NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGIES

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

Evaluation Committee Meeting – Tuesday 21 May 2019
3rd Committee meeting

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. **NICE email to company post ECM2**

3. **Company additional evidence submission**

4. **Company updated additional evidence submission**

5. **Evidence Review Group critique of the company's updated model –** prepared by ScHARR

6. **Evidence Review Group - additional analysis**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Patisiran treating hereditary transthyretin 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>Alnylam</td><td>
<u>4.12 Company's economic model</u>

ECD: The ERG explained that PND is not the best overall descriptor of the condition because it only captures mobility impairment (see Table 1); a model based on FAP stage would have also captured the autonomic symptoms.

Response: We request that the Evaluation Committee reconsider this opinion from the ERG, because—contrary to the suggestion of the ERG—the FAP staging system does not capture autonomic symptoms distinctly from polyneuropathy disability. Therefore, using FAP Stages instead of PND Scores would not have improved our model's ability to capture autonomic symptoms separately from polyneuropathy disability. On the contrary, the PND and FAP scoring systems are both predicated on mobility status. In fact, PND Scores and FAP Stages overlap to such a great degree that a mapping between these two systems has been formally defined in the literature (Table 1).

Table 1. Mapping of PND Score to FAP Stage
<table>
<tr><th colspan="2">PND classification</th><th colspan="2">FAP stage classification</th></tr>
<tr><th>Score</th><th>Symptoms</th><th>Stage</th><th>Symptoms</th></tr>
<tr><td>0</td><td>No impairment</td><td>0</td><td>No symptoms</td></tr>
<tr><td>I</td><td>Sensory disturbances but preserved walking capability</td><td>1</td><td>Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs</td></tr>
<tr><td>II</td><td>Impaired walking capability but ability to walk without a stick or crutches</td><td>2</td><td>Assistance with ambulation required; mostly moderate impairment progression to</td></tr>
</table>
</td><td>Thank you for your comment. The committee acknowledged comments from the company and the ERG, although accepted the company's staging based on PND scores, but on balance agreed that it did not capture all aspects of the condition, so was unlikely to reflect the true expected cost effectiveness. Please see section 4.12 of the Final Evaluation Document (FED).

Thank you for your comment. Autonomic neuropathy has been removed from Table 1. Please see section 2.3 of the FED.</td></tr>
</table>

Consultee	Comment	Response

IIIA	Walking only with the help of one stick or crutch		the lower limbs, upper limbs, and trunk
IIIB	Walking with the help of two sticks or crutches		
IV	Confined to a wheelchair or bedridden	3	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

FAP, familial amyloidotic polyneuropathy; PND, polyneuropathy disability.
Source: [Adams, 2013, Ando et al., 2013]

As shown in Table 1, although the FAP staging system does mention autonomic involvement, it does not separate autonomic function from the other criteria in each stage. Consequently, it cannot provide additional information on autonomic symptoms in comparison with the PND classification system. In particular, FAP Stages provide no way for a clinician to sub-classify patients on the basis of autonomic involvement independently of their mobility status. On the contrary, the FAP staging system clearly assumes that autonomic involvement correlates with mobility disability. We wish to emphasise that this essentially matches what the Committee heard about the PND scoring system from clinical experts, namely that improvements in polyneuropathy are correlated with autonomic symptoms (ECD pages 11 and 17).

Table 1 also shows that the only autonomic neuropathy referred to in the FAP classification relates to symptoms in the limbs [Ando et al., 2013]. Consequently, FAP staging does not include the gastrointestinal (GI) autonomic symptoms of hATTR amyloidosis such as diarrhoea, constipation and wasting, which clinical experts from the National Amyloidosis Centre (NAC) told us they believe to be the most important drivers of health-related quality of life (HRQoL) in this disease (as reported in our Company Submission [CS] Table D11, p 155). The patient expert statements received by the Committee for this HST evaluation also confirmed that GI-related symptoms had the greatest impact on their HRQoL; e.g., “The worst thing is the effect it has on my bowel movements. I have to be careful what I eat and have quick access to toilet facilities. This restricts where we travel and holiday types.”

ECD: *The clinical experts highlighted that changes in mobility are correlated with shifts in cardiac function and autonomic neuropathy so, although PND score is based on mobility impairment, it is indirectly predictive of harm and death. Despite this, the committee was concerned that the model*

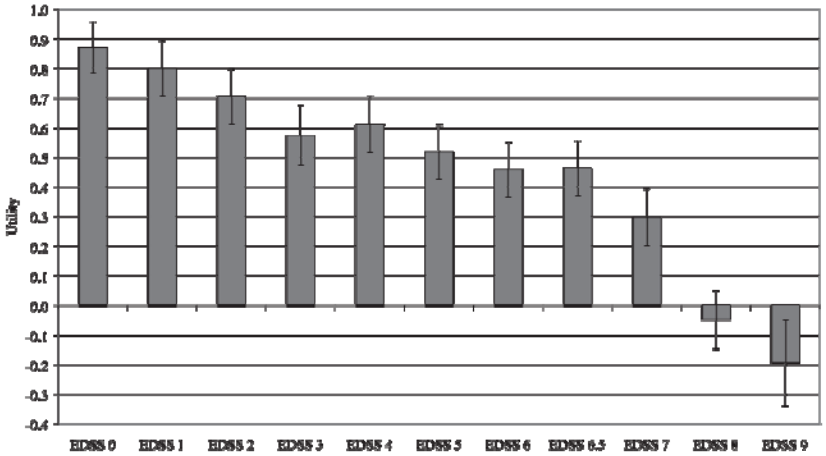
Consultee	Comment	Response
	relied on an assumed correlation between PND score and factors that patients have identified as particularly important, such as autonomic dysfunction and mortality (see section 4.7). The committee considered that although the model structure was broadly reasonable, it did not capture all aspects of the condition, so was unlikely to reflect the true expected cost effectiveness. **Response:** We acknowledge that autonomic dysfunction is important to patients, but there is no single measure, and thus no single model health state, that can capture the varied manifestations of a multi-systemic disease like hATTR amyloidosis. This reality was highlighted by Professor Philip Hawkins from the NAC in his comments at the HST hearing, and was acknowledged by the ERG in their comments to the Committee. This is because autonomic involvement includes such disparate effects as GI symptoms, orthostatic hypotension, and erectile dysfunction. Bouts of constipation, diarrhoea, and faecal incontinence can be so severe as to affect patients' nutritional status and result in life-threatening wasting. Orthostatic hypotension results in dizziness and/or fainting which in turn may lead to serious injury and hospitalization (e.g., due to falls). These effects are all clearly relevant to patients, as confirmed by the patient evidence presented at Committee; however, they also have an impact on overall HRQoL. Therefore, we believe we are justified in accommodating them in the model using EQ-5D scores, especially in light of the clear view from clinical experts that no single health state can capture the diversity of autonomic symptoms. Our rationale is that autonomic disability and any other aspects of HRQoL not explicitly defined in the PND scoring system would be encompassed by the EQ-5D data. The fact that no single assessment exists for hATTR amyloidosis is why the APOLLO trial included multiple endpoints, including measures of autonomic neuropathy and cardiac function. Patisiran demonstrated significant benefit versus placebo on all relevant measures of autonomic dysfunction, including modified Body Mass Index (mBMI), the Composite Autonomic Symptom Score 31 (COMPASS-31), and measures of orthostasis from the mNIS+7 (i.e., postural blood pressure; see CS Section 9.6) [Adams et al., 2018]. However, the multi-systemic nature of autonomic dysfunction and measurement across several different instruments presented challenges in modelling these changes using any single unified measure. We used EQ-5D-based utilities in our model as a necessary simplification of how the varied symptoms of hATTR amyloidosis—including autonomic dysfunction—affect patients' HRQoL. Importantly, this may underestimate the benefits of patisiran in the cost-effectiveness model, since all of these endpoints (including nutritional status/wasting) showed significant benefit in favour of patisiran versus placebo. Thus, even if there had been some way to incorporate autonomic	Thank you for your comment. The committee acknowledged comments from the company, but on balance agreed that the model structure was broadly reasonable, but it did not capture all aspects of the condition. It concluded that it would take this into account in its decision making. Please see section 4.12 of the FED.

Consultee	Comment	Response
	dysfunction more directly in the model, the ICER would have been lower. In other words, the absence of a viable method to directly model dysautonomia and the need to capture this indirectly via EQ-5D-based utilities means that we took a conservative modelling approach. The Committee's comment that our model did not capture all aspects of hATTR amyloidosis seems not to recognise that the directly measured EQ-5D data from APOLLO on which the model utilities were based would have encompassed a broad spectrum of patient-relevant symptoms of the disease.	Thank you for your comment. While the committee recognises that the EQ-5D captures a broad spectrum of relevant outcomes, it considered that there were some health-related benefits of treatment with patisiran that were not captured in the model. Please see section 4.31 of the FED.
Alnylam	**4.14 Disease progression** ***ECD:*** *It was assumed that [patients having BSC] could either stay in their current health state or progress to the next worst PND state during each cycle, but not move to an improved health state. This matrix was derived from the probability that a patient's PND state worsened between baseline and 18 months in the placebo group of APOLLO, and the estimated probability of crossing the NT-proBNP threshold of 3,000 pg/mL or more during any given 6-month cycle. The ERG noted that the method used to convert 18-month data from APOLLO to 6-month cycles was inappropriate because there were more than 2 health states, and that this produced a small bias in favour of BSC. It also noted that it may have been informative to use a 9-month time point (for NT-proBNP). The committee concluded that the company's method of modelling of health-state transitions introduced uncertainty into the model, especially for the extrapolated period for which no long-term data exists (see section 4.9).* **Response:** The model assumption that patients could not improve on BSC reflects the true clinical course of hATTR amyloidosis. Natural history studies have consistently shown that once patients start showing symptoms, their clinical state progressively worsens [Adams et al., 2015, Koike et al., 2012, Mariani et al., 2015, Ruberg et al., 2012]. Therefore, in the absence of disease-modifying	Comment noted. See section 4.14 of the FED. The committee acknowledged that the company's approach to adjusting the cycle were biased and that using the 18-month data directly would not have required conversion. The committee was aware of the uncertainties around modelling of health-state transitions but was also aware it had little impact on the cost-effectiveness.

Consultee	Comment	Response
	therapy (i.e., with BSC), it would not be realistic to model health-state improvement. Clinical experts from the NAC validated our extrapolation method for BSC, noting that it was supported by natural history data (see CS Table D11, p 154). We used 6-month cycles because this is the natural time period over which changes in a hATTR amyloidosis patient's course are recorded by doctors, as we were told by clinical experts from the NAC whom we consulted during model development. Prof. Hawkins' clinical expert statement for the HST evaluation confirmed, "In the UK, patients are assessed and followed-up 6 monthly at the NHS National Amyloidosis Centre …" Therefore, our use of 6-month cycles was consistent with the expert recommendation for state-transition modelling that cycle length should be short enough to represent the frequency of clinical events and interventions [Siebert et al., 2012]. The conversion from 18 months to 6 months is a challenging mathematical problem, as recognized by the ERG. In our response to the ERG (Priority Question B13), we explained that the alternate method they suggested for converting to 6-month cycles was not feasible in our case. As noted in the ECD, the ERG characterised the bias introduced by our approach as "small" and in favour of BSC—in other words, the ERG acknowledged that we took a conservative approach. It is therefore unreasonable for the ECD to use this point as justification for its recommendation. We disagree that it would have been informative to use a 9-month time point instead, since this was not a pre-specified final endpoint assessment and would thus have been less reliable. As we explained in our response to the ERG (Priority Question B11), APOLLO was designed so that all primary, secondary, and exploratory endpoints were evaluated as differences between baseline and 18 months in the patisiran and placebo groups. Using the 18-month data (i.e., the latest time point in the study) provides the clearest idea of treatment separation over time, thus allowing us to more accurately extrapolate the treatment benefits of patisiran relative to BSC than if we had used 9-month data. Taking all of these points into consideration, it is not justifiable to conclude that our method of modelling of health-state transitions introduced uncertainty into the model.	Please see section 4.14 of the FED.
Alnylam	**4.15 Health-state utilities** ***ECD:*** *The company capped the utility values so that they could not exceed a maximum (patisiran) or fall below a minimum (BSC) in each health state. It applied a further cap to ensure that the utilities for*	Thank you for your comment. The evaluation committee reviewed the changes provided by the

Consultee	Comment	Response
	each health state did not exceed those for the general population in England (using data from Kind et al., 1999). The ERG considered the regression to be unreliable because it: • *excluded important parameters (such as cardiac involvement)* • *included the interaction of time by treatment without the main terms (that is, time and treatment)* **Response:** We revised the regression analysis to include the parameters the ERG requested, including the time and treatment interaction terms, and submitted the results as part of our responses to the ERG. The ECD appears to ignore this. For full details of these revisions, we encourage the Committee to review these responses. Notably, the addition of these parameters decreased the ICER relative to our own base case; in other words, our original approach was more conservative than the ERG's approach which favours patisiran. Here again, it is unreasonable for the ECD to base its recommendation on this. ***ECD:*** *chose the minimum and maximum caps arbitrarily, which would not have been needed if the model had been correctly specified.* **Response:** We request that the Evaluation Committee not consider the ERG's characterisation of our selection of utility caps in its decision-making, because we did not choose our maximum and minimum caps arbitrarily—instead, the selection of caps was driven by the evidence. We defined our caps on the basis of the 25th and 75th percentiles of observed EQ-5D utility data from APOLLO, stratified by treatment arm and PND score (CS, pp 129–130). The purpose for this was to avoid ceiling effects by imposing the constraint that in the long term the utilities can never cross the limits of values measured in at least half of patients in each stratum over the available 18 months of observed data. Furthermore, we consulted clinical experts from the NAC about our selection of utility caps, and they supported our approach (CS Table D11, p 155). Consequently, the ECD conclusion on this point is incorrect. ***ECD:*** *… the ERG explained that, without the minimum and maximum caps, the utilities reached unrealistic values. For example, over time, patients with PND II in the patisiran arm were assumed to have the same utility as patients with PND 0 (that is, no symptoms).* **Response:** We strongly disagree that our regression analysis (as correctly specified) generates unrealistic values. The cited objection is that PND II patients could theoretically achieve the same utility as PND 0 patients over time, which the ERG discounted as being unrealistic. This point has	company for the 3rd evaluation committee meeting (May 2019) and accepted the revised model. The regression model included treatment group, time, PND score, NT-ProBNP, treatment-by-time interaction term. Please see section 4.15 of the FED. Thank you for your comment. The committee acknowledged comments from the company, but on balance it concluded that the use of 25th and 75th percentiles of observed EQ-5D to define minimum and maximum caps was arbitrary. Thank you for your comment. The evaluation committee has taken into account all factors that may affect its decision. It

Consultee	Comment	Response
	little practical relevance to the model results since only a very small percentage of patients accrue time in PND 0 in the model. This is evident with reference to Table 23 in our response to the ERG comments, which shows that the vast majority of patients are in PND I–IV. While it was necessary for the sake of realism to reflect the potential improvement of some patients to PND 0 (since this was observed for a number of patients in the patisiran arm of APOLLO), this applies to so few patients that it has negligible impact on the model results. Given the health-state distribution at model entry, most improvement in PND Score will be to PND I or II. Therefore, this comment in the ECD does not support the overall negative recommendation. It is important to recognise that, as seen in other more common systemic amyloidoses—like AL amyloidosis—it *is* possible for a diseased patient with hATTR amyloidosis to reach essentially perfect health. This point was specifically raised and discussed by Prof. Hawkins from the NAC during the Committee meeting in November. The ECD states, "The clinical experts explained that, based on response to chemotherapy in light chain amyloidosis (the most common form of systemic amyloidosis), they expected only around half of people remaining on treatment to return to what might be considered near-full heath. This is because the condition is often diagnosed at an advanced stage from which it may not be possible to return to PND 0 or FAP 0." However, while polyneuropathy and autonomic neuropathy are correlated in this disease, returning to PND 0 or FAP 0 may not be necessary to achieve comparable utility, because clinical experts from the NAC told us that (a) autonomic symptoms may progress at a different rate than PND score (a functional scale), and (b) they believe HRQoL is driven mainly by autonomic symptoms (diarrhoea, constipation, wasting) (CS Table D11, p 155). Therefore, the ECD comment implying that our model generated unrealistic utilities is misplaced because it incorrectly assumes that PND alone is driving HRQoL and hence utilities. We note that our approach is consistent with those taken for other serious progressive diseases. For example, the possibility of overlapping utility values in patients with different PND Scores can be compared with utility valuations for the Expanded Disability Status Scale (EDSS) in models for multiple sclerosis (MS). In their NICE submission for the MS therapy Ocrevus® (ocrelizumab), Roche included utilities derived from a UK survey by Orme et al. (2007) [NICE, 2018a]. As shown in Figure 1, this survey found considerable overlap in the 95% confidence intervals (CIs) of utilities for different EDSS scores [Orme et al., 2007]. Overlapping 95% CIs were seen even for EDSS scores with such radically different levels of disability as EDSS 3 (*Moderate disability in one functional system [FS], or mild disability in three or four FS. No impairment to walking* [Multiple Sclerosis Trust, 2018]) and EDSS 6.5 (*Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without*	acknowledged comments from the company, but on balance agreed that it was unlikely that someone with no symptoms would have the same utility as someone with PND II. However, the FED has been modified to reflect that only a few patients have been affected. Please see section 4.15 of the FED. The committee also acknowledged that in response to consultation the company provided a new scenario analysis in which the minimum and maximum caps were removed and any improvement in quality of life within a given PND stage was limited by time. The committee considered the updated scenario analysis in its preferred base-case. Please see section 4.15 of the FED.

Consultee	Comment	Response
	resting [Multiple Sclerosis Trust, 2018]). This means that we would expect to often find an MS patient with severe walking impairment equivalent to a hATTR amyloidosis patient in PND IIIb who had a higher utility than an MS patient with unimpaired walking ability, equivalent to a hATTR patient in PND 0 or I. The observed variability in utility within an EDSS score also implies that a given patient could change their utility without changing EDSS score.  Figure 1. Utilities derived from EQ-5D by EDSS in a UK survey of patients with multiple sclerosis. EDSS: Expanded Disability Status Scale; EQ-5D: EuroQoL 5 dimensions. Note: Error bars show 95% confidence intervals. Source: [Orme et al., 2007] In rendering a positive recommendation to the Ocrevus submission, the NICE Evaluation Committee accepted the structure of the Roche economic model and concluded that it was appropriate for decision-making [NICE, 2018b]. We believe that it would be inconsistent with past NICE decisions for the Committee to disallow the way we modelled utility (in terms of how utilities behave within and across PND Scores in our model) when our method is comparable to how utility values behave in the MS model accepted by NICE. We also disagree on principle with the interpretation that the need for utility caps means that our model was incorrectly specified or lacks face validity. In the absence of directly measured long-term utility values—a challenge often faced when modelling innovative therapies for rare diseases that are	Thank you for your comment. During consultation the company submitted a revised base-case that relied on a regression model. The committee accepted the company's updated modelling approach. Please see section 4.15 of the FED. Thank you for your comment. The comment about lack of

Consultee	Comment	Response
	new to market—it is logical to model utilities based on the best-fit function to the observed data over the period for which utility measurements are available, then to explicitly prevent clinically implausible values over the long term by setting reasonable caps grounded in actual data. This is the approach we took, with input from clinical experts at the NAC, and given the acknowledged limitations in the currently available data, we continue to believe it to be valid. ***ECD:*** *The committee noted that a utility could vary within the same health state depending on treatment group. The company explained that this was because PND score does not reflect all aspects of the condition; people may be in the same PND state but have improved autonomic symptoms if they are taking patisiran. The committee considered that this was at odds with what it had heard from clinical experts about improvements in polyneuropathy and autonomic symptoms being correlated (see section 4.7).* **Response:** As noted above, we acknowledge that polyneuropathy and autonomic symptoms are correlated in hATTR amyloidosis. However, correlation does not imply 1-to-1 correspondence, or mean that PND Score alone captures all aspects of change in autonomic symptoms that impact patients' HRQoL and hence utilities. On the contrary, it is entirely possible for a person's autonomic symptoms and thus HRQoL to change without a change in PND score. For example, a patient's diarrhoea may improve within a certain timeframe, thereby improving their HRQoL, even if they are not able to stop using a walking stick during the same period and therefore remain in the same PND state. Furthermore, given that PND Score (or, for that matter, a FAP Stage) is not a single unique point, but rather a broad category defined on the basis of patient ability to walk, a patient could experience improvement or worsening of polyneuropathy symptoms—and thus HRQoL—without changing PND Score. We specifically posed the question of whether it was reasonable to model utility changes within a PND Score to clinical experts from the NAC during model validation as part of our original CS. We checked again that this was a valid approach in a meeting with Professors Philip Hawkins, Mary M. Reilly and Julian Gillmore from the NAC on December 19, 2018, and they stated that they continue to agree with our position. To assess whether or not utility could improve without an improvement in PND Score, we performed a post hoc mixed-model repeated measures analysis on EQ-5D utility scores (UK valuation) from APOLLO for the subset of patients who remained in the same PND Score from baseline to 18 months. As shown in **Error! Reference source not found.**, whereas HRQoL worsened in placebo patients who did not change PND Score, utilities steadily improved in patients taking patisiran who remained in the same PND score. Furthermore, neither of these curves was approaching a plateau	face validity has been removed from the FED. Thank you for your comment. The committee accepted the company's updated analysis provided after consultation. Please see section 4.15 of the FED.

Consultee	Comment	Response
	by trial end, which supports our decision to include a time-dependent utility effect in the regression. These real data provide robust evidence to support change in utility over time within a PND health state and between treatment arms, demonstrating that the clinical experts from the NAC were correct in their validation of our approach, and conclusively refuting the criticism in the ECD of this aspect of our model.    We also wish to highlight that the patient expert statements reviewed by the Committee identified factors other than mobility status as the major drivers of HRQoL impairment in this disease, particularly autonomic symptoms. In fact, the main basis for the ERG's challenge of our use of PND Score to define health states is that the PND scoring system does not capture all autonomic symptoms. We are confident that the Committee will agree that it is not reasonable to, on the one hand, criticise our model for not explicitly defining health states on the basis of dimensions other than polyneuropathy disability, then on the other hand disallow our attempt to accomplish this by modelling utility variations within PND Scores (especially considering that the ERG did not find an alternative method acceptable to the Committee).	Thank you for your comment. After consultation the company provided new evidence. In its revised base case included an additional assumption because it stated that the model underestimated the benefit of patisiran on such a determinative feature of the condition as autonomic neuropathy captured by GI dysfunction. Therefore, the company included

Consultee	Comment	Response
	To test whether or not autonomic symptoms could improve without an improvement in PND Score, we analysed COMPASS-31 scores from APOLLO for the subset of patients who remained in the same PND Score from baseline to 18 months. COMPASS-31 is a measure of patient-reported autonomic symptoms, covering six domains: Orthostatic intolerance, Vasomotor, Secretomotor, Gastrointestinal, Bladder, and Pupillomotor. As shown in **Error! Reference source not found.**, whereas COMPASS-31 scores worsened (increased) in placebo patients who did not change PND Score, autonomic symptoms steadily improved (decreased) in patients taking patisiran who remained in the same PND score. This graph conclusively demonstrates that patients in the same PND Score do indeed experience ongoing improvement in autonomic symptoms over time if they are taking patisiran.    Given the importance of autonomic symptoms to HRQoL as highlighted by the NAC experts, **Error! Reference source not found.** also supplies a mechanistic explanation of why we observe that	further GI-related disutilities in the model. The evaluation committee considered evidence submitted by the company, the views of people, clinical experts and a review by the ERG and acknowledged the importance of capturing GI dysfunction in the model. Please see section 4.17 of the FED.

Consultee	Comment	Response
	utilities do in fact vary within the same PND Score (as seen in **Error! Reference source not found.**), and also why it is entirely plausible that patients with different PND Score could have the same utility. However, we would also like to point out that utility scores in the model are not fully independent of PND Score but instead are based on EQ-5D data gathered in APOLLO and stratified by PND Score. Thus, the influence of polyneuropathy on utilities is explicitly included in the model, with inclusion of an additional factor (i.e., time-varying change in utility score) to reflect the fact that EQ-5D-based utility scores are observed to change within a given PND Score. Therefore, there is no justification for the Committee's conclusion that the way we modelled utility was unreliable and highly uncertain; on the contrary, it is grounded in observed data and consistent with clinical expert opinion and patient testimony. The ECD conclusions on this point are unreasonable in our view. ***ECD:*** *It questioned the reliability of the method to generate the utilities and considered that it was unlikely that someone with no symptoms would have the same utility as someone with PND II.* **Response:** Above we have addressed the criticisms regarding the reliability of our method for generating utilities. Here we wish to reiterate that very few patients will improve to PND 0, and so, as explained above, the apparent issue relating to utilities in PND 0 has no meaningful impact on the model results. We should also emphasise that just because a patient in PND 0 may have no polyneuropathy impairment does not mean that they are disease-free or have no symptoms of any kind. As in the FAP staging system, patients with stage 0 disease already have evidence of amyloid deposits [Ando et al., 2013], so it is plausible that some level of impairment and thus impact on utility could already be detected. Consequently, this comment in the ECD lacks validity and does not support the overall negative recommendation for patisiran. ***ECD:*** *The ERG provided a scenario analysis in which the utility values did not change over time, effectively meaning that they were the same for each health state regardless of treatment.* **Response:** This scenario analysis from the ERG should not be considered by the Committee, because there should be no disagreement that utility values and HRQoL can change over time in the 18-month study period—this is empirically true, as was observed in the overall APOLLO trial population (i.e., modified intent-to-treat), consistent with the results for the subgroup of patients with no change in PND Score from baseline shown in **Error! Reference source not found.** and **Error! Reference source not found.**. Taking into account all of the evidence presented above, it is clearly	Thank you for your comment. The committee considered that it was unlikely that someone with no symptoms would have the same utility as someone with PND II. However, the FED has been modified to reflect that only a few patients have been affected. Please see section 4.15 of the FED. Thank you for your comment. The committee accepted the company's updated analysis provided after consultation. Please

Consultee	Comment	Response
	unrealistic to model a scenario in which utility values are static within each model health state. Furthermore, we specifically discussed this question with the clinical experts from the NAC at our meeting on December 19, 2018, and they continue to support our position. To further illustrate that (a) HRQoL changes over time within a PND Score, (b) HRQoL is consistently better in patients receiving patisiran than in those receiving placebo, and (c) the HRQoL difference between the two treatment arms continues to diverge over time, we analysed results from APOLLO on the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire for the subset of patients who remained in the same PND Score from baseline to 18 months. Change from baseline on the Norfolk QoL-DN was the highest-ranked secondary endpoint in the protocol-specified hierarchical order for statistical testing in APOLLO [Adams et al., 2018]. The Norfolk QoL-DN is a validated measure of HRQoL for hATTR amyloidosis, which captures patients' assessments of neuropathy symptoms as they relate to five HRQoL domains: physical functioning/large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy [Vinik et al., 2014]. **Error! Reference source not found.** shows that HRQoL improves in patients on patisiran and worsens in those taking placebo even within a given PND Score. 	see section 4.15 of the FED. The ERG scenario in which the utility values did not change over time is not discussed in the FED.

Consultee	Comment	Response
	[redacted] It is crucial to understand that a given PND Score (or, for that matter, a FAP Stage) is not a single unique point, but rather a broad category defined on the basis of patient ability to walk. Therefore, staying in a PND Score does not mean that the disease is stable—not only could autonomic symptoms change, but even the severity of polyneuropathy symptoms could change within a PND Score before having a large enough impact on functioning to require reclassification to the next higher or lower PND Score. We raised this question with clinical experts from the NAC during model development and again at our December meeting with Profs. Hawkins, Reilly and Gillmore, and these experts consistently supported our approach. The fact that disability can change without necessarily triggering a change in PND Score can also be seen by looking at the R-ODS scores from APOLLO for the subset of patients who remained in the same PND Score from baseline to 18 months (**Error! Reference source not found.**). R-ODS measures overall disability in terms of activity and social participation limitation [Regnault et al., 2017]. The graph shows that R-ODS was stable in the patisiran arm, which is not unexpected since both PND Score and R-ODS assess disability, and by definition this is the subgroup of patients without change in PND Score. What is striking in **Error! Reference source not found.**, however, is that R-ODS declined steadily in the placebo arm, indicating worsening disability, *even though this is a subgroup of patients who remained in the same PND Score from baseline*. This confirms that HRQoL—even HRQoL linked specifically to disability—can vary without being detectable by a change in PND Score. [redacted]	

Consultee	Comment	Response
	[redacted] Given the continuing separation of the utilities and other HRQoL measures between the patisiran and placebo arms shown in **Error! Reference source not found.** to **Error! Reference source not found.**, with patients on patisiran always faring better over time than patients on placebo, it is clearly reasonable to extrapolate these observed effects into the post-trial period (i.e., after 18 months) using regression analysis as we have done. ***ECD:*** *[The ERG] used a study by Stewart et al. (2017), which reported utilities according to FAP stage (for Val30Met mutations and 'other mutations' categories) valued using Brazilian tariffs. However, the committee was concerned that the Brazilian tariffs were very different from UK-specific tariffs, so reflected different cultural views and societal preferences.* **Response:** We agree with the Committee that the ERG's scenario using the Brazilian tariff data is not valid to consider in the context of this HST submission. Not only are the cultural views and societal preferences from the Brazilian study not representative of the UK, but also the distribution of TTR mutations (mostly V30M) and preferences of the patients are likely to be different and thus not relevant to the UK. ***ECD:*** *the company included a disutility for carers of 0.01 for patients with PND IV. The committee questioned whether this adequately reflected the carer burden reported in the Amyloidosis Research Consortium UK survey (see section 4.2).* **Response:** We acknowledge there may be underestimation of the burden experienced by caregivers, but more fully incorporating these effects may decrease the ICER for patisiran relative to BSC. Thus, our approach was likely conservative. We have addressed this concern in the revised analysis described on page **Error! Bookmark not defined.**, which did indeed yield more favourable	Comment noted. Thank you for your comment. In its revised base case, the company assumed 1 full-time caregiver in FAP stages 1 and 2, and 2 full-time caregivers in FAP stage 3 reflecting the additional care needs of people with more advanced disease. This was in line with

Consultee	Comment	Response
	results (i.e., a lower ICER) for patisiran. ***ECD:*** *The committee considered that the way the company had modelled utility was highly uncertain, and that the alternative source suggested by the ERG was equally flawed. It concluded that an alternative modelling approach may have resulted in utility values with greater face validity.* **Response:** We agree with the Committee that the ERG's approach to utilities was flawed, but trust that we have demonstrated in the preceding responses that our method is reasonable, as it reflects: • Actual utility data from APOLLO • The clinical reality that HRQoL changes within a given PND Score over time, as supported by a range of different measures • The continuing divergence of utilities and other HRQoL measures between the patisiran and placebo arms over the entire course of the APOLLO trial, representing ongoing improvement in patients taking patisiran and worsening in patients on placebo • Lower and upper limit values applied after regression analysis in the model in order to ensure that the benefits in each treatment arm will not become unreasonably low or high over time Importantly, all of these aspects of our methodology were validated with clinical experts from the NAC during model development for the CS. We discussed specific objections from the ECD during our December meeting with Profs. Hawkins, Reilly and Gillmore, and they supported our position. Furthermore, as explained above, our approach to utilities is consistent with the Roche Ocrevus submission, which NICE accepted. Taking all of these points into account, it is evidently not justifiable to render a negative decision on patisiran based on criticisms of our approach to utilities. It also does not appear to be reasonable to hypothesise that an alternative approach may have provided greater face validity without specifying what said approach would entail, especially since even the ERG was unable to offer a more satisfactory alternative. Therefore, we urge the Committee to revisit their conclusions about our approach to utilities and take these arguments into account in a re-evaluation of patisiran.	what the committee had accepted in NICE's highly specialised technology guidance on inotersen. The committee concluded it was satisfied with the company's updated model incorporation of revised caregiver disutilities. Please see section 4.20 of the FED. Comment noted.
Alnylam	**4.16 Mortality** ***ECD:*** *The ERG questioned the relevance of the Suhr study because the population was not clearly defined and there was uncertainty about the survival analysis. … The committee recognised the complexities of the company's approach and its limitations but concluded that this approach was*	Thank you for your comment. After consultation, the company implemented a new approach by modelling the effects of

Consultee	Comment	Response
	acceptable because of the lack of other evidence. **Response:** We agree with the ERG that uncertainty is introduced by use of the Suhr study [Suhr et al., 1994]. This is the only paper available in the literature that describes the relationship between the polyneuropathy in this disease and mortality, and the clinical experts from the NAC we consulted on model methodology considered this appropriate in the absence of other sources. They also agreed that in spite that in the UK the mortality is mainly due to cardiac symptoms, it is appropriate to include mortality associated to PND Score in the model even with the significant limitations of the Suhr data (see CS Table D11, p 154). The introduction of the Suhr data may overestimate the mortality associated to PND Scores in the UK and thus underestimate the cost-effectiveness of patisiran, meaning that the ICER is likely to be lower than the result of the base-case model in the CS. Profs. Hawkins, Reilly and Gillmore confirmed this hypothesis at a December 2018 meeting at the NAC. To address the ERG's concerns, we removed all mortality due to polyneuropathy (i.e., not using the data from Suhr et al. [1994]). As reported on page **Error! Bookmark not defined.** below, implementing this change yields a significant reduction in the ICER compared with the result of the base-case model in the CS. A multivariate analysis using data from APOLLO to model the effect of different degrees of polyneuropathy on survival was planned, but was not conducted due to the low number of deaths in APOLLO. In the absence of other data sources at the time of submission, it was not possible to model the effects (or even thresholds) of polyneuropathy or autonomic function on survival. Since in APOLLO patisiran had uniformly positive impacts on autonomic symptoms and wasting, which we did not model as survival gains in the model for the reasons stated above, our method clearly underestimated the cost-effectiveness of patisiran. It is unreasonable for the ECD to justify its conclusions based on this point.	treatment with patisiran and BSC on mortality using NT proBNP alone. The evaluation committee has considered all factors that affect its decision. It understood that in an exploratory analysis, the ERG showed the effect of using PND-related hazard ratios only. This was in line with what was accepted in NICE's highly specialised technology guidance on inotersen. The committee considered the advantages and disadvantages with each source of mortality data. It also recognised the uncertainties around the values but concluded that the use of PND-related mortality only, although not optimal, was acceptable for decision making. Please see sections 4.21 – 4.23 of the FED.

Consultee	Comment	Response
Alnylam	**4.17 Resource use** ***ECD:*** *The company used a Delphi approach to elicit experts' beliefs about resource use, in particular for cardiomyopathy-related costs. The ERG was concerned that the method is unlikely to have reflected the true expected cost and uncertainty. Moreover, the company included the costs of adverse events by assuming a constant rate of events (based on APOLLO) as well as a reduction over time (based on treatment discontinuation function; see section 4.13). The ERG considered that this was illogical because it meant that all patients would stop patisiran at the end of the time horizon and, at the same time, develop adverse events. Additionally, the committee was aware that the company proposed a homecare service for patients and noted that the costs for this were not included in its model. The committee concluded that there were some uncertainties in the company's resource use assumptions, and that it would take this into account in its decision making.* **Response:** We acknowledge there were limitations in our ability to define resource use, but wish to emphasise that the information we incorporated in the model was derived from asking some of the world's leading experts in the management of hATTR amyloidosis, who are thus uniquely well placed to advise on resource use in this condition. We presented multiple scenarios in addressing healthcare resource utilization in our responses to the ERG clarification questions and none of them has a meaningful impact on the ICER presented in the base-case model in the CS. In our view, it is therefore unreasonable for the ECD to justify its conclusion based on this point.	Comment noted. The committee was aware of the limitations of the resource use assumptions and took them into account into their decision-making. This means that it contributed to their recommendation but was not the sole factor driving their recommendation. The committee was also aware it had little impact on the cost-effectiveness.
Alnylam	**4.18 Discount rate** ***ECD:*** *The committee therefore concluded that patisiran does not meet the criteria for applying a discount rate of 1.5%. It concluded that a discount rate of 3.5% should be applied for both costs and health effects.* **Response:** Although we disagree that applying the same discount rate to costs and health effect because it discriminates against diseases affecting middle age and elderly patients, we have revised our final proposed model accordingly.	Comment noted.
Alnylam	**4.19 Other assumptions** ***ECD:*** *The ERG highlighted several additional assumptions and parameters that were uncertain and that it had addressed in its preferred analysis. In particular, in the company's analysis:*	Thank you for your comment. Section 4.19 of the ECD has been removed from the FED.

Consultee	Comment	Response
	• *the administration and premedication costs had not been adjusted by treatment compliance* • *one-off costs associated with progression of polyneuropathy had been double-counted* • *patisiran cost-savings had been double-counted by applying a treatment discontinuation function as well as a compliance rate. The ERG also recalculated the starting health-state distribution in the model according to the baseline data for PND and NT-proBNP in APOLLO. The committee considered the ERG's assumptions to be appropriate.* **Response:** We previously addressed these concerns in our response to the ERG comments. As confirmed by the ERG, implementing these changes did not substantially alter the ICERs: • Base-case: [redacted] • Correction of double-counting of one-off costs: [redacted] • Correction of double-counting of patisiran cost savings: [redacted]	Company provided a new model with new assumptions.
Alnylam	**4.21 Cost-effectiveness results** ***ECD:*** *The committee reiterated its views on the unreliability of the utility estimates and considered an ERG's exploratory scenario in which the change of utility over time was removed (see section 4.15). This scenario led to a substantial increase in the ICER compared with the ERG's preferred analysis ICER. The committee concluded that the most plausible ICER was likely to lie between the ERG's preferred analysis and the scenario in which the change in utility over time was removed. Both ICERs were substantially higher than the range that can be considered an effective use of NHS resources for highly specialised technologies.* **Response:** We categorically disagree with this conclusion, as it is based on a scenario that (a) is refuted by observed data from APOLLO, (b) conflicts with NAC clinical expert opinion, and (c) contradicts other arguments made by the Committee in the ECD. Regarding point (c), in Section 4.15 of the ECD the Evaluation Committee judged the ERG's approach to utilities to be flawed, and thus it is not reasonable to consider the ERG's exploratory scenario in which the change of utility over time within a given PND Score was removed. This scenario is clinically implausible because it implies that PND Score alone is able to capture all relevant aspects of hATTR amyloidosis patients' HRQoL, and thus that utilities would not change over time within a given PND Score. As shown in **Error! Reference source not found.**, this implication is demonstrably incorrect, refuted by data from the largest trial ever performed in this disease state. This scenario is also incompatible with expert clinical opinion from Profs. Hawkins, Reilly, and Gillmore, who are among the world's leading experts in this disease. It would also be inconsistent to criticise our use of PND Score to define health states	Thank you for your comment. The paragraph has been removed from the FED. See new cost-effectiveness paragraph in section 4.26 of the FED.

Consultee	Comment	Response
	because this system does not capture all aspects of the disease (including autonomic dysfunction), but then penalise us for attempting to address this issue by capturing the broad spectrum of symptoms via changing utilities within a given PND Score. We therefore urge that the Committee not consider this exploratory scenario among the possible range of ICER values. Doing so would conflict with observed clinical evidence and expert clinical opinion, and would therefore be unreasonable in our view.	
	4.22 Application of QALY weighting ***ECD:*** *[The Committee] understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with patisiran, and highlighted that these were below 10 (8.30) in the company's base case, the ERG's preferred analysis (6.85) and the ERG's exploratory analysis in which utility was constant over time (3.97). The committee concluded that there was no evidence to suggest that patisiran would meet the criteria for applying a QALY weight.* **Response:** The potential QALY gain for any therapy for hATTR amyloidosis is inherently limited by the fact that this disease predominantly strikes the elderly. The median age at symptom onset for hATTR amyloidosis patients in the UK with the underlying Thr60Ala mutation is 63 years (range: 45–78 years) [Sattianayagam et al., 2012]; with the Val122Ile mutation is 77 years (range: 47–92 years); and generally for non-Val122Ile mutations is 66 years (range: 41–82) years [Gillmore et al., 2017]. To use the same criteria for QALY gains in hATTR amyloidosis as for diseases of younger patients would discriminate against the elderly. As previously noted, the ERG's exploratory analysis in which utility was constant over time is based on a faulty assumption, disproved by actual data from APOLLO, so the calculated QALY gain of 3.97 should be disregarded. Therefore, the remaining QALY-gain estimates are quite close (8.30) to the threshold of 10 for applying QALY weighting. Moreover, as explained throughout this response, many aspects of the modelling approach we adopted were conservative (i.e., to the disadvantage of patisiran). In addition, much of the clinical benefit observed in the APOLLO trial cannot easily be modelled, especially with regard to the benefit of patisiran on the main determinant of HRQoL in this disease, namely autonomic functioning. Such limitations are common to cost-effectiveness analyses for specialised medicines for very rare diseases. In the case of patisiran, the QALY-gain estimates calculated in our base-case analysis and the ERG's analysis are not only close to the threshold for weighting, but they are also undoubtedly conservative. Therefore, it is probable that the 'true' QALY value meets or exceeds the threshold for weighting. Given the equity issue regarding the elderly patient population, we urge reappraisal of the	Thank you for your comment. The mean age of people in APOLLO (60.5 years) indicates that the majority of people were not elderly therefore the majority would have the potential accrue more than 10 QALYs with highly effective treatments. The threshold and the weighting could only be preferentially biased for populations that were not able to attain those QALYs because of their age. Please, see sections 52-54 in the Interim Process and Methods of the Highly Specialised Technologies Programme Patisiran was recommended, within

Consultee	Comment	Response
	eligibility of patisiran for QALY weighting	its marketing authorisation, as an option for treating hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy.
Alnylam	**4.25 Other factors** ***ECD:*** *The committee noted the potential equality issue raised by clinical experts and the company, and recognised that specific mutations were more common in some ethnic groups in the UK. It also considered whether the age of onset of the condition raised particular issues of equality. The committee concluded that its recommendations apply equally regardless of age or ethnicity, so a difference in disease prevalence in different age and ethnic groups does not in itself represent an equality issue.* **Response:** Although the recommendations do not differ by age, the application of the same threshold for QALY weighting for hATTR amyloidosis as for other conditions does raise equity issues, as described in our previous response, because it gives preference to therapies for younger patients. In addition, while the recommendations of the Committee would apply without regard to ethnicity, the higher prevalence of specific hATTR amyloidosis-associated mutations in some historically disadvantaged groups (e.g., Afro-Caribbean and Irish) could raise equality concerns relating to disproportionate harm on these communities if access to patisiran is not provided, when considered alongside other therapies for orphan indications that have been recommended by NICE.	Thank you for your comment. The mean age of people in APOLLO (60.5 years) indicates that the majority of people were not elderly therefore the majority would have the potential accrue more than 10 QALYs with highly effective treatments. The QALY weighting aims to recognise the additional value of technologies that provide a very large magnitude of health gain. Long enough to accrue more than 10 QALYs. Please see sections 52-54 in the Interim Process and Methods of the Highly Specialised Technologies Programme.

Consultee	Comment	Response
Alnylam	**4.27 Managed access** ***ECD:*** *the committee considered that the company's model, defined by a combination of the severity of polyneuropathy (PND score) and cardiomyopathy (NT-proBNP), did not adequately capture all aspects of the condition (including autonomic symptoms) that the clinical and patient experts considered to be a major part of hATTR amyloidosis. The committee explained that this had led to an inaccurate reflection of the true expected cost effectiveness (see section 4.12).* **Response:** Our model explicitly included a measure of polyneuropathy (PND Score) and cardiomyopathy (NT-ProBNP). As no single measure exists to capture autonomic dysfunction, it was not feasible to explicitly model this. However, we did capture the impact of autonomic dysfunction on HRQoL by use of EQ-5D-based utility scores directly collected in APOLLO. As previously explained, all of the HRQoL measures in the trial showed divergence over time between the patisiran and placebo arms. Thus, while we recognise (as confirmed by clinical experts from the NAC) that autonomic dysfunction has an impact on mortality, by not including this mortality source in our modelling of survival benefits we are actually underestimating the benefits and cost-effectiveness of patisiran. Consequently, this ECD criticism does not substantiate the overall negative recommendation. ***ECD:*** *It therefore noted that further data collection, as proposed in a managed access arrangement, would not be a possible route to resolving the key uncertainties associated with patisiran because it would not address the uncertainties in the economic model.* **Response:** We strongly disagree with this conclusion. In criticising our method for modelling health-state transitions (ECD Section 4.14), the Committee highlighted that uncertainty applied "especially for the extrapolated period for which no long-term data exists". This statement is incompatible with the suggestion that long-term data would be unhelpful to addressing uncertainties in the model. On the contrary, additional data, especially long-term data, are going to be extremely important in defining the true value of patisiran. We note that in his expert statement to the Committee, Prof. Hawkins reported, "The experience of my colleagues at the NAC treating patients through compassionate access (over one year) and Early Access to Medicine Schemes has been extremely favourable. Remarkable clinically significant improvements of well-being and function have occurred in a majority of cases, including regaining	Thank you for your comment. The committee was able to recommend patisiran as an option for treating hATTR amyloidosis as a cost-effective use of NHS resources. Managed access section has been deleted from the FED.

Consultee	Comment	Response
	the ability to walk unaided." This statement makes clear that long-term data gathered in clinical practice are going to be crucial in resolving remaining uncertainties associated with patisiran, providing yet another incentive to expand patient access to this therapy. The outright rejection of any value from any additional evidence or long-term data, especially from the EAMS program, directly conflicts with current clinical experience and is unreasonable. We urge the Committee to reconsider.	
Alnylam	**4.28 Conclusion** ***ECD:*** *[The Committee] noted that the clinical evidence suggested that patisiran provides considerable clinical benefits. However, it considered that these clinical benefits were not appropriately represented in the economic model because the model structure was based on a combination of polyneuropathy and cardiomyopathy, and did not capture autonomic symptoms. In addition, the company's approach to modelling utility was highly uncertain and the resulting utility values lacked face validity. The committee considered that the most plausible ICER lies between the ERG's preferred analysis and the exploratory scenario in which utilities did not change over time. Both of these ICERs were above the range that can be considered an appropriate use of NHS resources for highly specialised technologies. It also noted that patisiran did not meet the criteria for QALY weighting to be applied, and that there remained important uncertainties within the economic model. The committee therefore did not recommend patisiran as an option for treating hATTR amyloidosis.* **Response:** Given the clarifications provided above regarding the appropriateness of our approach to modelling utility, we feel justified in requesting a reconsideration of the validity of our approach, and respectfully request a reappraisal of this decision. In support of this request, we reconstructed the ERG's preferred model and also implemented additional changes recommended by the ERG in order to arrive at a new base case.	Thank you for your comment. Previous conclusion has been deleted from the FED as the committee realised a different conclusion after the 3rd evaluation committee meeting (May 2019). It concluded that some assumptions in the economic modelling are uncertain, particularly around the utility values and the modelling of mortality. Also, the range of cost-effectiveness estimates presented is somewhat higher than what NICE usually considers a cost-effective use of NHS resources. However, taking additional factors into account, such as uncaptured health-related benefits, the rarity and severity of

Consultee	Comment	Response
		the condition, the potential lifetime benefit for people with the condition and the innovative nature of the treatment, patisiran is recommended for use in the NHS. Please see sections 4.26-4.36 of the FED.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical expert 1 (endorsed by Royal College of Pathologist [RCP])	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 patisiran reduces disability and increases quality of life. It may provide long-term benefits but evidence for this lacking. It also concludes that there are uncertainties in the economic modelling as although the important aspects of the condition are captured, not all more subjective symptoms are covered. The cost effectiveness estimates are much higher than what NICE considers acceptable for highly specialised technologies. Patisiran is innovative but does not appear to provide value for money and therefore is not recommended for routine funding in the NHS.	Comment noted.
Clinical expert 1 (endorsed by RCP)	**Has all of the relevant evidence been taken into account?** The committee discussed and took into account relevant evidence with respect to patisiran, namely APOLLO comparing patisiran with placebo, a single arm phase 2 open label extension (OLE) study and the ongoing global OLE study. These studies are relevant to a UK population. The clinical effectiveness of patisiran is demonstrated in the APOLLO study. Long term data are being accumulated in the OLE study.	Comment noted.

Nominating organisation	Comment	Response
Clinical expert 1 (endorsed by RCP)	**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 87.8% was seen with Patisiran. 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, patisiran was associated with an ICER above £100,000 per QALY gained (which NICE considers acceptable).	Comment noted.
Clinical expert 1 (endorsed by RCP)	**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.	Comment noted.

Nominating organisation	Comment	Response
Clinical expert 2	**1) Potential for efficacy of patisiran in the longer term:** My expectation is that patisiran treatment, through substantially reducing the supply of the ATTR amyloid precursor protein (i.e. plasma TTR) by more than 80%, will lead to sustained benefit and likely further improvement in the function of organs and tissues affected by ATTR. This expectation is based on: 1. Experience in the National Amyloidosis Centre of thousands of patients with other types of amyloidosis, most notably more than 5000 patients with AL amyloidosis in whom amyloid precursor protein (light chain) knock-down through chemotherapy has been associated with hugely improved long term survival, ongoing gradual regression of amyloid, and ongoing gradual improvement in amyloidotic organ function. The rationale / plausibility for sustained benefit of patisiran in ATTR amyloidosis is completely analogous with knock-down treatments of all other types of amyloidosis. There is a very robust and consistent relationship between amyloid precursor protein supply and the course of amyloid deposition in all types. 2. Data from Alnylam's longer term studies of patisiran, which suggest that the benefit of patisiran is maintained and prolonged. 3. Very positive experience in the National Amyloidosis Centre among patients receiving patisiran via the compassionate access programme and EAMS. We have treated 30 patients with hereditary ATTR amyloidosis, ten for over one year. The treatment has been safe, and several of the ten patients who have been treated for one year have reported very significant improvements in mobility and nerve symptoms. The single patient who was wheelchair bound at the start of treatment is now able to walk with stick. [redacted]	Comment noted. The evaluation committee considered evidence submitted by the company, the views of people with the condition, clinical experts and a review by the ERG. The committee recognised that hATTR amyloidosis is a serious and debilitating condition, and that patisiran could be a promising treatment. During 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. Clinical evidence therefore suggests that, patisiran apart from stopping progression of the disease, has the potential to reverse it in the long-term. Please see sections 4.8 and 4.9 of the FED.

Nominating organisation	Comment	Response
	[redacted]	
Clinical expert 2	**2) Comments re PND score:** There has been some misconception regarding the correlation of the PND score value and other clinical measurements relating to amyloid associated organ dysfunction. Patients may improve very significantly on treatment whilst remaining within a particular PND grade since the latter is a useful but quite crude measure and does not capture many elements in the disease that are important to patients, particularly autonomic dysfunction, which causes many of the most unpleasant and disabling symptoms (eg incontinence). Alnylam's analysis shows that patients who remained within the same PND score on patisiran did experience a significant benefit in a wide range of measures versus those on placebo (EQ5D, Norfolk, Compass and RODS). It is clear then that patisiran treatment can improve symptoms over a relatively short 18 month period whilst not being associated with a change in PND score.	Thank you for your comment. The evaluation committee has considered all factors that may affect its decision. In particular, the committee acknowledged that there may be uncaptured benefits of treatment with patisiran.

Nominating organisation	Comment	Response
		Please see section 4.31 of the FED.

Comments received from members of the public

Role*	Section	Comment	Response
Healthcare industry (pharmaceutical)	Section 4.8	**Long term benefit of patisiran** In Section 4.8 of the ECD, the committee concludes that the evidence shows that patisiran offers considerable benefit for some patients. This is based on two main arguments: 1. Expectation of an increase over time in clinical benefit of patisiran, evidence for which includes: o A patient who has had patisiran for 4.5 years beginning to walk and work full time again; o Other improvements observed in some patients in clinical practice; o Medical images showing reduction of amyloid deposits in all organs for some patients. 2. Mean serum transthyretin (TTR) reduction at 18 months from the APOLLO study, from which the committee has concluded: o A TTR reduction of >80% represents a threshold above which o Patisiran is likely to have surpassed this threshold [redacted] contests the appropriateness and accuracy of both of these judgements Please see comment 8 'Expectation of an increase over time in clinical benefit of	Comment noted.

* 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.

Role*	Section	Comment	Response
		patisiran' for response to the first issue and comment 9 'Mean serum transthyretin (TTR) reduction at 18 months from the APOLLO study ' for response to the second.	
Healthcare industry (pharmaceutical)		**Treatment stopping rule** The ECD makes reference to the fact that the economic model did not include a formal stopping rule, reflecting the possibility of patients receiving patisiran indefinitely. However, patisirans marketing authorisation is for patients with hATTR amyloidosis at FAP stages 1 and 2. Clinical experts at the committee meeting have commented that it is possible that a patient benefitting from patisiran and their clinician would not want to stop treatment when that patient entered Stage 3. However, NHS England states that the wording of the marketing authorising was interpreted to mean that when patients progress to FAP stage 3, treatment should stop. The Summary of Product Characteristics is explicit about the license of the product: Onpattro [patisiran] is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy (European Medicines Agency, 2018) We are mindful that it is NICE remit to assess patisiran within its marketing authorisation as per the NICE scope, and have found no precedent where NICE have extended their remit to assess a treatment outside of its marketing authorization. The committee notes that: NHS England interprets the marketing authorisation that treatment ought to stop following progression to FAP stage 3; Alnylam applied no formal stopping rule in their model so patients could continue treatment indefinitely; [redacted] therefore believes that the committee is potentially introducing a significant uncertainty into their assessment of Alnylam model. The committee is attempting to use	Thank you for your comment. In the company's updated model, patients who reached PND IV (FAP stage 3) immediately stopped patisiran and subsequently had best supportive care (BSC). The committee acknowledged that, in addition, a stopping rule using data from APOLLO was also implemented, meaning that patients could stop in any health state based on a log-normal time-to-treatment discontinuation curve. The committee accepted the updated model for decision making Please see section 4.13 of the FED.

Role*	Section	Comment	Response
		an economic model generating ICERs predicated on treatment in Stages 1 through 3 to estimate the costs and benefits of funding a treatment for Stages 1 and 2 only. [redacted] urges the committee to resolve this ambiguity as it is required for NICE to review treatments within their license i.e. with a stopping rule applied to patients in FAP stage 3. Onpattro | European Medicines Agency. at Https://Www.Ema.Europa.Eu/En/Medicines/Human/EPAR/Onpattro#authorisation-Details-Section. Date of Issue: August 2018. N.d. The ECD makes two comments which are ambiguous regarding the clinical effect of patisiran. It would be helpful to have these sections reworded to remove the ambiguity.	
Healthcare industry (pharmaceutical)		**Suppression of amyloid production** The committee indicates that evidence showed that patisiran offers considerable benefit for some patients. This immediately follows a sentence which describes how while TTR production is supressed, the body is able to clear accumulated amyloid deposits. This gives the impression that the committee believes that there is evidence that patisiran can clear amyloid deposits, a belief supported by an earlier observation that the clinical experts described that a reduction of amyloid deposits in all organs has been seen in the medical imaging of some patients. To our best understanding of the evidence submitted by Alnylam, there is no direct peer-reviewed evidence of amyloid regression in patients on patisiran. [redacted] request the committee clarify whether the judgement that patisiran offers benefit for some patient was influenced by a belief that it could clear or reduce amyloid deposits. If so, [redacted] further request that the evidence on which the committee formed this judgement is made available, if it can be made public. Alternatively, these sections could be reworded to avoid ambiguity. The ECD makes two comments which are ambiguous regarding the clinical effect of patisiran. It would be helpful to have these sections reworded to remove the ambiguity.	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, clinical experts, NHS England and a review by the ERG. Taking into account all the information (including confidential information, which cannot be shared with the public) and patient testimonies the committee recognised that patisiran offers considerable benefit for patients and that in addition to stopping disease progression, patisiran has the potential to reverse it. Please see section 4.8 of the FED.

Role*	Section	Comment	Response
Healthcare industry (pharmaceutical)		**ECHO as measurement of TTR** The committee describe how Other outcomes collected in the trial included assessment of serum transthyretin (TTR) levels and cardiac function (through echocardiogram and cardiac biomarkers such as troponin I and N-terminal pro-B-type natriuretic peptide [NT-proBNP]). It is unclear whether the examples of cardiac function assessment are also supposed to apply to assessment of serum transthyretin. This would not be unexpected (as there is some literature on the use of echocardiogram for the assessment of TTR levels) (Tsang and Lang 2010), although the sentence overall is ambiguous without an Oxford comma. A reduction in echocardiogram measurements has not been established as a direct measure of amyloid removal as it is unclear what specifically is being measured, and therefore if the committee has understood echocardiogram to be a measure of both TTR levels and cardiac function more evidence would be required to conclude that the outcome of the echocardiogram is measuring TTR directly and not an unexpected confounder. [redacted] request the committee clarify whether they understand TTR levels to have been measured directly by echocardiogram, and if so to further clarify what evidence they have used to justify a link between echocardiogram measurements and amyloid removal. Alternatively, this section could be reworded to avoid ambiguity. Tsang, Wendy, and Roberto M. Lang 2010 Echocardiographic Evaluation of Cardiac Amyloid. Current Cardiology Reports 12(3): 272“276.	Thank you for your comment. Section 4.6 has been amended to avoid ambiguity.
Healthcare industry (pharmaceutical)		**Treatment discontinuation** The ECD does not specify which criteria were used to select the treatment discontinuation curve used. [redacted] wishes to draw the committee’s attention to whether the curve best reflecting the clinical context of hATTR disease was adopted to model treatment discontinuation, as this can significantly alter ICER and is a point of contention in many models involving discontinuation assumptions.	Thank you for your comment. In the company’s updated model, patients who reached PND IV (FAP stage 3) immediately stopped patisiran and subsequently had best

Role*	Section	Comment	Response
			supportive care (BSC). The committee acknowledged that, in addition, a stopping rule using data from APOLLO was also implemented, meaning that patients could stop in any health state based on a log-normal time-to-treatment discontinuation curve. The committee accepted the updated model for decision making. Please see section 4.13 of the FED.
Healthcare industry (pharmaceutical)		The ECD does not discuss patient and carer burden associated with patisirans mechanism of administration (once every 3 weeks by intravenous infusion), other than to note that infusion-related reactions are a relatively common adverse event. It is fairly concluded that continuous infusion is a relatively burdensome method of administration, and there is evidence that method of administration is important to patients; in a recent Amyloidosis Research Consortium UK patient survey (Amyloidosis Research Consortium UK, 2018 (Unpublished)), 50% of patients rated mode of administration as important or very important, and 59% rated place of administration as important or very important. In addition to the increased costs of infusion captured in the Alnylam economic model, there are also additional costs for patients and carers such as transport and the opportunity cost of paid employment foregone. This is notable, as this represents the only genuine reason for differences between the BSC arms of the patisiran submission and submissions for other hATTR therapies. It would be helpful if NICE could clarify what the value of patient choice would be with respect to avoiding the cost and burden of continuous infusion methods of administration.	Thank you for your comment. Section 2.8 has been amended. Please see the following sentence in section 2.8: "At the second meeting, the company explained that some patients already receive patisiran at home, after 3 infusions administered in the Centre and this is expected to become the routine place for patisiran administration in clinical practice."

Role*	Section	Comment	Response
		Amyloidosis Research Consortium UK. Burden of Disease and Perspectives on Treatment: Summary Report from Research with Hereditary Transthyretin Amyloidosis (HATTR) Patients and Carers. July 2018 (Unpublished). N.d.	
Healthcare industry (pharmaceutical)		**Expectation of an increase over time in clinical benefit of patisiran** [redacted] notes that a greater level of TTR reduction was observed among patients receiving patisiran between months 9 and 18 of the APOLLO study than was observed between baseline and month 9 of the study. It remains unclear how Alnylam has justified their claim that this rate of change will persist in the long term. Indeed, as the mechanism of action of patisiran is to reduce serum TTR levels it is logical that after the initiation of treatment, patients who discontinue due to adverse events and lack of response to treatment will no longer be assessed for outcomes from patisiran treatment. Therefore, it is intuitive that there will be an increased mean reduction in TTR levels once these discontinuers are no longer observed. However, once use of treatment has stabilised there is no basis to assume that TTR levels continue to reduce at the observed rate. [redacted] suggests that further consideration be given to the expectation of persistent reduction in TTR among patients receiving patisiran. With regards to the remaining evidence for long-term effect of patisiran, we note that these are anecdotal observations of single patients and it is not appropriate that they be reported under the clinical trial results heading. While patient experience is important, anecdotal reporting of a single patients experience may not be representative of the mean effect of treatment.	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, clinical experts, NHS England and a review by the ERG. Thank you for your comment. The issue of discontinuers was discussed in depth at the last meeting and the accepted model includes a waning of effect with time off treatment. Please see section 4.13 of the FED.
Healthcare industry (pharmaceutical)		**Mean serum transthyretin (TTR) reduction at 18 months from the APOLLO study** [redacted] notes the committees judgement that it is important that patisiran generates a clinical benefit above a threshold of 80.0% that clinical experts advised was needed to halt or reverse neuropathic progression. 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 [sic] is mediated through TTR, it is unsurprising that there will be an association between TTR levels and patient outcomes. However, there is no clear 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	Thank you for your comment. Section 4.8 of has been amended, the FED does not refer to a binary 80% threshold. Please see section 4.8 of the FED.

Role*	Section	Comment	Response
		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. 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 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 The claimed threshold is inconsistent even with the patisiran submission own data; the correlation plot showing TTR reduction against clinical response (Figure 1 in this document, Figure 3 in Adams et al, 2018) includes a number of patients who do not improve with a >80% reduction and some who do improve with a <80% reduction. In addition, the plot contains both placebo and active treatment arms, meaning that confounding could occur if both TTR reduction and outcomes are correlated with taking treatment (which we would expect them to be). If the committee are certain that a threshold is clinically justifiable, we would request that the correlation is presented using the active treatment arm only and with a more rigorous methodology. However even if a threshold is appropriate, the measurement of serum TTR levels in the submission is unclear and so it cannot be concluded that patisiran generates clinical benefit above this threshold. There is a general lack of scientific rigor, statistical methodology and consistency in the way that TTR reduction is measured and reported for patisiran. This has led to a number of apparent inconsistencies, which are described in comment 10 'inconsistencies in TTR reduction in submission' owing to space limitations	
Healthcare		**'Inconsistencies in TTR reduction in submission'**	Thank you for your

Role*	Section	Comment	Response
industry (pharmaceutical)		1. The 87.8% TTR reduction at 18 months is described in section 4.8 as being the mean reduction. This is not correct; the figure is actually the mean max reduction according to Alnylam other publications (Adams et al. 2018). This is not a measurement with a well-understood statistical interpretation, but we believe the mean max might refer to the highest individual datapoint per patient out of many possible datapoints, without consistency in timeframe of measurement. However, we are unaware of a statistical definition of mean max, cannot find any support for this statistical approach in references, and have been advised by statistical experts that it is not a valid way to report data and therefore are unsure if this interpretation is correct. Regardless, to describe it simply as the mean reduction would ignore this methodological debate. 2. Alnylam reports a mean TTR reduction of 83% and 84% at month 9 and month 18, without reporting data at the many other timepoints for which they measured TTR reduction. However, in the appendix to the NEJM article (Adams et al. 2018) it states that the TTR reduction measurements were taken post dose. It is typical to take biomarker measurements pre-dose as is done consistently in other clinical trials. Taking a sample post-dose may lead to a larger decrease due to immediate impacts of patisiran dosing, but it is not a valid methodology for determining reduction over time. We believe the pre-dose results of TTR reduction for patisiran at all timepoints should have been reported, and if this convention was purposefully not followed it should be highlighted and explained in the ECD why a different approach was used. 3. It is unclear what the most important timepoint is for measuring TTR reduction to predict clinical outcomes. In AL amyloidosis, survival is predicted based on Light chain precursor protein reduction at 3 months and 6 months, but no data has established a later timepoint for that disease. Taking into account the lack of information to know when the most appropriate timepoint of measurements to predict the best response, we believe the most appropriate measurements to report would be the pre-dose mean (not mean max) and median of the whole sample at month 3, 6, 9, 12, 15 and 18. [redacted] requests the committee reconsiders the appropriateness of an 80% TTR threshold, and the appropriateness of Alnylam reporting of their TTR outcomes which allow them to meet this threshold.	comment. Wording of section 4.8 has been specified to reflect 'mean maximum TTR'.

HIGHLY SENSITIVE

Summary of meeting with Alnylam on patisiran for treating hereditary transthyretin-related amyloidosis

This document summarises the issues discussed by NICE and Alnylam on 4 March 2019.

1. Marketing authorisation – NICE may only recommend treatments within their marketing authorisations. Therefore, the modelling must be commensurate (i.e. must include stopping rule once patients enter FAP III stage)

2. Uncertainties - model structure which is defined by PND and NT-proBNP score, but which excludes states or events associated with other key impacts of the disease, such as autonomic dysfunction, is a limitation that introduces uncertainty around the expected cost-effectiveness of patisiran. The committee considers that although the model structure is broadly reasonable, it does not capture all aspects of the condition, so is unlikely to reflect the true expected cost effectiveness. It concluded that it will take this into account in its decision making. The committee's preferred ICER was [redacted] per QALY gain (includes PAS discount) which included the following assumptions:

    a. utility regression model included all the terms (treatment group, time, PND score, NT-ProBNP, and a treatment-by-time interaction term)
    b. removed minimum and maximum utility caps based on using 25th and 75th percentiles of the EQ-5D score for each PND state across either treatment group at any assessment time (from the APOLLO)
    c. incorporated improvement in quality of life within a given PND stage that is limited at 5 years to reflect clinical practice
    d. included PND-related carer disutility (see para 4 below)
    e. corrected some errors (see ECD section 4.19)
    f. used a discount rate of 3.5% for costs and benefits (see ECD section **Error! Reference source not found.**)
    g. recalculated starting state distribution and removed a patient with FAP stage 3 (see ECD sections **Error! Reference source not found.** and **Error! Reference source not found.**)
    h. used a utility cap for the general population based on Ara and Brazier, 2010 (see ECD section 4.15)
    i. removed mortality effect for lower NT-proBNP states (see ECD section 4.16)

3. Managed access is not an option because committee agreed that further data collection would be unlikely to resolve the key uncertainties associated with

patisiran as those lie in the economic model (which structure did not adequately capture all aspects as discussed above).

4. Caregiver disutilities – the committee accepted the inotersen model which assumes 1 full-time caregiver for each patient in the first 2 stages of the disease and 2 carers at stage 3. For consistency, this approach could be used in patisiran.

[redacted]

6. Next steps

    a. Alnylam should revised their model to account for 1 and 4; model will be reviewed by ERG and NICE to see if corrections have been appropriately implemented

[redacted]

7. Timing with inotersen – NICE is running both appraisals patisiran and inotersen in parallel with the hope that both topics will be published concurrently. Any delay in negotiation would impact the release of final guidance and could jeopardise its concurrent release.

[redacted]

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April 15, 2019

RE: Additional evidence submission for patisiran – ID 1279

Dear Sheela:

Thank you for the opportunity to present additional evidence to the Committee to clarify and support the value proposition of patisiran.

Here, we have summarized the additional evidence on the changes to the CEA model below and have also included technical information that may help facilitate the ERG's validation of our model implementation. We believe that the revised cost-effectiveness analysis of patisiran in hATTR-amyloidosis described here summarizes the exchanges between Alnylam and NICE to date.

NICE has requested that Alnylam apply assumptions from the committee's preferred base case, which yielded an ICER of [redacted] per QALY gained; this estimate is inclusive of the original PAS discount considered by Committee. We were asked to implement the following changes from this preferred base case:

- Consider revising the simple PAS and move away from commercial arrangements
- Consider approaches to introduce the impact of autonomic neuropathy symptoms, highlighted by patients and clinicians as being of particular importance
- Consider a stopping rule in accordance with the marketing authorization: Patisiran to be stopped if patients enter FAP 3 (PND IV) stage
- Consider adding caregiver disutilities (point 4 in NICE document) to achieve consistency with the inotersen model. The committee accepted the inotersen model which assumes 1 full-time caregiver for each patient in the first 2 stages of the disease and 2 carers at stage 3.

Please find below a summary of the updates to the model in line with these requests. We also provide additional considerations regarding issues of equality between the patisiran and inotersen appraisals; these were the subject of our recent teleconference and email exchanges.

Stopping rule if patients transition into FAP Stage 3 / PND Score IV

As requested by NICE, a stopping rule was implemented in the model to simulate the impact of discontinuing patisiran treatment if patients progress to PND Score IV. In terms of implementation, patients are moved to an "off-treatment" section of the model after

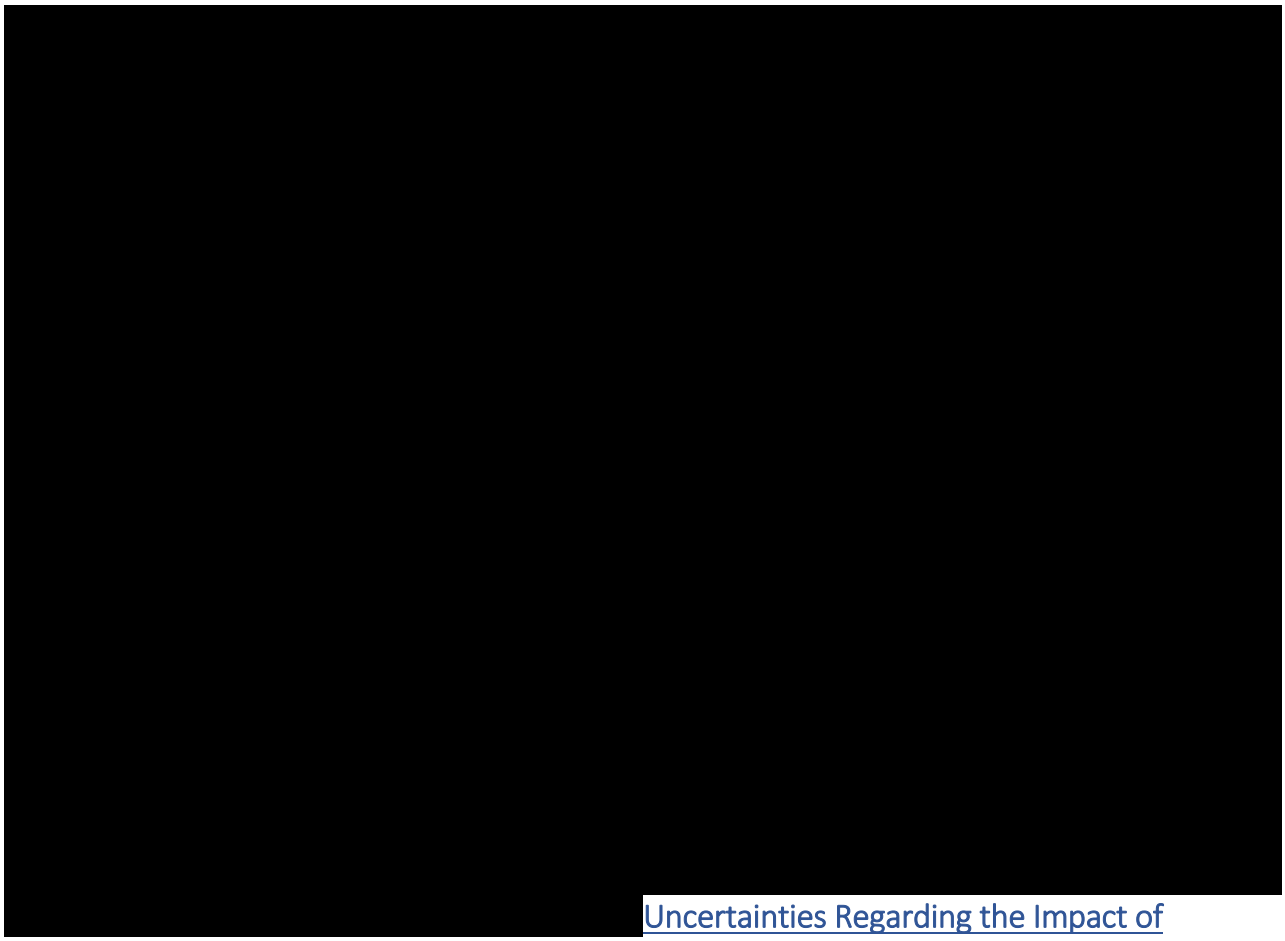
discontinuation where they are assumed to be treated with BSC. At this point, it was assumed that these patients experience decreased utility over time, in line with that observed with BSC. This was implemented in the model so that the utility for patients off-treatment is recalculated every cycle as the weighted contribution of the fraction of the cohort already off-treatment in the previous cycle (decreasing with the rate of BSC) and of the cohort discontinuing in the cycle. Additionally, the transition matrices were adjusted to avoid the possibility that patients could improve to a lower PND Score after reaching PND Score IV, which would have the effect of allowing patients to re-initiate treatment.

Please note that these assumptions are in line with those that have been implemented in the inotersen model, as described to us by NICE staff during our telephone and email exchanges. The specific implementation of the stopping rule is consistent with the one implemented in the inotersen model (described in slide 6 of the publicly-available presentation of the inotersen model for the Committee and in the email description we received from NICE).

Revised caregiver disutilities

As NICE requested, we have revised caregiver disutilities based on an assumption of one full-time caregiver for each patient with a PND Score of 1, II, IIIA, and IIB and two carers for patients with PND Score IV.

[redacted]



Uncertainties Regarding the Impact of Autonomic Symptoms

Testimony from clinicians and patients during the two HST Committee meetings described the importance of autonomic neuropathy on the lives of patients with hATTR amyloidosis. The literature reports that autonomic neuropathy is present in 56% to 65% of patients with hATTR[1]. In a UK conducted study of patients with the T60A mutation -- the most prevalent in the UK -- reported data show that 75% suffer autonomic neuropathy[2]. According to the literature regarding the natural history of the disease, alongside clinician and patient testimonies at the NICE HST Committee meetings, the most common symptoms of autonomic dysfunction are GI in nature (constipation, diarrhoea, alternating constipation and diarrhoea, vomiting). We agree that autonomic dysfunction and subsequent GI symptoms are profound and represent a significant part of the disease burden and reduced quality of life among patients in the UK.

Due to the multi-systemic nature of the disease, several dedicated instruments were deployed in the APOLLO study of patisiran to adequately capture these different aspects of disease. Patisiran demonstrated significant benefit versus placebo on all relevant measures of autonomic dysfunction, including modified Body Mass Index (mBMI), the Composite Autonomic Symptom Score 31 (COMPASS-31), and measures of orthostasis from the mNIS+7 (i.e., postural blood pressure; see CS Section 9.6)[5]. This observation was true whether patients worsen, improve, or stay in the same PND score from baseline (See Section 10.1.11 of the Company Submission and

Alnylam's ECD response). More importantly, among the endpoints directly related to autonomic symptoms such as COMPASS-31 and mBMI, patisiran patients consistently score better than those patients in best-supportive care arm (See Section 10.1.11 of the Company Submission). These positive results on measures of autonomic dysfunction were in part the basis on which the EMA granted 'accelerated review' for patisiran, were cited in the EMA's European Public Assessment Report, were used by the Committee on Orphan Medicinal Products (COMP) in its decision to grant and subsequently maintain (following in-depth review of APOLLO data) patisiran's orphan drug designation (see COMP's Orphan Maintenance Assessment Report), and were part of Alnylam's successful applications to the MHRA leading to patisiran's Promising Innovative Medicine (PIM) designation and subsequent Early Access to Medicines Scheme (EAMS) approval. There is robust evidence to support patisiran's beneficial impact on autonomic dysfunction.

We agree that the uncertainty stems from the lack of an obvious approach to incorporate these aspects of patisiran's benefit on autonomic dysfunction into the model, despite the abundance of clinical evidence. Although the impact of autonomic dysfunction is significant, it is extremely difficult to comprehensively incorporate aspects of autonomic dysfunction in the CEA model because autonomic dysfunction has multi-systemic impacts; subsequently, there is not a single measurement that captures all critical aspects. Indeed, the literature often defines autonomic dysfunction in different ways.

As a necessary simplification, we relied on the EQ-5D measurements from our APOLLO trial to proxy all other aspects of the disease the aspects of the disease that were not explicitly included in the CEA model (i.e., everything other than ambulatory and cardiomyopathy aspects of disease). However, as noted in our ECD reply and subsequent communications with NICE, we fully recognize that this simplifying assumption may be imperfect since it may substantially underestimate the true clinical effectiveness of patisiran on autonomic features of the disease. The HRQOL benefits observed on EQ-5D may not fully capture aspects of autonomic dysfunction, such as mortality due to wasting, which have been demonstrated across multiple endpoints in the APOLLO trial.

The two scales that are used in clinical practice are FAP stages and PND scores. Although FAP does mention autonomic symptoms, it only makes reference to symptoms related to the limbs[3]. Consequently, FAP staging (as used in the inotersen model) does not include the gastrointestinal (GI) autonomic symptoms of hATTR amyloidosis such as diarrhoea, constipation and wasting, which clinical experts from the National Amyloidosis Centre (NAC) told us they believe to be the most important drivers of health-related quality of life (HRQoL) in this disease (as reported in our Company Submission [CS] Table D11, p 155). The patient expert statements received by the Committee for this HST evaluation also confirmed that GI-related symptoms had the greatest impact on their HRQoL; e.g., "The worst thing is the [e]ffect it has on my bow[e]l movements. I have to be careful what I eat and have quick access to toilet facilities. This restricts where we travel and holiday types."

Consequently, in an attempt to address the Committee's concerns that the submitted patisiran CEA model does not take into account the autonomic symptoms, we sought to further capture the GI aspects of autonomic dysfunction in the updated model. Specifically, we investigated the

disutility of these GI symptoms present in patients with autonomic neuropathy and incorporated into the model the reported UK disutility for functional digestive disorders and 'other' intestinal disorders identified by ICD code[4].

As noted in the ERG's last review of this approach, the added disutility for autonomic dysfunction was only applied in the BSC arm, to reflect the efficacy shown by patisiran on a number of endpoints related to autonomic dysfunction in the APOLLO trial. However, we disagree with the ERG that the addition of this disutility implies a double-counting of non-PND-related utility impacts. Instead, we believe that this is an appropriate application of this disutility to mirror the characteristics of the prevalent genotype-phenotype makeup of the UK population. As noted in the literature, approximately three-quarters (75%) of patients in the UK suffer from autonomic neuropathy, due to the prevailing presentation of patients with a T60A mutation.[3] The patisiran APOLLO study was the largest ever global study of patients with this disease and enrolled a broad array of patient genotypes, but T60A patients represented a relatively small fraction of the overall trial population. Therefore, we believe EQ5D utilities in the overall APOLLO study cohort may indeed underestimate the amount of dysautonomia present in the UK population. Therefore, we enriched the disutility consequent to autonomic dysfunction in the model by applying UK disutility values related to digestive/intestinal disorders to try to adjust for differences between the APOLLO study population and the prevalent UK cohort.

We should also note that patisiran also impacts autonomic dysfunction by ameliorating wasting in this disease, as evidenced by the positive benefits on the modified Body Mass Index (mBMI). A 30-year natural history study of disease found that 41% of patients with hATTR amyloidosis with polyneuropathy died of inanition (i.e., wasting) consequent to autonomic neuropathy (Gertz, 1992). As mentioned earlier, it is exceedingly difficult to incorporate these benefits into the CEA model.

As a result, we believe that incorporating EQ5D-related dysautonomia in this latest revision of the CEA model is an appropriate estimation of the profound autonomic dysfunction experienced in the UK population and may still underestimate the benefit of patisiran on this feature of disease. The APOLLO trial clearly demonstrated a reduction in autonomic dysfunction (including GI abnormalities) in patients treated with patisiran, and a worsening in patients in the control arm. We believe our current attempt to address a source of modelling complexity is reasonable and transparent.

Time on treatment

Time-on-treatment in the inotersen model was estimated using a log-logistic curve, obtained by fitting trial data, to extrapolate and estimate discontinuation of inotersen over the course of the simulation. This approach was included in the implementation of the stopping rule when patients transition to FAP Stage 3 / PND Score IV (as described in slide 7 of the inotersen public slides for Committee and slide 8 of the inotersen public slides from the 1st Evaluation Committee Meeting).

Time-on-treatment in the patisiran model was included in the original submission, but was subsequently removed from the model in the ERG-preferred analysis (point 1-c, page 124, patisiran ERG report). At that time, we acknowledged the risk of bias raised by the ERG and accepted the request to remove time-on-treatment discontinuation from our model. However, upon further review during our technical exchanges with NICE, we believe that it is both appropriate and important to incorporate time-on-treatment estimations in our CEA model. In recent discussions with NICE, we have discussed the importance of appropriately simulating the effects of discontinuing patisiran treatment (i.e., transition to BSC) when patients reach PND Score IV. In parallel with this approach, we believe it is critical to consider time-on-treatment over the simulation to correctly understand the benefits of patisiran on patients, even if they may eventually discontinue.

Therefore, following recent exchanges with NICE we have re-implemented time-on-treatment in this latest version of the model. The impact is two-fold: (1) it helps estimate how patients perform on BSC whether they are discontinuing treatment for any reason or progressing to PND Score IV; (2) it improves the consistency of other assumptions that have been implemented elsewhere in response to requests from NICE (e.g. stopping rule). We considered the log-normal function to extrapolate discontinuation data for patisiran, because of the goodness of the fit and the plausibility of the long-term extrapolation. As noted by the ERG, this may be the most reasonable extrapolation curve that allows for a persisting, but decreasing rate of stopping treatment over time.

From an implementation perspective, patients who discontinue patisiran receive BSC, and therefore have transition probabilities and decreases in utility in line with BSC (i.e., the transition matrix for BSC is applied). The implementation parallels that similar to the stopping rule that was applied when patients progress to PND Score IV.

Mortality in hATTR-amyloidosis

As discussed with NICE in recent exchanges, assumptions regarding the leading cause of death in hATTR amyloidosis in the UK, and subsequently its implementation in the model, have significant impacts on the ICER. As documented in the extensive natural history of disease in the UK and the attestation of clinical experts, the leading cause of death of hATTR amyloidosis in the country is cardiomyopathy. In keeping with this, we believe that the most appropriate approach for modelling mortality in the UK population is to exclusively use cardiomyopathy. In the patisiran ECD, the ERG criticised the estimation of mortality by PND Score because of the weakness of the source[6] and the complexity of the method. As a part of the scenario analysis, the ERG considered a case in which PND Score-related mortality was removed from the model. This scenario is reasonable, since most patients with hATTR amyloidosis die from cardiac complications or wasting[7], rather than from polyneuropathy.

In contrast, the inotersen model entirely ignores mortality associated with cardiomyopathy. In the inotersen model, the hazard ratios for mortality (with respect to the mortality of the general population in England) are 2.01, 2.42 and 9.53 for FAP stages 1, 2 and 3, respectively (slide 21 of

the inotersen public slides for Committee). Ironically, these values were directly taken by the inotersen manufacturer from our own patisiran model "in an attempt to improve consistency with the ongoing NICE appraisal of patisiran" (slide 12 of the inotersen public slides for Committee). The effect of cardiomyopathy on mortality was entirely excluded from the inotersen model (slide 21 of the inotersen public slides for Committee), ostensibly due to the lack of any evidence on the impact of inotersen on any measures of cardiac amyloidosis. This approach was accepted by the ERG and the Committee based on the public slides for Committee.

We would like to reiterate our agreement with the ERG's statement that our incorporation of PND-Score related mortality was based on data from a small cohort study (Suhr et al., 1994); nonetheless, it was included in our submission for completeness. In addition to the weaknesses noted by the committee, we should also note that approximately one-third of the patients in this study had cardiac involvement, which is suggestive that these estimates of the mortality by PND Score may be confounded by the presence of cardiomyopathy.

Due to all of the weaknesses and uncertainties with the implementation of PND-Score related mortality in the model, and the uncertain generalizability to UK practice (both of which were previously highlighted as weaknesses by the ERG, the Committee, and the patisiran ECD), we believe the most appropriate approach would be simulate mortality in the CEA model through cardiomyopathy (i.e., NT-ProBNP) effects alone. Nonetheless, for illustration, we explore how different mortality assumptions in the model (with and without PND-Score related mortality) impact the ICER in the different scenarios presented below.

Base Case Results: All changes described above, with PAS, & mortality by NT-proBNP only

	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)
Patisiran	16.62	12.17	3.28	2.92	[redacted]	[redacted]
BSC	14.53	10.97	-7.11	-4.67	[redacted]	[redacted]
Difference						
Patisiran vs. BSC	2.09	1.20	10.39	7.59	[redacted]	[redacted]

	Undiscounted		Discounted	
ICER	**Cost/LY**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

Scenario Analysis 1: As above, but mortality by PND only, ignoring the important cardiac mortality among UK patients

	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)
Patisiran	14.25	10.81	4.75	3.76	[redacted]	[redacted]
BSC	11.05	8.92	-4.29	-3.00	[redacted]	[redacted]

Difference						
Patisiran vs. BSC	3.21	1.90	9.04	6.76	[redacted]	[redacted]

	Undiscounted		Discounted	
ICER	**Cost/LY**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

Additional Concerns: Toxicity and discontinuation effects on ICERs

There are critical differences between the patisiran and inotersen appraisals that have complicated the modelling approaches. These have been discussed in our correspondence and telephone discussions with NICE. We are concerned that there is a risk of decision-making based on paradoxical ICER outcomes. Specifically, the safety profile of the technologies has a significant impact on the modelling approach. The discontinuation rate for inotersen is three-times higher than that for patisiran (company submissions; SMPCs for both products). The SMPC for inotersen clearly lays out important safety concerns that require weekly monitoring of blood counts, among other parameters. This higher discontinuation rate effectively reduces the total modelled treatment costs for inotersen versus BSC with the paradoxical consequence of lowering the ICER.

To illustrate the impact of this paradox, we have provided to NICE and report again below a scenario that 'neutralizes' any differences in discontinuation rates between the products and applies the high toxicity-driven discontinuation for inotersen directly to the patisiran model. Specifically, we considered the log-logistic function, that was considered the most appropriate by the ERG, among the functions fitted on data from both NEURO-TTR and NEURO-TTR Extension study (Figure 15, page 127 of inotersen company submission; slides 7 of Inotersen Public Slides).

Revised Base Case: Base case shown above, with application of higher inotersen discontinuation rate

	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)
Patisiran	15.37	11.48	-1.33	-0.24	[redacted]	[redacted]
BSC	14.53	10.97	-7.11	-4.67	[redacted]	[redacted]
Difference						
Patisiran vs. BSC	0.84	0.51	5.79	4.43	[redacted]	[redacted]

	Undiscounted		Discounted	
ICER	**Cost/LY**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analysis 2: Revised base case shown immediately above, with mortality by PND only, ignoring the important cardiac mortality among UK patients

	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)
Patisiran	12.63	9.91	0.54	0.84	[redacted]	[redacted]
BSC	11.05	8.92	-4.29	-3.00	[redacted]	[redacted]
Difference						
Patisiran vs. BSC	1.58	0.99	4.83	3.83	[redacted]	[redacted]

	Undiscounted		Discounted	
ICER	**Cost/LY**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

Technical considerations: "hard coding" and "Markov errors"

In recent email exchanges with the NICE technical teams, it was noted that our previously submitted model had a technical issues. These include:

- Some of the changes in the new model seem to be hard-coded in – and there is not option to undo or modify them
- The inclusion of the stopping rule seems to have resulted in a situation in which the Markov trace no longer sums 1.0.

To address the first point, we have submitted alongside this letter an updated model in which the additional changes are coded as an option to be easily included/excluded from the analysis with a drop-down-list control.

Regarding the second point, we respectfully disagree that the model submitted on March 20th contains errors in the Markov trace. Due to the inclusion of the stopping rule requested by NICE, the Markov structure in the worksheet "Markov Patisiran" is now duplicated: in rows 5:86 we have the portion of the Markov trace for patients remaining on treatment and in rows 95:176 we have the portion of the Markov trace for patients off-treatments. When patients discontinue, they are transferred from the "on-treatment" portion to the "off-treatment" portion. The populations of the two portions of Markov trace (patients on- and off-treatment) are summing to 1.0 at every cycle of the simulation, as displayed in cells AB6:AB86. The model that is submitted alongside this letters reflects this.

Conclusions

We believe the revised model and updates address NICE's concerns discussed over the past weeks. Alnylam appreciates the tremendous time constraints all sides face and hope our response enables the appraisal to move forward positively. To conclude, we have attempted to modify the

model to reflect the preferences from NICE, and have provided additional evidence to address uncertainties raised in the ECD and in subsequent communications from NICE. Finally, we have removed the risk of perverse ICER outcomes due to toxicity differences between the technologies and feel our approach is reasonable for the Committee to consider, as the Committee has largely accepted these modelling assumptions in its appraisal of inotersen [redacted] Consequently, when applying consistent approaches, and removing the potential for toxicity-driven discontinuation to reduce the ICER for one technology, we are able to arrive at a potentially acceptable ICER for patisiran [redacted]. The successful EAMS program for patisiran, following its PIM designation from the MHRA, has provided patients with access to treatment without any service delivery burden relating to the provision of specialised services for amyloidosis. The 'real world' experience with patisiran from EAMS can provide further confidence to the Committee regarding the important clinical and patient benefits of treatment. We hope the totality of these factors can be considered by the Committee in its deliberations of patisiran treatment for this ultra-rare, progressively debilitating, ultimately fatal disease that robs dignity and quality of life from patients and their families.

To crystallize some of the technical topics further, we have listed the issues we discussed during our prior teleconferences and email exchanges with NICE in a simple table, below.

Please do not hesitate to contact me should you require additional information.

Kindest regards,

Anant Murthy, PhD

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1. Swiecicki PL, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid (2015), 22:2, 123-131.
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3. Ado et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet Journal of Rare Diseases 2013, 8:31
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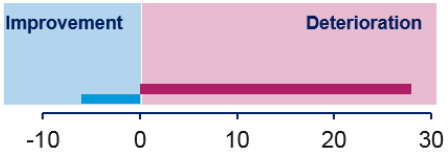
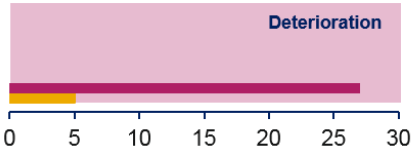
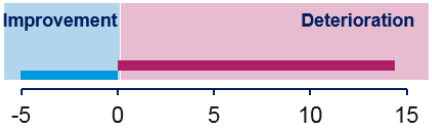
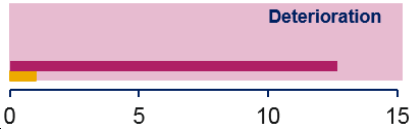
6. Suhr O, Danielsson A, Holmgren G, et al. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med.* 1994;235(5):479-485
7. Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl.* 2015;21(3):282-292

Dimensions	Patisiran	Inotersen
Key Elements in Pivotal trials[1-4]		
Treatment Discontinuations rate	**7%** Patisiran arm	**22.32%** Inotersen arm. Likely due AEs as reported in Akcea's submission and inotersen SmPC
mNIS+7 Difference vs placebo	-34 points Blue = Patisiran; Red = Placebo 	-19.7 points Yellow = Inotersen; Red = Placebo 
Norfolk QOL-DN Difference vs placebo	-21.1 points Blue = Patisiran; Red = Placebo 	11.7 points Yellow = Inotersen; Red = Placebo 
Proportion improving on mNIS+7 from baseline	56% vs 4%: 14 times greater % of patients improve vs placebo	36.5% vs 19.2%: 2 times greater % of patients improve vs placebo
Proportion improving on NORFOLK QOL-DN from baseline	51% vs 10%: 5 times greater % of patients improve vs placebo	50% vs 26.9%: 1.9 times greater % of patients improve vs placebo
Safety profile	Adverse event profile is similar to that observed with placebo. Most common AEs are peripheral edema and infusion-related reactions	Concerns with its safety profile especially; o Thrombocytopenia • Patients with platelet count >100 x10^9/L have to be monitored every other week • Patients with platelet count ≥75 to <100 x109/L have to be monitored every week and the dosing frequency should be reduced o Glomerulonephritis • UPCR and eGFR should be monitored every 3 months

CEA Models[6-7]	Patisiran	Inotersen

Data source and Implementation of QOL	Changes in EQ-5D-5L (direct changes observed in study used)	Changes in QoL obtained by mapping Norfolk QoL-DN into utility indexes, from tafamidis model[2] **(**changes in EQ-5D not available; SF-36 values from study not used)
Changing time-in-state utilities	Assumed to worsen over time with BSC and improve over time with patisiran treatment (direct changes observed in study used). These results are aligned with the results of all primary and secondary endpoints	Assumed to worsen over time with BSC and improve over time with inotersen treatment (***not*** consistent with changes observed in study; inotersen-treated patients continued to deteriorate in QOL)
Impact of the benefit of treatment after discontinuation	If the same logic is applied to the patisiran model, due to the low discontinuation rate observed in APOLLO compared to NEURO-TTR, 7% vs 22.32%, the impact of this in lowering the ICER is much smaller than that seen in the inotersen model. As such, patisiran is being penalized for being better tolerated than inotersen	A small disutility (-.0038), from the rate of change in the placebo arm of the NEURO-TTR study, is applied after inotersen discontinuation over time starting from a higher basis. This has the effect of modelling a slow 'waning' of efficacy after discontinuation, and thus patients in the inotersen arm of the model continue to accrue benefit (QALYs) after discontinuation at no cost. Therefore, with the high discontinuation rate of Inotersen, this yield an artificial ICER benefiting inotersen
Polyneuropathy Efficacy Parameter in Model	Changes in PND Score and/or FAP Stage (direct changes observed in study used)	Changes in Norfolk QoL-DN mapped to changes in FAP Stage (direct changes on PND Score and/or FAP Stage observed in study not used)
Cardiomyopathy Efficacy Parameter in Model	Changes in NT-ProBNP (direct changes observed in study used)	Not implemented (direct changes on NT-ProBNP from study not used)
Mortality Assumptions	Mortality based on contributions of polyneuropathy (i.e., PND Score) and cardiomyopathy (i.e., NT-ProBNP)	Mortality based on contributions of polyneuropathy (i.e., PND Score) – ***only***

Other Important Aspects	Patisiran	Inotersen
Promising Innovative Medicine (PIM) Designation	YES	NO
EAMS program	YES	NO
Cardiac data reported in the SmPC[1-2]	YES	NO
Annual NHS list price without simple PAS	Similar to Inotersen	Similar to Patisiran
German G-BA assessment	Considerable added clinical benefits	Non-quantifiable added clinical benefits

References:

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3. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):11-21
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5. Onpattro (patisiran) NICE Committee Papers
6. Tegsedi (inotersen) NICE Committee Papers

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April 24, 2019

RE: Additional evidence submission for patisiran – ID 1279

Dear Sheela:

We would like to extend our thanks to the NICE and ERG teams for sharing directional views on the latest evidence we have presented and sharing technical feedback on the implementation of these data in our model, during our teleconference on April 17th, 2019.

This letter is meant to address the useful points raised by NICE and the ERG during that teleconference. As we do not fully repeat information contained in our prior correspondence with NICE, this letter should be read in the context of our prior communications.

Based on the feedback we received during our last call, we have implemented the following revisions to the model:

- 5-year cap on within-state disutility among patients who receive BSC after they discontinue patisiran (with thanks to the ERG for pointing out our error in failing to include this previously)
- Autonomic-related disutility applied to patients who receive BSC after they discontinue patisiran (again, with thanks to the ERG for point this out).

Below, we have described how these revisions were implemented to facilitate the ERG's validation of these changes in our model. Subsequent to our implementation of these changes, we noted that there were still outstanding uncertainties in the estimate of our ICER and [redacted]

Base Case

NICE has requested that Alnylam apply assumptions from the committee's preferred base case. We were asked to implement the following changes from this preferred base case:

- Consider revising the simple PAS and move away from commercial arrangements
- Consider approaches to introduce the impact of autonomic neuropathy symptoms, highlighted by patients and clinicians as being of particular importance
- Consider a stopping rule in accordance with the marketing authorization: Patisiran to be stopped if patients enter FAP 3 (PND IV) stage

- Consider adding caregiver disutilities (point 4 in NICE document) to achieve consistency with the inotersen model. The committee accepted the inotersen model which assumes 1 full-time caregiver for each patient in the first 2 stages of the disease and 2 carers at stage 3.

These changes were implemented and described in our prior correspondence. We address below the points raised during our last teleconference.

Disutility After Discontinuation of Patisiran (Modelling of Patisiran to BSC transition)

As requested by NICE, a stopping rule was implemented in the model to simulate the impact of discontinuing patisiran treatment if patients progress to PND Score IV. In terms of implementation, patients are moved to an "off-treatment" section of the model after discontinuation where they are assumed to be treated with BSC. At this point, it was assumed that these patients experience decreased utility over time, in line with that observed with BSC. Additionally, the transition matrices were adjusted to avoid the possibility that patients could improve to a lower PND Score after reaching PND Score IV, which would have the effect of allowing patients to re-initiate treatment.

Please note that these assumptions are in line with those that have been implemented in the inotersen model, as described to us by NICE staff during our telephone and email exchanges. The specific implementation of the stopping rule is consistent with the one implemented in the inotersen model (described in slide 6 of the publicly-available presentation of the inotersen model for the Committee and in the emailed technical description we received from NICE).

As mentioned above, two technical changes to the model were implemented based on feedback from the ERG which both related to the simulation of patients who are treated with patisiran, but who subsequently discontinue treatment to receive treatment with BSC. Before addressing these two technical changes, we provide further clarification on the implementation of the utility profile for patients who have discontinued patisiran and describe the logical steps underlying the calculations. Please note that in this document all references to cell ranges are related to the updated model file that corresponds to the date of this letter. These may not coincide with cell ranges in the model submitted on April 15th or in prior versions because of the addition of the two technical changes discussed here.

After discontinuation of patisiran patients are assumed to have the same utility they had in the last cycle before discontinuation, but this utility starts decreasing with the same rate of change of BSC. This was based on guidance we received from NICE in teleconferences and further described to us via email on April 10th, 2019. The utilities for patients in the "off-treatment" state are calculated in cells EK96:EV176 of the "Markov Patisiran" worksheet. The rate of change of BSC is calculated in cells D65:D67 of the "QoL Data" worksheet. Three different rates are actually defined by the parameters "m_utility_changeDiscont_PND0_I", "m_utility_changeDiscont_PNDII", and "m_utility_changeDiscont_PNDIII_IV" as a function of the PND score. The reason for having three different parameters for the rate of change of BSC is explained below in the context of correcting the application of the disutility relating to autonomic dysfunction.

Due to the fact that utilities with patisiran are changing in time and that discontinuation from patisiran may occur at every cycle, the starting point for utilities after discontinuation is changing at

every cycle. This means that the actual utility for every patient in the "off-treatment" portion of the model is a function of the PND score and of the time from discontinuation. However, Markov models with cohort simulation have no memory, and therefore it would have been practically impossible (especially in light of the time afforded to us to respond to NICE's request) to keep track of the actual permanence of each patient in the "off-treatment" portion of the Markov trace. Therefore, an approximated solution was implemented, so that what is actually calculated in cells EK96:EV176 of the "Markov Patisiran" worksheet is the average utility of the cohort in the "off-treatment" portion (for each PND score). This average utility is recalculated every cycle as the weighted contribution of the fraction of the cohort already off-treatment in the previous cycle (they have the utility in "off-treatment" in the previous cycle) and the contribution of the cohort discontinuing in that same cycle (they have the utility of patisiran at the moment of discontinuation). For instance, the utility in cell EL97 is given by the weighted average of the patients "off-treatment" in the previous cycle (call AF96) with their utility (cell EL96) and of the patients entering "off treatment" (cell DK97) with their utility (cell EL7). The average utility is then deceased with the rate typical of BSC.

Next, we would like to extend our thanks to the ERG for noting that we had incorrectly estimated the 5-year cap (which was previously agreed to by NICE and the Committee) on the disutility associated with BSC-treated patients who were previously treated with patisiran. Due to time constraints and the lack of memory associated with our Markov model, we used an approximation to apply the agreed 5-year time limit of disutility among these patients. Just like the utility after discontinuation, the cap is calculated as an average for the entire cohort (for each PND score).

The average minimum value of the utility for each health state in the "off-treatment" section of the model is recalculated in each cycle as the weighted contribution of the cohort which is in the "off-treatment" portion of the model in the previous cycle and the contribution of the cohort which discontinues treatment in that same cycle. This calculation is added in the "Markov Patisiran" worksheet in cells DW92:EH176. The minimum utility for patients discontinuing in this cycle is calculated by subtracting the estimated change of utility in 5 years' time from the utility at the time of discontinuation. This calculation is added in the "Markov Patisiran" worksheet in cells DW2:EH86. Overall the columns DW:EI were added to the Markov trace of patisiran.

Autonomic-related disutility to reduce uncertainties regarding the impact of autonomic symptoms

As noted in our prior correspondence, patisiran also impacts autonomic dysfunction across a range of endpoints measured in the APOLLO trial. However, as noted previously it is exceedingly difficult to incorporate these benefits into the CEA model. As a result, we believe that incorporating EQ5D-related dysautonomia in this latest revision of the CEA model is an appropriate estimation of the profound autonomic dysfunction experienced in the UK population and may still underestimate the benefit of patisiran on this feature of disease. The approach taken is described in detail in our prior correspondence and we appreciated the opportunity to discuss this with you in our last teleconference.

We would like to thank the ERG for noting that we may have incorrectly implemented this change among the patients who discontinue patisiran and receive BSC. We corrected this error by applying dysautonomia-associated disutility at the same rate as the general decrease in utility due to BSC-

treatment from the moment the patient discontinues patisiran. In other words, the disutility associated with dysautonomia is added over the 5-year period of time after they discontinue patisiran. We reasoned that patients would not instantaneously accrue all dysautonomia-associated disutility at the time that patients discontinue patisiran, based on the significant reductions in dysfunction and improvement in functioning observed during the APOLLO trial. Instead, we assumed that this disutility, just like all other disutilities, would accrue over the 5-year period after patients discontinue patisiran to receive BSC. We implemented this by adding the disutility associated with dysautonomia in each PND Score, dividing this number by 10 (Two 6-month cycles per year multiplied by 5 years = 10) to calculate this disutility per cycle. From a practical point of view, this is implemented in "QoL Data" worksheet, by the definition of the parameters "m_utility_changeDiscont_PND0_I", "m_utility_changeDiscont_PNDII", and "m_utility_changeDiscont_PNDIII_IV"in cells D65:D67.

We agree with NICE that the overall uncertainty here stems from the lack of an obvious approach to incorporate the aspects of patisiran's benefit on autonomic dysfunction into the model, despite the abundance of clinical evidence. Although the impact of autonomic dysfunction is significant, it is extremely difficult to comprehensively incorporate aspects of autonomic dysfunction in the CEA model because autonomic dysfunction has multi-systemic impacts; subsequently, there is not a single measurement that captures all critical aspects. Indeed, the literature often defines autonomic dysfunction in different ways. In our model, we have used the directly-measured EQ5D quality of life data to capture the impact of these symptoms on patients, but we also recognize that this might be a necessary simplification of this complex disease. We believe the latest approach taken here can help to address the uncertainty and also note that similar concerns regarding autonomic dysfunction were not raised in the Committee's review of inotersen.

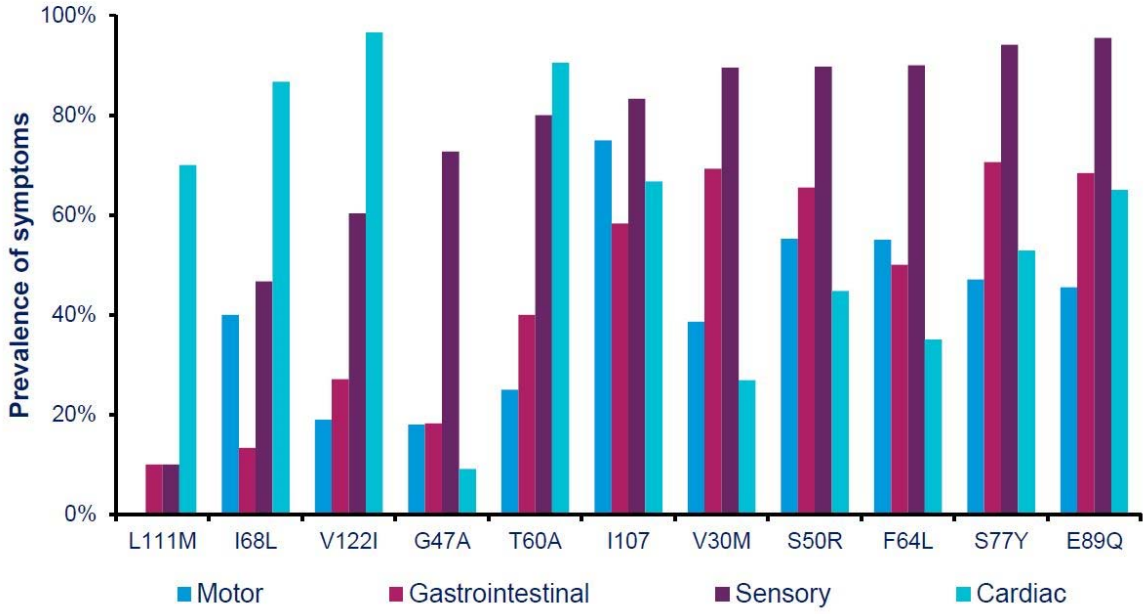
Mortality Assumptions

As discussed in our recent exchanges with NICE, assumptions regarding the leading cause of death in hATTR amyloidosis in the UK and the implementation of these assumptions in the model have significant impacts on the ICER. As documented in the extensive natural history of disease in the UK and consistent with the attestation of clinical experts, the leading cause of death of hATTR amyloidosis in the country is cardiomyopathy.

A question was raised by the NICE and ERG teams during our call on April 17th, 2019 about the generalizability of the cardiac mortality data source included in our submission (Gillmore et al., 2017), since that study largely comprised V122I and T60A mutations – two mutations that were not significantly represented in the patisiran APOLLO study.

Data from the international THAOS registry—the largest global hATTR amyloidosis registry—demonstrate that V122I and T60A are variants that present with a mixed phenotype. Nearly all patients with the V122I mutation had cardiac complications (96.6%), and the majority experienced neuropathy: 60.3% had sensory neuropathy, 19.0% motor neuropathy, and 27.1% GI (autonomic) symptoms. As such, even the V122I mutation, which was previously thought to be the most cardiomyopathy-specific pathogenic variant, should be recognized for its potential to cause a wide range of symptoms.

Mixed Phenotype Across Mutations of hATTR Amyloidosis – THAOS Registry (N=1744)

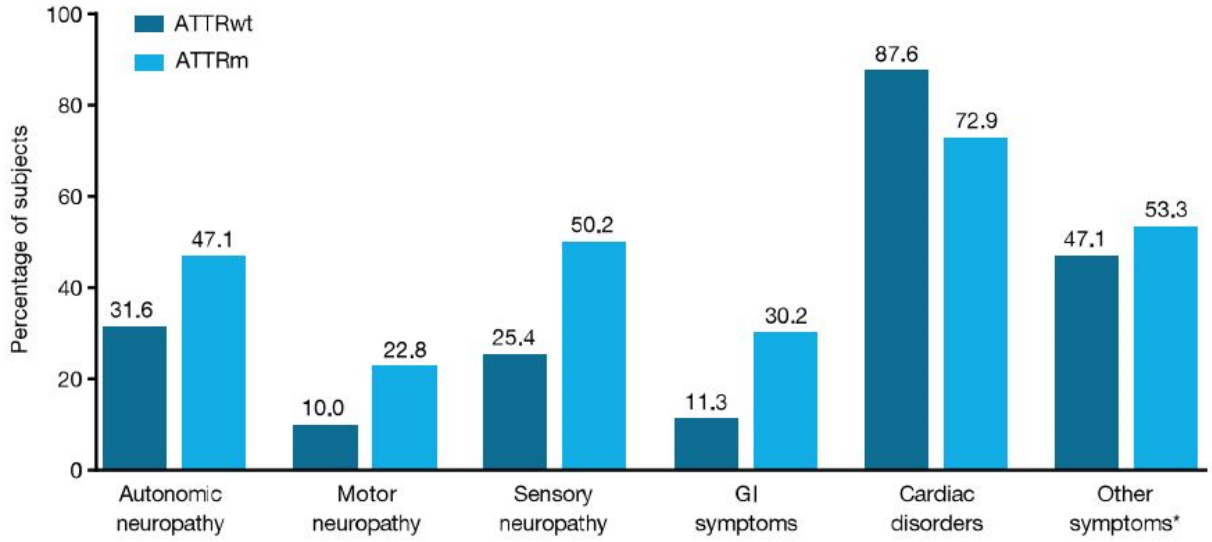


Source: Wixner et al. (2014) PMID: 24767411

Another recent (2018) analysis from the THAOS registry included 225 patients with hATTR amyloidosis, specifically with mutations historically considered to have predominantly cardiac manifestations (V122I, Thr60Ala, Leu111Met, or Ile68Leu). The study confirmed variability in the disease manifestations experienced by patients with these genotypes and reported that:

- 72.9% of patients had cardiac disorders
- 50.2% had symptoms of sensory neuropathy
- 22.8% had motor neuropathy
- 47.1% had symptoms of autonomic neuropathy
- 30.2% had GI symptoms
- 53.3% had other symptoms associated with hATTR amyloidosis (i.e., carpal tunnel, endocrine/metabolic disease, eye disease, genitourinary/reproductive disease, inflammatory disease, psychiatric diagnosis, respiratory disease, and others)[37] (see Figure).

Figure: Prevalence of symptoms among patients with historically classified cardiac mutations



Source: Khella et al. (2018) PMID not available[37]
ATTRm: mutated ATTR; ATTRwt: wild-type ATTR; **GI:** gastrointestinal.
*Other symptoms include carpal tunnel, endocrine/metabolic disease, eye disease, genitourinary/reproductive disease, inflammatory disease, psychiatric diagnosis, respiratory disease, and others.

In keeping with these published data, we believe that the patient population described in Gillmore et al., 2017 is broadly applicable to the patient population enrolled in the patisiran APOLLO study, since both groups of patients with hATTR amyloidosis present with a mixed phenotype disease comprising both polyneuropathy and cardiomyopathy features. We continue to believe that the most appropriate approach for modelling mortality consequent to hATTR amyloidosis in the UK population is to exclusively use cardiomyopathy (i.e., model the effects of patisiran and BSC on mortality through NT-ProBNP alone) and have presented these results as our base case.

However, we recognize that the Committee has already rendered a final decision on the acceptability of mortality estimates used in the inotersen submission, which assumed that PND Score was the sole driver of mortality in the UK based on published estimates that were included in our original submission (Suhr et al., 1994) despite those estimates being from Sweden. As noted by the Committee in its ECD for patisiran, this source of PND mortality estimates is highly uncertain and was taken from one paper in a population that may not be generalizable.

We also note that the effect of cardiomyopathy on mortality was entirely excluded from the inotersen model (slide 21 of the inotersen public slides for Committee), ostensibly due to the lack of any evidence on the impact of inotersen on any measures of cardiac amyloidosis. Nevertheless, criticism of this point appears absent in the inotersen FED and Committee papers, and the approach was accepted by the Committee.

Therefore, we understand that the Committee may decide to consider a scenario analysis using PND-Score only mortality from Suhr et al., 1994 to maintain consistency between the assumptions in the inotersen and patisiran models, so we have included this scenario below and in our model submission.

A point was also raised by the ERG during our last teleconference about life year gains in the BSC arm of our model if we assumed mortality based on NT-ProBNP alone (from Gillmore et al., 2017), rather than considering the contribution of PND Score on mortality (from Gillmore et al., 2017 or Suhr et al., 1994).

As noted in the table below, the choice to use either NT-ProBNP mortality alone (from Gillmore et al., 2017) or PND-Score mortality alone (from Suhr et al., 1994) both yield similar life years gained in the BSC arm in the patisiran model. Additionally, the estimated life year gains in the BSC arm using either mortality assumption is numerically similar to the estimated life years gained in the BSC arm of the inotersen model, as described in slide 30 of the public committee slides for inotersen. We also note that the life-year estimates for BSC in the inotersen model were not challenged and were accepted by the Committee.

In conclusion, we believe there is no inconsistency created by our simulation of mortality based on NT-ProBNP alone, since it yields the same expected life year gains as those observed in the inotersen submission. However, we maintain that the use of cardiac mortality (based on the observed NT-ProBNP data from the APOLLO trial and UK studies of hATTR patients) is more appropriate than the PND-only mortality from a dated, non-UK, small-sample study previously challenged in the patisiran ECD, although later accepted in the inotersen FED.

	Patisiran: NT-ProBNP only	**Patisiran** PND Score only	**Inotersen** ERG Preferred Analysis	**Inotersen** Revised company base case
Life Years Gained in BSC arm	[redacted]	[redacted]	[redacted]	[redacted]

Impact of time-on-treatment and drug-related toxicity on ICERs

There are critical differences between the patisiran and inotersen appraisals that have complicated the modelling approaches. These have been discussed in our correspondence and telephone discussions with NICE.

We are concerned that there is a risk of decision-making based on paradoxical ICER outcomes. Specifically, the safety profile of the technologies has a significant impact on the modelling approach. The discontinuation rate for inotersen is three-times higher than that for patisiran (company submissions; SMPCs for both products). The SMPC for inotersen clearly lays out important safety concerns that require weekly monitoring of blood counts, among other parameters. This higher discontinuation rate effectively reduces the total modelled treatment costs for inotersen versus BSC with the paradoxical consequence of lowering the ICER.

To illustrate the impact of this paradox, we have provided to NICE and report again below scenarios that 'neutralize' any differences in discontinuation rates between the products.

Specifically, we considered the log-logistic function for inotersen, that was considered the most appropriate by the Committee, among the functions fitted on data from both NEURO-TTR and NEURO-TTR Extension study (Figure 15, page 127 of inotersen company submission; slides 7 of Inotersen Public Slides). This setting is labelled as the "inotersen log-logistic" in the updated model.

The use of this setting allows for perhaps the most equitable comparison of the ICERs of these two therapies by comparing the cost and effectiveness of these therapies vs. BSC without projected duration on treatment confounding these different estimates due to differences in drug-related toxicity and consequent discontinuation. We urge the Committee to consider this as an important analysis part of the base case to highlight the profound impact that toxicity and discontinuations can have on estimated ICERs for these therapies. The ICERs reported below illustrate this further.

[redacted]

		Mortality Assumption	
		Cardiac (NT-ProBNP) mortality alone (APOLLO plus Uk study Gillmore et al., 2017)	PND-Score mortality alone (Study of Swedish patients; Suhr, 1994)
Time on treatment assumption	APOLLO Log-Normal	[redacted]	[redacted]
	Inotersen Log-Logistic	[redacted]	[redacted]

Conclusions

We believe the revised model and clarifications following our last teleconference address NICE's concerns discussed over the past weeks. Alnylam appreciates the tremendous time constraints all sides face and hope our response helps reduce the uncertainty inherent in appraisals of medicines for extremely rare diseases. Should any of our technical explanations be insufficiently clear, we of course continue to remain available for discussion with the ERG and NICE. We appreciate that the time constraints pose challenges for all.

To conclude, we have attempted to modify the model to reflect the preferences from NICE, and have provided additional evidence to address uncertainties raised in the ECD and in subsequent communications from NICE. Finally, we have removed the risk of perverse ICER outcomes due to toxicity differences between the technologies and feel our approach is reasonable for the Committee to consider, as the Committee has accepted many of the modelling assumptions in its appraisal of inotersen [redacted] Consequently, when applying consistent approaches, considering the specific phenotype of UK patients with hATTR amyloidosis and consequent mortality risk, we are able to arrive at a potentially acceptable ICER for patisiran [redacted].

The successful EAMS program for patisiran, following its PIM designation from the MHRA, has provided patients with access to treatment without any service delivery burden relating to the provision of specialised services for amyloidosis. The 'real world' experience with patisiran from EAMS can provide further confidence to the Committee regarding the important clinical and patient benefits of treatment.

We hope the totality of these factors can be considered by the Committee in its deliberations of patisiran treatment for this ultra-rare, progressively debilitating, ultimately fatal disease that robs dignity and quality of life from patients and their families.

To crystallize some of the technical topics further, we have provided in our prior correspondence additional technical detail alongside a simple table that highlights important factors to consider.

Please do not hesitate to contact me should you require additional information.

Kindest regards,

Anant Murthy, PhD

Patisiran for treating hereditary transthyretin-related amyloidosis: A Highly Specialised Technology Appraisal

Addendum - ERG critique of the company's updated model

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30th April 2019

1. Introduction

The current NICE Evaluation Consultation Document[1] (ECD) for patisiran makes the following recommendation:

"Patisiran is not recommended, within its marketing authorisation, for treating hereditary transthyretin-related amyloidosis in adults" (NICE ECD,[1] December 2018).

Following the second NICE Appraisal Committee meeting on 12th February 2019, NICE asked the company to consider the following amendments to their health economic analysis:

- Consider revising the simple PAS and move away from commercial arrangements
- Consider approaches to introduce the impact of autonomic neuropathy symptoms, highlighted by patients and clinicians as being of particular importance
- Consider a stopping rule in accordance with the marketing authorisation: Patisiran to be stopped if patients enter FAP stage 3 (PND IV)
- Consider adding caregiver disutilities to achieve consistency with the inotersen model. The committee accepted the inotersen model which assumes 1 full-time caregiver for each patient in the first 2 stages of the disease and 2 carers at stage 3.

In April 2019, the company submitted an additional evidence submission[2] containing new analyses undertaken using an updated version of the company's model. The executable model was provided for scrutiny by the ERG.

The company's new analyses based on the updated model include the following:

[redacted]

(b) An assumption that mortality risk does not increase with increasing PND score
(c) Additional disutilities applied to the BSC group which are intended to reflect the additional impact of GI-related autonomic dysfunction
(d) A stopping rule in which patients discontinue patisiran on progression to PND IV and the re-introduction of the log normal time-to-treatment discontinuation function applied to all other model health states
(e) The inclusion of caregiver disutilities based on the inotersen model.

This addendum provides a summary and critique of the company's new analyses. Section 3 presents further analyses undertaken by the ERG using the company's updated model.

Following further communication between the company, NICE and the ERG, the company submitted an amended version of the updated model; all results presented in this addendum are based on this amended version of the updated model.

2.1 [redacted]

2.2 Exclusion of PND-related mortality risks

The company's updated model makes the assumption that mortality risk for patients with hATTR amyloidosis does not increase with increasing PND score. Hence, within the company's new analyses, the hazard ratios (HRs) for mortality for all PND states are set equal to 2.01 (the HR used by the company to characterise mortality risk in patients with hATTR amyloidosis relative to mortality in the general population), unless the patient has an NT-proBNP level ≥3,000pg/mL. The company's additional evidence submission states that this assumption has been made because *"As documented in the extensive natural history of disease in the UK and the attestation of clinical experts, the leading cause of death of hATTR amyloidosis in the country is cardiomyopathy"* (Company's additional evidence submission,[2] April 2019). The company's additional evidence submission also highlights that the ERG report criticised the source of PND-related mortality (Suhr *et al*[3]) and the complexity of the method used by the company to derive mortality risks conditional on the model health states. The company also notes that the ERG's exploratory analyses included a scenario in which PND-related mortality was removed from the model.

As described in the original ERG report, the HRs are "chained" together – for example, the HR for mortality in state PND IIIa and NT-proBNP≥3,000pg/mL is calculated as the product of: (i) the HR for hATTR amyloidosis versus general population mortality; (ii) the HR for PND IIIa/b versus PND 0-II and (iii) the HR for NT-proBNP≥3,000pg/mL versus NT-proBNP<3,000pg/mL. These HRs are assumed to be constant over time. Table 1 presents the HRs for death according to PND score and NT-proBNP level applied in the company's original model alongside those applied in the company's updated model. Figure 1 presents the modelled survival trajectories for the patisiran and BSC groups

including both PND and NT-proBNP risks (as per the company's original model), and including NT-proBNP risks only (as per the company's updated model).

Table ***2*** shows the impact of re-introducing the PND-related HRs for death on the results of the company's updated model (in line with the company's original model).

Table 1: HRs for death applied in company's original model and company's updated model

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

Figure 1: Company's new and original mortality projections

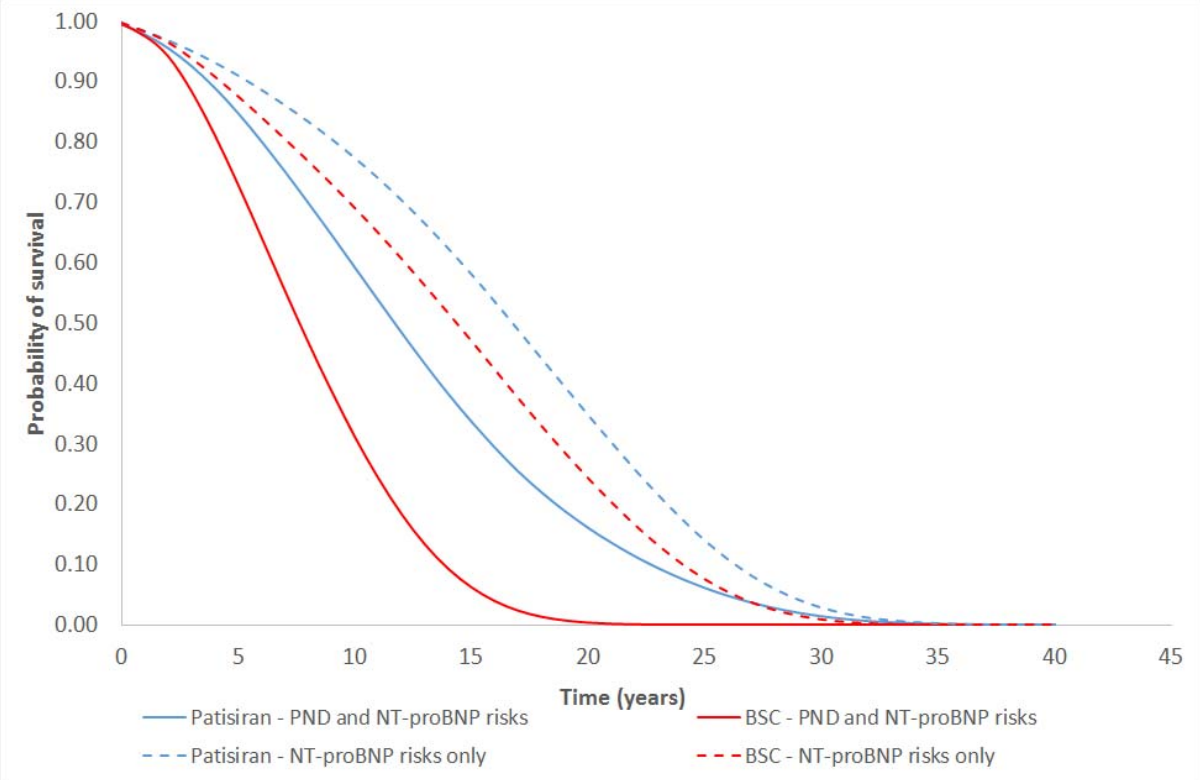

Table 2: Company's updated model results – with/without PND-related mortality HRs

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – including NT-proBNP risks only							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – including PND and NT-proBNP risks							
Patisiran	12.79	4.58	[redacted]	4.52	6.21	[redacted]	[redacted]
BSC	8.27	-1.63	[redacted]	-	-	-	-

‡ *Undiscounted*

As shown in Table 1, the removal of the PND-related mortality HRs from the company's updated model leads to a lower modelled risk of death for patients in all health states, except for PND0-II, NT-proBNP<3,000pg/mL. In turn, this leads to a marked increase in the expected survival durations for patients in both the patisiran and BSC groups (see Figure 1). As shown in

Table ***2***, removing the PND-related mortality HRs has a substantial impact on the model results:

- Mean survival for the BSC group is increased from 8.27 (original model) to 14.53 years (company's new model). This represents an increase of 6.27 years.
- The incremental QALYs gained for the patisiran group are increased – this is a consequence of the extended survival in the BSC group together with the company's assumptions of time-dependent HRQoL and the assumption that BSC-treated patients cannot transition to improved health states. The ERG notes that according to the company's model, per-cycle QALY gains in the BSC group become negative after 4 cycles (2 years) and remain negative for every subsequent cycle. The assumption of increased survival for these patients therefore increases the number of QALYs lost by patients receiving BSC.
- Mean costs for the BSC group are more than doubled (BSC costs including PND and NT-proBNP risks = [redacted]; BSC costs including NT-proBNP risks only = [redacted]). This is a consequence of extended survival for BSC and the assumption that BSC-treated patients cannot transition to improved health states. Under the company's new scenario, virtually all of the extended survival time for BSC patients is spent in PND IV (the worst and most expensive health state).
- When both PND and NT-proBNP mortality risks are included in the company's updated model, the ICER for patisiran versus BSC is [redacted] per QALY gained. When only NT-proBNP risks are applied, the ICER is reduced to £80,730 per QALY gained.

The ERG's critique of the evidence used to inform this aspect of the model and the methods used to derive HRs can be found in the ERG report (Section 5.3.3, critical appraisal point 5). The ERG agrees that there is uncertainty regarding the expected survival duration of patients with hATTR amyloidosis. However, the ERG has several concerns regarding the appropriateness of the company's new mortality assumptions.

- As described above, the company's new survival assumptions have a substantial impact upon the expected survival, QALYs, costs and cost-effectiveness estimates.
- According to the ECD, the Appraisal Committee previously accepted the company's original approach to modelling mortality risks. The ECD states: *"The clinical experts agreed with the company's approach of combining both the effect of polyneuropathy and cardiac involvement, and explained that patients usually die from cardiac complications. They noted that the hazard ratios for each PND/NT-proBNP combination were largely plausible. In its preferred analysis, the ERG assessed the impact of removing the mortality effect in patients with no cardiac involvement. The committee recognised the complexities of the company's approach and its limitations, but concluded that this approach was acceptable because of the lack of other evidence"* (NICE ECD,[1] Section 4.16).
- The company's original submission included details relating to the company's efforts to validate their original model (see CS,[4] Section 12.2.5, Table D11). The CS states that the clinicians that the company consulted: (i) agreed with the inclusion of mortality due to PND; (ii) agreed with the use of Suhr *et al*[3] (in the absence of other sources), and (iii) believed that the estimated survival gains for the BSC group were *"within the realm of plausibility."* Given that the estimated mean survival gains for the BSC group in the updated model have increased by 6.27 years compared with the original model, the ERG considers it unlikely that the company's clinical advisors would still believe that the company's modelled survival estimates remain plausible. However, the company's additional evidence submission does not provide any information regarding this, and the CS provided little information regarding the questions that the company asked the clinicians when attempting to validate the original model.
- In April 2019, inotersen received a positive recommendation from NICE.[5] The inotersen model used the PND-related HRs derived from the original patisiran model[4] (applied to states defined by FAP), but did not include additional mortality risks for patients with NT-proBNP NT-proBNP<3,000pg/mL.
- Additional information provided by the company in late April 2019 (page 7) suggests that the inclusion of NT-proBNP-related mortality only or using PND-related mortality only within the patisiran model produces similar survival estimates for BSC (14.53 years versus 11.05 years). The ERG disagrees with the company's view that these estimates are similar.

- The company's additional evidence submission highlights that the ERG presented an analysis in which PND-related mortality risks were removed (see ERG report, Table 34, exploratory scenario analysis 11). The ERG notes that this analysis was presented to highlight the significant impact of the assumption of time- and state-dependent improvements in HRQoL for patisiran and time- and state-dependent worsening in HRQoL for BSC on the ICER for patisiran.
- The ICER patisiran model[6] included mortality risks associated with increasing FAP stage and cardiac involvement.

The ERG believes that the company's updated mortality assumptions are inconsistent with the assumptions previously agreed by the Appraisal Committee, the company's clinical advisors, the NICE inotersen model[5] and the ICER patisiran model.[6] As such, the ERG does not consider the company's updated mortality assumptions to be reasonable. However, for the sake of consistency with the NICE inotersen appraisal, Section 3 presents additional ERG analyses in which only PND-related mortality risks are applied within the model (NT-proBNP risks are removed).

2.3 Additional GI-related disutilities applied to the BSC group

The company's updated model includes time- and state-dependent utilities based on a regression model fitted to EQ-5D data from APOLLO. Within the patisiran group, HRQoL in each state is assumed to increase at a constant rate for 5 years and subsequently plateau; within the BSC group, HRQoL is assumed decrease at a constant rate for 5 years and subsequently plateau. The ERG believes that the duration over which these increases/decreases in HRQoL in each state are applied has been accepted by the NICE Appraisal Committee. The company's updated model includes an additional assumption whereby patients with PND>I in the BSC group incur further time-independent GI-related disutilities, based on values taken from a UK catalogue of utility values for chronic conditions in the UK (Sullivan *et al*[7]). Patients in PND II are assumed to incur a disutility of -0.0727 during each model cycle (based on the reported disutility for "ICD-9 564 Funct Digestive Dis Nec"). Patients in PND IIIA to IV are assumed to incur a disutility of -0.1243 during each model cycle (based on the reported values for "ICD-9 564 Funct Digestive Dis Nec" plus "ICD-9 569 Oth Intestinal Disorders"). Amongst others, these ICD codes include some forms of constipation, irritable bowel syndrome, post-gastric surgery syndromes, vomiting and other disorders post-surgery, diarrhoea, megacolon, and neurogenic bowel.

The company's updated utility profiles for the BSC group are illustrated in Figure 2 (note – the utility values shown assume that no patient changes health state over time). The impact of these GI-related disutilities on the ICER for patisiran versus BSC are shown in Table 3. As shown in the table, the inclusion of these additional disutilities for BSC increases the magnitude of the QALY losses in the BSC group and reduces the ICER for patisiran versus BSC by around [redacted].

Figure 2: Company's updated utilities for BSC group (excluding caregiver disutilities)

Table 3: Company's updated model results – with/without additional GI-related disutilities

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – time-dependent utilities capped at 5-years, with GI-related disutilities							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – time-dependent utilities capped at 5-years, no GI-related disutilities							
Patisiran	16.62	4.04	[redacted]	2.09	7.47	[redacted]	[redacted]
BSC	14.53	-3.43	[redacted]	-	-	-	-

‡ Undiscounted

The ERG has several concerns regarding the inclusion of these new GI-related disutilities:

- The ERG understands that the company's approach to modelling improvement (patisiran) or worsening (BSC) in EQ-5D within each PND health state over time is an attempt to reflect those aspects of hATTR amyloidosis which are not captured in the company's definition of the model health states (i.e. by PND or NT-proBNP). The extrapolation of EQ-5D over time within a health state is unconventional and the ERG believes that this approach leads to a lack of clarity regarding the actual health state that is being valued. The ERG also notes that if the company's inclusion of further GI-related disutilities in the updated model is intended to quantify other

factors which are not reflected in the definition of PND- and NT-proBNP-related health states, this then means that it is unclear what the time-dependent utilities are intended to reflect. The ERG believes that the inclusion of both effects on HRQoL may represent double-counting and, as such, may overestimate the negative health impact of the disease on patients treated with BSC. This is an area of uncertainty and there are no data to support or refute this.

- The company's additional evidence submission[2] does not provide any information regarding whether the health states valued in Sullivan *et al*[7] reflect the specific health impacts which they consider are not captured in the existing time- and state-dependent utilities.
- The company's updated model applies the additional GI-related disutilities from Sullivan *et al*[7] to every BSC patient with PND>1 at all timepoints. This appears to imply that: (i) all BSC patients with PND>1 will experience these symptoms indefinitely, and that (ii) none of the impact of GI-related symptoms is reflected in the time- and state-dependent EQ-5D estimates. Given that hATTR amyloidosis is a progressive disease in which symptoms accumulate over time, this assumption is unlikely to be reasonable.
- The application of constant disutilities to all patients with PND>I together with the time- and state-dependent EQ-5D estimates is inconsistent with the predictions of the company's regression model fitted to EQ-5D data from APOLLO.
- The company's updated model does not apply the additional GI-related disutilities to those patients who have discontinued patisiran. This implies that even after discontinuation, patisiran provides a lifetime protective effect against GI-related autonomic dysfunction. The ERG believes that if it is appropriate to include these GI-related disutilities, they should be applied to all patients who are receiving BSC, irrespective of whether they have previously received patisiran.
- The amended version of the company's updated model includes GI-related disutilities for patisiran discontinuers, but includes an additional assumption that these GI-related symptoms do not manifest fully after discontinuation. The ERG notes that this assumption favours patisiran as it still assumes some degree of protective effect of the drug following discontinuation.

2.4 Discontinuation of patisiran

The company's updated model includes a stopping rule whereby patients discontinue patisiran upon progression to PND IV. The company has also re-implemented the time-to-treatment discontinuation function applied in the original model.[4] The company's updated analysis assumes that:

(i) Patients in any health state can discontinue patisiran, with per-cycle probabilities determined by the log normal time-to-treatment discontinuation function fitted to data from APOLLO

(ii) Patients who reach PND IV will immediately discontinue patisiran and subsequently receive BSC

(iii) The prognosis of patients who have discontinued patisiran is governed by the BSC transition probabilities

(iv) HRQoL for patisiran discontinuers is assumed to decrease according to the slope of the time-dependent HRQoL functions for BSC, starting from the patient's last "on treatment" utility value. This is applied using a weighted average contribution of the fraction of the cohort already off-treatment in the previous cycle and of the cohort discontinuing in the current cycle.[2]

(v) In the company's updated model, patisiran discontinuers do not incur any the additional GI-related disutilities described in Section 2.3.

(vi) In the amended version of the company's updated model, patisiran discontinuers do not incur the full GI-related disutilities; instead, they incur 10% of the full GI-related disutilities. In addition, lower limits for utilities for patisiran discontinuers were calculated using complex formulae which attempt to estimate a weighted average between the cohort discontinuing in the current cycle and the cohort already off-treatment in the previous cycle.

The impact of the PND IV stopping rule and the re-introduction of the APOLLO time-to-treatment discontinuation function on the ICER for patisiran versus BSC is shown in

Table **4**.

Table 4: Company's updated model results – with/without discontinuation

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – time to treatment discontinuation curve and PND IV stopping rule							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model –PND IV stopping rule only							
Patisiran	16.74	4.33	[redacted]	2.21	9.00	[redacted]	[redacted]
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – time to treatment discontinuation curve only							
Patisiran	17.94	6.95	[redacted]	3.41	11.45	[redacted]	[redacted]
BSC	14.53	-4.50	[redacted]	-	-	-	-

‡ Undiscounted

With respect to the inclusion of the stopping rule and time-to-treatment discontinuation curve from APOLLO, the ERG notes the following:

- As described above, the ERG believes that if it is considered appropriate to apply the additional GI-related disutilities to the BSC group, these should also be applied to patients who have discontinued patisiran (at the point of discontinuation).
- The simultaneous application of the time-to-treatment discontinuation function from APOLLO and the company's PND IV stopping rule may overestimate the joint discontinuation risk.
- The company's approach for estimating HRQoL in patisiran discontinuers is problematic given the company's assumptions regarding time- and state-dependent utilities. The appropriate approach for implementing the company's intended assumptions regarding HRQoL (i.e. no rebound effect on HRQoL after discontinuation) would require the use of tunnel states which account for the subsequent HRQoL trajectory of patients in a given health state who discontinue patisiran at each timepoint in the model. This would require the use of tunnel states which explicitly account for changes in HRQoL for incident and prevalent discontinuers. This could be implemented using a semi-Markov or patient-level simulation approach; however, the ERG does not believe that it is possible to appropriately implement the company's intended assumptions using the company's existing Markov model structure.
- Following receipt of the updated model, the ERG asked the company to clarify the assumptions underpinning their implementation of post-discontinuation utility in the model. In response, the company stated that these were the same as those used in the NICE inotersen model. The ERG does not believe that this claim is accurate. The company's amended model includes complex formulae which attempt to approximate the appropriate approach described above. The ERG was unable to fully understand the logic underpinning the company's calculations.
- The impact of this structural issue cannot be fully assessed using the company's model structure.

2.5 Inclusion of caregiver disutilities

The company's updated model includes caregiver disutilities; these were taken from the Akcea model developed to inform the NICE appraisal of inotersen.[8] The impact of including these disutilities on the ICER for patisiran is shown in Table 5.

Table 5: Company's updated model results – with/without caregiver disutilities

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – including caregiver disutilities from inotersen model							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**

BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – no caregiver disutilities							
Patisiran	16.62	4.31	[redacted]	2.09	7.14	[redacted]	[redacted]
BSC	14.53	-2.83	[redacted]	-	-	-	-

‡ *Undiscounted*

The NICE Final Evaluation Document (FED) for inotersen[5] states the *"The committee accepted the company's revised approach and concluded that it was appropriate to assume 1 carer in stages 1 and 2, and 2 carers in stage 3 of the model."* The ERG believes that for the sake of consistency, it is reasonable to include these additional caregiver disutilities in the patisiran model.

2.6 Use of inotersen time-to-treatment discontinuation function

The company's additional evidence submission highlights that discontinuation rates were higher for inotersen compared with patisiran and presents an analysis in which the time-to-treatment discontinuation function for inotersen is applied to the patisiran group. This reduces the ICER for patisiran. The ERG believes that it is inappropriate to use the inotersen time-to-treatment discontinuation function as this relates to a different technology. The ERG believes that these analyses should be disregarded.

3. Additional analyses undertaken by the ERG

The ERG has undertaken additional exploratory analyses using the amended version of the company's updated model. All of the ERG's exploratory analyses have the following features:

(i) GI-related disutility is applied equally to patients receiving BSC and to patients who have discontinued patisiran. This is applied outside of the minimum/maximum utility caps.

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

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

(iv) All analyses include the current PAS for patisiran.

The following analyses were undertaken using this amended version of the model:

- Exploratory analysis 1. This analysis applies features (i) to (iv) within the company's updated base case model (NT-proBNP mortality only).
- Exploratory analysis 2a. This analysis applies features (i) to (iv) and includes both PND- and NT-proBNP-related mortality.
- Exploratory analysis 2b. This analysis is the same as 2a, with GI-related disutilities halved.

- Exploratory analysis 2c. This analysis is the same as 2a, with GI-related disutilities removed.
- Exploratory analysis 3a. This analysis applies features (i) to (iv) and includes both PND-related mortality only.
- Exploratory analysis 3b. This analysis is the same as 3a, with GI-related disutilities halved.
- Exploratory analysis 3c. This analysis is the same as 3a, with GI-related disutilities removed.

The results of the analyses are presented in Table 6.

Table 6: Additional analyses of the company's updated model undertaken by the ERG

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's updated model base case							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Exploratory analysis 1. Updated model, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	16.62	3.55	[redacted]	2.09	8.23	[redacted]	[redacted]
BSC	14.53	-4.67	[redacted]	-	-	-	-
Exploratory analysis 2a. Updated model, PND and NT-proBNP mortality HRs, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	12.79	4.37	[redacted]	4.52	6.00	[redacted]	[redacted]
BSC	8.27	-1.63	[redacted]	-	-	-	-
Exploratory analysis 2b. Updated model, PND and NT-proBNP mortality HRs, GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)							
Patisiran	12.79	4.47	[redacted]	4.52	5.73	[redacted]	[redacted]
BSC	8.27	-1.25	[redacted]	-	-	-	-
Exploratory analysis 2c. Updated model, PND and NT-proBNP mortality HRs, no GI-related disutilities applied for discontinuers or BSC							
Patisiran	12.79	4.58	[redacted]	4.52	5.46	[redacted]	[redacted]
BSC	8.27	-0.88	[redacted]	-	-	-	-
Exploratory analysis 3a. Updated model, PND mortality HRs only, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	14.25	4.09	[redacted]	3.21	7.09	[redacted]	[redacted]
BSC	11.05	-3.00	[redacted]	-	-	-	-
Exploratory analysis 3b. Updated model, PND mortality HRs only, GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)							
Patisiran	14.25	4.25	[redacted]	3.21	6.75	[redacted]	**£125,256**
BSC	11.05	-2.50	[redacted]	-	-	-	-
Exploratory analysis 3c. Updated model, PND mortality HRs only, no GI-related disutilities applied for discontinuers or BSC							
Patisiran	14.25	4.41	[redacted]	3.21	6.42	[redacted]	[redacted]
BSC	11.05	-2.01	[redacted]	-	-	-	-

As shown in Table 6, including PND-related mortality, with or without additional risks for patients with high NT-proBNP, leads to ICERs which are higher than those presented in the company's additional evidence submission. The ERG believes that some caution should be given to the interpretation of results generated using the company's model due to the method used to calculate post-discontinuation

utilities. An exploratory "worst-case" scenario analysis conducted by the ERG, in which the utility profile for patisiran discontinuers was set equal to that for the BSC group, produced ICERs which were around [redacted] higher than those presented in Table 6. Whilst this aspect of the company's model is incorrectly implemented due to its structural limitations, it may not have a large impact on the estimated ICER for patisiran.

4. References

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Addendum – Additional analyses requested following the third HST Appraisal Committee meeting

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22nd May 2019

This document provides estimates of undiscounted QALY for the full range of ERG scenarios considered during the third Appraisal Committee meeting.

Scenario description			**Undiscounted QALYs**		
ERG addendum table reference	**Description**	**ICER (for reference)**	**Patisiran**	**BSC**	**Incremental**
2	Company, base case	£80,730	5.08	-7.11	12.19
2	Company, NTproBNP+PND mortality risks	[redacted]	5.99	-2.25	8.24
3	Company, no GI disutilities	[redacted]	5.08	-5.43	10.52
4	Company, PND IV stopping rule only	[redacted]	5.50	-7.11	12.61
4	Company, time on treatment curve only	[redacted]	9.78	-6.91	16.70
5	No caregiver disutilities	[redacted]	5.43	-4.48	9.91
6	ERG analysis 1	[redacted]	4.35	-7.11	11.46
6	ERG analysis 2a	[redacted]	5.70	-2.25	7.96
6	ERG analysis 2b	[redacted]	5.84	-1.80	7.64
6	ERG analysis 2c	[redacted]	5.98	-1.35	7.34
6	ERG analysis 3a	[redacted]	5.28	-4.29	9.57
6	ERG analysis 3b	£125,256	5.50	-3.67	9.16
6	ERG analysis 3c	[redacted]	5.72	-3.04	8.77