National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation (HST)

Inotersen for treating hereditary transthyretin-related amyloidosis

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

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Ionis Pharmaceuticals	Yes, we believe that the topic should be referred to NICE to ensure that appropriate hATTR patients have access to inotersen as soon as possible after marketing approval for the UK is granted, as there is a significant unmet need in this patient population.	Comment noted.
	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	Highly appropriate. Phase III RCT has demonstrated a significant disease modifying effect with reasonable safety	Comment noted.
	National Amyloidosis Centre, UCL	Entirely appropriate and urgently required	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	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	Ionis Pharmaceuticals	The wording of the remit does reflect the issues of clinical and cost-effectiveness about inotersen.	Comment noted.
	Amyloidosis Research Consortium UK	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.
	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.

Section	Consultee/ Commentator	Comments [sic]	Action
	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	Ionis Pharmaceuticals	It is expected that inotersen will be granted marketing authorization for the UK in [redacted], so there is an urgency about this proposed evaluation in order to provide patient access to inotersen as soon as possible following regulatory approval.	Comment noted.
	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	High urgency	Comment noted.

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	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.
	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 inotersen was only submitted to the EMA in November 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	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

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			inotersen and patisiran are evaluated by NICE, they will be considered in separate evaluations.

Comment 2: the draft scope

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Background information	Ionis Pharmaceuticals	The background information is a good summary of the disease, its manifestations and impact on patients symptoms. However, the devastating nature of the disease and its toll on patients and their caregivers quality of lives is not adequately described.	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.
	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

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			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/ British Society for Haematology	This is fine but I would suggest removing the doxcycline data which is very weak	Comment noted. The reference to doxycycline with 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

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			genetic mutation that is uncommon in England.
The technology/ intervention	Ionis Pharmaceuticals	The description of the technology is accurate.	Comment noted.
	Amyloidosis Research Consortium UK	As further background, we suggest clarifying that a marketing authorisation application to the EMA has been submitted for inotersen.	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.
	Association of British Neurologists	Yes but should mention that regular treatment will probably need to continue life long	Comment noted. No action required.
Population	Ionis Pharmaceuticals	The population is defined appropriately; there are no sub-groups that would require separate consideration as inotersen has the potential to benefit all patients with this disease.	Comment noted.

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	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 inotersen in order to prevent deterioration of neuropathy and maximise the clinical benefit. However, inotersen offers the potential to be a valuable treatment option for all patients within this population.	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. It was agreed at the scoping workshop that there are no important differences expected between subgroups of the population that 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/	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	Comment noted. It was agreed at the scoping workshop that

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	British Society for Haematology	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]*	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 subgroups of the population that require separate consideration.
Comparators	Ionis Pharmaceuticals	There are no approved treatments for hATTR; the potential comparators listed are a range of off-label and experimental treatments which lack robust evidence of clinical effectiveness, and liver transplantation. "Best alternative care" is supportive care, symptomatic treatment (depending on the manifestation of the disease), and, in many patients, off-label diflusinal. Detailed responses to the question of appropriate comparators are listed below in the "Questions for consultation".	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.
	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.	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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		Symptom management approaches form the basis of standard care alongside diflunisal. These approaches do not delay the course of the 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

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			primarily comprises 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.

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Outcomes	Ionis Pharmaceuticals	In addition to the outcomes listed, patient preferences are important outcomes to measure, to ensure that the “burden of treatment” does not have an impact on overall treatment benefits.	Comment noted. The outcomes have been updated following discussion at the scoping workshop. Aspects of the burden of treatment are captured by the adverse effects of treatment and quality of life outcomes included in the scope. No action required.
	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 outcomes in the scope. 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

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			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 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.	Comment noted. The outcomes have been updated following

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		Serum transthyretin may be useful to be monitored as an early indicator of treatment efficacy 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	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.
	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

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			the scope, as it overlapped with the motor function and quality of life outcomes.
Economic analysis	Ionis Pharmaceuticals	As hATTR is a life-long disease, a lifetime horizon is the most appropriate time horizon.	Comment noted.
	National Amyloidosis Centre, UCL	Considerable urgency	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	Ionis Pharmaceuticals	There are no equality issues or concerns observed in the draft scope document.	Comment noted.
	Amyloidosis Research Consortium UK	We have not identified any equality issues	Comment noted.

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	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	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. The population has been broadened and no longer specifies polyneuropathy.
Innovation	Ionis Pharmaceuticals	Inotersen has the potential to dramatically change patients' lives for the better. Evidence from the pivotal clinical study demonstrates halting or significant slowing of disease progression – something that has not been	Comment noted.

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		achievable before. In addition, a significant number of patients experienced improvement in their neuropathy and HRQoL with inotersen treatment. Inotersen is the first investigator product to show clinical improvement in hATTR in a pivotal trial. The mechanism of action of inotersen is a novel approach to halt disease progression that has not previously been available to treat this patient population. The clinical results, based on two primary end-points (mNIS+7, a gold-standard clinical assessment of motor, sensory and autonomic neuropathy, and Norfolk QoL-DN, a patient-reported measure of health-related quality of life) demonstrated that inotersen can have a significant and substantial impact on health-related benefits. The inclusion of inotersen in the treatment paradigm for hATTR patients will radically change the way the disease is treated and how patients, their families, and their physicians view their condition, and their potential to live a full and fulfilling life. For the first time, patients with hATTR will have a treatment that allows them to remain independent and productive members of their family, community and society.	
	Amyloidosis Research Consortium UK	Yes, we consider inotersen 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	Comment noted.

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		effective and unlicensed drug, diflunisal. The complications, effects and progressive nature of the disease have a profound impact on patients' and their families' lives. In providing an effective disease-modifying option, inotersen represents a significant step change in the potential management of hATTR and in meeting the unmet need of this patient population. Inotersen has shown considerable effect on polyneuropathy and other measures. We do not have full knowledge of inotersen's potential to reverse advanced polyneuropathy. However, in offering an option that can stabilise and stop further deterioration inotersen 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 innovation, both for this disease and for novel RNA inhibiting pharmacology generally. The treatment can greatly reduce disease progression.	Comment noted.
	National Amyloidosis Centre, UCL	Completely innovative with potential to halt the decline in 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.
	Association of British Neurologists	Yes this is a major step-change in treatment in an inherited condition. 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	Comment noted.

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		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	Ionis Pharmaceuticals	Have all relevant comparators for inotersen been included in the scope? Which treatments are considered to be established clinical practice in the NHS for hereditary transthyretin-related amyloidosis: • Are tafamidis and diflunisal comparators? Tafamidis is licensed in the UK for the indication of the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. However, tafamidis was only studied in a randomized controlled trial in patients with the Val30Met mutation which only enrolled patients with early stage 1 disease. Therefore its not an appropriate comparator for all hATTR patients within the proposed labelled indication of inotersen. In addition, it failed to meet either of its two primary endpoints (NIS-LL and Norfolk QoL-DN) in the Phase 3 trial. Lastly, since its marketing authorisation in 2011, tafamidis has yet to receive a positive review by NICE (or SMC, or AWMSG) for reimbursement by the NHS in the UK. It is our understanding that tafamidis is not established clinical practice in the NHS for hATTR, therefore it cannot be considered a standard of care, nor a comparator to inotersen. Diflunisal was studied in a similar patient population to that studied in the inotersen pivotal study. However, the diflunisal phase 3 study had a very high dropout rate (~50% at 1 year) which may affect generalizability of the data. In addition, as an NSAID, it may not be suitable for patients with significant renal or cardiac impairment, both of which are common in hATTR. Therefore, despite diflusinal's widespread use in the target patient population, because of its limited evidence of clinical effectiveness, it cannot be considered a comparator to inotersen.	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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		• Are other experimental treatments such as doxycycline plus tauroursodeoxycholic acid comparators? Other experimental treatments should only be considered comparators to inotersen if they have demonstrated evidence of efficacy in treatment of the target patient population and if they are established clinical practice. A Phase II study of doxycycline plus tauroursodeoxycholic acid in hATTR did not show positive results, and it is our understanding that it is not established clinical practice in hATTR. Therefore, this experimental regimen cannot be considered a comparator to inotersen. • Is liver transplantation a comparator? While liver transplantation is a recognised treatment for hATTR and has demonstrated slowing or halting of disease progression in a subset of patients, no randomised, controlled trials have been conducted to provide data on comparative efficacy or health-related quality of life. The best outcomes with liver transplant are seen in early onset Val30Met mutation patients with a short duration of disease symptoms. Patients with non-V30Met mutations, cardiomyopathy involvement, low mBMI, and long durations of symptoms have poorer outcomes. As liver transplantation is only a rarely used option for a very small percentage of the target patient population, it cannot be considered standard of care or a relevant comparator to inotersen. • Are there any other treatments that should be included as comparators? There are no other currently approved treatments that are being regularly used on-label or off-label for the treatment of hATTR. Other treatments in development will likely be considered comparators to inotersen once they have been approved and established themselves as part of the treatment paradigm for hATTR.	

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		Are the outcomes listed appropriate? • Is serum transthyretin a relevant outcome? Serum transthyretin (TTR) is a biomarker of interest in the treatment of hATTR. In the pivotal NEURO-TTR study, in the Inotersen-Ionis treatment group, robust reduction in circulating TTR levels was observed throughout the 15-month treatment period and was correlated with clinical improvement measured by the two primary end-points in the study. Positive data was also demonstrated with patisiran for similar endpoints in a similar patient population thereby validating reduction of TTR as a biomarker for effectiveness of treatment in hATTR. The exact relationship between reduction in serum TTR and slowing or halting of disease progression has yet to be established, however, based on the data we have generated it is likely that there is a threshold effect rather than a direct proportionality between TTR reduction and clinical benefit. • Which elements of autonomic function are affected by the condition and might be improved by inotersen? hATTR causes accumulation of amyloid deposits in multiple organ systems, particularly the nervous system, gastrointestinal (GI) tract, kidney, and heart, and autonomic dysfunction manifests in a number of ways, including: • GI dysfunction with malabsorption, constipation, diarrhea, loss of appetite, nausea, vomiting • Orthostatic hypotension • Sexual dysfunction • Urinary retention and/or incontinence with recurrent UTI which may contribute to renal impairment • Impaired renal autoregulation which may affect renal function	Serum transthyretin has been added to the outcomes in the scope. Postural hypotension and effects on the gastrointestinal system have been included as

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		By decreasing the amount of liver-derived TTR protein circulating in the plasma inotersen reduces the formation of TTR amyloid fibril deposits and thus can slow or halt disease progression and its various autonomic manifestations. Hence we anticipate that inotersen will have a positive impact on progression of all or most of the symptoms of autonomic neuropathy. • Would inotersen have an effect on cardiomyopathy outcomes? Yes. More than 60% of patients in the NEURO-TTR study had cardiac disease at baseline. Amyloid deposits in cardiac muscle contribute to increased left ventricle mass and interventricular septum thickness. In the pivotal NEURO-TTR study, inotersen showed significant improvement in both left ventricle mass and interventricular septum thickness compared to placebo in patients that had considerable cardiomyopathy as indicated by a IVS thickness ≥1.5 cm. These findings are consistent with the efficacy outcomes in an independent, investigator initiated study of inotersen in patients with TTR (hereditary and wild type) cardiomyopathy being conducted at Indiana University School of Medicine. Inotersen-treated patients with cardiac disease at baseline achieved statistically significant benefit compared to placebo in both primary endpoints (mNIS+7 and Norfolk QoL-DN). 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? In the pivotal NEURO-TTR study, inotersen demonstrated significant benefit in mNIS+7 (primary end-point) scores across all stratification sub-groups and important disease sub-groups.	examples of autonomic function in the scope. Cardiac function has been added to the outcomes in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Inotersen also demonstrated significant benefit in Norfolk QoL-DN (primary end-point) scores across all stratification sub-groups and important disease sub-groups. There is no evidence to suggest that there are identifiable sub-groups of patients in whom inotersen is expected to provide greater clinical benefits or value for money. There are several genetic mutations that patients with hATTR can have. The clinical benefit of inotersen was seen in all patients irrespective of the type of genetic mutation. As hATTR can affect adults who are independent and employed, there is value in helping these patients remain at work and independent through an effective treatment that can be self-administered, at home or at work. In addition, keeping later stage hATTR patients more functionally independent will likely allow for their carers to remain in employment. Would inotersen be used at a particular stage of the disease? Slowing or halting disease progression through reduction of formation of TTR amyloid fibril deposits can benefit patients in all stages of disease. In the pivotal NEURO-TTR study, patients with Stage 1 and Stage 2 disease, but not Stage 3, were included. However, because inotersen blocks production of TTR, it should decrease continuous amyloid deposits which drive the disease and therefore theoretically should be effective in Stage 3 patients as well.	It was agreed at the scoping workshop that there are no important differences expected between subgroups of the population that require separate consideration.

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		Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Inotersen has the potential to dramatically change patients' lives for the better in a population that currently has significant unmet need. Evidence from the pivotal clinical study demonstrates halting or significant slowing of disease progression – something that has not been achievable before. In addition, a significant number of patients experienced improvement in their neuropathy and HRQoL with inotersen treatment. Inotersen is the first investigator product to show clinical improvement in hATTR in a pivotal trial. The mechanism of action of inotersen is a novel approach to halt disease progression that has not previously been available to treat this patient population. The clinical results, based on two primary end-points (mNIS+7, a gold-standard clinical assessment of motor, sensory and autonomic neuropathy, and Norfolk QoL-DN, a patient-reported measure of health-related quality of life) demonstrated that inotersen can have a significant and substantial impact on health-related benefits. The inclusion of inotersen in the treatment paradigm for hATTR patients will radically change the way the disease is treated and how patients, their families, and their physicians view their condition, and their potential to live a full and fulfilling life. For the first time, patients with hATTR will have a treatment that enables them to remain independent and productive members of their family, community and society.	

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		The self-administered treatment can benefit both early stage patients who do not need to take time off work or away from family activities to travel to an infusion center, and later stage, less mobile patients who might have difficulty in making the same journey.	
	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. 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	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. 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.

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		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	Cardiac function has been added to the outcomes in the scope.
	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	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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		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 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