033
32331	-0.248	0.024
33321	-0.095	0.022
32233	-0.426	0.016
33223	-0.273	0.014
33133	-0.5	0.007
33231	-0.3	0.005
33313	-0.208	-0.009
32332	-0.319	-0.026
33322	-0.166	-0.028
33232	-0.371	-0.045
32333	-0.484	-0.071
33323	-0.331	-0.073
33331	-0.358	-0.082
33233	-0.536	-0.09
33332	-0.429	-0.132
33333	-0.594	-0.177

Highly Specialised Technology
Inotersen for treating hereditary transthyretin amyloidosis [ID1242]
Evaluation consultation document

Dr Carol Whelan's response on behalf of British Society of Heart Failure and Royal College of Physicians, January 2019.

Within this evaluation document, the committee has accurately described the condition, hereditary transthyretin-related amyloidosis, its burden on patients and their carers and the unmet need of this disease. The increasing burden as the disease progresses on patients and importantly, their family members who provide care, in terms of independence, dignity, ability to work and carry out daily activities is described. There is no treatment at present. With best supportive care, the disease progresses with the patient ultimately bedbound.

The committee concludes that clinical trial evidence demonstrates that inotersen slows progression of the disease considerably. It is uncertain whether this is maintained long-term. It also concludes that there are uncertainties in the economic modelling particularly around utility values, numbers of carers, mortality and stopping treatment. The cost effectiveness estimates are much higher than what NICE considers acceptable for highly specialised technologies. Inotersen is innovative but does not appear to provide value for money and therefore is not recommended for routine funding in the NHS.

- Has all of the relevant evidence been taken into account?

The committee discussed and took into account relevant evidence with respect to inotersen, namely NEURO-TTR comparing inotersen with placebo, and the NEURO-TTR extension study. These studies are relevant to a UK population. The clinical effectiveness of inotersen is demonstrated in the NEURO-TTR study. Long term data are being accumulated in the extension study.

- Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

These summaries are reasonable interpretations.
A mean TTR reduction of 74% was seen with inotersen. A threshold for TTR knockdown at 80% for clinical effectiveness is discussed. It should be noted that this percentage has not been validated in TTR amyloidosis, although it is accepted that the higher the knockdown in all types of amyloidosis, the higher the percentage of patients whom are likely to benefit in terms of halting or reversing progression of disease. The turnover and production of TTR varies from patient to patient so some may derive benefit from a knockdown lower than 80% while other patients may require a much higher level of knockdown to gain the same benefit.

The company's base case as well as the ERG's analysis, are described. In both scenarios, inotersen was associated with an ICER well above £100,000 per QALY gained (which NICE considers acceptable).

- Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

I agree that these recommendations are sound and a suitable basis for guidance to NHS England at present.

C Whelan

January 2019

Inotersen for treating hereditary transthyretin-related amyloidosis

ERG critique of new economic evidence submitted by the company in response to the ECD

Produced by Aberdeen HTA Group

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Date completed 25 January 2019

Version 1

Contains

Commercial in confidence (CiC) data are highlighted in blue throughout the report

Academic in confidence (AiC) data are highlighted in yellow throughout the report

This report provides the ERG's brief commentary and critique of revised economic evidence submitted by the company (Akcea therapeutics), and revised economic model, received by the ERG on 16/01/2019 in response to the ECD and in advance of the second AC meeting for this appraisal.

This ERG commentary and critique should be read in conjunction with the company's submitted evidence: document: *ID1242 Inotersen ECD company response v0.1 JE 090119 [AIC]*.

The company's revised evidence updates 1) the model base case assumptions, in part reflecting the committee's preferred analyses, as outlined in the ECD; 2) estimates of Coutinho (FAP) stage specific healthcare resource use costs, utilities and mortality hazard ratios in an attempt to improve consistency with the ongoing NICE appraisal of patisiran, and 3) to provide further information clarifying areas of uncertainty raised in the ECD.

Contents

Summary of changes from committee's preferred ICER in ECD

The ERG has used the company revised model to re-produce the committee's preferred base case ICER from the ECD. The ERG are satisfied that the company's amendments relate only to the documented changes as described in their response to the ECD.

The company have made a number of changes to parameter inputs, which taken together have substantially reduced the ICER from £646,767 per QALY gained [ECD preferred assumptions, (NICE, 2018)] to £150,636 (company's revised preferred assumptions). The company present all of their analyses using both log logistic and exponential extrapolation curves to reflect treatment discontinuation. This document reports all ICERs using the log-logistic curve as this was the preferred extrapolation approach in the ECD.

The preferred ICER quoted in the ECD reflects the following assumptions (NICE, 2018)

1. One carer assumed for all disease stages
2. Incorporation of costs and utilities associated with adverse events
3. Discontinuation modelled using a log-logistic curve
4. Utilities sourced from Faria et al, linear calculation (Faria & Palmer, 2012)
5. A discount rate for costs and QALYs of 3.5% per annum
6. Compliance rate of [redacted]
7. Health state resource use costs as used in the company's originally submitted analysis

The company have implemented points 3, 5 and 6 as outlined above, and these issues are not discussed further. For point 1, the ECD preferred an assumption where the disutility of one carer was applied across all Coutinho (FAP) stages. However, the company's revised analysis applies carer disutility assuming one carer for patients in Stage 1 or 2 disease, and 2 carers for patients in Stage 3. For point 2, the company have not updated costs and utilities of adverse events to reflect the ERG values used to inform the ECD preferred ICER. The ERG have updated all analyses in this report accordingly, and note that the impact on the ICER is minimal. For point 4, health state utility values sourced from Faria et al. were preferred in the ECD. However, the company have provided a revised analysis attempting to translate utilities sourced from Stewart et al (Brazilian tariffs as per original company submission) to corresponding UK values. Additionally, the company have applied a treatment specific adjustment to health state utility values, allowing increasing and decreasing utility over time

in state for the inotersen and BSC arms of the model respectively. The rationale is to align assumptions with those used in the patisiran evaluation. For point 7, the company have provided updated health state costs in an attempt to align with the costs used for the patisiran appraisal (this includes application of a 43% reduction in health state costs (stages 1 and 2 only) for the inotersen arm of the model).

Each of the company's amendments to the model are described and justified in the company's response to the ECD, with sensitivity analyses presented around the company's preferred assumptions for each change made.

In this report, the ERG present the impact of each parameter change from the starting the ECD preferred ICER of £646,767. Where the ERG disagrees with the company's assumptions or data inputs, the impact of both company and ERG preferred analyses ICER is reported.

Table 1 below illustrates the results of the various analyses. Each amendment is described in more detail and critiqued in the sections that follow.

Table 1 Summary of changes made post ECD

Analysis No.	Analyses Description [A]	Comparator	£	Q	LYG	diff £	diff QALY	diff LYG	ICER
1.	ECD preferred assumptions (NICE, 2018)	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£646,767
Healthcare Resource Use Costs:									
2.	43% reduction in health state costs (inotersen arm FAP 1 and 2)	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£623,299
3.	Co. revised health state costs (based on patisiran appraisal)	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£504,334
4. (2+3)	Co. revised health state costs + 43% reduction for inotersen (FAP 1 and 2)	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£406,813
5. (ERG correction to 3)	ERG revised health state costs (map PND1 to FAP 1) (Adams, 2013)	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£471,602
6. (ERG preferred correction to 3)	ERG revised health state costs (map PND 1 and 2 to FAP 1) (Adams, et al., 2016)	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£473,653
7. (2+5)	ERG revised health state costs (maps PND 1 to FAP 1) + 43% inotersen reduction in FAP 1 and 2	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£457,131
8. (2+6)	ERG revised health state costs (maps PND I and II to FAP 1) + 43% inotersen reduction in FAP 1 and 2	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£456,077
9.	ERG: Apply patisiran one-off health state costs, with 43% inotersen reduction [B]	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£640,210
10. (7+9)	ERG: Map PND 1 to FAP 1 + patisiran one off costs + 43% discount	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£450,574
11. (8+9) (ERG preferred cost revisions)	Map PND 1 and 2 to FAP 1 + patisiran one off costs + 43% discount	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£449,520

Analysis No.	Analyses Description [A]	Comparator	£	Q	LYG	diff £	diff QALY	diff LYG	ICER
Mortality									
12.	Co. updated HRs from patisiran assessment *(Maps PND 1 to FAP 1)*	BSC	[redacted]	[redacted]	11.062				
		Inotersen	[redacted]	[redacted]	13.001	[redacted]	[redacted]	1.939	£570,431
13.	ERG updated HRs from patisiran assessment *(Maps PND I and II to FAP 1)*	BSC	[redacted]	[redacted]	11.028				
		Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£572,303
Transition probabilities									
14.	Co. removal of BSC transitions from FAP 2 to FAP 1	BSC	[redacted]	[redacted]	7.120				
		Inotersen	[redacted]	[redacted]	8.484	[redacted]	[redacted]	1.364	£596,436
Utilities									
15.	Company revised FAP stage utility mapping (average of 16 and 17 below)	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£367,314
16.	FAP stage 3 mapped to EQ-5D state '33311'	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£400,290
17.	FAP stage 3 mapped to EQ-5D state '31332'	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£339,357
18.	Co. treatment arm specific adjustment of utility by time in state *(denotes ERG preferred utility assumptions – Faria et al. with time in state adjustment)* [C]	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£503,547
19. (15+18)	Company revised utility assumptions (combined)[C]	BSC	[redacted]	[redacted]	7.541	-	-		
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£344,433
Number of carers accruing disutility by FAP stage									
20.	Co. revised approach Stage 1&2 = 1 carer; Stage 3 = 2 carers.	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£562,779
Overall combined analyses:									
21. (4+12+14+19)	Company preferred base case analysis (as stated in documentation) [C]	BSC	[redacted]	[redacted]	10.510				
		Inotersen	[redacted]	[redacted]	12.502	[redacted]	[redacted]	1.991	£150,636

Analysis No.	Analyses Description [A]	Comparator	£	Q	LYG	diff £	diff QALY	diff LYG	ICER
22. (4+12+14+19 + ERG minor correction (See text)	ERG minor corrections to company revised base case [C]	BSC	[redacted]	[redacted]	10.510				
		Inotersen	[redacted]	[redacted]	12.502	[redacted]	[redacted]	1.991	£150,968
23. (11+13+18)	ERG preferred analysis [C]	BSC	[redacted]	[redacted]	11.028	-	-		
		Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£281,571
24. (11+13)	ERG preferred analysis, without time in state utility adjustment [C]	BSC	[redacted]	[redacted]	11.028	-	-		
		Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£367,993
25. (10+13+18)	ERG preferred analysis, with HRU costs mapped from PND I to FAP 1 [C]	BSC	[redacted]	[redacted]	11.028	-	-		
		Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£282,059
Additional exploratory analyses around removing stopping rules on entry to Stage 3 disease									
26.	Allow treatment continuation in stage III (Applied to ECD preferred assumptions)	BSC	[redacted]	[redacted]	7.541				
		Inotersen	[redacted]	[redacted]	8.819	[redacted]	[redacted]	1.278	£682,213
27. (22+26)	Allow treatment continuation in stage III (Applied to Company preferred case) [C]	BSC	[redacted]	[redacted]	10.510	-	-		
		Inotersen	[redacted]	[redacted]	12.502	[redacted]	[redacted]	1.991	£172,732
28. (23+26)	Allow treatment continuation in stage III (Applied to ERG preferred case) [C]	BSC	[redacted]	[redacted]	11.028	-	-		
		Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£306,318
29. (24+26)	Treatment continuation in stage III applied to ERG alternative case *(no adjustment of time in state utility)*	BSC	[redacted]	[redacted]	11.028	-	-		
		Inotersen	[redacted]	[redacted]	12.939	[redacted]	[redacted]	1.911	£407,952

BSC: Best Supportive Care; ECD: Evaluation Consultation Document; ERG: Evidence Review Group; FAP: Familial Amyloid Polyneuropathy (considered equivalent to Coutinho stage in the ERG report); ICER: Incremental Cost-Effectiveness Ratio; LYG: Life Years Gained; PND: modified polyneuropathy disability score; QALY: Quality Adjusted Life Years

[A] Analyses will differ slightly to those generated using the company submitted model because a number of minor corrections made by the ERG were not replicated in the company's revised model submission. These include: A) a typographical error updating the one-off costs on entry to Stage 2 disease, B) Full incorporation of adverse event data costs and utilities, as per the ERG and ECD preferred analyses at committee stage. The ERG note that these discrepancies have minimal impact on the ICERs overall.

[B] A minor error was noted on the Markov cohort trace for the 'one-off' transition costs applied. This has been corrected by the ERG to enable exploration of the impact of including an inotersen specific reduction (43%) for one-off transition costs to stages II and III. This helps to improve alignment with the patisiran assessment.

[C] Note: each run of the model that requires a re-generation of utilities using the company simulation generates slightly different estimates of the ICER. Whilst variation is minimal, it may preclude re-production of the exact ICERs reported in the table above from a single model file for analyses that use time-varying utilities.

Healthcare resource use costs:

Two changes have been made to health state costs used in the model to better align the resource use assumptions between the inotersen (NICE, 2018) and patisiran (NICE, 2018b) appraisals. In addition, the ERG note that a minor typographical error in the one-off costs for progression to Stage II disease, identified in the original ERG report (page 117, Table 38), has not been rectified in the latest company submission. The ERG have made this correction again to all analyses in this report. This discrepancy has minimal impact on the ICER and is not discussed further. The changes made, including the ERG's critique are as follows:

Sources of resource use costs per FAP stage

Costs applied to each Coutinho (also referred to as FAP) stage have been updated to ensure consistency with the patisiran evaluation. These health state costs were collected using a Delphi panel of N=7 experts, conducted for the manufacturer of patisiran.

Table 5 of the company's submission details the revised health state costs used in the model. These have been sourced from NICE documentation pertaining to the evaluation of patisiran, specifically committee meeting presentation slides, which indicated a range of health state costs, per six-monthly model cycle for polyneuropathy (£234 to £82,424). These have been applied in the company's model, assuming that a) £234 relates to Stage 1 disease, b) £82,424 relates to Stage 3 disease and c) the appropriate Stage 2 cost is an interpolation of the two extremes, using weightings across stages from the originally submitted health state costs. Costs were then converted from six-monthly (as reported for patisiran) to four-weekly cycles, as required for use in the inotersen model.

The ERG have re-examined the publicly available NICE documentation regarding patisiran and have identified an error in the mapping approach to health state costs in the company's submission. The company appear to have mapped PND stage 0 costs (from patisiran) to FAP stage 1 for use in the model (i.e. £234 per six month patisiran cycle). This is not consistent with either of the mapping processes suggested by the literature (Adams, 2013) (Adams, et al., 2016). A more accurate description of the relevant PND stage specific, poly-neuropathy health state costs (from the patisiran appraisal) can be found in the patisiran ERG report. The six-monthly costs are quoted as £233.80, £1,825.50, £2,499.25, £4,553.52, £7,203.59 and £82,423.93 for PND 0, I, II, IIIA, IIIB, and IV, respectively (Source: page 92, Table 22 of the

patisiran ERG report). These health state costs can be mapped to FAP stage using published information (Adams, et al., 2016) where PND stage I and II match to FAP stage 1 and PND stages IIIA and IIIB match to FAP stage 2. This is the ERG's preferred approach. An alternative matching approach is suggested by an earlier study (Adams, 2013), and the ERG explore the impact of using this in sensitivity analysis. The different potential stage specific costs, sourced from the patisiran documentation are compared in Table 2, which also details the process for mapping between PND and FAP costs using the most recent consensus (Adams, et al., 2016).

Table 2 FAP stage specific costs based on mapping PND to FAP stage

PND	PND state description	FAP (Adams, et al., 2016)	FAP stage description	Company's original submission (4-weekly stage cost)	Company's revised submission (4-weekly stage cost)	ERG preferred 4-weekly stage costs, corrected mapping using (Adams, et al., 2016) [A]
0	No impairment	**0**	No symptoms	N/A	N/A	N/A
I	Sensory disturbances, preserved walking capability	**I**	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs	£393.33	£36	(£1,825.50 + £2,499.25)/2/26*4 = **£332.67**
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	£1,306.86	£8,548.26	(4553.52 + 7203.59) /2/ 26*4 = **£904.39**
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	£1,744.63	£12,680.62	£82,423.93/26*4 = **£12,680.60**

FAP: Familial Amyloid Polyneuropathy (considered equivalent to Coutinho stage in the ERG report); ICER: Incremental Cost-Effectiveness Ratio; LYG: Life Years Gained; PND: modified polyneuropathy disability score;

[A] An alternative mapping from PND to FAP stage has been suggested in an older study (Adams, 2013) which maps as follows (PND I→ FAP 1; PND II,IIIA,IIIB → FAP 2; PND IV → FAP 3). This approach generates FAP specific 4-weekly stage costs of £280.85, £731.10 and £12,680.60 for FAP stages 1, 2 and 3 respectively. These data have been considered in a sensitivity analysis in Table 1 above.

The ERG agree with the company that it is appropriate to use health state costs, sourced from the patisiran appraisal, and mapped between PND and FAP stage. These costs improve alignment between the appraisals, are sourced from UK based clinicians, and are costed using UK national average unit cost information. They are therefore the most appropriate data available for populating the economic model. The ERG note that correcting the company's mapping approach between PND and FAP, and updating this according to most recent consensus (Adams, et al., 2016) generates substantially different health state costs compared to those reported in the company submission. This is particularly true for Stage 2 FAP costs which are substantially lower compared with the company's interpolation approach. The company's approach substantially over-estimates the difference between stage 1 and stage 2 costs, but under-estimates the difference between Stages 2 and 3. The ERGs approach and correction to health state costs generates an ICER which is more favourable to inotersen compared to the company's amendments.

One off stage progression costs

The ERG note that one-off costs for stage progression are also available from the patisiran documentation, sourced from the same Delphi study as the per-cycle health state costs. Given that the Delphi study was conducted with UK clinicians and resource use costed using UK sources, the ERG considers this to be a more appropriate source of one-off stage progression costs for use in the model. A comparison of the one-off transition costs used in the company submission, and the patisiran assessment are provided in Table 3 below.

Table 3 One-off poly-neuropathy stage progression costs

PND stage	FAP stage (Adams, et al., 2016)	One-off polyneuropathy costs applied in inotersen model	ERG revised one-off poly-neuropathy costs, sourced from BSC arm of patisiran appraisal [C]
PND 0	0	N/A	N/A
PND I	1	N/A	N/A [A]
PND II			
PND IIIA	2	**£2,029.21** [B]	(£8,075.69 + £9,938.22)/2 = **£9,006.96**
PND IIIA			
PND IV	3	**£4,525.50**	**£10,783.92**

[A] Not applicable: Data are available to map using the algorithm, but are not relevant to the inotersen model as progression to FAP stage 1 is not possible.

[B] Note that this value was originally quoted as £1,218.88, but was based on a typographical error, as described in the original ERG report. The correct cost (£2,029.21) has been used for the ERG analyses. The discrepancy has minimal impact on the ICER.

[C] The ERG also notes that these one-off stage transition costs were also reduced by a further 43% in the patisiran arm of the patisiran model, but that this transition cost reduction was not replicated in the company's ECD response for inotersen.

Applying a 43% reduction to health state costs in the inotersen arm of the model

In addition to the change to health state costs, the company have applied a 43% reduction to the inotersen health state costs for FAP stages I and II only, again informed by the patisiran appraisal. The adjustment is applied for the full duration of health state occupancy in FAP Stages 1 and 2, and is applied only to the proportion of the inotersen cohort that are on treatment. The application of the adjustment is consistent with the approach taken for the patisiran appraisal. The ERG note that the true percentage reduction is likely to be highly uncertain and has not been subjected to sensitivity analysis. The ERG have therefore conducted a further exploratory analysis illustrating the impact of removing the percentage discount applied to the inotersen (proportion on treatment) arm of the model.

The ERG also note that the 43% reduction was also applied to one-off poly-neuropathy costs in the patisiran appraisal, a discount which has not been replicated in the company's revised analysis, though the functionality exists to do so. The ERG believe that in order maintain consistency between the appraisals, it is appropriate to apply the 43% reduction in a similar manner for the one-off poly-neuropathy costs in the inotersen (proportion on treatment) arm of the model. The impact on the ICER has been described in Table 1.

Impact of changes to cost parameters on the ICER

The ERG have made 3 amendments to cost parameters in the company's revised submission: a) correcting the mapping between PND and FAP stage, following the most up to date consensus (Adams, et al., 2016) and using more detailed, publicly available data from the ERG report for the patisiran appraisal; b) implementing one-off costs from the patisiran appraisal on progression to FAP stages 2 and 3 and c) applying a reduction to one-off progression costs of 43% in the inotersen arm of the model to improve consistency with the modelling approach used in the patisiran appraisal. The combined impact of these changes is to reduce the ICER from £646,767 (ECD preferred assumptions) to £449,520 per QALY gained.

Revised mortality hazard ratios used in the model

The company have updated the mortality hazard ratios (by disease stage relative to the general population) to align with the patisiran appraisal, and have conducted deterministic

sensitivity analyses around these parameters (See Table 3 of the company submission). The motivation to update the hazard ratios was to exclude mortality due to cardio-myopathy.

The hazard ratios have been changed from 5, 10 and 19 in the original submission to 2.01, 2.42 and 9.53 (as per the patisiran preferred assumptions) for stages 1, 2 and 3 respectively. The HR of 2.42 for FAP stage 2 was obtained by taking a weighted average of PND stages II, IIIa and IIIb. Given the most recent consensus mapping described in Table 2 above, the ERG believe it would have been more appropriate to map PND stages IIIa and IIIb to FAP stage 2 (Adams, et al., 2016). Using this approach, the HR for FAP stage 2, relative to the general population, would be 2.62 (as quoted for PND stage III on page 8 of the company submission). The ERG have implemented this update, but note that the adjustment has had minimal impact on the ICER.

With the implementation of the minor update noted, the approach taken by the company to revise mortality hazard ratios appears reasonable and is consistent with the assumptions used for the patisiran appraisal. The revised mortality hazard ratios are substantially lower across all stages relative to the original assessment, meaning that a greater proportion of the cohort remain alive to benefit from inotersen treatment, generating greater life year and hence QALY gains, leading to a moderate reduction in the ICER from £646,767 to £570,431 (company HRs) or £572,303 (ERG updated HRs).

Adjusted transition probabilities for the BSC arm of the model

The company have added an additional amendment to the BSC arm of their model to prevent the cohort from transiting from Stage 2 to Stage 1 disease beyond the 66 week follow up of the Neuro-TTR study. The implication is that the BSC transition probability over the extrapolation phase changes from [redacted] to 0%. The ERG are satisfied that the stated amendment has been correctly implemented in the model, but raise concerns about its appropriateness. The amendment appears akin to removing any placebo effect (or random fluctuation in health state transitions arising from the imperfect mapping between TQoL score and FAP stage) from the BSC arm of the model, but not doing likewise in the inotersen arm. The impact is that improvement in FAP stage is only possible in the inotersen arm. This would appear to create a bias in favour of inotersen, as one would anticipate to see some placebo effect or random variation in both arms. Furthermore, the observation of possible transition from Stage 2 to 1 in the BSC cohort is more likely due to random variation in the

subjective TQoL score and the somewhat arbitrarily defined TQoL thresholds used to define health state occupancy in the model. It may also be the result of a small proportion of patients adapting to their condition, reflected in improvements in TQoL score. Both of these effects might be expected to occur equally in both arms of the model, independently of treatment effect, and so to remove them from the BSC arm only may create a bias in favour of inotersen.

The ERG acknowledges the company's argument that the approach was implemented in the patisiran evaluation and was not challenged in the patisiran ECD. However, the ERG feel that it is more methodologically sound to retain the effect as per the original company submission. The ERG also note that the company's amendment has a moderate impact on the ICER, reducing it from £646,767 to £596,436.

Amendments to utility parameters

Revised health state utilities applied to FAP stage in the model:

In response to the ECD, the company have attempted to generate stage specific utilities that are more applicable for use in the UK setting. The rationale for the company's approach is to generate utilities that would be close to the values that might be obtained were raw data available from the THAOS registry, by FAP stage, to which UK tariffs could be applied. The company note that access to the registry data was not available.

The company's revised approach to health state utilities attempts to match the mean Brazilian values obtained from the THAOS registry (Stewart, et al., 2013) to mean UK values. This is done by 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. The company have taken the utility score from Stewart et al for each stage, and found the EQ-5D health profile with Brazilian valuation closest to these means. UK tariffs are then applied to the selected EQ-5D profile to approximate the mean UK health state utility value by stage. The ERG are concerned that the approach is uncertain and has limited face validity. The approach assumes a single state profile can be used to approximate the expected difference in mean UK and Brazilian utility values by stage. It does not account for the distribution of profiles underpinning the mean Brazilian values reported by Stewart et al., or variability in preference patterns for different dimensions of the EQ-5D between the UK and Brazil. The approach is

un-validated and generates potentially strange health state classifications. For example, one of the states selected for mapping FAP stage III utility is 31332, which specifies 'no problems' with self-care. This lacks face validity and is unlikely to reflect the health status of someone with Stage III disease. Similar critiques could be applied to the EQ-5D profiles applied to the utility calculations for each FAP stage.

The ERG acknowledge that the range of utility values between best and worst states with the UK tariff is substantially wider than the Brazilian tariff, and it may be reasonable to assume greater between stage differences might be expected if raw data from the THAOS registry were available on which to apply UK tariffs. However, the approach taken generates further uncertainty and the ERG do not believe that it is any more robust than any of the other methods considered (Using Stewart et al utilities directly, or using Faria et al mapping from TQoL to EQ-5D). All approaches are associated with limitations. The ERG are not convinced that the company have provided a strong enough case to move away from the ECDs preferred utilities (mapping from TQoL to EQ-5D using the linear function described in Faria et al), despite their limitations. The alternative utility sources available are provided in Table 4 below for comparison.

Table 4 Alternative utility sources for use in the economic model

FAP stage	Revised company submission (Stewart, et al., 2013) utilities translated to UK values)	Original company submission, Brazilian tariffs (Stewart, et al., 2013)	Faria linear map from TQoL score to EQ-5D utility (Faria & Palmer, 2012)
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

Allowing increasing / decreasing utility for inotersen / BSC within state

The company have provided a revised analysis in which the QALYs in the Markov trace are adjusted to allow utility within state for inotersen patients to increase over time. Conversely, utility is assumed to decrease over time for both the proportion of the cohort who discontinue inotersen and the BSC cohort. The motivation for this amendment was to align the inotersen model with the assumptions used for the patisiran appraisal. The ERG accepts the company's

rationale but also notes that the ECD for patisiran indicates that the committee questioned the reliability of the method used to generate the utilities. To enable the application of increasing / decreasing utility within stage, the company have implemented the following:

They calculated the change in TQoL score between baseline and 66 week follow-up for each treatment arm in the Neuro-TTR study. The data suggest that there is possibly a within stage treatment benefit that is not captured in the original QALY calculations, and it is assumed that this accrues linearly over time. The improvement in TQoL over the duration of the study (inotersen) and deterioration in TQoL (BSC) are translated into expected differences in EQ-5D utility over a 66 week period using the linear mapping function from Faria et al. The translation results in a +0.0002 utility increment (inotersen on treatment) and -0.0038 utility decrement (inotersen treatment discontinued and BSC), applied to each 4-week cycle that a patient remains within state in the model. As it is not possible to track patients in a Markov cohort, the company have carried out a patient level simulation outside the Markov model (using Visual Basic), to account for 'time in state' and to estimate cycle specific health state utility values by treatment arm, that are dependent on time in state. The utilities from the simulation study are then applied to the Markov cohort trace. It is the ERGs understanding that within state utility increases over time in the inotersen arm, but is capped at the baseline utility of the next best state. Conversely, within stage utility declines over time in the BSC (and inotersen discontinued) arm but is capped at the utility of the next worst state. Furthermore, the utility in Stage 1 is capped at general population values, and the utility in Stage 3 is capped at -0.093. Presumably this lower bound is chosen as it is similar to the average health state utility for stage 3 disease, as per the company's revised approach to obtaining health state utility.

The company argue that the analysis has clinical validity and has been ratified by clinicians. The ERG accepts that intuitively, one might expect to see a faster reduction in the QoL (within state) for those receiving BSC compared to treatment with inotersen. However, to assume that inotersen utility increases linearly whilst on treatment over the full duration of time in state, in what is essentially a progressive disease, where inotersen is claimed to slow the rate of progression rather than reverse it, appears to be counter-intuitive. The ERG believes that a more conservative assumption might have been to assume that the rate of utility decline within stage is slower for inotersen than BSC. This approach would be more congruent with the reduction in the rate of TQoL deterioration observed for inotersen vs.

BSC in the NEURO-TTR study (See Figure 6, page 67 of the original company submission). In particular, the ERG feels that the assumption of linear changes in utility extrapolated indefinitely beyond 66 weeks is highly uncertain, and has questionable face validity. It is also unclear to the ERG how the 'within state' TQoL changes (used to adjust utility by time in state) were calculated by the company, and whether the application of this adjustment potentially double counts some of the utility benefit already reflected in the lower rates of transition through the FAP stages in the inotersen arm of the model. The ERG therefore explore the impact of including and excluding the time in state utility adjustments on its preferred base case assumptions.

Carer dis-utility (number of carers modelled by FAP stage)

The ERG acknowledges that carer dis-utility is an important model parameter and decisions regarding the number of carers in each FAP stage can have substantial impacts on the ICER. The company's revised, preferred base case analysis assumes that patients will require one carer in Stages 1 and 2, but will require 2 carers in Stage 3 reflecting the additional care needs of patients with more advanced disease. The company's assumption reduces the ICER from £646,767 to £562,779 per QALY gained. However, the ERG also note that the ECD provides a clear steer that the committee '*concluded that as a reasonable estimate it would prefer to assume 1 carer in every stage of the model'.* To maintain consistency with the preferred assumptions of the ECD, the ERG's preferred analyses apply the disutility for one carer across all FAP stages.

Impact of utility changes on the ICER

In general the model results are highly sensitive to different utility assumptions. The company's preferred utility assumptions: A) Brazilian utilities (Stewart, et al., 2013) translated to UK values, and B) Increasing and decreasing utility over time for the inotersen and BSC cohorts respectively lead to a substantial reduction in the ICER compared with the ECD preferred approach from £646,767 to £344,433 per QALY gained.

By contrast, the ERGs preferred utility assumptions: a) using state specific utilities mapped from TQoL to EQ-5D using a linear approach (Faria & Palmer, 2012) and B) allowing utilities for inotersen and BSC to increase and decrease respectively within state lead to an ICER of £503,547 per QALY gained. The ERG prefer the use of increasing / decreasing utilities within state because it improves consistency with the patisiran appraisal, but note that

removing the within state adjustment reverts the ICER back to the ECD preferred utility assumptions (ICER = £646,767). The ERG prefer the use of Faria et al. utilities, despite their limitations and narrower range between stages. In light of the substantial uncertainty surrounding the most appropriate values, those from Faria et al. are likely to generate conservative estimates of the ICER.

In summary, the ERG note that there is substantial uncertainty surrounding utility parameters. There is wide variation in the ICER arising from different plausible assumptions regarding utility data, all of which are associated with respective advantages and disadvantages.

Assumptions regarding treatment stopping rules:

In the company's model, inotersen treatment is only provided in Stage 1 or 2 disease, and is assumed to be discontinued upon progression to Stage 3. This assumption is in line with inotersen's marketing authorisation. However, the ERG note that some patients and clinicians may still wish to continue treatment into Stage 3 disease if patients are deemed to continue benefiting from treatment. As an exploratory analysis, the ERG have considered the impact of removing the stopping rule from the model. Doing so increases the ICERs to £682,213, £172,732 and £306,318 for the ECD preferred, company preferred and ERG preferred analyses respectively. It should be noted that analyses around stopping rules are exploratory in nature and do not reflect the ERGs preferred assumptions.

ERG conclusions

There remains substantial unresolved uncertainty surrounding the most likely ICER for inotersen compared to BSC in this population. The key drivers of uncertainty in the model are state specific utility and cost data, as well as the appropriateness of treating costs, utilities and transition probabilities differently in the different arms of the model. Doing so may improve clinical face validity but runs the risk of introducing further bias into the estimates of the ICER. The ERG accept that many amendments to the model are made in an attempt to align assumptions between the inotersen and patisiran appraisals. The company's preferred assumptions generate a base case ICER of £150,636 (£150,968 when implementing minor adjustments to adverse events and correcting minor typographical input errors), substantially lower than the preferred ECD ICER of £646,767. The ERGs preferred assumptions and

corrections result in an ICER of £281,571 per QALY gained. Removing a time in state utility adjustment from the ERGs preferred assumptions increases the ICER further to £367,993.

In summary, the key areas of unresolved uncertainty that committee should consider are:

1. Whether the patisiran stage specific costs are an accurate reflection of UK specific resource use by FAP stage
2. Whether it is appropriate to adjust cost data, but more importantly utility data, to assume treatment specific effects within stage.
3. Whether it is appropriate to adjust out transition probabilities from FAP stage 2 to 1 in the BSC arm of the model (which may be due to random variation in the TQoL scores used to map to FAP stages), without making a similar adjustment in the inotersen arm.
4. There remains substantial uncertainty regarding utility assumptions, specifically whether a wider utility range between states (as per the company's revised approach) or a more conservative range (as per Faria et al.) is more appropriate. The ERG re-iterate that there are substantial limitations associated with all approaches in the absence of access to the raw EQ-5D response data from the THAOS registry.

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Sent via email 28 January 2019:

Dear Luke,

NICE technical team have now had an opportunity to review the consultation response to the ECD along with the ERG response. We are concerned that there is an outstanding issue that would need to be resolved before we take this topic back to committee. Both NICE technical team and ERG have been struggling to review the additional information presented in section 5 in the response document. We would like to give you an opportunity to address this issue before the February committee meeting, which would ensure your case will be presented to the committee suitably.

The ECD response document (section 5, pages 10-12) indicates that change in TQoL score between baseline and week 66 was used to estimate 4 weekly changes in utility within FAP stages. The document notes that the TQoL score of patients stable on inotersen improved by an average of 0.66 points, whilst those on BSC deteriorated by 10.96 points.

1. Is this analysis of change restricted to people with no change in Stage between baseline and weeks 66, in both the inotersen and BSC arms? We would need to see some more details on the sample and numbers stable in Stage 1 and 2 by treatment arm.
2. Could you please provide further reassurance that the approach used does not lead to any double counting of the utility benefit associated with slowed progression through the stages.
3. Could you please justify the same increment and decrement being applied in Stage 1 and 2, given Stage 1 incorporates a broader range of TQoL scores than Stage 2 and contribute more data to the average change?
4. What is the justification of applying the within stage increments/decrements beyond week 66?

Please note, in order to ensure we are able to continue with the February meeting, the information will be required to reach us by **noon, 30 January 2019**. We are happy to further discuss with you any questions you may have during the call scheduled for tomorrow morning.

Kind regards,
Orsolya Balogh

Orsolya Balogh, PhD
Health Technology Analyst – Technology Appraisals

Dear Sheela,

Thank you for the opportunity to address your outstanding questions in anticipation of taking this topic back to committee. I hope the below satisfies you that the approach taken in the submission is justified.

Background to inclusion of the change

We feel it may be helpful to include some contextual details to explain why these parameters were included in the response to the ECD.

Alongside the submission for inotersen (Tegsedi), another HST is being undertaken for a treatment with the same indication and a similar economic model.

In the interests of consistent consideration of assumptions in the same disease area and therefore a fair and balanced appraisal, it was agreed with NICE that it would be reasonable to adjust assumptions regarding the best supportive care (BSC) group to align for both assessments: the BSC group should be identical between submissions because the BSC group in both models are untreated Stage 1 and 2 hATTR. Any inconsistency would mean that NICE had accepted different assumptions in one submission to another, which would go against the principle of transparency and consistency.

One such amendment was the way utilities vary within a Stage. In our original submission, we assumed that there was no variation in utility except between Stages. However, Alnylam argued that this was clinically unjustified; patients do not 'jump' between Stages from one day to the next, but instead progress from a less severe form of the disease with a Stage to a more severe form of the disease within the same Stage, before transitioning from one stage to the next. In addition, there was evidence that treatment may offer improved patient outcomes, allowing within Stage improvement. The time-in-state utilities approach captures this important outcome. As this argument is clinically reasonable, captured an outcome of critical importance to patients and satisfied NICE's objective of aligning BSC groups, Akcea agreed to implement the change in their next version of the model. We will not describe here the implementation of the change in the model, as we believe your clarification questions relate to the parameterisation rather than implementation of the change, although are happy to provide further details if this would be helpful.

We would like to emphasise that the impact of the inclusion of time-in-state utilities is relatively minimal; removing this assumption entirely changes the ICER from £150,636 to £157,668. This revision was not due to the availability of new data, rather adopting a clinically reasonable, and methodologically more appropriate approach. Therefore, we hope that – even if further clarifications of the below are required – it does not affect the ERG's view of the appropriateness of taking this topic back to committee.

Question 1 - Is this analysis of change restricted to people with no change in Stage between baseline and weeks 66, in both the inotersen and BSC arms? We would need to see some more details on the sample and numbers stable in Stage 1 and 2 by treatment arm.

The original analysis was **not** restricted to those with no change in Stage between baseline and week 66, but looked at all patients on a particular arm. The reason for this decision was:

1. As far as we could understand, this is in line with the approach accepted in the patisiran submission. Importantly, we corrected a criticism of the patisiran model, which was that patients in worse Stages were able to have QoL higher than in better Stages if they did not change Stage for a long time (for example, Stage 2

patients with better QoL than Stage 1 patients). Whilst we are seeking to be consistent, we also expect this amend to be made in the patisiran model.

2. Patients would drop out of the trial if they ever entered Stage 3. Consequently, a per-stage approach would risk ignoring changing utilities in Stage 3. This is especially important from a payer's point of view as inotersen is not given in Stage 3, so a utility decrement in Stage 3 is likely to increase ICER relative to no utility decrement in Stage 3.
3. Numbers of completely stable patients are small in some subgroups. For example, [redacted]; by including all possible patients the hope was that it was clear we were not exploiting random variation in the data to produce better ICERs.

Table 1 provides the raw data for TQoL score by submission arm used in the submission (ie **not** restricted to those with no change in Stage). These data were not split by Stage for the reasons given above. Note that the 'n' here refers to the number of patients who gave a usable TQoL value at this stage of the trial, not the total number of patients still enrolled in the trial.

Table 1 – Raw data used for original values

	Baseline TQoL	Wk35 TQoL	Wk66 TQoL	Baseline n	Wk35 n	Wk66 n
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 splits the same data out by Stage as requested, identifying the TQoL and number of patients in each Stage at each timepoint. Note that 'Stage 3' refers to TQoL scores above 91 as per Faria et al (2012)'s proposed mapping; as described above there are no actual Stage 3 patients in the NEURO-TTR trial as inotersen is discontinued in Stage 3, so this group is used as a proxy for entry into Stage 3.

Table 2 – Split of original raw data by Stage

	Baseline TQoL	Wk35 TQoL	Wk66 TQoL	Baseline n	Wk35 n	Wk66 n
Inotersen - Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen - Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen - 'Stage 3'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - 'Stage 3'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

We believe from your requests that you were expecting to see numbers stable in each Stage, even though this was not the approach we actually adopted. Table 3 shows the number of patients stable in each Stage, meaning the number who begin the NEURO-TTR trial in a particular Stage and remained in that Stage at week 66. Note that as no patients both began and finished the trial in placebo Stage 3 there is no way to calculate the average TQoL of such a patient – we would highlight that this will heavily and inaccurately penalise inotersen when using a 'stable in stage' strategy as the reason no patients are stable on 'Stage 3' placebo is that they all enter actual Stage 3 by week 66 (demonstrating a very serious worsening of TQoL).

Note that [redacted];we explain this in our response to question 3.

Table 3 – TQoL of stable patients only

	Baseline TQoL	Wk35 TQoL	Wk66 TQoL	Baseline n (start trial in this Stage)	Wk66 n (finish trial stably on this Stage)
Inotersen - Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen - Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen - 'Stage 3'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - Stage 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - Stage 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - 'Stage 3'	[redacted]			[redacted]	[redacted]

Question 2 - Could you please provide further reassurance that the approach used does not lead to any double counting of the utility benefit associated with slowed progression through the stages.

The main risk of 'double counting' in this model is if the difference in TQoL at baseline and Week 66 in Table 1 is driven mainly by placebo patients transitioning more quickly through Stages than inotersen patients, rather than arising from better utility within-stage as suggested by Table 2 and Table 3.

To be explicit, the data show that inotersen causes **both** a slowed progression through Stages and better utility within Stage, and therefore it is actually appropriate to apply two sources of on-inotersen improvement; what we understand by the query is that the ERG are concerned that *the same* improvement is being counted twice, which would be incorrect and is not the case here.

Table 4 demonstrates that taking any stable subset of patients from the NEURO-TTR trial retains approximately the same ICER. As there is no possibility of double-counting utilities in the case of looking only at the stable patients, we believe this should reassure the ERG that our approach is robust to the possibility of double counting. However, we believe our original approach – which is robust to the missing data in Stage 3 – is still the most appropriate for the base case because it does not exclude the information that 'Stage 3' placebo patients do actually get worse.

Table 4 – Evidence of robustness of ICER to double-counting tests

Scenario	**ICER**
Base case	£150,636
Utility change based on stable Stage 1 patients in Table 3 only	[redacted]
Utility change based on stable Stage 2 patients in Table 3 only	[redacted]
Utility change based on stable 'Stage 3' patients in Table 3 only (assuming no change for placebo patients as insufficient data for meaningful analysis)	[redacted]
Utility change based on stable 'Stage 3' patients for inotersen patients and Stage 2 patients for placebo in Table 3	[redacted]

Question 3 - Could you please justify the same increment and decrement being applied in Stage 1 and 2, given Stage 1 incorporates a broader range of TQoL scores than Stage 2 and contribute more data to the average change?

Referring again to Table 3, [redacted]

[redacted]

Therefore, we believe our approach of not differentiating utility decrement by Stage is the most appropriate way of handling this data, and as demonstrated in Table 4 the model is not especially sensitive to decrement parameterisation. Table 5 demonstrates [redacted].

Table 5 – Evidence of robustness of ICER to different increments

Scenario	ICER
Base case	£150,636
[redacted]	[redacted]
[redacted]	[redacted]

Question 4 - What is the justification of applying the within stage increments/decrements beyond week 66?

As with any HTA submission, Akcea has extrapolated the results of the 66 weeks of the NEURO-TTR study to model the likely outcomes of giving the treatment over a patient lifetime. Typically, the justification for extrapolating results is partly based on clinical plausibility and partly on statistical observation and inference.

It is clinically plausible that the within-stage increment/decrement would continue beyond week 66, as Akcea has argued that the mechanism is related to the presence or absence of the drug. That is, without inotersen patients will continue to get worse, as hATTR is a progressive condition and there is nothing preventing the progression after week 66. Similarly, the improvement in quality of life on inotersen is caused by the presence of inotersen, and therefore can be expected to remain for as long as inotersen provides clinical benefit. Note that the NEURO-TTR extension study provides further evidence of ongoing clinical benefit of inotersen.

Statistically, looking at Table 2 and Table 3 shows a general trend of patients improving on inotersen and getting worse on placebo. There is no evidence of 66 weeks being an inflection point, or of a slowdown in the rate of improvement / worsening between weeks 35 and 66. A conservative approach in this situation would be to assume that there is no difference between week 66 and subsequent weeks without evidence, and we do not believe such evidence exists.

Conclusion

Once again, many thanks for the opportunity to address your outstanding questions. We hope that we have addressed both your specific queries and the context in which we made decisions leading up to our specific implementation. Please do not hesitate to request clarification on any issue, and we will do our best to respond subject to patient data protection issues.

We would reiterate that this is a relatively minor assumption with respect to its impact on the ICER, and hope that it would not prevent taking this topic back to committee as planned.

Best wishes,

Claire Grant

Director of Market Access and Policy UK, Ireland and Nordics

Inotersen for treating hereditary transthyretin-related amyloidosis

ERG addendum

Critique of the company's response to additional queries on revised evidence post ECD

Produced by Aberdeen HTA Group

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Background:

Following the company's initial response to the ECD, NICE and the ERG requested further clarification (four specific queries) regarding the parameterisation of the within-state, per-cycle utility changes applied to a) inotersen on treatment (+0.0002 per 4-weekly cycle within state) and b) BSC and inotersen off treatment (-0.0038 per 4-weekly cycle within state). The company's revised approach post ECD seeks to standardise the modelling approaches and assumptions used for both the patisiran and inotersen appraisals. This document details the ERG's understanding of the company's (Akcea therapeutics) response to additional queries, dated January 30th, 2019 as follows:

Queries 1 & 2 & 3: Using changes in TQoL across FAP stages (between baseline and week 66) to predict within state utility changes per cycle.

These queries sought further clarity on the data used to obtain within state utility adjustment, and sought assurance that there was no risk of the calculations underpinning the within-state adjustment counting some utility benefit (inotersen) or decline (BSC) that is already counted in the transitions through the FAP stages 1 to 2 (according to the model transition probabilities). The ERG believe the magnitude of any bias would be small, but requested additional data to ratify that belief. The ERG also note that any potential for bias would be mitigated if the calculated 'within state' utility changes for stages 1 and 2 were based on trial participants who remained stable in state between baseline and week 66.

The ERG agrees with the company's justification for not providing a stage specific analysis in stage 3 because a) it would not be possible given the NEURO-TTR baseline population and b) inotersen treatment is not given in stage 3, meaning that utility decrements are applied equally to both arms. The company have clarified that their analysis was not stage specific, but have now provided further data on the mean TQoL scores at baseline and 66 weeks for patients who remain stable within each stage.

Table 1 below details the 4-weekly cycle specific utility increments and decrements that might have been applied in the model, by stage, if the stage specific data had been used. The ERG note that using the 'stable in stage' approach to obtain per cycle utility changes would lead to a greater improvement per cycle in Stage 1 for inotersen, [redacted]. However, given the time available to critique the company submission, it was not possible to update the VB programming to explore the

impact of applying these stage specific values. However, the company have provided analyses illustrating the impact of applying the stage 1 changes to all, and the stage 2 changes to all. The ERG provide similar analyses on our preferred ICER for the committee's information.

Table 1 Comparison of different approaches to obtain 'within state' utility changes per cycle

Within state utility adjustment assumption:	TQOL (BL)	TQOL (Week 66)	EQ-5D (BL)	EQ-5D (Week 66)	4 weekly change	ICER: company preferred assumptions (as per company response letter)	ICER: ERG preferred assumptions
Company preferred 'within state' utility adjustment							
Inotersen	[redacted]	[redacted]	0.6400	0.6438	0.0002	[redacted]	[redacted]
BSC	[redacted]	[redacted]	0.6374	0.5752	-0.0038		
Apply Stage 1 stable only							
Inotersen	[redacted]	[redacted]	0.7735	0.7852	0.0007	[redacted]	[redacted]
BSC	[redacted]	[redacted]	0.7940	0.7705	-0.0014		
Apply Stage 2 stable only							
Inotersen	[redacted]	[redacted]	0.5194	0.4949	-0.0015	[redacted]	[redacted]
BSC	[redacted]	[redacted]	0.5698	0.5057	-0.0039		
Remove within state adjustment completely							
	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]

N/A: Not applicable.

Query 4: Long term extrapolation

The ERG sought further clarity from the company regarding the extrapolation of within state utility changes for the full duration of the model, despite data only being available over 66 weeks. The ERG agree with the company's assertion that it is feasible to assume clinical benefit on treatment would apply beyond the trial time horizon, and indeed their data provided in response to ECD show maintenance of TQoL benefits versus projected placebo continuation out to 104 weeks. However, there remains uncertainty, as in many HTA models, regarding the maintenance of benefit in the long-term, and a decision is required as to whether the committee feel long term extrapolation of within state utility benefit is a plausible assumption.

Conclusion:

The ERG note that the company's response has helped to clarify the approach taken to 'within state' utility adjustments. The ERG note that the impact on the ICER is quite small,

but not insignificant when the estimated stage 2 decrements are applied to all in stage 1 and 2. This is the more pessimistic analysis and may be considered conservative. The ERG re-iterate that removing the assumption of 'within state' utility adjustment entirely, increases the company's preferred ICER from £150,636 to [redacted] (see company response letter) and the ERG's preferred ICER form £281,571 to [redacted] (see Table 1 of the ERG's report). Applying stage specific increments and decrements, based on patients stable in stage 1 and 2, would have the impact of increasing the ERG's preferred ICER to between [redacted] (applying within state adjustments based on stage 1 stable to all) and [redacted] (applying stage 2 to all).