National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tafamidis for treating transthyretin amyloid cardiomyopathy

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 *It is important that appropriate topics are referred to NICE to ensure that NICE*	British Society for Heart Failure	Yes.	Thank you. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?	Pfizer	We believe it is appropriate to refer this topic to NICE for evaluation under the Single Technology Appraisal (STA) programme, because: • **Process:** There are a number of cardiology services currently diagnosing and managing patients with ATTR-CM. An increase in the rate of new diagnoses of ATTR-CM is likely to further expand this number of centres that work alongside the National Amyloidosis Centre (NAC). Therefore, tafamidis would not meet the HST criterion that care should be focused in very few centres. o *Prevalence:* Case series reported by the NAC suggest that 997 patients with ATTR-CM were seen between 2005 and 2017,(1) however there are no reports of a point prevalence for the disease in the UK. The number of new diagnoses made each year is increasing rapidly, in part due to the availability of nuclear scintigraphy as a diagnostic test. The rate of increase is expected to accelerate further with the availability of a disease-modifying treatment. • **Timely:** A marketing authorisation for tafamidis in ATTR-CM is expected imminently, therefore this appraisal would align with NICE's published procedural and methodological guidelines regarding completion of appraisals as close to marketing authorisation as possible. • **Priority**: Assessment of tafamidis aligns with NICE's topic selection prioritisation criteria (2) and the 10 year NHS Long Term Plan (3), because if recommended, can offer significant health benefit to UK patients, support a care pathway designed around patients, and help frail and older people stay healthy and independent.	Thank you for your comments. At the decision point 4 meeting, it was agreed that a referral as a Single Technology Appraisal (STA) should be sought.
	Genetic Alliance UK	As tafamidis is the only medicine specifically designed to treat this condition and due to, in the context of a HSS, the small number of patients, this is an appropriate topic for HST evaluation.	Thank you for your comment. At the decision point 4

Section	Consultee/ Commentator	Comments [sic]	Action
			meeting, it was agreed that a referral as a Single Technology Appraisal (STA) should be sought. It was considered that the Highly Specialised Technology (HST) criteria were not met primarily because the population with wildtype transthyretin amyloid cardiomyopathy is likely to be large and underdiagnosed. Further, clinical experts noted at the scoping workshop that treatment was unlikely to be concentrated in a few highly specialised centres but instead delivered locally
	Amyloidosis Research Consortium UK	Yes.	Thank you. No action required.
	UK ATTR Amyloidosis	Yes.	Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Patient Association		
Wording *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	British Society for Heart Failure	Yes.	Thank you. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	We agree that the wording in the draft remit appropriately reflects the issues NICE should consider.	Thank you for your comment. No action required.
	Genetic Alliance UK	The wording of the remit matches the current format.	Thank you for your comment. No action required.
	Amyloidosis Research Consortium UK	Yes.	Thank you. No action required.
	UK ATTR Amyloidosis Patient Association	Yes.	Thank you. No action required.
Timing Issues	British Society for Heart Failure	Urgent – very rare but fatal progressive disease.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
What is the relative urgency of this proposed appraisal to the NHS?	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	We believe that there is a strong rationale for an urgent STA evaluation of tafamidis for ATTR-CM by NICE for the following reasons: • **Significant unmet need**. ○ *Survival:* The prognosis of ATTR-CM is poor, with median survival from diagnosis ranging from 2.3 to 4.8 years.(4-6) ○ *Morbidity:* Patients experience progressive deterioration in physical and health-related quality of life.(7) Significant caregiver burden has also been observed with a negative impact on their physical and emotional well-being.(8) ○ [redacted] • **Lack of current treatments for patients in the UK** In the existing treatment paradigm, the main aims of treatment are to manage the symptoms of congestive heart failure and prevent arrhythmogenic complications.(9, 10) As such, patients do not have access to any treatments that could improve their quality and/or length of their life.	Comment noted. No action required.
	Genetic Alliance UK	Tafamidis is the only medicine developed specifically to treat ATTR-CM. It is therefore 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. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Amyloidosis Research Consortium UK	Urgent, due to there being no other licensed treatment and significant patient unmet need due to disease-related symptoms and emotional burden.	Comment noted. No action required.
	UK ATTR Amyloidosis Patient Association	From the point of view of the patients, it is urgent, since there is no available treatment at present.	Comment noted. No action required.
Additional comments on the draft remit	British Society for Heart Failure	No.	Thank you for your comment. No action required.
	Alnylam Pharmaceuticals	-	-
	Pfizer	No additional comments.	Thank you for your comment. No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	-	-
	UK ATTR Amyloidosis	-	-

Section	Consultee/ Commentator	Comments [sic]	Action
	Patient Association		

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information *Consider the accuracy and completeness of this information.*	British Society for Heart Failure	Brief background. It should be noted that an important TTR variant in the UK, V122I is associated with isolated cardiomyopathy without neuropathy so the table in the Technology Section –Intervention: Comparators: hereditary ATTR-CM needs to be corrected.	Thank you for your comment. The background section of the scope has been updated accordingly. No change has been made to the comparators section. Explanation provided in the comparator section below.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	We believe that the majority of the background information is accurate and complete, however we believe that the following information should be also considered: • **Prevalence estimates** ○ We agree that it is difficult to reliably estimate the prevalence of ATTR-CM. We would also like to highlight the largest UK series, which included 997 patients that attended the NAC between 2005-2017.(1)	Thank you for your comments. No change has been made to the prevalence estimates as the scope specifies by wildtype and hereditary types. The numbers given in the

Section	Consultee/ Commentator	Comments [sic]	Action
		• **Hereditary ATTR-CM** ○ We agree that Val122Ile is the most common variant causing hereditary ATTR-CM; occurring in 64% of patients with hereditary ATTR-CM. It is thought to be the 4th most common cause of all heart failure among Afro-Caribbean patients in the UK.(11) In addition, we note that approximately 30% of patients with hereditary ATTR-CM have the T60A mutation.(1) ○ We would disagree that "many people with polyneuropathy as a result of transthyretin amyloidosis also have cardiomyopathy". We believe the overlap seen in the patisiran and inotersen clinical trials (APOLLO and NEURO-TTR, respectively) is likely to be an over-estimate due to the broad and non-specific diagnostic criteria used. The largest report of patients with Val122Ile ATTR-CM in the UK suggests that neurological symptoms were absent in all.(11)	scope were deemed reasonable by clinical experts at the scoping workshop. The background section has been updated to state that 'a small proportion of people with cardiomyopathy as a result of transthyretin amyloidosis also have polyneuropathy.' and 'Reported median survival is 2.1 years following diagnosis for people with the Val122Ile variant **and 3.4 years for people with the T60A variant.'** (addition in bold)
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	Suggest some edits to the background text. Transthyretin amyloidosis (ATTR) is caused by the production of abnormal transthyretin (TTR) proteins in the liver. These abnormal TTR proteins are unstable and readily misfold into amyloid fibrils and go on to accumulate as deposits in the tissues of the body (amyloidosis)[1]. Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of transthyretin amyloidosis in which	Thank you for your comment. The background section of the scope is intended to provide a brief overview of the disease area. The background section

Section	Consultee/ Commentator	Comments [sic]	Action
		amyloid fibrils accumulate in the heart[1], causing the heart tissue to thicken and stiffen[2]. Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care. Patisiran and inotersen have marketing authorisations for treating hereditary transthyretin related amyloidosis (hATTR). The marketing authorisations state that the technologies should be used for the treatment of hATTR in patient with polyneuropathy, but because ATTR is a multisystemic disease, many patients with polyneuropathy as a result of transthyretin amyloidosis may also have cardiomyopathy. Both technologies are currently being evaluated by NICE for hATTR.	has been updated to state that 'a small proportion of people with cardiomyopathy as a result of transthyretin amyloidosis also have polyneuropathy.' and 'Reported median survival is 2.1 years following diagnosis for people with the Val122Ile variant **and 3.4 years for people with the T60A variant.'** (addition in bold)
	UK ATTR Amyloidosis Patient Association	-	-
The technology/ intervention *Is the description of the technology or technologies accurate?*	British Society for Heart Failure	The table, Intervention: Comparators: needs to be corrected as Patisiran and Inotersen cannot be used as comparators in this V122I ATTR-CM, an important variant for ATTR-CM in the UK as no neuropathy is present.	Thank you for your comment. Clinical experts at the scoping workshop said that there is a small proportion of people who have ATTR-CM with associated neuropathy in the UK who would potentially

Section	Consultee/ Commentator	Comments [sic]	Action
			be eligible for treatment with inotersen or patisiran, subject to ongoing NICE evaluation. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE evaluation)". It is recognised that patisiran and inotersen are not relevant comparators for the treatment of ATTR-CM without associated neuropathy. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	We agree with the description of the technology and suggest further detail is added:	Thank you for your comments. Details about the effectiveness

Section	Consultee/ Commentator	Comments [sic]	Action
		• Tafamidis has been shown to reduce the progressive morbidity and mortality in patients with ATTR-CM.(12) The ATTR-ACT trial investigates the efficacy and safety of tafamidis in ATTR-CM patients and includes an open label extension (OLE) for up to 60 months. The OLE collects safety and efficacy data. The endpoints include all-cause mortality, incidence of treatment emergent adverse events, CV-related hospitalisation, change in KCCQ, NYHA.(13)	of the intervention are not included in the scope. No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	Suggested some edits. Tafamidis (Vyndaqel, Pfizer) binds to transthyretin (TTR) in the blood. This binding stabilises the shape of TTR, preventing it from misfolding and forming amyloid fibrils. In turn, this then stops the formation of amyloids.	Comment noted. The technology section is intended to give a brief overview of the intervention. No action required.
	UK ATTR Amyloidosis Patient Association	Yes.	Thank you. No action required.
Population *Is the population defined appropriately? Are there groups within*	British Society for Heart Failure	Yes.	Thank you. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
this population that should be considered separately?	Pfizer	We agree with the definition of the population and is aligned with the planned marketing authorisation.	Thank you for your comment. No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	Yes.	Thank you. No action required.
	UK ATTR Amyloidosis Patient Association	Population defined appropriately.	Thank you for your comment. No action required.
Comparators *Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	British Society for Heart Failure	The only standard treatment currently used in the NHS for ATTR-CM is supportive therapy with diuretic management.	Thank you for your comment. It is acknowledged that patisiran and inotersen are not currently used in clinical practice in England. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals

Section	Consultee/ Commentator	Comments [sic]	Action
			have been included "(subject to ongoing NICE evaluation)". No action required.
	Alnylam Pharmaceuticals	See comments to questions below.	Thank you.
	Pfizer	We agree that tafamidis should be compared against "established clinical management without tafamidis", however, • We believe that there is no difference between established clinical management between wild-type and hereditary patients. • We interpret "clinical management" to mean the symptomatic control of the symptoms of ATTR-CM using loop diuretics and anticoagulants. • We agree with the scope that transplantation is not widely used in UK clinical practice. • *Patisiran and inotersen:* These products should not be considered as comparators for the tafamidis STA as they are not licensed for wild-type ATTR-CM and limited efficacy data exists for their use in a predominantly cardiac phenotype hereditary population. ○ Although the APOLLO and NEURO-TTR trials reported that approximately half of hereditary ATTR patients with PN may have cardiac symptoms, these patients were not diagnosed using established criteria for ATTR-CM. ○ Unlike ATTR-ACT [tafamidis], the endpoints selected in APOLLO [patisiran] and NEURO-TTR [inotersen] did not reflect how a patient diagnosed with ATTR-CM feels, functions and survives. The NICE Methods Guide gives preference to these endpoints.(14)	Thank you for your comments. No action required. Thank you for your comment. At the scoping workshop clinical experts said that there is a small proportion of people who have ATTR-CM with associated neuropathy in the UK who would potentially be eligible for treatment with inotersen or

Section	Consultee/ Commentator	Comments [sic]	Action
		○ Given the lack of commonality in endpoints between APOLLO, NEURO-TTR and ATTR-ACT, an indirect treatment comparison between patisiran, inotersen and tafamidis is not feasible. ○ In turn, this lack of relative efficacy would not allow for a fair comparison of patisiran and inotersen to tafamidis in a cost effectiveness model, and would introduce significant uncertainty that could not be addressed. *Please also refer to our detailed response in consultation question 2 and 4 for further detail*	patisiran, subject to ongoing NICE evaluation. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE evaluation)". It is recognised that patisiran and inotersen are not relevant comparators for the treatment of ATTR-CM without associated neuropathy. The clinical experts at the scoping workshop noted that established criteria for diagnosing ATTR-CM was used in

Section	Consultee/ Commentator	Comments [sic]	Action
			the NEURO-TTR [inotersen] clinical trial. No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	No. Patisiran and inotersen are not standard treatments for ATTR-CM and should not be considered comparators. The comparator is mostly likely best supportive care.	Thank you for your comment. At the scoping workshop clinical experts said that there is a small proportion of people who have ATTR-CM with associated neuropathy in the UK who would potentially be eligible for treatment with inotersen or patisiran, subject to ongoing NICE evaluation. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals

Section	Consultee/ Commentator	Comments [sic]	Action
			have been included "(subject to ongoing NICE evaluation)". It is recognised that patisiran and inotersen are not relevant comparators for the treatment of ATTR-CM without associated neuropathy. No action required.
	UK ATTR Amyloidosis Patient Association	Yes.	Thank you. No action required.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	British Society for Heart Failure	Yes.	Thank you. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.

	Pfizer	We broadly agree with the outcomes list and suggest the following are added so that all aspects of disease relevant to the patient are captured, in line with the NICE Methods Guide (14):
		• *Patient function*:
		  ○ Six-minute walk test (6MWT).
		  ○ New York Heart Classification to measure functional ability.
		• *Patient survival:*
			Thank you for your comment.
			At the scoping workshop, clinical and patient experts said that cardiac function (such as global longitudinal strain or brain

Section	Consultee/ Commentator	Comments [sic]	Action
		All-cause mortality in addition to CV-related mortality, which is already listed in the draft scope.	natriuretic peptide (BNP) level) and symptoms of heart failure (such as breathlessness) should be added to the scope. The scope has been updated accordingly.
	Genetic Alliance UK	The outcomes listed are appropriate. We suggest the addition of: fatigue, breathlessness, limited capacity to exercise (6-minute walk tests carried out with ATTR patients have demonstrated limited functional capacity), and swelling. All of these outcomes have a significant impact on the ability of the patient to carry out every-day activities.	Thank you for your comment. At the scoping workshop, clinical and patient experts said that cardiac function (such as global longitudinal strain or brain natriuretic peptide (BNP) level) and symptoms of heart failure (such as breathlessness) should be added to the scope. The scope has been updated accordingly.
	Amyloidosis Research Consortium UK	Mostly. The primary endpoint in the study was a pooled analysis of mortality and cardiovascular-related hospitalisations, so it may be more appropriate to list these together rather than individually.	Thank you for your comment. At the scoping workshop, clinical and

Section	Consultee/ Commentator	Comments [sic]	Action
		We do not recall carer QoL data being collected in the study but nonetheless this is an important outcome measure. Similarly, we do not recall adverse effects of treatment being an outcome in the study, but nonetheless is a very important outcome measure.	patient experts said that cardiac function (such as global longitudinal strain or brain natriuretic peptide (BNP) level) and symptoms of heart failure (such as breathlessness) should be added to the scope. The scope has been updated accordingly.
	UK ATTR Amyloidosis Patient Association	Yes.	Thank you. No action required.
Economic analysis *Comments on aspects such as the appropriate time horizon.*	British Society for Heart Failure	No comments.	Thank you. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	• As ATTR-CM is a life-long disease, a lifetime horizon is the most appropriate time horizon. • In addition, to fully encompass the impact of ATTR-CM on the patient and the healthcare system, we would like to include in the cost effectiveness model:	Thank you for your comment. As stated in section 5.1.9 of NICE's methods guide, the reference-case on costs is that of the NHS and personal social

Section	Consultee/ Commentator	Comments [sic]	Action
		○ The cost of disease to the patient and their carers (e.g. costs to travel to appointments, costs to adapt their homes), as well as any impact on their work. ○ Carer's quality of life. ○ The system impact of delayed vs. early diagnosis. *Data to support these scenarios will be derived from a UK patient and carer burden study and a cost of illness study.*	services. Therefore, the company's base case analysis should only include costs from this perspective. No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	This seems appropriate.	Thank you for your comment. No action required.
	UK ATTR Amyloidosis Patient Association	-	-
Equality *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between*	British Society for Heart Failure	V122I ATTR is present in the Afro-Caribbean population in the UK. It is important that this hereditary ATTR-CM group is not disadvantaged by inaccurate comparators (only comparator = supportive medical therapy with diuretics). Currently quoted comparators for hereditary ATTR-CM, Patisiran and Inotersen cannot be used in this condition as there is no associated neuropathy.	Thank you for your comment. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. The scope has been updated to specify that

Section	Consultee/ Commentator	Comments [sic]	Action
people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*			patisiran and inotersen are only potential comparators for people with a mixed phenotype. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	• We note that some *TTR* variants are common in selected populations within the UK: ○ The most common *TTR* variants associated with hereditary ATTR-CM are Val122Ile, which is prevalent in the Afro-Caribbean population (6), and T60A, prevalent in the white Caucasian population and endemic to parts of Northern Ireland.(15) Numerous other rare TTR variants are also associated with ATTR-CM and afflict specific minority groups.(16) The proposed scope is within the equality legislation, as both wild-type and hereditary ATTR-CM patients are included.	Thank you for your comment. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
• *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*			
	Genetic Alliance UK	The burden of this condition disproportionally affects males from the BAME community or from a BAME heritage usually after the age of 60 years old.	Thank you for your comment. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. No action required.
	Amyloidosis Research Consortium UK	No issues with equality.	Thank you for your comment. No action required.
	UK ATTR Amyloidosis Patient Association	-	-
Other considerations	British Society for Heart Failure	-	-

Section	Consultee/ Commentator	Comments [sic]	Action
Suggestions for additional issues to be covered by the proposed appraisal are welcome.	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	No other considerations.	Thank you for your comment. No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	It is important to delineate between hTTR polyneuropathy associated with patisiran and inotersen and hTTR cardiomyopathy associated with tafamidis.	Thank you for your comment. The marketing authorisations for patisiran and inotersen are referred to in the scope and it is noted that only a small proportion of people with cardiomyopathy as a result of transthyretin amyloidosis also have polyneuropathy.
	UK ATTR Amyloidosis Patient Association	-	-

Section	Consultee/ Commentator	Comments [sic]	Action
Innovation *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)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*	British Society for Heart Failure	Yes.	Thank you. No action required.
	Alnylam Pharmaceuticals	None.	Thank you. No action required.
	Pfizer	We believe that tafamidis is innovative and will be a 'step-change' in the management of ATTR-CM compared to current treatments, and is therefore eligible for an Accelerated Access Collaborative designation.(17) Our justification for this is provided below: • **Firstly, tafamidis has high potential for major improvement in patient relevant outcomes.** We expect tafamidis to provide significant additional QALY gains to ATTR-CM patients that would transform their treatment approach.(12) • **Secondly, tafamidis has the potential to transform service delivery**. Delayed diagnosis is thought to be a major reason for shortened survival of patients with cardiac amyloidosis (18, 19). On average, patients experience >3 years delay in reaching a diagnosis from the onset of symptoms.(20) Furthermore, the median survival of affected individuals varies in the UK between 2.3 to 4.8 years. Given the delay in diagnosis, it can be expected that patients will already have advanced disease, and may have developed significant morbidity at the point of treatment initiation.(4, 6, 21) The availability of a disease-modifying treatment will likely result in greater disease awareness, and raise the index of suspicion among physicians, leading to higher rates of diagnosis. If patients are diagnosed earlier and treated with tafamidis, patients can expect improved survival and quality of life.	Comment noted. The company and other stakeholder submissions can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment. The Accelerated Access Product Selection Process has not been launched yet and the criteria for transformative designation are yet to be released. However, it is not an alternative route to market - an

Section	Consultee/ Commentator	Comments [sic]	Action
		• **Finally, introduction of tafamidis aligns with a key priority in the NHS Long Term Plan (3).** If recommended, tafamidis can help frail and older people stay healthy and independent for longer. To demonstrate that tafamidis will transform the care pathway for ATTR-CM, Pfizer is working collaboratively with NHS Partners to collect additional real-world evidence. The objectives of these studies are to: • **Patient and carer burden:** Understand the impact of ATTR-CM on the quality of life of UK patients and their carers; including the societal impact, utility and qualitative insights into the patient experience of the disease. • **Resource use:** Estimate the healthcare system impact of early vs. delayed diagnosis. • **Service provision:** [redacted] These studies will help to quantify the potential savings to the NHS that would otherwise be spent on repeated secondary care attendances without a diagnosis and treating late stage disease. We intend to incorporate the outputs of these studies into the cost effectiveness model for tafamidis and understand their impact on the cost per QALY.	assessment of clinical and cost effectiveness by NICE is still required No action required.
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	It has the potential to be transformative for patients and carers and therefore could be considered to be innovative.	Comment noted. The company and other stakeholder submissions can

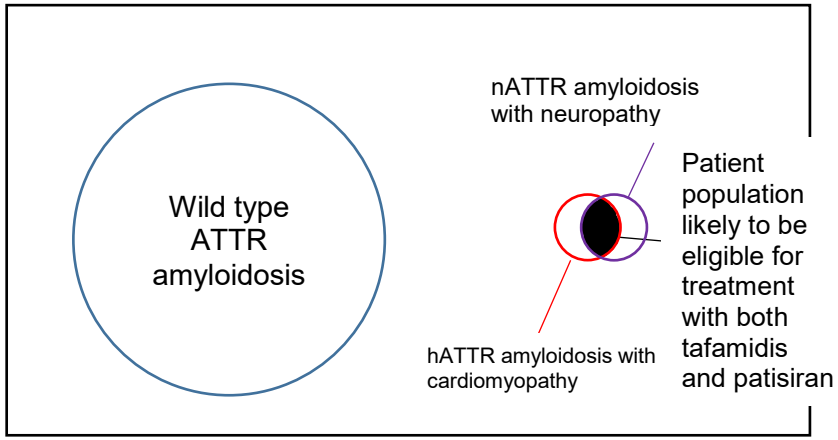
Section	Consultee/ Commentator	Comments [sic]	Action
			expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment. No action required.
	UK ATTR Amyloidosis Patient Association	-	-
Questions for consultation *Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes*	British Society for Heart Failure	-	-
	Alnylam Pharmaceuticals	Please our responses to questions for consultation, below.	Thank you.
	Pfizer	See response to questions below.	Thank you.

Section	Consultee/ Commentator	Comments [sic]	Action
to the planned time lines).			
	Genetic Alliance UK	-	-
	Amyloidosis Research Consortium UK	There is no specific question driving at the impact of the disease on patients, caregivers, families, etc. It would be good to see one added. Hereditary ATTR cardiomyopathy is easier to diagnose than wild-type due to family history. Wild-type is harder to diagnose as often goes mis- or undiagnosed and is treated, usually unsuccessfully, as other forms of heart failure. In hereditary ATTR, family members may be more likely to seek a formal diagnosis if they know an effective treatment is available, but this would most likely be a very small number. The availability of a new treatment alone is unlikely to result in more wild-type patients receiving treatment, unless there are concurrent improvements in diagnosis/detection. Treatment after diagnosis amounts to symptom management and best supportive care. Although there is the National Amyloidosis Centre (NAC), most patients are managed at local centres. One could make a strong argument however that complex cases should be seen at the NAC.	Comments noted. The impact of the disease on patients and caregivers will be explored by the appraisal committee. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Patisiran and inotersen not indicated for ATTR – CM. Tafamidis would fit well into the current pathway. Liver transplant unlikely to be a suitable comparator given rarity. There are no obvious sub-groups although in clinical practice, doctors and patients will discuss pros and cons of treatment and only those patients most likely to be benefit would be considered for treatment.	
	UK ATTR Amyloidosis Patient Association	-	-
Additional comments on the draft scope	British Society for Heart Failure	No.	Thank you. No action required.
	Alnylam Pharmaceuticals	▪ **If a specific treatment for this condition became available, is the number of people diagnosed expected to increase?** *hATTR: It is possible that there might be a minor increase in the number of people diagnosed with hATTR but we would expect any increase to be small and limited because:*	Thank you for your comments. No action required.

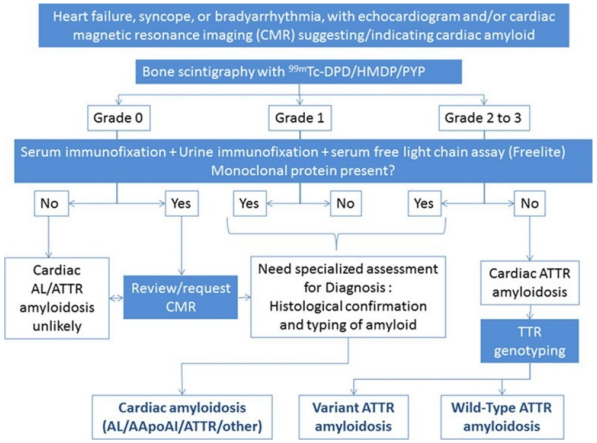
Section	Consultee/ Commentator	Comments [sic]	Action
		1) *Clinical experts (from the National Amyloidosis Centre and other sites in the UK) have indicated to us that they do not believe that there is a 'large pool' of undiagnosed hATTR patients in the UK* 2) *Novel hATTR treatments were licensed in 2018 (i.e., patisiran and inotersen) and, as a result, much of the increased diagnosis that accompanies new treatments due to higher disease awareness in the UK will likely already have occurred by the time tafamidis is made available in the UK*	
	Alnylam Pharmaceuticals	▪ **If a specific treatment for this condition became available, is the number of people diagnosed expected to increase?** *wtATTR: It seems likely that there would be a large increase in the number of people diagnosed with wtATTR because:* 1) *There is increasing evidence that wtATTR is much more common than previously thought. Studies have reported a wtATTR prevalence of 13% among patients with heart failure with a preserved ejection fraction (Gonzalez-Lopez et al., 2015) and Pfizer has estimated 'that there are about probably 100,000 potential patients in the U.S.' with 'only about 1% of these patients [being] diagnosed today' (*https://seekingalpha.com/article/4236494-pfizer-inc-pfe-ceo-albert-bourla-q4-2018-results-earnings-call-transcript?part=single*)* 2) *If approved, tafamidis would become the first licensed treatment ever for wtATTR and this would likely result in significantly increased awareness of the condition. Pfizer has stated its intention to make improving diagnosis of wtATTR 'a key focus of [its] launch plans'*	Thank you for your comment. The background section of the scope has been updated to include: 'The number of new diagnoses made each year, in particular for wildtype ATTR-CM, is increasing rapidly, in part due to the wider availability of diagnostic tests."
	Alnylam Pharmaceuticals	▪ **Would some of the people eligible for treatment with patisiran and inotersen be eligible for treatment with tafamidis (and vice versa)? Are heart or liver transplantation relevant comparators? Are there**	1) Thank you for your comment. Please

Section	Consultee/ Commentator	Comments [sic]	Action
		any other treatments that should be included specifically as comparators? *We do not believe that patisiran or inotersen should be a comparator in this appraisal because:* *1) As NICE states in the draft scoping document, the appraisals for patisiran and inotersen are 'in development' and neither is currently used as 'established clinical management' in the NHS.* *2) We believe that only a very small minority of people eligible for treatment with patisiran would be eligible for treatment with tafamidis (and vice versa) in England. This is because:* *a. The vast majority of patients eligible for treatment with tafamidis under a cardiomyopathy label will be patients with wtATTR (please see answer to question above). Neither patisiran nor inotersen are licensed for the treatment of wtATTR* *b. It is possible that tafamidis will not be granted a license for the treatment of cardiomyopathy in hATTR. In the NEJM paper outlining the results of the ATTR-ACT trial (Maurer et al., 2018), Figure 3 shows that tafamidis did not achieve statistical significance at the 95% level for a difference in Hazard Ratios vs. placebo in the hATTR patients studied. If tafamidis is not granted a license for cardiomyopathy in hATTR, there will be no 'overlap' in patient eligibility* *c. If tafamidis is granted a license for the treatment of cardiomyopathy in hATTR, it will remain the case that patisiran is licensed to treat hATTR in patients with Stage 1 and Stage 2*	see response in the comparator section above. No Action required. 2A). Thank you for your comment. Please see response in the comparator section above. No Action required. 2B & 2C). Thank you for your comment. Clinical experts at the scoping workshop said that there is a small proportion of people who have ATTR-CM with associated neuropathy in the UK who would potentially be eligible for treatment

Section	Consultee/ Commentator	Comments [sic]	Action
		neuropathy. Therefore, the only 'overlapping' patient pool will be hATTR patients with a mixed phenotype. This is represented in the illustrative diagram below (Figure 1).  *Please note that we are aware that 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.* *The answer above is based on the fact that, to our knowledge, tafamidis is not currently being used in the NHS to treat neuropathy in hATTR patients because it received a negative reimbursement decision from AGNSS in 2013. This negative decision appears to have been due to 'the lack of a significant difference between tafamidis and placebo in the primary analysis' of the pivotal FX-005 trial and a lack of trial evidence in patients*	with inotersen or patisiran, subject to ongoing NICE evaluation. It is understood that patisiran and inotersen are not relevant comparators for the treatment of ATTR-CM without associated neuropathy. No action required. .

Section	Consultee/ Commentator	Comments [sic]	Action
		with mutations other than V30M (Tafamidis for TTR FAP Evidence Review Group assessment of manufacturer submission, 2013). To our knowledge, there are no reasons for NICE or the NHS to reverse this reimbursement decision and so we assume that tafamidis will continue to not be used to treat the neurological impairment of patients with hATTR amyloidosis.	
	Alnylam Pharmaceuticals	▪ **Where do you consider tafamidis will fit into the treatment pathway for treating transthyretin amyloid cardiomyopathy?** *Our best estimate at this time (i.e., without knowing what license tafamidis will be granted), based on our discussions with key UK experts in hATTR is that:* ▪ *Patisiran will be the first line therapy for hATTR patients with 'pure' neuropathy and for hATTR patients with mixed neuropathy and cardiomyopathy* ▪ *Tafamidis will be the first line therapy for wtATTR patients and for hATTR patients with 'pure' cardiomyopathy* *This answer is based on the fact that, to our knowledge, tafamidis is not currently being used in the NHS for hATTR patients with polyneuropathy because it received a negative reimbursement decision from AGNSS in 2013. This negative decision appears to have been due to 'the lack of a significant difference between tafamidis and placebo in the primary analysis' of the pivotal FX-005 trial and a lack of trial evidence in patients with mutations other than V30M (Tafamidis for TTR FAP Evidence Review Group assessment of manufacturer submission, 2013). To our knowledge, there are no reasons for NICE or the NHS to reverse this reimbursement decision and so we assume that tafamidis will continue to not be used to treat the neurological impairment of patients with hATTR amyloidosis.*	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Alnylam Pharmaceuticals	▪ **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).** *We agree that an STA seems an appropriate process for appraising this topic*	Thank you for your comment. No action required
	Pfizer	**Any additional comments on the draft scope** **DETAILED RESPONSE TO CONSULTATION QUESTIONS** **1. How is transthyretin amyloid cardiomyopathy diagnosed in the NHS? Are there any differences in how wild-type and hereditary ATTR cardiomyopathy are diagnosed?** Endomyocardial biopsy (EMB) with histological testing was previously considered the gold-standard method of diagnosing cardiac amyloidosis.(22) A preliminary diagnosis of cardiac amyloidosis would then be followed by characterisation of the amyloid type and several techniques have been described to achieve this including immunofixation, immunoglobulin free light-chain assay and mass spectroscopy.(23) In 2016, specialist centres across Europe and the United States (including the NAC in the UK) produced a report outlining details of a consensus non-invasive pathway for diagnosis involving nuclear scintigraphy and a screen for monoclonal proteins (serum and urine immunofixation electrophoresis and serum free light-chain assay) (Figure 1). When combined, these non-invasive tests offer 100%	1.Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		specificity in diagnosing ATTR, both among 1217 patients with histology from any organ and in 374 patients with EMB sourced histology.(24) There is a paucity of data to establish the uptake of this non-invasive diagnostic algorithm in the NHS since its publication in 2016.(24) *Figure 1. Diagnostic algorithm for patients with suspected cardiac amyloidosis(24)*  Presently, the NAC is commissioned to provide diagnostic and management advice services for the national caseload of patients with amyloidosis. They receive referrals from a range of specialties, most commonly cardiologists and haematologists, for patients with ATTR-CM.(5) During a period between 2002 and 2011, prior to the establishment of the non-invasive diagnostic pathway for ATTR-CM, 47% of 102 patients referred with wild-type ATTR-CM had amyloid	

Section	Consultee/ Commentator	Comments [sic]	Action
		proven on a biopsy performed locally prior to initial assessment at the NAC.(5) In the current non-invasive diagnostic era, several cardiology services are diagnosing patients with ATTR-CM; however, few data are available to inform how many patients are diagnosed locally. In the non-invasive diagnostic algorithm,(25) there is a group of patients that may be diagnosed without ambiguity based on a Perugini grade >2 nuclear scan and the absence of a monoclonal protein on serum and urine immunofixation and serum free light-chain assay. These tests are straightforward and the infrastructure to perform them (gamma camera, access to radiopharmacy) is thought to be available in 131 out of 155 NHS providers based on data from the NHS Diagnostic Imaging Dataset 2017-18. Another group of more complex patients in the diagnostic algorithm are those with indeterminate results (low cardiac uptake/ Perugini grade 1 on nuclear scintigraphy and/ or positive monoclonal protein screen). According to the published algorithm these patients require specialized assessment to determine the amyloid type,(25) and this process is likely to require the expertise of the national centre of excellence. Once the diagnosis of ATTR-CM is confirmed, the final diagnosis of hereditary or wild-type disease is made by genetic testing with sequencing of the transthyretin (TTR) gene. A diagnosis of hereditary ATTR amyloidosis is supported by a TTR gene mutation.(16) Prior to this final diagnostic step, a common non-invasive diagnostic algorithm exists for both hereditary and wild-type ATTR cardiac amyloidosis. **a. If a specific treatment for this condition became available, is the number of people diagnosed expected to increase?**	1A. Thank you for your comment. The background section of

Section	Consultee/ Commentator	Comments [sic]	Action
		The absence of disease-modifying treatments in ATTR-CM has likely held back awareness of the disease among clinicians,(26) resulting in a significant under-diagnosis of the disease. A wide range of evidence from screening studies,(27, 28) autopsy data,(29) and annual trends in the rate of new diagnoses of ATTR-CM (Figure 2), suggest that it is more common than is currently recognised. Current estimates of the burden of ATTR-CM in various populations studied include: wild-type ATTR in 13% of patients hospitalised for heart failure with preserved ejection fraction (HFpEF);(27) ATTR found in 16% of patients undergoing transcatheter aortic valve implantation for severe aortic stenosis;(30) and hereditary ATTR-CM in 5% of patients with hypertrophic cardiomyopathy as defined by European Society of Cardiology guidelines.(28) Cardiac deposits of wild-type transthyretin amyloid have been found in as many as 20% of unselected elderly subjects suggesting that TTR amyloid in the heart may not always give rise to overt symptoms.(31).(32) However, in a study of HFpEF patients without antemortem suspicion of amyloid, 17% had left ventricular wild-type TTR amyloid deposition at autopsy.(29) In the past decade, the availability of cardiac magnetic resonance imaging and nuclear scintigraphy using technetium-labelled DPD to diagnose ATTR-CM non-invasively has resulted in a 30-fold increase in the diagnosis of the condition at the National Amyloidosis Centre (Figure 2).(4) Prior to 2001, 0.5% (1 in 200) of patients seen at the NAC were diagnosed with wild-type ATTR amyloidosis, compared to 18% (1 in 5) in 2016.(33) This upward trend in new diagnoses is expected to continue or accelerate as a result of the availability of disease-modifying therapy (subject to	the scope has been updated to include: 'The number of new diagnoses made each year, in particular for wildtype ATTR-CM, is increasing rapidly, in part due to the wider availability of diagnostic tests."

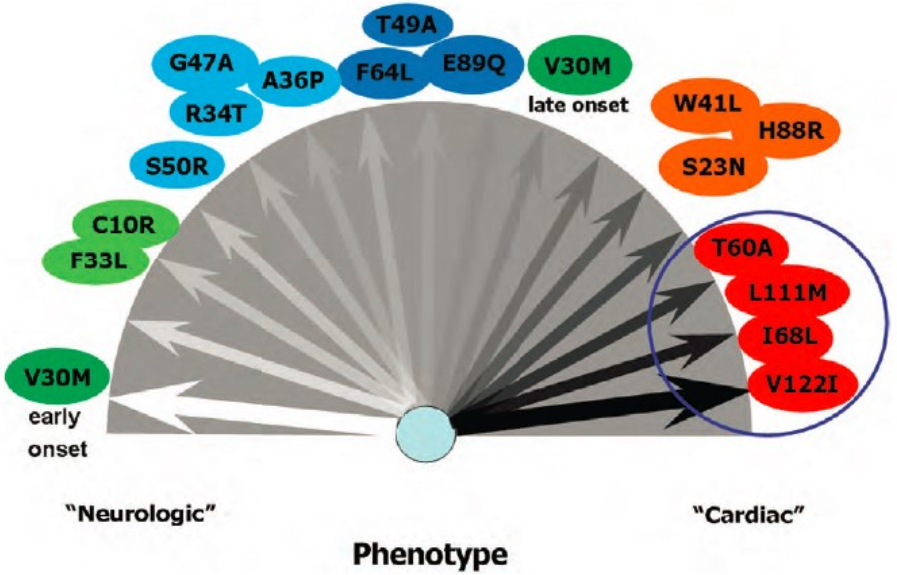
Section	Consultee/ Commentator	Comments [sic]	Action
		NICE evaluation) and widespread adoption of nuclear scintigraphy in heart failure services **<u>Figure 2. New diagnoses of ATTR-CM by genotype at the NAC (academic in confidence)</u>** <u>Reproduced from slides presented at an advisory board(20)</u> [Figure provided but not reproduced here as data academic in confidence]	
	Pfizer	**2.Following diagnosis, how is transthyretin amyloid cardiomyopathy managed? Please answer separately for wild-type and hereditary ATTR cardiomyopathy if appropriate.** There are currently no approved pharmacological treatments for this progressive and fatal disease. Symptom management of heart failure and arrhythmias is the mainstay of treatment in ATTR-CM,(23) owing to the absence of disease-modifying therapies. The use of conventional heart failure and anti-arrhythmic medications can be harmful in ATTR-CM, complicating management of the disease. Many are either used with extreme caution or contraindicated altogether.(23, 34) Patients with ATTR-CM often rely on a higher heart rate to maintain their cardiac output due to a fixed stroke volume that may be seen with thickened ventricular walls.(35) Heart failure therapies that slow heart rate (beta-blockers), or exert negative inotropic effects (ACE inhibitors, Ca-channel blockers), are potentially hazardous and may cause symptomatic hypotension and even cardiogenic shock.(35) Digoxin is also contraindicated in ATTR-CM due to its affinity for amyloid fibrils, which it binds to, increasing the possibility of toxic effects.(23) Against this background, judicious use of loop diuretics forms the mainstay of	2. Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		pharmacological treatment to relieve the symptoms of heart failure in ATTR-CM. The use of diuretics may be supplemented with strict fluid balance and involvement of a specialist heart failure nurse, for daily weight monitoring and diuretic dose titration according to symptoms and renal function.(36) Atrial fibrillation is common in ATTR-CM, as are other arrhythmias, increasing the risk of thromboembolic complications. There are no absolute contraindications to anticoagulation in this setting and a low threshold for initiation is recommended.(36) Routine pacemakers for bradycardia are considered appropriate but the role of implantable cardiac defibrillators is not defined in this population.(36) The only treatment option that offers an opportunity for disease modification is organ transplantation in patients with hereditary ATTR-CM. Orthotopic liver transplantation can remove the source of amyloidogenic variant transthyretin,(37, 38) but is rarely performed in the UK as outcomes are poor outside the setting of the Val30Met mutation that is endemic to areas of Portugal (but uncommon in the UK).(39, 40) Heart transplantation has also been performed in the UK for both hereditary and wild-type ATTR-CM patients with severe heart failure, but is generally not feasible due to the advanced age of potential transplant recipients, their co-morbid burden of illness and the scarcity of donor organs.(41) Diflunisal is a non-steroidal anti-inflammatory drug (NSAID) that has been used off-label to treat ATTR patients with both neuropathy and cardiomyopathy. It is bound by TTR in the plasma and therefore acts as a stabiliser,(42) reducing the rate at which TTR is broken down into its constituent subunits. Comprehensive data in ATTR-CM are lacking, although diflunisal was given to 13 patients in a single-arm cohort study	

Section	Consultee/ Commentator	Comments [sic]	Action
		at a low dose and in combination with a proton pump inhibitor.(43) Its safety was confirmed in this setting; however, an association between long term use and renal dysfunction was reported that may be prohibitive in the context of pre-existing renal impairment.(43) Diflunisal has not been approved to treat ATTR in any form and is associated with the typical NSAID-related adverse events, including gastrointestinal bleeding, renal dysfunction and worsening heart failure.(36) The management of hereditary ATTR-CM differs in one important regard. Once a diagnosis is made on *TTR* genotyping, genetic counselling of family members and routine monitoring for asymptomatic carriers should be offered.(44) **a. Is the disease managed at local centres?** In the absence of any disease-modifying treatment for ATTR-CM, the mainstay of management involves the use of loop diuretics to relieve the symptoms of congestive cardiac failure.(36) The titration of diuretic therapy, alongside the treatment of arrhythmias and prevention of their complications, fall within the routine practice and expertise of cardiologists. The management of heart failure caused by ATTR-CM occurs in local or regional heart failure or cardiomyopathy services in the NHS. Where patients with hereditary ATTR-CM have multi-system manifestations, multidisciplinary input is more often sought. The management of this more complex multi-system disease is more appropriately, and likely to be, led by the national centre of excellence.	2A. Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pfizer	**3.How long would treatment with tafamidis be expected to continue for in clinical practice?** It is expected that tafamidis would be continued lifelong in patients with ATTR-CM. The inclusion criteria of the ATTR-ACT trial included patients with NYHA class I-III at randomisation, and these patients were allowed to continue treatment if they progressed to NYHA class IV. In ATTR-ACT, the proportion of patients that discontinued the study due to adverse events that were related to the study drug was 21.2% in the pooled tafamidis group and 28.8% of patients in the placebo group. The most frequently reported adverse events leading to discontinuation in any treatment group were cardiac failure, congestive cardiac failure, cardiac amyloidosis and disease progression.(12)	Thank you for your comments. No action required.
	Pfizer	**4.Which treatments are considered to be established clinical practice in the NHS for treating transthyretin amyloid cardiomyopathy? Please answer separately for wild-type and hereditary ATTR cardiomyopathy if appropriate.** Please see the response to question 2 outlining how the disease is managed in the NHS and what treatments are considered to be established. **a.Would some of the people eligible for treatment with patisiran and inotersen be eligible for treatment with tafamidis (and vice versa)?** Patisiran and inotersen have each been studied in patients with hereditary transthyretin amyloidosis with polyneuropathy only.(45,	4. Thank you. Response provided in the comparator section above. No action required. 4A.Thank you for your comment. Clinical experts at the scoping workshop said that there is a small proportion of people who have ATTR-CM

Section	Consultee/ Commentator	Comments [sic]	Action
		46) Neither patisiran or inotersen have been investigated in the treatment of patients with wild-type ATTR amyloidosis, therefore it is anticipated that these patients would not be eligible for either treatment. Wild-type ATTR-CM is more common than the hereditary form of the disease; the largest series of patients reported from the NAC suggests that patients with wild-type ATTR-CM make up 68% of the overall population.(1) Furthermore, the prevalence of the wild-type population is expected to increase at a greater rate than hereditary ATTR-CM if current trends in diagnoses continue (Figure 2). In hereditary ATTR amyloidosis, mutations in the *TTR* gene can be associated with a spectrum of disease ranging from a predominantly neurological condition, to a mixed neurological and cardiac phenotype, to an exclusively cardiac phenotype.(47) The most common mutations found among patients with ATTR-CM in the UK are V122I and T60A, which are causative in around 64% and 30% of patients with the hereditary form of the disease.(1) The phenotypic expression of both mutations is thought to manifest in a predominant or exclusive cardiac disease (Figure 3).(47) In the largest series of patients with V122I ATTR amyloidosis in the UK (n=72) seen at the NAC, the majority of patients were in New York Heart Association class II and III (92%), but no single patient exhibited signs of peripheral neuropathy.(6) **Figure 3. Possible Spectrum of Genotype-Phenotype Correlations in ATTR.** Mutations associated with a predominant or exclusive cardiac phenotype are circled in blue. Reproduced from Rapezzi et al(47)	with associated neuropathy in the UK who would potentially be eligible for treatment with patisiran or inotersen, subject to ongoing NICE evaluation. It is understood that patisiran and inotersen are not relevant comparators for the treatment of ATTR-CM without associated neuropathy. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		 Patients with hereditary ATTR amyloidosis and a mixed phenotype may be eligible for treatment with patisiran or inotersen (subject to ongoing NICE evaluation). There is however difficulty in extrapolating the results of NEURO-TTR and APOLLO to patients with a mixed phenotype as neither trial defined subpopulations with cardiac disease based on consensus diagnostic standards,(25) or indeed cardiac symptoms such as heart failure. Therefore, neither study provides evidence of safety or efficacy of treatment in a population with ATTR-CM. The apparent large cardiac subpopulations enrolled in phase 3 trials of both patisiran and inotersen are unexpectedly large (53-63% of patients with ATTR-PN enrolled), and inconsistent with the literature around the phenotypic expression of these mutations.(6, 47) This inconsistency is due to the	

Section	Consultee/ Commentator	Comments [sic]	Action
		broader definition of cardiac involvement in APOLLO and NEURO-TTR than is considered diagnostic of ATTR-CM.(25) In the phase 3 APOLLO trial of patisiran, investigators defined a cardiac sub-population (left ventricular wall thickness ≥13 mm in the absence of a history of aortic valve disease or hypertension) that included 126 patients (56%). Similarly, investigators in the NEURO-TTR trial of inotersen defined a cardiomyopathy subgroup population based on left ventricular wall thickness ≥13 mm, no history of persistent hypertension and availability of echocardiogram imaging. This cardiomyopathy sub-population in NEURO-TTR included 108 patients (63%). Importantly, in both trials the definitions of these cardiac sub-populations were not made based on consensus diagnostic criteria for ATTR-CM, that requires either nuclear scintigraphy imaging of the heart or histological confirmation, in combination with other tests.(25) Furthermore, the trial definitions for the cardiac subpopulations did not specify any cardiac symptoms consistent with cardiomyopathy (e.g., symptoms of heart failure). Finally, the endpoints assessed in APOLLO and NEURO-TTR were reflective of the disease burden of patients with ATTR-PN, and did not include any clinical cardiac endpoints such as CV-mortality, CV-related hospitalisation or functional cardiac measures such as the Kansas City Cardiomyopathy Questionnaire. As such a methodologically valid indirect comparison of the inotersen/ patisiran and tafamidis is not possible. **b. Are heart or liver transplantation relevant comparators?** Organ transplantation is the only disease-modifying approach currently available for ATTR-CM patients. As the liver is the primary	The clinical experts at the scoping workshop noted that established criteria for diagnosing ATTR-CM was used in the NEURO-TTR [inotersen] clinical trial. No action required. 4B. Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		site of TTR production, liver transplantation may be helpful for patients with hereditary ATTR-CM, where the donor liver would produce normal wild-type TTR instead of mutant TTR protein. Thus, the aim of liver transplantation is to reduce the supply of abnormal TTR (leading to TTR misfolding) and prevent the formation of further amyloid deposition in other organs. Liver transplantation can lead to stabilisation of ATTR-CM, with the success rate highest for patients early in the course of disease before there has been extensive damage to cardiac tissue. In practice, liver transplant for ATTR-CM is almost never performed in the UK and tends to be reserved for younger patients with the Val30Met mutation that is endemic in parts of Portugal, but extremely rare in the UK.(36, 40) In patients with mutations other than Val30Met, cardiac disease may progress further following liver transplantation.(40) Combined heart-liver transplantation or heart transplantation in isolation have been suggested as a potential alternative for selected patients but are also rarely performed in the UK, due to the advanced age of eligible patients.(48) **c. Are there any other treatments that should be included specifically as comparators?** In the absence of any disease-modifying therapies for ATTR-CM, there are no relevant comparators for tafamidis.	4C. Thank you for your comment.
	Pfizer	**5.Are the outcomes listed appropriate? Please answer separately for wild-type and hereditary ATTR cardiomyopathy if appropriate.** **a. Are there any other outcomes that should be included?** As described in the draft scope table, to fully reflect the patient experience, we propose the addition of outcomes that measure	At the scoping workshop, clinical and patient experts said that cardiac function (such as global longitudinal strain or brain

Section	Consultee/ Commentator	Comments [sic]	Action
		how patients function and survive (e.g. All-cause mortality, NYHA over time, 6MWT). These outcomes apply for wild-type and hereditary ATTR-CM.	natriuretic peptide (BNP) level) and symptoms of heart failure (such as breathlessness) should be added to the scope. The scope has been updated accordingly.
	Pfizer	**6.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?** The ATTR-ACT study was not powered to evaluate response by subgroups; however, pre-specified exploratory analyses were conducted to explore efficacy analyses. All pre-defined subgroup analyses in ATTR-ACT study, including those based on TTR status (wild-type vs hereditary ATTR-CM) and NYHA class (I or II vs III), showed a consistent benefit of tafamidis, except for one subgroup analysis involving the frequency of CV-related hospitalisation in patients with NYHA class III heart failure at baseline. This finding may be explained by the fact that patients with a more advanced stage of disease (such as NYHA class III heart failure) who received tafamidis (for whom a subgroup analysis indicated a benefit with respect to mortality) had a longer period of time in which to incur hospitalisations than patients who received placebo. This benefit was accompanied by a longer disease duration, so patients with NYHA class III heart failure who received tafamidis could have been more vulnerable to health events that warranted hospitalisation than those who received placebo. That said, we caution about overinterpretation of results from one subgroup analysis. These	Thank you for your comments. At the scoping workshop the clinical experts suggested that subgroup analysis by New York Heart Classification class would be appropriate. The scope has been updated accordingly.

Section	Consultee/ Commentator	Comments [sic]	Action
		findings may be attributable to chance and should be considered to be hypothesis-generating.(49) These data, in combination with an understanding of the progressive nature of the disease and the mechanism of action of tafamidis (stabilisation of TTR tetramers), highlight the importance of an early diagnosis in ATTR-CM.(12) Tafamidis is therefore expected to offer the greatest benefit to patients when administered early in the disease course, when underlying pathology may be more easily reversed compared with later stages.(50) In the accompanying editorial to the ATTR-ACT publication,(50) it was suggested that tafamidis may allow the activation of local recovery processes that result in remodelling of amyloid deposits, a reduction in the strain on cardiac walls, and ultimately clinical benefit. Once irreversible organ damage has occurred, disease-modifying treatments may be less likely to be effective as the opportunity to reverse pathological ventricular remodelling is lost. There is likely to be a 'point of no return' in patients with advanced disease,(18) where the degree of cardiac damage and dysfunction drives the outcome, regardless of treatment effects on further amyloid deposition. It is unclear whether a lack of response to treatment occurs among patients with symptoms of advanced disease consistent with NYHA IV classification, however, it is not possible to draw conclusions around benefit and risk in this sub-population as they were excluded at baseline from ATTR-ACT.	
	Pfizer	**7.Where do you consider tafamidis will fit into the treatment pathway for treating transthyretin amyloid cardiomyopathy?** We would expect tafamidis to be the first line treatment for ATTR-CM in conjunction with symptomatic management of heart failure and its complications. There are currently no approved disease-modifying	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		pharmacological treatments for ATTR-CM. Following a diagnosis, the aims of treatment are the management of symptoms of heart failure and prevention of arrhythmogenic complications. Judicious use of diuretics forms the mainstay of treatment to relieve the symptoms of heart failure in ATTR-CM. Atrial fibrillation is common in ATTR-CM, as are other arrhythmias, increasing the risk of thromboembolic complications. There are no absolute contraindications to anticoagulation in this setting and a low threshold for initiation is recommended.(36) It is therefore expected that tafamidis (subject to ongoing NICE evaluation) would be the 1st line and only available treatment option for patients with wild-type or hereditary ATTR-CM.	
	Pfizer	**8.NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** **a. could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tafamidis will be licensed;** As stated in our response to the draft scoping table, it has been observed that some common variants, such as V122I, occur more commonly in the Afro-Caribbean population in the UK(11). The proposed scope is within the equality legislation, as both wild-type and hereditary ATTR-CM patients are included.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		b. could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; A recommendation in line with the draft scope (wild-type and hereditary ATTR-CM patients) would ensure that the principles of the Equality legislation are upheld. **c. could have any adverse impact on people with a particular disability or disabilities.** See response to 8(b)	
	Pfizer	**9.Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** See response to 8(b)	Thank you.
	Pfizer	**10.Do you consider tafamidis 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)?** Tafamidis is an innovative therapy. It provides significant reductions in mortality and morbidity for a fatal disease that until now has had no viable treatment options.(12) Tafamidis therefore represents an	Comment noted. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a

Section	Consultee/ Commentator	Comments [sic]	Action
		important advance for patients, their families and caregivers. Pfizer are working closely with the MHRA and NHS England to provide access to tafamidis for patients with ATTR-CM, prior to its marketing authorisation. [redacted] The ATTR-ACT study showed that tafamidis significantly reduced the hierarchical combination of all-cause mortality and cardiovascular-related hospitalisation (primary analysis) in ATTR-CM patients (p=0.0006).(12) Secondary endpoints included separate analyses of the 2 components of the primary endpoint, where a 30.2% reduction in risk of all-cause mortality (HR=0.698, 95% CI 0.508, 0.958, p=0.0259) and a 32.4% reduction in risk of CV-related hospitalisation (RR=0.6761, 95% CI 0.5639, 0.8107, p<0.0001) were observed in the pooled tafamidis group compared to placebo-treated patients.(12) The mortality benefit from tafamidis was observed across all subgroups (TTR genotype, NYHA class, tafamidis dose) and fewer cardiovascular-related hospitalisations were seen in all subgroups with the exception of patients in the NYHA class III group.(12) The greater hospitalisation rate observed in this group may be attributed to longer survival of the active treatment arm during a more severe period of disease.(12) In analyses of the key secondary endpoints, a statistically significant and clinically meaningful difference was observed favouring the tafamidis-treated group versus the placebo-treated group on functional (6MWT) and quality of life (KCCQ-OS) measures (p<0.0001 for both endpoints), as assessed by the change from Baseline to Month 30. [redacted]	significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] In summary, the benign safety profile and robust efficacy results in the ATTR-ACT study indicate that tafamidis is the first effective therapy for patients with ATTR-CM.(12, 50) Tafamidis represents a paradigm shift in the management of the disease- it represents the first and only treatment option that moves beyond symptomatic management to modification of disease progression and maintenance of physical/ psychosocial functioning. This paradigm shift in the treatment of the disease will reduce some of the substantial burden of ATTR-CM on patients and their caregivers.(8)	
	Pfizer	**11.Do you consider that the use of tafamidis can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** It is widely acknowledged that the absence of a disease-modifying treatment for ATTR-CM has held back awareness of the disease among clinicians.(18, 26) The lack of an approved treatment is likely to be a contributor, albeit one of many, to the significant under-diagnosis of the disease in the UK, that is supported by a range of evidence from screening studies,(27, 28) autopsy data,(29) and national trends in new cases (Figure 2). If current trends in new diagnoses made at the NAC continue, the prevalence of ATTR-CM will increase by at least 2.5-fold in 5 years. This increase is likely to be an under-estimate if there is availability of an approved treatment (subject to NICE appraisal) combined with widespread adoption of nuclear scintigraphy in heart failure services around the UK, both of which are likely to accelerate the upward trend in new diagnoses (Figure 2).(18)	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		With the use of non-invasive nuclear scintigraphy as standard,(25) the availability of tafamidis (subject to NICE evaluation) is likely to increase the identification of patients with early-stage ATTR-CM. Given the progressive nature of ATTR-CM, this is fortunate as delays to diagnosis, currently thought to be >3 years on average, represent a missed opportunity for disease modification should tafamidis become available. UK data suggest that >20% of patients with wild-type ATTR-CM are already in NYHA classification III or IV heart failure at diagnosis.(4) The corresponding figure for patients with V122I hereditary ATTR-CM is 40%, suggesting these patients have more advanced disease at diagnosis. A system shift to earlier diagnosis is likely to result in a benefit for all patients with ATTR-CM, but the greatest benefit will be seen among those with hereditary ATTR-CM and the V122I mutation.(4)	
	Pfizer	**12. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Pfizer are working with a number of NHS Partners to generate data around patient/ carer burden and healthcare resource utilisation stratified by disease stage. Using NYHA as measure of disease stage, these data will provide evidence of the benefits of diagnosing ATTR-CM at an early point where there is an opportunity for disease modification. System improvements in diagnosis resulting from the availability of disease-modifying treatment, will in turn lead to earlier diagnosis. The sequelae for health-related benefits are that a great proportion of patients will have an opportunity to reverse pathological ventricular remodelling with treatment, and fewer patients will have extensive cardiac damage that is irreversible.	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pfizer	**13.To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** The principal barriers to adoption of tafamidis in clinical practice are under-diagnosis and delayed diagnosis of ATTR-CM in the UK. [redacted] Treatment with tafamidis will offer the greatest benefits in patients with early-stage disease, due to the progressive nature of the disease and the mechanism of action of tafamidis. Therefore, it is critical to reduce the time to diagnosis for patients to receive the maximum benefit from treatment. [redacted] NICE quality standards from 2018 support timely referral of all patients with suspected heart failure for specialist assessment and transthoracic echocardiography.(51) Implementation of these guidelines in practice has shown that early involvement of a heart failure specialist is associated with better outcomes for patients, who experience reduced all-cause and CV-related hospitalisations.(52) The same study evaluating the implementation of the NICE quality standards in practice highlighted a key difference in the management of patients with heart failure and a reduced ejection fraction (HFrEF), compared to those with a preserved ejection fraction (HFpEF).(52) While those with HFrEF routinely received early and ongoing management from a	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		multidisciplinary team, those with HFpEF were usually discharged back to the General Practitioner with a management plan.(52) It is within this group of patients with a diagnosis of HFpEF that ATTR-CM is thought to be widely underdiagnosed. Screening studies using nuclear scintigraphy have found evidence of ATTR-CM in as many as 13% of patients hospitalised for HFpEF.(27) If there is to be a system improvement in diagnosis rates for ATTR-CM, coupled with a reduction in the delay to diagnosis, it will be important for clinicians to have an appropriate index of suspicion for the disease in this population. Physician education will be critical to highlight that the disease is far commoner than previously thought, that early diagnosis will lead to better patient outcomes, and that a simple nuclear test offers comparable sensitivity and specificity as an endomyocardial biopsy (when used with a monoclonal protein screen). Early use of nuclear scintigraphy among patients with suspected cardiac amyloidosis offers a safe, cheap and effective method of diagnosing both cardiac amyloidosis and differentiating its subtypes.(4, 53)	
	Pfizer	**14. NICE intends to appraise this technology through its STA Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).** Please see response in the draft scope table	Comment noted. No action required.
	Pfizer	**15.NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-**	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. **a. Would it be appropriate to use the cost comparison methodology for this topic?** We do not believe that it would be appropriate to undertake a cost comparison for this topic, as no data is available to show that tafamidis is clinically equivalent to a relevant comparator for the treatment of ATTR-CM. **b. Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Not applicable. Please see response to question 15a **c. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Not applicable. Please see response to question 15a **d. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** Not applicable. Please see response to question 15a	
	Genetic Alliance UK	-	-

Section	Consultee/ Commentator	Comments [sic]	Action
	Amyloidosis Research Consortium UK	None.	Thank you. No action required.
	UK ATTR Amyloidosis Patient Association	-	-

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

- British Association for the Study of the Liver (BASL)
- Department of Health and Social Care (DHSC)