

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Evaluation consultation document

**Inotersen for treating hereditary transthyretin-
related amyloidosis**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using inotersen in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the [committee papers](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of inotersen in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using inotersen in the context of national commissioning by NHS England.

For further details, see the [interim process and methods of the highly specialised technologies programme](#).

The key dates for this evaluation are:

Closing date for comments: 9 January 2019

Second evaluation committee meeting: 12 February 2019

Details of membership of the evaluation committee are given in section 6.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Recommendations

- 1.1 Inotersen is not recommended, within its marketing authorisation, for treating polyneuropathy in adults with hereditary transthyretin-related amyloidosis.
- 1.2 This recommendation is not intended to affect treatment with inotersen that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Hereditary transthyretin-related amyloidosis is a rare condition that severely affects the quality of life of people with the condition, and their families and carers. Current treatment is supportive care.

Clinical trial evidence shows that inotersen slows progression of the disease considerably. But it is uncertain whether this is maintained in the longer term.

The assumptions in the economic modelling are uncertain, particularly around utility values, number of carers, mortality and stopping of treatment. Also, the cost-effectiveness estimates for inotersen are much higher than what NICE considers acceptable for highly specialised technologies.

Although inotersen slows progression of the disease and is innovative, it does not appear to provide value for money in the context of a highly

specialised service. Therefore inotersen is not recommended for routine funding in the NHS.

2 The condition

2.1 Hereditary transthyretin-related (hATTR) amyloidosis is an ultra-rare condition caused by inherited mutations in the TTR gene. This causes the liver to produce abnormal TTR protein, which accumulates as deposits in body tissues (amyloidosis). These deposits can disrupt the structure and damage the function of affected tissues.

2.2 Because hATTR amyloidosis can affect tissues throughout the body, people may have a range of symptoms relating to 1 or more systems. Affected systems can include the autonomic nervous system, peripheral nerves, heart, gastrointestinal system, eyes and central nervous system. The effects and complications of the condition can lead to death within 3 to 15 years of symptoms developing. At the time of the evidence submission, there were thought to be around 150 people with hATTR amyloidosis in the UK.

2.3 Neuropathy in hATTR amyloidosis can be classified according to walking ability (described by Coutinho et al.1980):

- Stage 1: people do not need help with walking and have mostly mild sensory, motor neuropathy in the lower limbs, and autonomic neuropathy
- Stage 2: people need help with walking, there is progression in the lower limbs and symptoms develop in the hands (weakness and muscle wasting).
- Stage 3: people are wheelchair bound or bedridden and have severe sensory and motor neuropathy of all limbs, and autonomic neuropathy

2.4 People may mainly have symptoms of polyneuropathy or cardiomyopathy, but most patients seen in the NHS will have symptoms of both over the

course of the condition. In the UK, the most common genetic mutations associated with both polyneuropathy and cardiac involvement are Val122Ile (39%), Thr60Ala (25%) and Val30Met (17%). The Val30Met mutation is associated with higher survival rates. Val122Ile is primarily associated with cardiomyopathy.

- 2.5 Current treatment options for people with hATTR amyloidosis are limited. They mainly focus on symptom relief and supportive care including pain management, nutritional and mobility support, and lessening the effects of the condition on other organs (for example, pacemakers, arrhythmia management). There are no disease-modifying treatments for people with hATTR amyloidosis that is being treated in the NHS. Other pharmacological treatments may be used, including difflunisal, which is sometimes used outside of its marketing authorisation to treat hATTR amyloidosis. It is contraindicated in people with cardiac impairment and those taking anticoagulants.
- 2.6 Liver transplant, which prevents the formation of additional amyloid deposits, might be an option for some people. However, a transplant can only be done early in the course of the disease, and outcomes are poor in people with cardiac involvement, so it is rarely done in England.
- 2.7 The National Amyloidosis Centre in London provides the only highly specialised service for people with amyloidosis and related disorders in the UK. People with hATTR amyloidosis are assessed (for overall clinical status, neuropathy progression and cardiac involvement) and followed up every 6 months at the centre, and treatment is started there.

3 The technology

- 3.1 Inotersen (Tegsedi, Akcea Therapeutics) is a novel, first-in-class 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide that inhibits production of transthyretin (TTR) in adults with hereditary transthyretin-related (hATTR) amyloidosis. Inotersen has a marketing authorisation for

‘the treatment of stage 1 or stage 2 polyneuropathy in adults with hATTR amyloidosis’.

- 3.2 The most frequent adverse reaction listed in the summary of product characteristics is injection site reactions (50.9%). Other commonly reported adverse reactions are nausea (31.3%), anaemia (27.7%), headache (23.2%), pyrexia (19.6%), peripheral oedema (18.8%), chills (17.9%), vomiting (15.2%), thrombocytopenia (13.4%) and decreased platelet count (10.7%). In the main clinical trial for inotersen (the NEURO-TTR study) there was 1 death, which was considered to be related to inotersen. The main safety concerns with inotersen treatment are glomerulonephritis and thrombocytopenia, therefore enhanced monitoring (platelet count, urine protein to creatinine ratio and estimated glomerular filtration rate [eGFR]) has been implemented. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.3 Inotersen is self-administered once weekly by subcutaneous injection. The price of inotersen per weekly dose (284 mg) is £5,925 (excluding VAT; company submission). The company has a commercial arrangement, which would apply if the technology had been recommended.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Akcea Therapeutics, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Burden of disease

- 4.1 The patient and clinical experts explained the all-consuming nature of hereditary transthyretin-related (hATTR) amyloidosis. They highlighted that the condition affects all aspects of the lives of patients, and their families and carers. It is a multi-system condition, which has a considerable effect on patients' independence, dignity, and their ability to work, take part in family and social life, and carry out daily activities. They also highlighted that patients need a high level of care as the condition progresses. The clinical experts explained that the clinical signs of hATTR amyloidosis are heterogeneous, and can be associated with a very wide range of impairments.
- 4.2 The neurological deficit associated with hATTR amyloidosis progresses to the legs and the upper limbs. A survey by Amyloidosis Research Consortium UK collected information on 101 patients and 51 carers with experience of the condition. It showed that 86% of patients have numbness, tingling or pain in the lower part of their body, and 74% have muscle weakness and difficulty walking or climbing stairs. Autonomic symptoms typically include dizziness or fainting, vomiting, severe diarrhoea or constipation or both, and neurogenic bladder; 38% of patients in the survey reported having faecal or urinary incontinence that considerably impairs their quality of life. Symptoms may severely affect professional and social life. The patient experts explained that the condition may affect many members of the same family. Patients have often been carers for their parents, and they may also be concerned about their children developing the condition in the future.
- 4.3 The condition places a significant burden on family members because they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own. Carers of people with hATTR amyloidosis reported that dealing with gastrointestinal problems

(especially diarrhoea), patients' mental functioning and the combination of symptoms is particularly difficult. The committee concluded that hATTR amyloidosis is a rare, serious and debilitating condition that severely affects the lives of patients, families and carers.

Unmet need

4.4 The clinical experts explained that hATTR amyloidosis is a progressive and relentless condition, and currently there are no treatments available to treat the underlying cause. The condition is usually not diagnosed immediately, there is typically a delay of 4 years from the first symptoms appearing to getting a diagnosis. As a result, at the time of diagnosis, the condition is likely to be advanced and the survival rate poor. Patient experts also explained that they have mixed experiences of symptom and disease management approaches, and that new treatments offer considerable hope to them and to their families. Patients and carers value efficacy, convenience, and a low risk of side-effects. However, they are likely to accept risks if they are outweighed by treatment benefit. The clinical experts also expected that better communication and predictive testing would help to diagnose the condition earlier. Patients might be able to fully recover if a disease-modifying treatment was available. The committee recognised that there is a significant unmet need for effective treatment options for hATTR amyloidosis.

Impact of the new technology

Clinical evidence

4.5 The company's clinical evidence came from 2 studies:

- NEURO-TTR was a double-blind, randomised, placebo-controlled study which assessed the efficacy of inotersen (n=113) compared with placebo (n=60) when administered for 65 weeks (15 months). After NEURO-TTR ended, patients could enter the extension study for long-

term follow-up. Also, patients on placebo could switch to treatment with inotersen.

- The NEURO-TTR Extension study was an open-label study that evaluated the long-term efficacy and safety of inotersen. Information about the extension study is considered academic in confidence by the company, so cannot be presented here.

The committee discussed the generalisability of the trials. It acknowledged that 6 patients in NEURO-TTR were recruited from the UK. It also discussed the genetic mutations of patients in the trials and in UK clinical practice. The committee understood that the most common genetic mutations in patients in NEURO-TTR were Val30Met (52%), Thr60Ala (13%) and Leu58His (6%), which the clinical experts considered to reflect those usually seen in the UK. The ERG noted that patients in the inotersen arm had had cardiomyopathy symptoms for longer (45 months) than those in the placebo arm (34 months). The company highlighted that this would potentially have biased the results against inotersen. The committee therefore concluded that the trial population was generalisable to patients in UK clinical practice. It also understood the limitations of developing an evidence base for an ultra-rare condition and was satisfied that it had been presented with the best available evidence.

Study outcomes

- 4.6 The primary outcomes in NEURO-TTR were mean change from baseline in neurological impairment as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) and the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) score at 15 months. The mNIS+7 is a composite measure of neurological impairment including motor, sensory and autonomic polyneuropathy assessment. Norfolk QoL-DN is a patient-reported measure validated in patients with hATTR amyloidosis with polyneuropathy. It is designed to capture the effect of neuropathy on quality of life. A decrease in mNIS+7 score indicates a reduction in neurological impairment and a decrease in Norfolk QoL-DN total score

indicates an improvement in quality of life. Other outcomes included the assessment of serum transthyretin (TTR) levels, neurological impairment, cardiac function, autonomic function, weight loss, motor function, quality of life and safety. The company explained that the studies were powered to detect changes in both primary outcomes.

- 4.7 The committee discussed whether the outcomes captured all aspects of the condition. The clinical experts explained that hATTR amyloidosis is a systemic condition and its main features are peripheral neuropathy, and autonomic and cardiac symptoms (see section 2.2). They further explained that mNIS+7 is a comprehensive measure of neurological impairment that has been specifically modified from the original NIS+7. It was modified to better characterise and quantify sensory function at multiple sites, autonomic function and nerve conduction changes associated with progression of hATTR amyloidosis, and to capture gastrointestinal dysfunction. The committee was aware that the Norfolk QoL-DN was developed in people with diabetes. However, the clinical experts explained that the autonomic symptoms seen in diabetes, such as gastrointestinal symptoms, are similar to those seen in hATTR amyloidosis. The committee acknowledged that it was difficult to capture all aspects of a condition that has such a big impact on patients. But it concluded that the outcome measures used in the clinical trial captured the condition reasonably well and included most aspects of importance to patients.

Results

- 4.8 During the 15 months of the NEURO-TTR study, a statistically significant difference in favour of inotersen was seen, that is, there was a slower rate of disease progression in patients who had inotersen than in patients who had placebo. The mean increase from baseline in the mNIS+7 composite score in the placebo arm was 24.9 compared with 4.2 in the inotersen arm at week 66. The least squares mean (LSM) difference between groups was 19.73 points ($p < 0.001$). The difference was statistically significant in

all components of the mNIS+7 score and for the subgroups analysed. The committee was aware that a 2-point change was considered the minimum clinically important difference, based on a consensus report of the Peripheral Nerve Society. For the change from baseline in Norfolk QoL-DN score at 15 months, there was little change in the inotersen arm (-0.08), but an increase of 10.8 was seen in the placebo arm (LSM difference between arms of 11.68, $p < 0.001$). No minimal clinically important difference for the Norfolk QoL-DN is reported in the literature. Patient experts noted that slowing disease progression is of value to them and their families and carers because without treatment, progression to the later, debilitating stages of the disease can be rapid. Therefore to remain in the earlier stages of the disease, with a better quality of life, for longer, would benefit patients and their families and carers. But the ERG explained that no evidence was provided suggesting that inotersen completely stops peripheral neuropathy in hATTR amyloidosis. Inotersen greatly slowed the progression of neuropathy but did not reverse the disease. The committee concluded that the evidence showed that inotersen had considerable benefit in slowing disease progression, but it did not stop progression.

- 4.9 The mean serum TTR reduction over 15 months exceeded 70% in the inotersen group, ranging from 68.41% in week 13 to 74.03% in week 65. In the placebo group, mean serum TTR decreased by 8.5% in week 3 and then remained constant throughout the study period. Differences in LSMs between the arms for change in TTR concentration from baseline were statistically significant ($p < 0.001$) at all time points. The clinical experts expressed their view that circulating TTR reduction is the preferred surrogate marker for amyloidosis and they considered this to be an important indicator of disease response to treatment. They also stated that, in general, people whose TTR serum level decreased by 80% have a better prognosis than people with smaller reductions in TTR serum levels. The committee understood that inotersen did not decrease the TTR serum level by 80%. It therefore concluded that even with inotersen treatment

there is disease progression and people progress into more severe stages.

Long-term benefits of inotersen

4.10 The main clinical trial providing evidence for inotersen was 15 months long. The committee also considered results from the extension study (considered academic in confidence by the company, therefore not presented here; see section 4.5). The committee discussed the likelihood of inotersen being beneficial for a longer period of time and its effects on disease progression. The clinical experts explained that, based on other forms of amyloidosis, if production of amyloid protein is stopped clearance of amyloid deposits from the organs can lead to improvements in clinical outcomes, although this can take many years. Circulating TTR reduction is considered to predict such improvement. The committee recalled that circulating TTR was reduced by about 70% in patients on inotersen treatment (see section 4.9) in the clinical trial. This was less than the optimal percentage suggested by the clinical experts, and it therefore noted that long-term clearance of amyloid may not be achieved. The committee noted that further data are being collected in the extension study, but concluded that there was insufficient evidence on the long-term benefits of inotersen. It therefore remained uncertain whether the clinical benefit would be maintained in the long term.

Adverse events

4.11 Treatment-emergent adverse events were seen in almost all patients in either the placebo or inotersen arm of NEURO-TTR. Most of these events were mild or moderate. Five deaths occurred in the inotersen arm and 1 death (from intracranial haemorrhage caused by severe thrombocytopenia [a reduced number of blood platelets]) was considered to be related to the study drug. There were no deaths in the placebo arm. After monitoring of platelet levels was implemented (see section 3), no other severe thrombocytopenia events occurred in NEURO-TTR. The company and clinical experts explained that platelet numbers may reduce

gradually in some people who have inotersen and sudden falls are not expected; therefore bi-weekly monitoring is appropriate. People whose platelets decrease may have their dose of inotersen reduced by increasing the interval between doses, but are expected to be able to return to the licensed dosing schedule when their platelet numbers increase. The committee also understood that in the clinical trial people accepted the increased monitoring because it allowed them to stay on inotersen. The committee acknowledged that the major safety risks associated with inotersen can be effectively managed with routine monitoring in clinical practice. Therefore it concluded that inotersen has an acceptable safety profile.

Cost to the NHS and value for money

Economic model

4.12 The company did a de novo cost-effectiveness analysis comparing inotersen with best supportive care. The cost-effectiveness results were estimated using a cohort-based Markov state transition model. The Coutinho et al. disease staging system (see section 2.3) was used to define health states 1 to 3 and the model also incorporated a death state. Patients could enter the model in health state 1 or 2. A lifetime time horizon (41 years) was adopted to fully capture the effect of the disease and mortality, and a cycle length of 4-weeks was modelled. The company explained that the choice of model structure was based on a model submitted to the Advisory Group for National Specialised Services for a closely related disease area (Vyndaqel [tafamidis] for the treatment of transthyretin amyloidosis in adults with stage 1 symptomatic polyneuropathy). The committee was satisfied that the model structure reflected the course of the condition.

Model assumptions

Starting and stopping treatment

- 4.13 In the model patients could start treatment in either stage 1 or stage 2. The company's model also included a stopping rule; patients were assumed to stop treatment on entering stage 3. The committee noted that this was in line with inotersen's marketing authorisation, which says that inotersen is indicated for stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis. The clinical experts explained that if a patient continues to benefit from treatment, both patients and clinicians would be reluctant to stop treatment in stage 3. However, NHS England stated that it interpreted the wording of the marketing authorisation to mean that treatment should stop when the condition progresses to stage 3. But the committee acknowledged that if treatment was continued in stage 3 in the model, the costs would increase but there would be no additional clinical benefit, so the incremental cost-effectiveness ratio (ICER) would substantially increase. The committee acknowledged that the stopping rule applied in the model may not reflect how the treatment would be used in UK clinical practice, and concluded that this was an additional source of uncertainty.
- 4.14 In addition to stopping treatment on entry into stage 3, patients could stop treatment for other reasons. The committee noted that alternative assumptions around treatment stopping had a considerable effect on the ICER. The clinical experts stated that there is no compassionate use of inotersen in the UK, so they had no knowledge of stopping rates in clinical practice. The clinical and patient experts explained that patients would want to stay on treatment if they believed that they were benefitting from it. In the model, survival curves for time to discontinuation were fitted to data from the NEURO-TTR and NEURO-TTR Extension studies. The company preferred to use exponential curves to predict when treatment would stop. The ERG suggested that the most reasonable extrapolation curve would be one that allows for a persisting but decreasing rate of

stopping treatment over time, and therefore preferred the log-logistic curve. The clinical experts agreed that they would expect only a small number of people to stop inotersen, and that the rate was likely to be higher in the first months and then decrease over time. The committee concluded that the log-logistic curve best reflected the likely rate of stopping of inotersen in clinical practice over time.

Mortality

- 4.15 Parameters used to inform mortality in the model were based on a Delphi panel of 4 clinical experts. The experts were asked to source likely mortality hazard ratios by disease stage relative to general population mortality. The clinical experts explained that the hazard ratios for mortality in the model appeared plausible, but acknowledged the considerable uncertainty around this parameter because it was based on expert opinion rather than published data. The committee concluded that the hazard ratios were highly uncertain and that it would like to see scenario analyses using lower hazard ratios in the model for the next committee meeting.

Carers

- 4.16 In its base case, the company assumed that every patient had 2 full-time carers. The patient experts explained how important carers are for people with hATTR amyloidosis. It noted that patients in stage 1 need minimal support from carers, but the need for support gradually increases in stage 2. In the advanced stage of the condition 24-hour care is essential because of immobility and possible loss of eyesight, combined with other symptoms such as incontinence. The patient experts explained that as the condition progresses relatives who provide care may not be able to provide sufficient support, and therefore professional carers are needed. Clinical experts explained that this is the picture for most patients in the severe disease stage, and that multiple carers are needed to provide round the clock care. The ERG explained that it was appropriate to consider carer disutility in the model, but because patients spend most time in the stage 1 and stage 2 health states in the model, assuming

2 full-time carers throughout the entire model period was inappropriate. The committee agreed with the ERG and concluded that as a reasonable estimate it would prefer to assume 1 carer in every stage in the model.

Adverse event utilities and costs in the model

4.17 The committee discussed uncertainties around the utilities and costs of adverse events in the model. It understood that the company considered most of the adverse events to be mild (serious adverse events less than 5%) or manageable by increased monitoring. Therefore it did not include utility decrements or costs associated with the most serious adverse events in the model. In an exploratory analysis the ERG applied disutilities and costs associated with adverse events in the model. The ERG explained that the changes did not have a major effect on the ICER. However, it concluded that for clarity it would prefer disutilities and costs of adverse events to be included in the model.

Source of utility data

4.18 The company stated that there were no algorithms to map Norfolk QoL-DN to the EQ-5D, therefore published literature was used for health state utilities in the model. The company used the utilities from a study by Stewart et al. 2017, which reports utilities according to Coutinho stages (for Val30Met mutations and 'other mutations') using a Brazilian value set. The ERG argued that using EQ-5D values based on Brazilian general population preferences was questionable because there are important differences in preferences for health states between the UK and the Brazilian populations. The ERG also noted that a standard decrement for any level 3 response was not applied in the Brazilian value set, but was used in the UK value set, meaning that poorer health states are valued substantially lower in the UK tariffs compared to the Brazilian tariffs. The committee concluded that the utility values used in the model were highly uncertain.

- 4.19 The company explained that utility values estimated by applying the UK tariff to the raw EQ-5D response data from the THAOS registry (a global, multicentre, longitudinal observational registry for all patients with hATTR amyloidosis) would have been preferred. The committee heard that this registry is owned by another company and therefore it might not be possible to get access to these data. It asked for these data to be provided, if available, for the next committee meeting.
- 4.20 The committee discussed the alternative utility sources used in the ERG's exploratory analyses. In particular, a study by Faria et al. (2012), which reported utility values by disease stage as used in the tafamidis appraisal (see section 4.12). The committee understood that utilities from Faria et al. were based on mapping from total quality of life (TQoL; based on defined TQoL score cut-offs on the Norfolk QoL-DN questionnaire) to the EQ-5D. The ERG explained that the lowest possible EQ-5D based utility was above 0, and therefore utility gains might be underestimated with this method. Alternatively the SF-36 data from NEURO-TTR could be mapped to EQ-5D but this would only provide utility values for stages 1 and 2. The committee acknowledged that there were advantages and disadvantages with each source of utility data, and recognised the uncertainties around the utility values used in the model. It concluded that it would have preferred to see the UK tariff applied to the raw EQ-5D data from the THAOS registry, but without these data, it preferred to use values from Faria et al.

Discount rate

- 4.21 The committee was aware that NICE's [guide to the methods of technology appraisal](#) (2013) and its [interim process and methods of the highly specialised technologies programme](#) (2017) specify that the discount rate that should be used in the reference case is 3.5% for costs and health effects. However, it also states that a non-reference-case rate of 1.5% for costs and health effects may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely

impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to significant irrecoverable costs. The company, in its base case, incorporated a discount rate of 1.5% for costs and health effects. It justified this change from the reference case, stating that the benefits of treatment were expected to be substantial and sustained over a lifetime. Firstly, the committee recalled its discussions around long-term benefits (see section 4.10) and its conclusion that it remained uncertain whether the clinical benefit seen would be maintained in the long term. Secondly, it did not consider that there was sufficient evidence to conclude that patients who had treatment would be considered to have 'normal or near-normal health'. This is because patients are often diagnosed at an advanced stage of disease and because inotersen slows, but does not stop, disease progression. Thirdly, the committee accepted that inotersen was unlikely to meet the requirement that health benefits must be sustained over at least 30 years. However, it considered that this criterion unfairly penalises people with hATTR amyloidosis because they are older and so would have a life expectancy of less than 30 years even in the absence of this condition. The committee noted that the criterion that health benefits must be sustained for 30 years is included when deciding whether a lower discounting rate can be justified because cost-effectiveness analyses are particularly sensitive to the choice of discount rate when benefits are accrued over a very long time. The criterion does not therefore penalise people with hATTR amyloidosis because of the age at which they are diagnosed. The committee therefore concluded that there was no justification for changing from the reference case discount rate of 3.5% for costs and health effects.

Cost-effectiveness results

4.22 The committee considered the results of the economic analysis, taking into account the company's base case, and ERG exploratory scenario analyses. It noted that the company's most optimistic scenario resulted in

an ICER of £369,569 per quality-adjusted life year (QALY) gained. The committee's preferred base case was associated with an ICER of £646,767 per QALY gained, with the following assumptions:

- In the model 1 carer was assumed based on the ERG's exploratory analysis (see section 4.16).
- Amendments to the costs and disutility of adverse events were applied based on the ERG's exploratory analysis (see section 4.17).
- Discontinuation was modelled using a log-logistic curve based on the ERG's exploratory analysis (see section 4.14).
- Utilities were based on Faria et al., linear calculation was based on the ERG's exploratory analysis (see section 4.20).
- Costs and QALYs were discounted at 3.5% per year (see section 4.21).
- The compliance rate was as used in the company's base case (information about compliance rate is considered academic in confidence by the company, therefore cannot be presented here).
- Healthcare resource use costs for treating different disease stages were as used in the company's base case.

4.23 The committee recalled the uncertainty around some of the model inputs, and noted that the ICER from its preferred analysis and the ICERs from the ERG's scenario analyses were all substantially higher than what is considered an effective use of NHS resources for highly specialised technologies.

Application of QALY weighting

4.24 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of

the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It 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 inotersen, and highlighted that these were below 10 in the company's base case, the ERG's base case and the ERG's exploratory analysis that was the most plausible to the committee (the exact QALY gains are considered commercial in confidence by the company, so cannot be reported here). The committee concluded that there was no evidence to suggest that inotersen would meet the criteria for applying a QALY weight.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

- 4.25 The committee discussed the effects of inotersen beyond its direct health benefits and the testimony of the patient experts. It understood from patient and clinical experts that all aspects of patients', families' and carers' lives are affected by the condition. It noted that there is a significant negative financial effect for families if they have to give up work to provide full-time care or need to employ professional carers. The patient experts explained that inotersen has changed their experience of living with hATTR amyloidosis. The committee concluded that hATTR amyloidosis affects patients beyond direct health benefits, but that quantifying this was difficult. It concluded that it was highly unlikely that the effects would be sufficient to overcome its concerns about the difference between the preferred ICER and values considered an effective use of NHS resources for highly specialised technologies.
- 4.26 The committee noted that inotersen can be taken at home, which is an advantage for those who would struggle to travel to hospital. Patients or carers would need to be trained to administer the subcutaneous injections

and regular blood monitoring. Patients with weakness in their hands from neuropathy would need a carer or district nurse to give the medication.

Other factors

- 4.27 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.
- 4.28 The committee discussed the innovative nature of inotersen, noting that it is the first licensed 2'-O-2-methoxyethyl phosphorothioate antisense oligonucleotide and its mechanism of action is distinct from all previous treatments for hATTR amyloidosis. The company considered that inotersen is a step-change in managing hATTR amyloidosis. The patient experts explained that having a treatment available would give people with the condition hope – both for themselves and for family members who may be affected in the future. The committee concluded that inotersen is innovative.

Managed access

- 4.29 The committee reiterated the uncertainties associated with inotersen. It recalled that, although the clinical evidence might be associated with uncertainties, it was satisfied that the trial outcomes captured the main aspects of the condition, that is, peripheral neuropathy, and autonomic and cardiac symptoms. It also considered that inotersen provided some benefit in slowing disease progression. However, the committee considered that the estimates of costs and benefits provided by the model were uncertain because of a lack of robust evidence to inform several of the key input parameters. It therefore noted that further data collection, as proposed in a managed access arrangement, would not be a possible

route to resolving uncertainties in the evidence base because it was not going to address the uncertainties in the economic model. The committee acknowledged that long-term data were already being collected and would be available in the future. It concluded that inotersen could not be recommended and that a managed access arrangement would be unlikely to resolve the uncertainties.

Conclusion

- 4.30 The committee recognised that hATTR amyloidosis is a devastating condition, with a debilitating effect on patients and a significant emotional and financial impact on their families. It was convinced that the evidence showed inotersen slowed disease progression, which had considerable benefit to patients, but noted that there was insufficient evidence on the long-term health benefits; patients on inotersen treatment slowly progressed to the more severe stages of the disease. The committee considered that the company's assumptions in the model around utility values, number of carers, mortality and stopping of treatment were highly uncertain. The committee considered that the ERG's ICER was the most plausible, but this was higher than what is usually considered an appropriate use of NHS resources for highly specialised technologies. It also noted that inotersen did not meet the criteria for a QALY weighting to be applied. The committee concluded that inotersen at its current price was not cost effective compared with current practice. Therefore it did not recommend inotersen as an option for treating hATTR amyloidosis.
- 4.31 The committee requested further clarification and analyses from the company, which should be made available for the second appraisal committee meeting, and should include:
- Lower hazard ratios to predict mortality in the model (see section 4.15).
 - EQ-5D values estimated by applying the UK tariff to the raw EQ-5D response data from the THAOS registry– if data are available (see section 4.19).

5 Proposed date for review of guidance

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

December 2018

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

[Committee members](#) are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Orsolya Balogh

Technical lead

Frances Nixon

Technical adviser

Joanne Ekeledo

Project manager

ISBN: **[to be added at publication]**