National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation (HST)

Patisiran for treating hereditary transthyretin-related amyloidosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Alnylam Pharmaceuticals	We believe it is appropriate to refer this topic to NICE for evaluation under the HST programme. The evaluation addresses a priority health issue in the UK, as patients with hATTR amyloidosis face a rare, genetic, progressive, debilitating and ultimately fatal disease for which very few effective treatment options exist. It is also timely given that the pivotal, registration-enabling, phase 3 trial of patisiran recently reported positive safety and efficacy outcomes, and both the EMA and the FDA have granted accelerated reviews as a result. Alnylam has recently filed to the EMA its application for a marketing authorisation in Europe and we expect approval and launch in the UK in 2018. A timely HST review by NICE would be aligned with NICE's published procedural and methodological guidelines regarding the completion of appraisals as close to marketing authorisation as possible. Additionally, it is important to point out that:	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		• hATTR is a genetic, progressive and deadly ultra-orphan disease[1, 2] and diagnosis and treatment are concentrated at one specialist centre of excellence in the UK (National Amyloidosis Centre, UCL, NAC) • Patients with the disease face significant morbidity (including reduced activities of daily living, substantial caregiver impact, and reduced employment/productivity, among others)[1, 3-6] • Recently-published phase 3 data from the APOLLO study demonstrate important clinical benefit including evidence of halting disease progression[7] • The small number of patients concerned is estimated to be well below 200 in the UK[2]. UK clinical experts at the NAC estimate that ~150 patients are currently known[8]. Lastly, we agree that the Highly Specialised Technology Programme is the appropriate method of evaluation given the small target patient group, the concentration of treatment at very few centres within the NHS, the distinct clinical make-up of patients in the UK (specific hATTR genotypes), the severely disabling and deadly nature of the disease, and the highly specialised service involved in the care of these patients.	
	Amyloidosis Research Consortium UK	Yes. There are currently no approved treatments for this patient population. Current standard of care is sub-optimal for this patient population and as such this evaluation is a high priority.	Comment noted.
	National Amyloidosis Centre, UCL	Essential. Phase II RCT has shown a very substantial disease reversing effect with excellent safety	Comment noted.

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	National Amyloidosis Centre, UCL	Entirely appropriate and urgently required	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	Highly appropriate as this is a devastating disease and the phase 3 trial looks promising	Comment noted.
	Association of British Neurologists	Yes very appropriate	Comment noted.
	Genetic Alliance UK	This is an appropriate topic for the HST programme, as it meets all the criteria for prioritisation.	Comment noted.
Wording	Alnylam Pharmaceuticals	We agree that the wording in the draft remit appropriately reflects the issues NICE should consider.	Comment noted.
	Amyloidosis Research Consortium UK	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]* Yes, the remit is appropriate.	Comment noted.
	National Amyloidosis Centre, UCL	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]* Fine	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	National Amyloidosis Centre, UCL	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]* Yes. No comments	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]* Yes	Comment noted.
	Association of British Neurologists	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]* Yes	Comment noted.
	Genetic Alliance UK	This is the standard wording.	Comment noted.
Timing Issues	Alnylam Pharmaceuticals	We believe that there is a strong rationale for an urgent HST evaluation of patisiran by NICE for the following reasons: • **Morbidity and mortality of hATTR amyloidosis:** There are currently dozens of patients in the UK suffering from hATTR amyloidosis.[3] The hATTR genotypes prevalent in the UK cause severe morbidity and mortality[1, 2]. A study by Dungu et. Al (2016) suggested that survival after diagnosis in some groups of UK hATTR patients was only 2.6 years[1]. There is clearly an urgent unmet need.[2,3,7] • **Lack of current treatments for patients in the UK:** UK hATTR patients currently have very limited treatment options available[3-4].	Comment noted.

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		While tafamidis is mentioned in the background information relating to this consultation, the registration trial evidence supporting its use is limited to stage 1 patients only[5], and only patients suffering from the V30M genotype were included in its pivotal randomized control trial[4, 6]. Importantly, V30M is not the dominant variant of the disease in the UK[4] and there are patients whose disease has progressed beyond the limited stage 1 population on which the evidence for tafamidis is based[5]. The registration trials of tafamidis also excluded patients suffering from cardiac symptoms, which is the primary phenotype observed in the UK[4]. As a consequence, tafamidis is only licensed by the EMA for early stage patients and it is not approved for funding by the NHS. *Next*, organ liver transplantation is also referred to in the background information, however it is very rarely performed in the UK, as outcomes are poor in patients with cardiac involvement, guidelines suggest transplantation only in early onset patients, and donor availability is often limited[4, 7-8]. The prior AGNSS review of hATTR and more recent expert opinion from clinicians at the NAC have confirmed also this.[3] *Finally*, although referenced in the background information, diflunisal is not licensed for the treatment of hATTR[9], is not routinely accessible based on feedback from clinicians[3], is contraindicated in patients with advanced cardiac disease, and is not used in patients taking anticoagulants (e.g., those in atrial fibrillation)[9]. Consequently, an urgent clinical need remains for the specific UK patient population. • **EMA and FDA fast-tracking:** Following the publication of positive safety and efficacy outcomes from the phase 3 trial, the EMA has granted patisiran an accelerated assessment for patients with hATTR amyloidosis and the FDA has awarded it fast track designation in recognition of the potential 'step change' in treatment it offers.	

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		Additionally, an application for marketing authorisation was recently submitted to the EMA and the FDA. An immediate referral for evaluation under HST would allow for NICE guidance to be issued shortly after marketing authorization and UK launch. [redacted]	
	Amyloidosis Research Consortium UK	The drug has recently been submitted for marketing authorisation to the EMA and will be considered under the Accelerated Approval process. A prompt recommendation by NICE on the commissioning status of this drug as soon as possible following (assumed) marketing authorisation is of high importance to avoid any unnecessary delay in patient access.	Comment noted.
	National Amyloidosis Centre, UCL	Extremely urgent. This is the first treatment to demonstrate reversal of a progressive and quite rapidly fatal disease.	Comment noted.
	National Amyloidosis Centre, UCL	This evaluation is very urgent since there are no existing efficacious treatments for hereditary ATTR amyloidosis, which is a gradually progressive and ultimately fatal disease associated with a very poor quality of life.	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	Current treatment for FAP is very suboptimal and there is a very real clinical need for new treatments.	Comment noted.

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	Association of British Neurologists	Patients with this condition suffer progressive deterioration and die within a few years. Delay in commissioning will result in more deaths and irreversible disability. As the drug has recently been submitted to the EMA through the accelerated access process, a decision by NICE on the commissioning status of this drug soon is very important to avoid access delays for patients.	Comment noted.
	Genetic Alliance UK	Although the Marketing Authorisation application for patisiran was only submitted to the EMA in December 2017, it has been granted accelerated assessment due to the severity of the condition and the high unmet need. It is appropriate that the medicine be appraised quickly in order for patients who would benefit from the treatment to gain access as soon as possible.	Comment noted.
Additional comments on the draft remit	National Amyloidosis Centre, UCL	TTR-lowering agents (inotersen and patisiran) offer the first hope of arresting disease progression and in the case of patisiran, bringing about genuine clinical improvement without any adverse safety concerns.	Comment noted.
	Genetic Alliance UK	It is not clear whether these medicines are intended to be evaluated as two linked but separate HST evaluations or as a single combined multiple HST evaluation. We would welcome some clarity on this, the methodology to be followed, and whether an MHST would also consider tafamidis (licensed in the EU but not commissioned in England) and diflunisal (used off-label).	Comment noted. There is no multiple technology evaluation process within the HST programme. If both inotersen and patisiran are evaluated by NICE, they will be considered in separate evaluations.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alnylam Pharmaceuticals	We believe that the majority of the background information is accurate and complete, however we believe the following important factual corrections should be made: • The background information should **include more information on the cardiac consequences of hATTR amyloidosis** (e.g., cardiomyopathy, heart failure), which are very significant in the UK hATTR population because of the genotypes prevalent here[1]. The current background focuses almost exclusively on neuropathy (e.g. the first sentence states that hATTR is 'also known as familial amyloid polyneuropathy') which is not correct and not representative of the clinical picture seen in the UK. The background information section as written is misleading without modifications to reflect the actual disease course and the specific cardiac manifestations of hATTR most relevant to the UK population. • We suggest the following text: o *Hereditary transthyretin (TTR)-mediated amyloidosis (hATTR amyloidosis) is a rare, life-threatening, autosomal dominant multi-systemic disease caused by mutations in the TTR gene that results in progressive, chronically debilitating morbidity and mortality[2-5]. hATTR amyloidosis is an orphan disease, with an estimated prevalence of 1/100,000 in EU [6]. The most common manifestations of hATTR amyloidosis are polyneuropathy and cardiomyopathy.* o *Historically, two clinical syndromes of hATTR amyloidosis have been described: hATTR amyloidosis with polyneuropathy*	Comment noted. The background section of the scope is intended to provide a brief summary of the disease and how it is managed. It is not designed to be exhaustive; consultees are able to expand on the condition and its treatment in their evidence submissions.

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		(previously known as familial amyloidotic polyneuropathy, or FAP) and hATTR amyloidosis with cardiomyopathy (previously known as familial amyloidotic cardiomyopathy, or FAC), both of which are characterized by amyloid deposits comprised of both mutant and WT TTR[7]*. However, while patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients with hATTR amyloidosis manifest signs and symptoms of both polyneuropathy and cardiomyopathy over the course of their disease, and therefore it is more appropriate to refer to one hereditary disease with a spectrum of clinical manifestations rather than attempt to classify the disease into two distinct syndromes*[8]*.* • The background information should make clear that the pivotal trial evidence and the EMA license for tafamidis does not include the hATTR genotypes present in the UK population[1]. The background information should also make clear that tafamidis was not approved for funding in the UK and is therefore not available for UK patients[1,9,11]. Finally, the background information should make clear that liver transplantation is not a viable option for the majority of UK patients because of its poor outcomes in patients with cardiac involvement[1, 9-10]. This was also the conclusion of the Evidence Review Group's prior AGNSS assessment of treatment options for patients with hATTR[1]. We believe that the **number of UK hATTR patients stated in the background information** is potentially an underestimate. Input from the National Amyloidosis Centre suggests that ~150 patients are currently	The background section of the scope clarifies that tafamidis is not used in clinical practice in England. In addition, the text has been updated to note that liver transplantation is only an option for people with a specific genetic mutation that is uncommon in England.

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		known[11], and the European prevalence figure of <1 in 100,000 people could potentially apply to the UK population[6].	The background section has been updated to include the estimate of the population agreed at the scoping workshop (150).
	Amyloidosis Research Consortium UK	With reference to the section on current treatment options we wish to clarify that liver transplantation is only an option for a very small minority of patients. We understand from clinical experts that it is only very rarely considered in the UK (1-2 patients every few years).	Comment noted. The background section of the scope has been updated to note that liver transplantation is only an option for people with a specific genetic mutation that is uncommon in England.
	National Amyloidosis Centre, UCL	*[Consider the accuracy and completeness of this information]* Fine	Comment noted.
	National Amyloidosis Centre, UCL	*[Consider the accuracy and completeness of this information]* Yes	Comment noted.
	Royal College of Pathologists/	This is fine but I would suggest removing the doxcycline data which is very weak	Comment noted. The reference to doxycycline with

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	British Society for Haematology		tauroursodeoxycholic acid has been removed from the scope.
	Association of British Neurologists	Generally good, except exact incidence and prevalence figures need checking as well as at risk population as that will be relevant going forward. Also in the UK as the predominant genotype is TTR Ala60 (not suitable for liver transplantation), liver transplantation is very rarely indicated.	Comment noted. The estimate of population with the disease has been updated. The background section of the scope has been updated to note that liver transplantation is only an option for people with a specific genetic mutation that is uncommon in England.
The technology/ intervention	Alnylam Pharmaceuticals	We believe that the description of patisiran is **accurate but not complete and would suggest that the following is added**: Patisiran is a double-stranded siRNA designed to treat hATTR amyloidosis that is caused by mutations in the TTR gene that lead to the formation of amyloid deposits containing both wild-type and mutant TTR. Patisiran is formulated as a lipid nanoparticle to target delivery of the siRNA to hepatocytes in the liver, the primary source of TTR protein. Upon binding and activation of the RNA-induced silencing complex (RISC) in the cytoplasm within hepatocytes, patisiran specifically binds to a genetically conserved sequence in the 3' untranslated region of wild-type and mutant TTR mRNA. The RISC/siRNA enzyme complex catalytically degrades wild-type and	Comment noted. The aim of the technology section of the scope is to give a broad overview of the technology. No action required.

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		mutant TTR mRNA, resulting in a reduction of wild-type and mutant TTR protein synthesis. Positive safety and efficacy outcomes from the phase 3 APOLLO trial were recently reported and demonstrated significant improvements versus placebo across a range of neurological, quality of life, and cardiac parameters[1]. The EMA has granted Patisiran an accelerated assessment for patients with hATTR amyloidosis and the FDA has awarded it fast track designation based on the pivotal trial results. Applications for a marketing authorisation have been submitted to both regulatory agencies.	
	Amyloidosis Research Consortium UK	As further background, we suggest clarifying that a marketing authorisation application to the EMA has been submitted for patisiran.	Comment noted. This information is not included in scopes. No action required.
	National Amyloidosis Centre, UCL	*[Is the description of the technology or technologies accurate?]* Fine	Comment noted.
	National Amyloidosis Centre, UCL	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted.

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	Association of British Neurologists	Yes but should mention that regular treatment will probably need to continue life long	Comment noted. No action required.
Population	Alnylam Pharmaceuticals	We **do not believe that the population is defined appropriately, as it is inconsistent with the population defined in the overall remit**. The population should be defined as **'adults with hereditary transthyretin-related amyloidosis (hATTR)'** as stated in the draft remit. Discussions with UK experts, as well as recently published academic literature, suggest that most UK patients manifest both cardiac and neuropathic manifestations of their disease[1-2]. As a consequence, defining the UK hATTR population as one with only polyneuropathy would be misleading and we suggest the wording above.	Comment noted. The technology will be evaluated within its marketing authorisation, taking into account the age of patients in the NHS and in the trials. The population has been amended to remove the reference to polyneuropathy.
	Amyloidosis Research Consortium UK	We suggest clarifying that the population concerned is adult only. We do not think there are groups within this population that should be considered separately. Ideally patients should have the opportunity to benefit from the earliest possible use of drugs such as patisiran in order to prevent deterioration of neuropathy and maximise the clinical benefit. However, patisiran offers the potential to be a valuable treatment option for all patients within this population.	Comment noted. The population has been left broad, because definitions of the age at which someone is considered an adult differ. It was agreed at the scoping workshop that there are no important differences expected between subgroups of the population that

Section	Consultee/ Commentator	Comments [sic]	Action
			require separate consideration.
	National Amyloidosis Centre, UCL	*[Is the population defined appropriately? Are there groups within this population that should be considered separately?]* Fine	Comment noted.
	National Amyloidosis Centre, UCL	*[Is the population defined appropriately? Are there groups within this population that should be considered separately?]* Yes	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	The number of patients with FAP in the UK is probably less than one hundred. There is some disease heterogeneity in the mutation, age of presentation, degree of cardiac involvement. The mechanism of action of both drugs should not be affected by the mutation, the role of treatment in more advanced disease, older patients and cardiomyopathy hasn't really been studied yet. My view is that indications are likely to expand as more *[note: comment ends here]*	Comment noted. It was agreed at the scoping workshop that there are no important differences expected between subgroups of the population that require separate consideration.
	Association of British Neurologists	*[Is the population defined appropriately? Are there groups within this population that should be considered separately?]* Yes	Comment noted.
	Genetic Alliance UK	We understand that this medicine (as well as the comparators) is substantially more effective if given in the early stages of the condition, before organs become too damaged. It may therefore be necessary to consider early and late treated patients separately.	Comment noted. It was agreed at the scoping workshop that there are no important differences expected between

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			subgroups of the population that require separate consideration.
Comparators	Alnylam Pharmaceuticals	We do not believe the comparators listed in the draft scope are appropriate based on the opinion of clinical experts. Instead, we believe **that symptomatic control of the symptoms of hATTR is the standard treatment currently used in the NHS** and would therefore be the most appropriate **'best supportive care'** comparator. Ando et al. have published on some of the 'best supportive care' treatments currently used[1] (see Table 1) Table 1: Treatment for clinical symptoms of hATTR amyloidosis[1]	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises supportive care and treatment of symptoms.

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<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Symptom</th><th>Treatment</th></tr>
<tr><td>Arrhythmias</td><td>Pacemaker implantation, pharmacotherapy</td></tr>
<tr><td>Cardiac failure</td><td>Diuretics, angiotensin converting enzyme inhibitors</td></tr>
<tr><td>Orthostatic hypotension</td><td>Droxidopa, midodrine, amezinium metisulfate, fludrocortisone, plastic stocking, abdominal belt, elevating head</td></tr>
<tr><td>Gastrointestinal disorders (not severe)</td><td>Polycarbophil calcium, metoclopramide</td></tr>
<tr><td>Severe diarrhea</td><td>Loperamide</td></tr>
<tr><td>Neuropathic pain</td><td>Pregabalin, gabapentin, amitriptyline, duloxetine</td></tr>
<tr><td>Carpal tunnel syndrome</td><td>Surgery</td></tr>
<tr><td>Dry mouth</td><td>Potassium dihydrogen phosphate, cevimeline</td></tr>
<tr><td>Hypoglycemia</td><td>Glucose loading</td></tr>
<tr><td>Renal failure</td><td>Hemodialysis</td></tr>
<tr><td>Urinary incontinence</td><td>Distigmine</td></tr>
<tr><td>Anemia</td><td>Erythropoietin, iron</td></tr>
<tr><td>Hypothyroidism</td><td>Levothyroxine</td></tr>
<tr><td>Ocular amyloidosis</td><td>Vitrectomy, trabeculectomy</td></tr>
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To the list in the table above, UK clinical experts have informed us that they also use codeine phosphate and/or octreotide to treat diarrhoea in hATTR amyloidosis[2].
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Section	Consultee/ Commentator	Comments [sic]	Action
		• We **do not agree that diflunisal** – which is a nonsteroidal anti-inflammatory drug (NSAID) repurposed as a TTR tetramer stabilizer – **is an appropriate comparator**. First, it is not licensed for the treatment of hATTR amyloidosis and is not reliably accessible in the UK, according to UK clinical experts[2]. Next, it is contraindicated in patients with severe heart failure and it is not used in patients taking anticoagulants (e.g. those in atrial fibrillation)[2-3]. Many UK patients with hATTR will have cardiac manifestations of disease that evolve to heart failure[2, 4-5]. As patients with hATTR amyloidosis are at risk of cardiovascular and renal issues due to the disease itself, many patients may be poor candidates or completely ineligible for diflunisal. Third, there are no data available to suggest that diflunisal offers the potential for an improvement in neurologic impairment nor the cardiac manifestations of the disease[2]. Specifically, there are no data on its efficacy or safety in patients suffering from cardiac symptoms due to hATTR amyloidosis. • We **do not agree that organ liver transplantation (OLT) is an appropriate comparator** because it is very rarely performed in UK hATTR patients[2,4]. Liver transplantation is a high-risk option and is generally only effective in halting or slowing disease progression for a limited subset of patients at an early stage of disease. The chronic immunosuppressive medications required to prevent rejection increase post-transplantation risk[6-7]. OLT is not recommended for patients with cardiac involvement due to continued progression of cardiac disease observed post-transplant[6]. Finally, due to the limited availability of donor livers, liver transplantation is also not an option for all patients, as some potential candidates may not find a match before progressing beyond the point where transplant is possible, and there are known inequalities in access to donors among specific ethnic groups in the UK. Taken together, OLT cannot be considered	

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		standard of care and should not be a comparator here. This conclusion is supported by findings from the AGNSS Evidence Review Group's prior assessment of hATTR in 2012[4], and is consistent with the input provided to us from UK clinical experts. • We **do not agree that tafamidis is an appropriate comparator** because it was rejected for NHS funding by AGNSS and is therefore not used in the UK. Importantly, the pivotal tafamidis trial studied a patient population with the early onset V30M mutation[4, 8], which is uncommon in the UK.[2] There is limited published evidence of the efficacy of tafamidis in other hATTR genotypes, and the registration trial of tafamidis excluded patients suffering from cardiac symptoms, and as such the evidence does not sufficiently relate to the specific UK patient population[4] • We do **not agree that experimental treatments such as doxycycline plus tauroursodeoxycholic acid are relevant comparators** because there is very limited evidence for their efficacy in hATTR amyloidosis. The study referenced in the background information section of the remit refers to an uncontrolled phase 2 study that did not include UK centres of patients[9]. That study included only 20 patients, of which only 17 had hATTR amyloidosis, and of these, approximately one-third were of the V30M genotype that is uncommon in the UK. Only half of the enrolled patients were able to tolerate six months of treatment, with two patients discontinuing treatment due to poor tolerability within just one month of treatment initiation. Moreover, clinical experts in the UK confirm that these drugs are not used in clinical practice[2], and **as such this is not a relevant comparator.**	

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	Amyloidosis Research Consortium UK	We consider that only routinely used and licensed treatments should be appropriate comparators. We therefore do not consider there to be any disease-modifying treatments that would be appropriate comparators in this evaluation. Tafamidis is licensed for this population, but it is not approved for use on the NHS. Clinical experts confirm that it is not used in practice and therefore does not form part of current standard of care. Doxycycline is not licensed for this population. Clinical experts confirm that it is not used in practice and therefore does not form part of current standard of care. Liver transplantation is only best alternative care for a very small minority of this patient population with very early stage polyneuropathy. While it may in theory be an option, personal preference, concern over transplant-related risks and shortage of organ availability mean that in practice it only rarely occurs. We understand from clinical experts that hATTR patients have only very rarely received this treatment in recent years. It is not therefore a suitable comparator. Clinical experts confirm that most patients in this population (approximately 80%) are treated with diflunisal and supportive care to manage the symptoms of polyneuropathy. Diflunisal is used in practice for patients who are not on anticoagulants. However, diflunisal is unlicensed for this patient population and there is only limited evidence of its effectiveness. There are furthermore availability issues with diflunisal. Clinical experts note that while it is the standard of care it is not the treatment of choice, due to its limited activity/effectiveness and lack of licensing status. As such we do not think it is an appropriate comparator for this evaluation. Symptom management approaches form the basis of standard care alongside diflunisal. These approaches do not delay the course of the	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises supportive care and treatment of symptoms.

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		disease but can alleviate disabling manifestations and improve quality of life, for example, by reducing neuropathic pain (e.g. gabapentin) and improving autonomic function, particularly GI symptoms (e.g. immodium, codeine, erythromycin and rarely colostomy), cardiac function (e.g. diuretics) and blood pressure control. The evaluation should consider the main symptom management approaches as standard treatment / best alternative care for most patients.	
	National Amyloidosis Centre, UCL	There are no standard treatments in the NHS. Tafamidis has a very weak and questionable benefit and is not supported by the NHS. Liver transplantation is ineffective in the vast majority (~99%) of UK patients. Diflunisal is not funded by NHS, and in NAC experience of a few dozen patients is ineffective. Doxycycline / tauroursodeoxycholic acid not used in UK	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises supportive care and treatment of symptoms.
	National Amyloidosis Centre, UCL	No comparators Tafamadis not in use in UK Diflunisal not efficacious and little used in UK Liver transplantation not applicable to most UK patients with hereditary ATTR amyloidosis	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises

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			supportive care and treatment of symptoms.
	Royal College of Pathologists/ British Society for Haematology	There are problems with all these comparators as: tafamadis is not available in the UK, difflunasil is used but difficult to access, not NHS funded (and has been used speculatively for 10-15 years with almost no evidence of benefit). At present OLTx would be regarded as the 'best' option for young patients with TTR Met 30 but in practice exceptionally few patients are offered this (due to limitations in patient suitability for major surgery, lack of benefit in the majority of mutations seen in the UK and donor organ shortage). In general the data for both OLTx and TTR stabilisers suggests slowing of disease progression is the best that these therapies could offer.	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises supportive care and treatment of symptoms.
	Association of British Neurologists	Liver transplantation is the most appropriate comparator which is used almost exclusively in TTR Met 30 which is extremely rare in the UK. Liver transplantation is not suitable for the vast majority of UK patients. The other comparators are the amyloid-stabilising treatments (diflunisal, or tafamadis) which may slow progression of the disease if given early but do not give improvement or stop progression. In the UK tafamadis is not licensed so is not a relevant comparator. Difflunisal is used but has limited effectiveness, has availability issues and is contraindicated in patients on anticoagulation and with significant gastrointestinal issues so many patients do not tolerate this long term.	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises supportive care and treatment of symptoms.
Outcomes	Alnylam Pharmaceuticals	The outcomes listed in the draft scoping document (e.g. neurological impairment, quality of life) are comprehensive and appropriate and many of them were in fact specific endpoints in the pivotal APOLLO trial of patisiran.	Comment noted. The outcomes have been updated following

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		In answer to NICE's specific questions on outcomes: 1. **Yes, we believe that serum transthyretin is a relevant outcome.** It is hypothesized that reducing circulating TTR levels will reduce TTR amyloid deposition and could lead to stabilization or improvement of disease in patients with hATTR amyloidosis. Patisiran has been studied in patients with hATTR amyloidosis and has demonstrated rapid and sustained knockdown (KD) of serum TTR in the phase 2 open-label extension (OLE) and the phase 3 APOLLO studies. Data from these studies suggest that the degree of TTR KD is associated with change in neurological impairment (mNIS+7) and support the therapeutic hypothesis that reduction of circulating TTR levels is associated with clinical benefit among patients with hATTR amyloidosis. 2. **Yes, we believe that autonomic function is relevant. A broad range of autonomic function is affected by hATTR amyloidosis and the APOLLO trial examined the impact of patisiran vs. placebo across six autonomic domains** (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, pupillomotor) using the Composite Autonomic Symptom Score (COMPASS)-31 questionnaire.[1] **3. Yes, patisiran does have an effect on cardiomyopathy outcomes.** Cardiac function was assessed through echocardiograms and cardiac biomarkers (troponin I and N-terminal pro-brain-type natriuretic peptide) in the APOLLO Phase 3 trial[1]. Exploratory analysis in the pre-specified APOLLO cardiac subpopulation showed that patisiran was associated with statistically and clinically significant reductions in NT-	discussion at the scoping workshop. Serum transthyretin has been added to the outcomes in the scope. Postural hypotension and effects on the gastrointestinal system have been included as examples of autonomic function in the scope. Cardiac function has been added to the outcomes in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		proBNP, LV wall thickness and longitudinal strain and with an improved 10-MWT gait speed[2]	
	Amyloidosis Research Consortium UK	The outcome measures listed in the table on page 2-3 are comprehensive and appropriate. Autonomic and cardiac functions are also relevant outcomes for the evaluation. Serum transthyretin is a relevant outcome in so far it is a marker of treatment efficacy, however the extent of its correlative effect on clinical benefit needs to be carefully considered. It is our view that the disease severity and quality of life outcome measures are the most relevant clinical improvement measures for this evaluation and the key outcomes from a patient perspective. In addition, the evaluation should consider preference-based measures, taking into account a broad view of the advantages and disadvantages of the drug from a patient preference perspective. This might include a range of factors including efficacy, side-effects, approaches to risk, and convenience /lifestyle/family considerations.	Comment noted. The outcomes have been updated following discussion at the scoping workshop. Cardiac function has been added to the scope as an outcome. Serum transthyretin has been added to the outcomes in the scope. Aspects of treatment burden are captured by the adverse effects of treatment and quality of life outcomes included in the scope. No action required.
	National Amyloidosis Centre, UCL	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* OK	Comment noted. The outcomes have been updated following

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			discussion at the scoping workshop.
	National Amyloidosis Centre, UCL	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. The outcomes have been updated following discussion at the scoping workshop.
	Royal College of Pathologists/ British Society for Haematology	These look fine: neurologic impairment is an umbrella term covering symptoms of polyneuropathy resulting in autonomic, sensory and motor deficits. HRQOL is important. The disability is secondary to neuropathy plus often devastating loss of muscle and flesh weight producing additional marked predilection to infectious complications and severe fatigue, and in some mutations cardiac and vitreous amyloid. Both disability and mortality are very important but one would expect a considerable lag phase before seeing changes in these after starting effective treatment and the effect is likely to be highly dependent on how advanced the disease is at starting treatment.	Comment noted. The outcomes have been updated following discussion at the scoping workshop.
	Association of British Neurologists	Generally outcomes listed are appropriate. Serum transthyretin may be useful to be monitored as an early indicator of treatment efficiacy in reducing transthyretin but it does not necessarily equate to clinical outcomes and should not be a primary outcome. Postural hypotension and gastrointestinal autonomic function are important to measure. Cardiac outcome measures are also essential	Comment noted. The outcomes have been updated following discussion at the scoping workshop. Serum transthyretin has been added to the outcomes in the scope. Postural hypotension and effects on the

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			gastrointestinal system have been included as examples of autonomic function in the scope. Cardiac function has been added to the outcomes in the scope.
	Genetic Alliance UK	The outcome measures included are broadly appropriate but very general. We would also suggest inclusion symptoms due to amyloid deposits in the heart, eye, kidneys, thyroid gland, adrenal glands and blood vessels. It will be important to measure the outcomes listed (such as neurological impairment and motor function) using tools which reflect the real benefit to patients, not just those endpoints which are easily measurable. We note that disability has been listed as an outcome for (we believe) the first time in an HST scope. In the past disability has largely been used to support and provide context to the specific clinical outcomes, not as an endpoint in its own right. We would welcome clarity on how this change in methodology will be used and measured.	Comment noted. The outcomes have been updated following discussion at the scoping workshop. Effects of amyloid deposits in other organs and tissues, including the eye has been added to the outcomes in the scope. The disability outcome has been removed from the scope, as it overlapped with the motor function and quality of life outcomes.
Economic analysis	Alnylam Pharmaceuticals	We agree with the components of the scope relating to value for money and the impact beyond direct health benefits. Due to the several disability caused by hATTR amyloidosis, including burden on families and caregivers, there are	Comment noted.

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		potentially important indirect benefits associated with new treatments for hATTR amyloidosis.	
	National Amyloidosis Centre, UCL	There is massive unmet need in this hitherto irreversibly progressive neurological and cardiac disease, and utmost urgency for patents to access this treatment.	Comment noted.
	National Amyloidosis Centre, UCL	The number of patients is small and the total cost burden of the drug to the NHS over and above the current NHS cost of standard of care ought to be minimal	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	Untreated FAP results in a slow death with eventual total dependency. The current results from clinical trials will need to be extrapolated considerably to predict benefits over the 10 to 15 year period which is currently regarded as the life expectancy from diagnosis in FAP.	Comment noted.
	Association of British Neurologists	This treatment is likely to be very expensive, but is also offering an enormous improvement in treatment of this disease compared with previous standard treatment.	Comment noted.
Equality and Diversity	Alnylam Pharmaceuticals	A timely HST review would support NICE's commitment to promoting equality. In particular, as noted above, patisiran targets a hereditary, genetic disease with specific genotypes among UK patients. The most common genetic variants associated with hereditary ATTR amyloid with signs and symptoms of cardiomyopathy are TTR V 122I, present in Afro-Caribbeans[1], and TTR T60A, present in many populations with a frequency of up to 1% in one North Western Irish study[2]. Numerous other rare TTR variants are also associated with ATTR amyloid cardiomyopathy[3] and afflict specific minority groups.	Comment noted. The committee will consider any potential equality considerations identified throughout the appraisal and whether the recommendations make it more difficult for a particular group to access treatment.

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	Amyloidosis Research Consortium UK	We have not identified any equality issues	Comment noted.
	National Amyloidosis Centre, UCL	The UK population of patients with hereditary ATTR amyloidosis is very small indeed, in the order of less than 100 patients. One particular mutation (V122I) predominantly affects older black people, a proportion of whom seem in the NAC experience to be somewhat reluctant to seek medical care.	Comment noted. The committee will consider any potential equality considerations identified throughout the evaluation and whether the recommendations make it more difficult for a particular group to access treatment.
	Royal College of Pathologists/ British Society for Haematology	I don't think there are specific issues here	Comment noted.
	Association of British Neurologists	I anticipate no significant problems concerning equality.	Comment noted.
Other considerations	Alnylam Pharmaceuticals	On the last page of the NICE draft Scope there is an error which should state patisiran rather than eteplirsen – "patient population for which eteplirsen will be licensed". Thank you in advance for correcting this error.	Comment noted. This section contained questions for consultation and is not included in the final scope.

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	Association of British Neurologists	The drug should be used at the early symptomatic stage. It is likely efficacious at all stages. This treatment should also be considered for patients with transthyretin-associated cardiomyopathy even if they do not (yet) have significant polyneuropathy.	Comment noted.
Innovation	Alnylam Pharmaceuticals	**Yes, we believe that patisiran is innovative and that, if licensed, will be a 'step-change' in the management of the condition.** The technology targets the disease at its source by inhibiting the production of transthyretin, slowing the progression of the disease. This disease is extremely debilitating and progressive and the current standard of care in the UK is symptom management. If approved, patisiran will be the first ever medicine to work through RNA interference (RNAi). The discovery of RNAi was awarded the 2006 Nobel Prize for Physiology or Medicine[1]. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, it makes it possible to address diseases with no or few treatment options. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, target the cause of diseases by potently silencing specific mRNAs, with the goal of preventing disease-causing proteins from being made. UK clinicians and scientists played an important role in the development of this platform for use as medicines in humans. The design and initiation of the first in-human clinical trials for this entirely new class of medicines was the result of substantial research, care and deep expertise for which Alnylam	Comment noted.

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		came to the UK specifically. World renowned UK clinicians and scientists played, and continue to play, a significant role in the development of Alnylam's RNAi platform. As a result, Alnylam's ex-US clinical development and regulatory headquarters are located in Maidenhead, Berkshire, and the progress in the development of patisiran was supported by the involvement of the UK scientific and medical communities. The data from the pivotal Phase 3 APOLLO trial, in which patisiran met its primary endpoint with a 33.99 point mean difference relative to placebo (p-value 9.26 E-24)[2] and a negative 6.0 point mean change (improvement) relative to baseline in mNIS+7 at 18 month[2], suggest that patisiran has the potential to have a significant benefit to the health of patients with hATTR amyloidosis. In light of these results, the EMA has granted patisiran an accelerated assessment for patients with hATTR amyloidosis and the FDA has awarded it fast track designation. Applications for marketing authorisation have been submitted to both agencies, and a UK launch is anticipated in 2018.	
	Amyloidosis Research Consortium UK	Yes, we consider patisiran to be genuinely innovative. The technology itself is innovative in the way it offers a new first-in-class treatment approach for this disease. To date there are no alternatives that inhibit the production of transthyretin, slowing the progression of the disease and reducing the polyneuropathic effects experienced by patients. This patient population has very significant unmet need. The disease is extremely debilitating and progressive for which current standard of care is predominantly limited to symptom management with or without a minimally effective and unlicensed drug, diflunisal. The complications, effects and progressive nature of the disease have a profound impact on patients' and their families' lives.	Comment noted.

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		In providing an effective disease-modifying option, patisiran represents a significant step change in the potential management of hATTR and in meeting the unmet need of this patient population. Patisiran has shown considerable effect on polyneuropathy and other measures. We do not have full knowledge of patisiran's potential to reverse advanced polyneuropathy. However, in offering an option that can stabilise and stop further deterioration patisiran can make a considerable improvement to patients' quality of life. It can also significantly reduce patients' reliance on and use of supportive care resources.	
	National Amyloidosis Centre, UCL	This represents a seminal and utterly remarkable innovation, both for this disease and for novel RNA inhibiting pharmacology generally. This really represents a new dawn in medical treatment, and a huge step change in the management of hereditary ATTR amyloidosis. This disease has essentially been untreatable hitherto, and reversal of its clinical manifestations during the 18 month RCT is almost miraculous	Comment noted.
	National Amyloidosis Centre, UCL	Completely innovative with massive potential to genuinely improve the health of this group of patients (i.e., those with hereditary ATTR amyloidosis)	Comment noted.
	Royal College of Pathologists/ British Society for Haematology	This is exceptionally innovative. It provides an entirely new technology which may well be applicable to other diseases associated with production of damaging protein in the future.	Comment noted.
	Genetic Alliance UK	We understand that if granted a marketing authorisation, patisiran will be the first licensed medicine using RNA interference, an innovative approach to treating genetic conditions which truly represent a step change both for patients with this condition and genetic conditions more broadly.	Comment noted.
	Association of British Neurologists	Yes this is a major step-change in treatment in an inherited condition.	Comment noted.

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		It is innovative as it is a gene silencing drug. Previous treatments only slowed progression but did not prevent disability and death (except the rare patients who benefitted from liver transplantation in the UK population). This new treatment gives complete clinical stabilisation in most patients without any further progression, and may give some sustained improvement. This will also reduce other supportive medical care patient currently need.	
Questions for consultation	Alnylam Pharmaceuticals	1) Please refer to the comparator section of Table *"Comment 2: the draft scope"* for answers to the questions regarding comparators 2) Please refer to the outcomes section of Table *"Comment 2: the draft scope"* for answers to the questions regarding the appropriateness of outcomes *3) Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?* a. Patients with polyneuropathy symptoms and patients with polyneuropathy and cardiomyopathy symptoms will benefit from patisiran regardless of the stage of the disease. *4) Would patisiran be used at a particular stage of the disease?* a. Patisiran is expected to be used in all stages of the disease.	Comment noted. It was agreed at the scoping workshop that there are no important differences expected between subgroups of the population that require separate consideration.
	Royal College of Pathologists/ British Society for Haematology	Tafamidis is a TTR stabiliser and the only currently licenced treatment for FAP but is not available in the UK so not a fair comparator. It's mode of action is entirely different. Given the way the studies were designed it is more or less possible to compare outcomes. Diflunasil is an old drug which has been repurposed for the treatment of FAP – it is not licensed and is extremely difficult to access and has only been studied in one randomised control trial. Anecdotal longer term experience with stabilisers has been disappointing as the disease has progressed.	Comment noted. Attendees at the scoping workshop agreed that established clinical management is the most appropriate comparator; it was understood that this primarily comprises

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		There is no rational for considering other experimental treatments here. OLTx is the current gold standard treatment for a small subset of young patients with TTR Met 30 but is not an option for the majority of UK patients I cannot think of any other treatments beyond good supportive care in FAP – which is all the majority of patients are currently offered Serum TTR levels are an extremely relevant biomarker – as this is the fibril precursor protein. We know from the much commoner acquired amyloidosis that reduction of the fibril precursors: clonal serum free light chains in AL and serum amyloid A protein in AA amyloidosis are extremely powerful predictors of long term outcomes. Autonomic dysfunction has better potential to improve the peripheral nerve function and improvements can result in improved incontinence (bowel and bladder), improved nutritional status, muscle bulk and mobility and better immune function. There is potential for improvement in cardiac innervation and a reduced chance of fatal arrthymias. In practice assessment of autonomic function is complex – requiring specialist input time consuming and not robustly reproducible. The clinically relevant endpoint are affected by other factors such as peripheral neuropathy and nutritional status and may be best looked at as part of composite outcomes related to nutrition, mobility and QoL. Analogy with AL amyloidosis strongly suggests that the marked reduction in circulating TTR may very well produce cardiac responses to treatment The studies looked at patients with relatively early disease but in my view the dramatic reductions in circulating TTR and improvements in neuropathy scares over the study period combined with the promising safety profile suggest that treating more advanced disease would be entirely rational	supportive care and treatment of symptoms. Serum transthyretin has been added to the outcomes in the scope. Postural hypotension and effects on the gastrointestinal system have been included as examples of autonomic function in the scope. Cardiac function has been added to the outcomes in the scope.

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	Pfizer	In 2011, tafamidis received a marketing authorisation for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Following a negative reimbursement decision by the Advisory Group on National Specialised Services (AGNSS) in 2013, and to Pfizer's best knowledge, tafamidis is not currently being used by patients' cared for by the NHS in England and Wales.	Comment noted.
Additional comments on the draft scope	Amyloidosis Research Consortium UK	We agree with the strategy to combine the scoping consultation for inotersen and patisiran. We understand that NICE has only limited resources for conducting HST evaluations. Given the similarities between the drugs, with respect to the intended population and treatment effects we believe it would be sensible, where possible, to consider the two drugs together. However, despite these similarities we strongly believe that both drugs have important roles to play in the treatment of patients with hATTR. They should therefore not be considered as equivalent. From a patient perspective the different administration method for these drugs are a critical consideration to factor in alongside the differences in their potential efficacy benefits and side-effects. For many patients, regular infusions in hospital (patisiran) will not be feasible or desirable, while for other patients the patisiran regimen may be feasible and/or preferred over inotersen after consideration of all the factors associated with both treatments. Both drugs offer considerable benefits and a significant step change in the management of hATTR. ARC UK believes it is important that both drugs should be available for patients and their clinicians to choose from, based on personal preference and logistical feasibility. We hope that the companies manufacturing these two drugs will work with NICE and NHS England to find	Comment noted. There is no multiple technology evaluation process within the HST programme. If both inotersen and patisiran are evaluated by NICE, they will be considered in separate evaluations.

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		an affordable and cost-effective solution to give patients access to both options as swiftly as possible.	
	Association of British Neurologists	These two treatments have very similar dramatic benefits and it is appropriate to consider both together and for both to be available as there may be reasons that one is preferable over the other for individual patients.	Comment noted. There is no multiple technology evaluation process within the HST programme. If both inotersen and patisiran are evaluated by NICE, they will be considered in separate evaluations.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
British Association for the Study of the Liver