NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator, and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Pfizer**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Cardiomyopathy UK
   b. UK ATTR Amyloidosis Patients' Association
   c. British Cardiovascular Society *(response endorsed by the Royal College of Physicians)*
   d. British Society for Heart Failure
   e. NHS England
   f. National Amyloidosis Centre, at UCL

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tafamidis for treating transthyretin amyloid cardiomyopathy

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

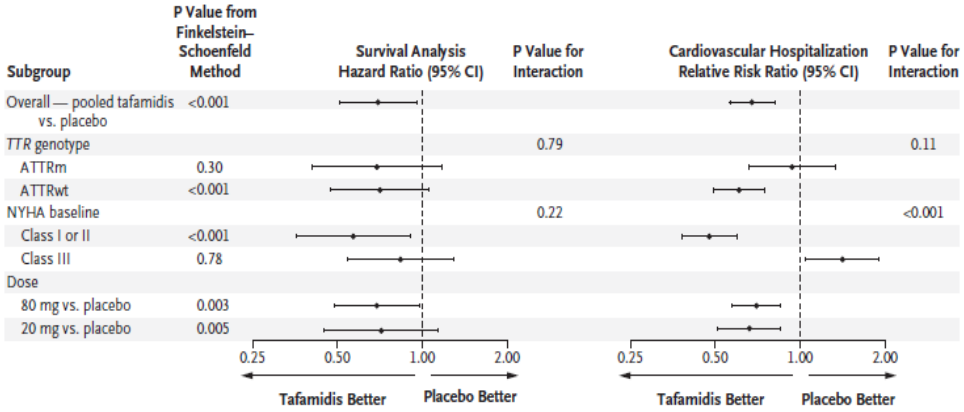
Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

Comments received from consultees

Consultee	Comment [sic]	Response
Pfizer	Accuracy and speed of diagnosis The committee concluded that "Accurately diagnosing ATTR-CM is challenging and can take a long time." (Section 1; Page 3) and "Without validated and objective measures for assessing ATTR-CM, identifying people who need treatment and those who are benefiting from treatment will continue to be a challenge" (Section 3.27; Page 25). The company suggests that these conclusions are not supported by the evidence. In 2016, a group of amyloid experts published a non-invasive diagnostic algorithm for ATTR-CM which was validated and found to have a specificity and positive predictive value for ATTR-CM of 100%.This algorithm has been implemented at 17 EAMS sites across the UK using diagnostic equipment for nuclear scintigraphy and laboratory tests that are standard at most NHS hospitals. The aforementioned diagnostic algorithm is now supplemented by comprehensive international expert recommendations on diagnosis that are endorsed by multiple professional societies from across Europe and the United States. The confirmatory tests in the diagnostic algorithm for ATTR-CM (nuclear scintigraphy, blood and urine tests for monoclonal protein) can be performed in a single day. The huge delays in establishing the diagnosis of ATTR-CM following presentation with cardiac symptoms (prior to 2019 the average delay in the UK was >3 years with 40% waiting >4 years), is likely the result of a low index of suspicion for the condition among cardiologists interacting with undiagnosed ATTR-CM patients in their daily practice and/ or clinical inertia in diagnosing ATTR-CM because of the lack of available treatment options. Historical UK data demonstrate the feasibility of rapid diagnosis as one third of patients received a diagnosis within 6 months from the onset of symptoms. Rapid diagnosis could be expanded to most patients providing the equity of access to confirmatory diagnostic tests achieved through EAMS could be replicated going forwards (reducing the requirement for every patient to travel to a single centre).	Comments noted. The committee agreed that the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM but recognised that diagnosis can still take a long time (see FAD section 3.3). The committee noted that these diagnoses were made at a specialist centre and questioned if the reduced delays to diagnosis achieved at the National Amyloidosis Centre (NAC) could be achieved at other centres in clinical practice (see FAD section 3.8) See above response and FAD section 3.8 The ERG highlighted that the trend of earlier diagnosis seen during the EAMS period could be explained by improvements in diagnostic tools since the ATTR-ACT trial (see section 3.3). It noted that when ATTR-CM is suspected the diagnostic

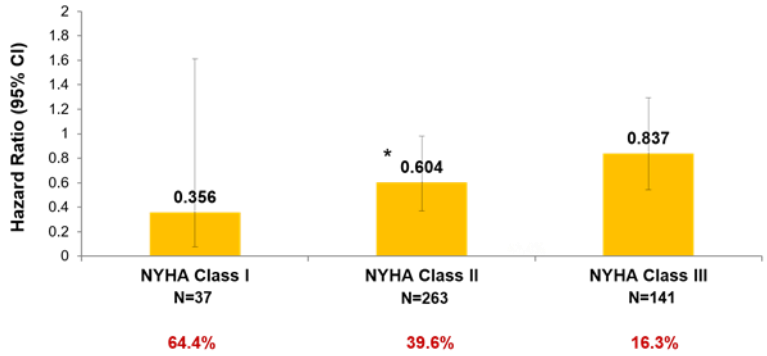
Consultee	Comment [sic]	Response
	Data from the EAMS support the positive impact of tafamidis on early diagnosis in terms of both reducing the delay to diagnosis and identifying patients earlier in their disease course.	pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur. The committee acknowledged this, and agreed it was not possible to entirely attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis (see FAD section 3.8). The committee acknowledged that although this data was informative, the EAMS data can only demonstrate that diagnosis delay was reducing when tafamidis was available through EAMS, and not that tafamidis was the cause for this reduction (see FAD section 3.8).
Pfizer	Treatment benefits across subgroups defined by NYHA classification and genotype The ACD contains the following statements which highlight uncertainty around the effectiveness of tafamidis in subgroups of the ATTR-ACT study. The conclusions of the committee within themselves are not consistent and are also not consistent with the observed results in either the subgroups or the overall trial population. These statements (see Footnote) call into question the efficacy of the medicine. The positive benefit risk profile of tafamidis has already been determined by the EMA. As acknowledged by the committee, subgroup analyses were not powered to assess efficacy but rather are evaluated for consistency of the treatment benefit. We do not believe it is appropriate to use subgroup analyses to undermine results observed in the overall population or draw conclusions on subgroups when consistent results were observed. Taken together the following statements (see Footnote) from the committee are inconsistent and raise concerns about the effectiveness of tafamidis in NYHA class 1, 2 and 3. The ATTR-ACT study only enrolled patients in NYHA Class 1, 2 and 3 and showed a 30% reduction in mortality (p=0.0259) and a 32% reduction in CV-related hospitalisation (p<0.0001) compared with placebo in the overall population. Despite these findings of a significant and clinically meaningful treatment benefit among patients treated with tafamidis, the committee have suggested the benefits are unclear in patients across the spectrum of NYHA classes that make up the totality of the enrolled trial population.	Comments noted. The committee agreed that although the subgroup results added a degree of uncertainty around the clinical effectiveness results for tafamidis it accepted that they were underpowered. It concluded that the subgroup results would not be considered in its decision making (see FAD section 3.11).

Consultee	Comment [sic]	Response
	There is no scientific basis to support the committee's conclusion that there is a high level of uncertainty in the clinical effectiveness of tafamidis in patients with hereditary ATTR-CM. When testing for statistical interactions between subgroups, no significant interactions were observed between hereditary and wild-type ATTR-CM for all-cause mortality and CV-related hospitalisation (both components of the primary endpoint). The magnitude of reduction in all-cause mortality was in fact higher among patients with hereditary ATTR-CM (31.0%) than observed in those with wild-type ATTR-CM (29.4%). Similarly, no significant interaction was observed between NYHA I/II and NYHA III for all-cause mortality supporting a consistent treatment effect across NYHA classes. The P value for interaction was significant between NYHA I/II and NYHA III for CV-related hospitalisation. This is thought to be attributable to patients living longer in a more advanced health state in the tafamidis treatment arm (as a consequence of the reduced mortality). Figure 1. Overall and subgroup results for all-cause mortality and cardiovascular related hospitalisations  Footnote omitted – see company's response to ACD	
Pfizer	NYHA classification and stopping rule The committee has concluded that the NYHA classification system has limitations, therefore, those that benefit most cannot be accurately identified and a stopping rule based on NYHA classification is not appropriate. The company disagrees with this	Comments noted. Although the committee acknowledged the views from clinical experts that NYHA is used widely in heart failure trials, it maintained its view that its use

Consultee	Comment [sic]	Response
	conclusion. NYHA classification is suitable to define a stopping rule because it is widely used in clinical practice, has been extensively validated and has been used in previous NICE recommendations. Furthermore, data from ATTR-ACT supports the use of the stopping rule and the EMA guidance is supportive, to some extent, of a stopping rule in NYHA IV. NYHA classification is the most widely used functional classification in heart failure. It has been extensively validated and has been shown to correlate with quality of life, quantitative assessment of cardiopulmonary performance such as peak VO2, and prognosis. Furthermore, NYHA classification is repeatedly used in NICE guidelines to describe the severity of heart failure and to define populations eligible for treatment with heart failure therapies. There is clear biological rationale for expecting that the treatment effect size of tafamidis may differ by severity of disease in ATTR-CM. NYHA classification is the most widely used measure of severity in ATTR-CM. Therefore, as agreed with the EMA based on scientific advice, it was deemed appropriate to pre-specify a subgroup analysis by severity using NYHA classification. The limitations of the NYHA classification system do not introduce difficulty in identifying who benefits from tafamidis treatment. The ATTR-ACT study results are applicable to a broad population diagnosed with ATTR-CM by established criteria in whom tafamidis reduces all-cause mortality by 30% and reduced CV-related hospitalisation by 32%. There are no data to support the use of tafamidis in patients in NYHA IV, who have symptoms at rest, because this group were not enrolled in the ATTR-ACT study. When patients did progress to this advanced stage of disease, they discontinued treatment at a median of [redacted] days after entering NYHA IV classification. This observation suggests that discontinuations in practice mirror an NYHA IV stopping rule, confirming feasibility in clinical practice. The trial evidence showing very high and rapid discontinuation of tafamidis in NYHA IV reflects published guidance around management of end stage heart failure, which suggests medicines optimisation is recommended once reversible causes of heart failure are excluded. Stopping unnecessary medicines that do not contribute to symptomatic improvement is recommended. Given that tafamidis is such a treatment, i.e. it offers no short-term symptomatic relief but addresses the underlying disease mechanism in reducing cumulative exposure to transthyretin amyloid over time, it is felt that a stopping rule at NYHA IV would be clinically appropriate.	for measuring the severity of ATTR-CM had limitations. Despite this it acknowledged there was insufficient evidence available from the trial to consider an alternative measure (see FAD section 3.6). The committee understood that there was limited evidence to support the use of tafamidis in NYHA class 4 because ATTR-ACT did not recruit people whose disease was classed as NYHA class 4. It acknowledged the company's view that the proposed stopping rule reflected treatment stopping in ATTR-ACT, in which most people stopped tafamidis quickly after progressing to NYHA class 4. It also acknowledged comments from the clinical experts suggesting that people whose disease was classed NYHA 4 would be very unwell and likely moved onto best supportive care. However, it noted that tafamidis' marketing authorisation did not include a treatment stopping rule based on NYHA classes. It also considered that using the NYHA classification to accurately identify people who need treatment had limitations. So, it concluded that it would not consider starting and stopping rules for tafamidis based only on the NYHA classification system in its decision making (see FAD sections 3.7 and 3.15) Comment noted. The committee acknowledged that tafamidis' marketing authorisation states that

Consultee	Comment [sic]	Response
	The randomised controlled trial evidence for tafamidis supports the effectiveness of the medicine in NYHA classes I-III. As the committee highlight, the European Medicines Agency Summary of Product Characteristics supports starting tafamidis as early as possible in NYHA I/II and recommends a physician decision on starting and maintenance in NYHA III. Therefore, it should be appropriate to specify a stopping rule in NYHA IV where there is no evidence of treatment benefit. Footnote omitted – see company's response to ACD	treatment should be started as early as possible. But, it was aware that tafamidis' marketing authorisation does not specify a treatment starting rule based on the NYHA classification system. Also, it agreed that, using the NYHA classification alone to accurately define the population who were eligible to receive tafamidis identify people who need treatment had limitations (see FAD section 3.6). So, it concluded not to considered treatment starting or stopping rules based on the NYHA classification system in its decision making (see FAD section 3.7). See above response in relation to the committee's view on applying a treatment stopping rule in NYHA class 4.
Pfizer	NYHA classification as a measure of clinical effectiveness We are concerned by the following statement which does not reflect the evidence submitted by the company: "The committee noted the high level of uncertainty, specifically: measuring the clinical effectiveness of tafamidis using the NYHA classification system (Section 3.23; Page 22)" This statement is factually incorrect, the clinical effectiveness of tafamidis was not measured using the NYHA classification system in the clinical evidence package. NYHA classification was an exploratory endpoint in the ATTR-ACT study and it was a stratification factor used for the primary analyses. The clinical effectiveness of tafamidis was measured using a combination of all-cause mortality and CV-related hospitalisation.	Comments noted. The committee maintained its view that using the NYHA classification to measure and categorise the severity of ATTR-CM had limitations (see FAD section 3.6). The committee was aware of and considered the clinical evidence and the ATTR-ACT trial primary and secondary outcome results (see FAD sections 3.9 and 3.10).
Pfizer	Differentiating amyloid deposits from amyloidosis The following statement in the ACD is misleading as it is not aligned with clinical practice: "The clinical experts……noted that transthyretin amyloid deposits are often an incidental finding in people having DPD scans. They explained that the population they see in practice had a range of amyloid deposits, sometimes because of older age, for example. Also, there is no defined point at which amyloid deposits become amyloidosis. So, it is unclear why some amyloid deposits progress to amyloidosis and others do not. Also, because other common comorbidities can	Comments noted. The committee heard conflicting views from the company and clinical experts present at the appraisal committee meeting regarding the interpretation and implications from an increased availability of DPD scans. It was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NHYA class 1, and that an accurate diagnosis cannot be formally established

Consultee	Comment [sic]	Response
	lead to increased breathlessness and decreased mobility, a definitive ATTR-CM diagnosis is challenging." (Section 3.3; Page 6). It is misleading to suggest that ATTR deposits are often an incidental finding in patients undergoing DPD scans. Based on the validated diagnostic algorithm developed by the NAC and other centres, patients are only eligible for a DPD scan if they meet the following criteria: "Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/ or cardiac magnetic resonance imaging suggesting/ indicating cardiac amyloid". Therefore, by definition, if patients are investigated according to this algorithm, DPD scans are only undertaken in symptomatic individuals with a clinical phenotype, consequently identification of amyloid deposits cannot be incidental. This algorithm has been safely and effectively implemented at 17 UK cardiology centres in EAMS, to identify patients aligned with the EMA indication, and without any evidence of misdiagnosis or misclassification. The suggestion that cardiologists specialising in heart failure or cardiomyopathy are not able to identify patients with a clinical phenotype on the basis of structural changes on imaging or cardiac signs/ symptoms undermines a core component of their routine practice.	without a number of procedures (such as biopsy and scintigraphy). The committee acknowledged this and agreed that even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM. So, it concluded that it was unclear if the availability of improved tests for diagnosing ATTR-CM would lead to an overdiagnosis of amyloidosis (see FAD section 3.4).
	If a DPD scan is performed for another indication, for example the investigation of bone disease, a patient may have an incidental finding of cardiac amyloid deposits. However, this would never equate to a diagnosis of amyloidosis in the absence of the clinical phenotype described in the algorithm (Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/ or cardiac magnetic resonance imaging suggesting/ indicating cardiac amyloid).	See above response and FAD section 3.4
	While common comorbidities can lead to breathlessness, the diagnostic algorithm restricts DPD scans to patients with the clinical phenotype of cardiac amyloidosis that must be evident on echocardiogram and/ or cardiac magnetic resonance imaging. This statement has therefore introduced unfounded uncertainty as to the ability of clinicians to correctly identify the disease that is not supported by evidence.	The committee heard comments from the clinical experts and the NHS England representative who explained that when amyloidosis is suspected people are referred to the NAC for more rigorous testing (see FAD section 3.4).
Pfizer	Treatment benefits in NYHA I The ACD states: "The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment" (Section 3.6; Page 9). This statement is directly contradicting the conclusion from the EMA and is not aligned with published data from ATTR-ACT.	Comments noted. The committee was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NHYA class 1, particularly if they do not have heart failure (see FAD section 3.4).
	This statement directly contradicts the European Medicines Agency Summary of Product Characteristics which states, "Vyndaqel should be started as early as	The committee acknowledged tafamidis' marketing authorisation states that treatment should be

Consultee	Comment [sic]	Response
	possible in the disease course when the clinical benefit on disease progression could be more evident." The evidence from the ATTR-ACT study suggests the medicine offers the greatest magnitude of benefit for the primary outcome measure in patients with NYHA I classification (Figure 2). A diagnosis of ATTR-CM in NYHA class I is not a benign condition, in ATTR-ACT, [redacted] NYHA I patients in the placebo arm died and [redacted] underwent heart transplantation during the 30-month trial period. Patients with NYHA Class 1 are also not asymptomatic- they must have a clinical phenotype for a diagnosis, this would include cardiac remodelling on echocardiogram or magnetic resonance, they may have clinical signs of heart failure or a previous hospitalisation for heart failure- treatment with diuretics may reduce the functional limitation for a time limited period before progression of disease. Delaying treatment while patients progress to a functional limitation is counter to international clinical consensus and deprives patients of an opportunity to halt progression of their disease in an early stage and reduce mortality. Figure 2. All-cause mortality by NYHA class 	started as early as possible. But, it was aware that tafamidis' marketing authorisation does not specify a treatment starting rule based on the NYHA classification system. Also, it agreed that, using the NYHA classification alone to accurately define the population who were eligible to receive tafamidis identify people who need treatment had limitations (see FAD section 3.6). So, it concluded not to consider treatment starting or stopping rules based on the NYHA classification system in its decision making (see FAD section 3.7)..
Pfizer	The impact of tafamidis on early diagnosis The ERG and subsequently the committee concluded that diagnosis times are unlikely to change if tafamidis were approved: "The ERG highlighted that the trend of earlier diagnosis seen during the EAMS period could be explained by improvements in diagnostic tools since the ATTR-ACT trial (see section 3.3). Also, it noted that awareness of ATTR-CM had increased after patisiran and inotersen were introduced (see section 3.4). So, diagnosis times are unlikely to substantially change if tafamidis was to be recommended by NICE" (Page 10). The company are	Comments noted. The committee agreed that the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM but recognised that diagnosis can still take a long time (see FAD section 3.3). It also noted that these diagnoses were made at a specialist centre and questioned if the reduced delays to diagnosis

Consultee	Comment [sic]	Response
	concerned that this is not a reasonable conclusion, given past trends, current licensed treatments and the evidence submitted by the company from the EAMS programme. Nuclear scintigraphy is the diagnostic tool referred to in the ACD; this tool was introduced into routine practice at the NAC in 2012. Average delays to diagnosis remained >3 years despite the introduction of scintigraphy at the NAC. The company presented NHS evidence to NICE in order to support the impact of tafamidis during EAMS on early diagnosis. We compared the proportion of patients diagnosed in NYHA I/II classes at the NAC (since the introduction of nuclear scintigraphy) and those treated during EAMS. A greater proportion of patients treated in EAMS were NYHA I/II compared with NAC diagnoses before EAMS (86% versus 75%, respectively). Patisiran and inotersen are unlicensed for ATTR-CM so cannot be linked to an increased awareness of ATTR-CM or a change in the time to diagnosis. They have not been introduced in ATTR-CM beyond a clinical trial setting at the NAC and remain investigational treatments in this setting. Any disease awareness activities suggesting these medicines are applicable in ATTR-CM would constitute promotion outside of a license.	achieved at the NAC could be achieved at other centres in clinical practice (see FAD section 3.8). It questioned whether recommending tafamidis would further improve awareness and reduce diagnosis times (see FAD section 3.8). It acknowledged that although the EAMS data was informative, it could only demonstrate that diagnosis delays were reducing when tafamidis was available through EAMSs, and not that tafamidis was the cause for this reduction. So, it concluded that there was not enough evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD section 3.8). A small proportion of people with ATTR-CM also have polyneuropathy (mixed clinical features), for which NICE has recommended patisiran and inotersen (see FAD section 3.5). The committee agreed that the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM but recognised that diagnosis can still take a long time (see FAD section 3.3).
Pfizer	Misinterpretation of published data The committee “noted that data from the National Amyloidosis Centre suggested that a third of people had an accurate ATTR-CM diagnosis within 6 months. It acknowledged this was an improvement on current diagnosis delays, but recognised these diagnoses were made at a specialist centre and questioned if this could be done in clinical practice.” (Section 3.7; Page 10). This is a misinterpretation of the data published by the National Amyloidosis Centre (NAC) and suggests the opposite, that reducing delays to diagnosis below 6 months is feasible in clinical practice. This is a misinterpretation of the data published by the National Amyloidosis Centre (NAC). The data from the NAC showed that the observed mean delay to diagnosis was >3 years and one third of these patients were diagnosed in less than 6 months. This one third of patients is from the same groups of patients that the significant	Comments noted. The committee acknowledged that if average diagnostic delays could be reduced to less than 6 months it would represent a substantial improvement. However, it noted that awareness of ATTR-CM had improved (see FAD section 3.3) and questioned whether recommending tafamidis would further increase awareness and reduce diagnosis times. The committee concluded that there was not enough evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD section 3.8).

Consultee	Comment [sic]	Response
	delays to diagnosis were calculated from, therefore they do not represent an improvement on current delays in diagnosis. The third of patients that were diagnosed in less than 6 months does, however, demonstrate that with greater suspicion of disease and local access to diagnostic tests (referral into a single national centre no longer being required), that the average diagnosis could be less than 6 months in the future due to the introduction of tafamidis. These data informed the company assumption that the expected reduction in time to diagnosis could be reduced from greater than 3 years to less than 6 months (ACD Section 3.18 page 18-19). This reduction in time to diagnosis is further supported by institutional data from the EAMS centres showing reductions in diagnostic delays to <6 months. In EAMS we also observed a greater proportion of patients diagnosed in early stage disease (NYHA I/II) compared with NAC diagnoses before EAMS (86% versus 75%, respectively).	
Pfizer	Clinical relevance of the primary outcome measure in ATTR-ACT The committees' concerns regarding the trial outcomes are unclear, all-cause mortality and cardiovascular-related hospitalisation are highly relevant, hard clinical endpoints and are considered as composite primary endpoints in other cardiovascular related trials. In these statements (see Footnote) the committee are suggesting that all-cause mortality and cardiovascular-related hospitalisation are measures not used in clinical practice. The company considers these endpoints to be highly relevant in clinical practice. If the concern is the combination of these endpoints using the Finkelstein-Schoenfeld method, we would respectfully highlight the company submission data where we presented components of the primary outcome measure separately. These results mirror those of the combined endpoint- i.e. patients treated in the pooled tafamidis arm experienced significant reductions in both all-cause mortality (HR 0.698, 95% CI 0.508, 0.958, p=0.0259) and CV-related hospitalisations (RR 0.68, 95% CI 0.56, 0.81, p<0.0001) when considered separately. Combining endpoints in commonly known methods such as major adverse cardiovascular events (MACE) use a time to event function. The Finkelstein-Schoenfeld method does exactly the same but prioritises mortality in a hierarchical fashion. The ATTR-ACT study underwent scientific advice with the EMA where this	Comments noted. The committee considered that although the components which made up the primary outcome were clinically relevant to patients and clinicians, it questioned whether the combined measure would be considered in clinical practice (see FAD section 3.10).

Consultee	Comment [sic]	Response
	validated measure was agreed. In addition, both heart failure treatments previous appraised by NICE included primary composite endpoints with both survival and hospitalisation. Footnote omitted – see company's response to ACD	
Pfizer	Hierarchy of submitted clinical evidence The company is concerned that the data from the RCT has been dismissed by the committee and the absence of a specific findings in EAMS prioritised (see footnote). The EAMS was not intended to provide evidence to support the efficacy of tafamidis, the purpose was to provide access to a medicine that did not yet have a marketing authorisation. The longest duration of treatment when the scheme closed on 17th February 2020 was 6 months. The evidence supporting the additional benefits of tafamidis when started in patients with NYHA I/II classification comes from the ATTR-ACT study and is represented in Figure 1. In a hierarchy of evidence, we suggest this randomised controlled trial data should be prioritised for consideration over the absence of real-world efficacy data in the EAMS that was not designed for this purpose. Footnote omitted – see company's response to ACD	Comments noted. The committee considered all of the evidence presented. The committee considered the clinical results in the overall population from ATTR-ACT trial (see FAD sections 3.9 and 3.10). It also agreed that it would not consider the subgroup analyses in its decision making because the subgroup results were underpowered (see FAD section 3.11). It considered the EAMS data in the context of the company's position on the potential to attribute benefits from future early diagnosis to tafamidis (see FAD section 3.8).
Pfizer	Continuation of treatment benefit The committee concluded that despite the ERG analyses "had limitations….they provided realistic alternatives to the company's overly optimistic analyses" and "that the ERG's analyses were appropriate for decision making" (Section 3.16; Page 16-17). The company believes the relevant merits of the company analyses have not been taken into consideration compared to the extensive limitations associated with the ERG analyses. The committee has acknowledged that ATTR-ACT was unique in that it had complete follow-up, by which we mean there was no censoring or loss to follow-up within the trial period. As a result, the impact of tafamidis discontinuation on efficacy was accounted for within the predicted OS curves which were aligned with the observed data. However, this has only been reflected in the consideration of the limitations of the ERG analysis and not when considering the company analysis. Tafamidis works by reducing cumulative exposure to amyloid, therefore, if patients discontinue in earlier NYHA stages they would have a better prognosis than a	Comments noted. The committee acknowledged the company's argument and considered the limitations of the ERG's alternative analyses, but it agreed that the company's approach of assuming continued treatment benefits without a cost was overly optimistic (see FAD sections 3.16 and 3.17). The committee acknowledged comments received at consultation from the NAC which suggested that

Consultee	Comment [sic]	Response
	patient that had been on BSC. This impact would become greater the longer a patient has been on tafamidis, as an equivalent patient on BSC would have experienced continued disease progression, as opposed to the tafamidis patient who had controlled disease whilst on treatment and discontinued in NYHA I-III for a reason other than progression of disease. This expected separation of overall survival and treatment discontinuation was observed within ATTR-ACT and the long-term extension, which provides a clear rationale for a separation of overall survival and treatment duration in the extrapolated curves. Therefore, given the complete follow-up in the data, the clinical rationale that patients discontinuing tafamidis cannot be considered equal to patients who have never received tafamidis, and the trend observed in the long-term data, the company analysis provides the most accurate modelling of the observed data without the introduction of arbitrary assumptions. A constant rate of discontinuation in NYHA I-III was observed in ATTR-ACT which is contrary to the conclusion from the clinical expert comment in Section 3.15 of the ACD. Observed data from the trial should be considered the most appropriate evidence to inform any modelling assumptions. This constant rate of discontinuation observed in the 30-month data was consistent with the extension study beyond the 30-month trial period (Technical Engagement Response Appendix Figure 1) and was supported by exponential having the best statistical fit. Therefore, in the absence of any clear explanation on why this long-term trend would suddenly change after the observation period, a constant rate of discontinuation is appropriate. This demonstrates that the first ERG analysis is unrealistic and not reflective of the observed data from the RCT. It should be noted, that the plateau observed in the end of the extension data is not informative given the low number of patients at risk. The significant limitations associated with the second ERG analysis were acknowledged by the ERG in their report “i) upon discontinuation, tafamidis patients immediately experience the same events and accrue QALYs in the same way as BSC patients, with no transition period; ii) that the prognosis of each patient upon discontinuation is equivalent to the mixture of patients in BSC (NYHA classification mix) at each respective time of discontinuation; iii) despite the complete follow-up (no censoring) up to 30 months in ATTR-ACT, the impact of the observed discontinuation is not reflected in any capacity in the extrapolation”. Considering these limitations, the ERG included their first analysis where treatment discontinuation was assumed to plateau in their preferred analysis. However, the extent of these limitations does not appear to have been fully reflected in the	ATTR-ACT had not revealed anything about how tafamidis works. The group stated that a recent publication had shown that disease stabilisation does not necessarily inhibit amyloid formation, so the mechanism underlying tafamidis’ proposed benefit is unclear. The committee concluded that assuming continued treatment benefits without a cost was overly optimistic and would lead to an underestimated incremental cost-effectiveness ratio (ICER) (see FAD section 3.16).

Consultee	Comment [sic]	Response
	committee conclusions and therefore cannot be considered appropriate for decision making compared to the company analysis.	
Pfizer	Overall survival extrapolation The committee "concluded that the reason for using generalised gamma functions to model overall survival was unclear and agreed to consider only the log-normal extrapolation functions in its decision making." Section 3.17; Page 17. The company acknowledges the rationale for the change in survival model following the submission of the updated data cut was potentially unclear, please see further rationale below. The company acknowledges the rationale for the change in survival model following the submission of the updated data cut was potentially unclear. Please see further rationale below. Despite all placebo patients crossing over to tafamidis at 30 months, there has been a continued separation in the survival curves observed within the long-term extension, with the initial long-term extension data cut observing a HR of 0.64 (0.47 - 0.85); 36% reduction in risk of death compared to 0.70 (0.51 – 0.96) in the initial trial period. This observed increase in efficacy is expected to increase further over time given those with NYHA III are associated with higher risk of mortality, therefore, in the long term there will be a shift in the population to a greater proportion of those that were NYHA I/II at baseline (who derive the greatest benefit from tafamidis). These long-term trends and clinical rationale suggest that the curves most likely do not reflect the full survival gains expected from tafamidis. Therefore, given the minimal difference between the log-normal and generalised gamma both in terms of visual and statistical fit to the observed data, the more 'optimistic' curve was felt to be the most appropriate.	Comments noted. The committee agreed that there was insufficient justification to model overall survival using generalised gamma extrapolation functions and agreed to consider only the log-normal extrapolation functions in its decision making (see FAD section 3.18).
Pfizer	Improvements in diagnosis delay and impact on costs 'The ERG highlighted that it was unclear how the company had estimated that diagnosis delays could be reduced by 2.5 years and how potential cost savings of £20,000 had been estimated' (Section 3.18; Page 18-19). The committee subsequently concluded "that the company's early diagnosis assumptions were not appropriate for decision making because there was not enough evidence to support them." (Section 3.18; Page 19). The company acknowledged it would not be possible to provide hard empirical estimates for the assumptions related to early	Comments noted. The committee agreed that because there was not enough evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays, it was highly uncertain if any costs could be avoided. So, it concluded that it was highly uncertain whether any additional cost savings resulting from earlier diagnosis could be attributed to tafamidis (see FAD section 3.19).

Consultee	Comment [sic]	Response
	diagnosis, however there is rationale for the estimates proposed by the company, and it is not appropriate to conclude there would be no impact. The NAC data demonstrate huge delays in establishing the diagnosis of ATTR-CM following presentation with cardiac symptoms, with this taking >4 years in >40% of patients (average >3 years) on a background of a median 17 hospital attendances during the 3 years before diagnosis. Encouragingly, one third of patients in the same report were diagnosed rapidly within 6 months from the onset of cardiac symptoms. This rapid diagnosis in one third of patients before the availability of tafamidis demonstrates the feasibility of early diagnosis. In the tafamidis EAMS scheme, we observed an 18% increase in the diagnosis of patients in early stage disease (NYHA I/II) versus ATTR-ACT and an 11% increase versus the NAC. In some EAMS centres, initial anecdotal data suggest that the average delay to diagnosis was reduced to <6 months. Compared with the historical average of >3 years at the NAC, these data support at least a 2.5 year reduction in the average delay to diagnosis. This reduction is likely to result from the availability of the first treatment for ATTR-CM which is no longer an academic diagnosis, a greater index of suspicion of the disease coupled with equitable access to confirmatory diagnostic tests across the UK. In terms of costs, the 3-years prior to diagnosis involves 17 hospital attendances across inpatient admissions, outpatient and emergency department visits, with further touch points in the 4th and other years prior to diagnosis. In addition to these attendances, many of which are avoidable, healthcare resource utilisation during the period also includes procedures and investigations. Some examples of unnecessary procedural/ investigation costs incurred during the diagnostic odyssey are coronary angiograms (one of the patient experts during the ACM described his experience of this test), implantation of cardiac defibrillators and repeated imaging investigations when cycling through secondary care specialist clinics (cardiac MRI, cardiac CT). Cost savings submitted by the company were estimated on the basis of these avoidable costs that have been quantified in terms of the proportion of patients they apply to and their reference costs. There are also the cost implications of misdiagnosis during this delay. Data from outside the UK suggests as many as 45% of patients received ≥1 misdiagnosis, of which 77% received treatment for these misdiagnoses, which demonstrate avoidable treatment costs during the delay to diagnosis. The range of scenarios provided in Technical Engagement Response Appendix C and D demonstrate the direction and impact of a reduction in the delay to diagnosis	

Consultee	Comment [sic]	Response
	by 2.5 years, which may be conservative given the historical data from the NAC and comparisons with the findings from EAMS.	
Pfizer	Adverse impact of diagnosis delay on QoL The committee concluded that the QALY "gain for reduced anxiety or depression for all patients was not a reasonable approach because it was not supported by any evidence' Section 3.18; Page 18-19. The company acknowledges the lack of supporting evidence for the assumption. However, it cannot be concluded that a delayed diagnosis has no impact on patient quality-of-life. It should be acknowledged by the committee that a patient experiencing symptoms such as breathlessness, fatigue and pain whilst having multiple touch points with different specialities over an extended period of time with no diagnosis would clearly have a negative impact on a patients' quality-of-life.	Comments noted. The committee considered if being diagnosed with a serious cardiac condition could negatively affect a person's mental wellbeing and acknowledged it may change the way they view themselves, and how their families perceive them. The company explained that it had not investigated the effects of a diagnosis of ATTR-CM on psychological wellbeing. So, the committee agreed that it was highly uncertain whether any additional quality of life benefits resulting from earlier diagnosis could be attributed to tafamidis (see FAD section 3.19).
Pfizer	Mechanism of action The following statement in the ACD is not evidence based "The clinical expert explained that new research had changed their understanding of the way that tafamidis treats ATTR-CM. They suggested that the mechanism by which it works may not be as innovative as was originally thought." (Section 3.26; Page 24) There is no peer-reviewed, published evidence to contradict the mechanism of action of tafamidis established over a decade of clinical development activity in ATTR-CM and in 9 years post-marketing data in ATTR polyneuropathy. The clinical experts stated in the ACM that they have conducted a "test tube experiment" at the NAC that casts doubt over the mechanism of action of tafamidis. These data have neither been peer-reviewed or published and should not have been considered by the committee. We respectfully cannot see any plausible link between this clinical input around the mechanism of action and the innovative nature of tafamidis and request it is withdrawn from the committee's conclusion. Within the ATTR-ACT clinical trial there is robust direct evidence of target engagement supporting the mechanism of action; stabilisation of the TTR protein was observed in 86% of patients in the pooled tafamidis group and 3.5% of those in the placebo group ($p<0.0001$).	Comments noted. Comments received at consultation from the NAC noted a recent publication which had suggested that disease stablisation does not necessarily inhibit amyloid formation, and because of this the mechanism underlying the proposed benefit of tafamidis is unclear. The committee acknowledged the company's and research group comments, and considered that the relevant benefits of tafamidis were captured in the economic model (see FAD section 3.26).
Pfizer	Factual accuracy	Comments noted.

Consultee	Comment [sic]	Response
	The following statement is factually inaccurate: "The company estimated that it took 3 years or more for a person to be accurately diagnosed with ATTR-CM." (Section 3.3; Page 6) The 3-year average delay to diagnosis was not an estimate and was not provided by the company. These data are from a cohort study of patients diagnosed with ATTR-CM at the NAC. In that study, the average delay to diagnosis was >3 years, one third of patients were diagnosed in less than 6 months demonstrating the feasibility of early diagnosis, however 40% waited for >4 years. Data from the tafamidis EAMS supports the positive impact of tafamidis on early diagnosis in terms of both reducing the delay to diagnosis and identifying patients earlier in their disease course.	The FAD has been updated to state "data from the National Amyloidosis Centre (NAC) showed that on average it took 3 years or more for a person to be accurately diagnosed with ATTR-CM" (see FAD section 3.3).
Pfizer	Factual accuracy The company has not suggested that patients should start in NYHA I/II and discontinue in NYHA III. As stated in Section 3.6; Page 8: "The company submission included analyses with these starting and stopping rules: • people whose disease is classed as NYHA 1 or 2 can start tafamidis • people whose disease is classed as NYHA 1, 2 or 3 can keep taking tafamidis and • people should stop tafamidis if their disease progresses to NYHA 4. The ERG explained that it had concerns about the clinical relevance of only allowing people whose disease is classed as NYHA 1 or 2 to start treatment." This statement is a misrepresentation of the company submission. This issue was raised at technical engagement where the company agreed 'that it would not be clinically appropriate for patients in NYHA III to not be eligible to start treatment but for NYHA I/II patients to remain on treatment upon progression to NYHA III'. The company also reiterated that 'the NYHA I/II subgroup was presented in the manufacturers submission (MS) to demonstrate the additional health gains expected in the overall population once tafamidis becomes available'. It is unclear why, when this issue was clarified and effectively resolved that is has still been included in discussion within the ACD in this context.	Comments noted. The committee agreed that subgroup results were underpowered and concluded it would not consider them in its decision making. The FAD has been updated accordingly (see FAD section 3.11).
Pfizer	Factual accuracy The following statement is factually inaccurate "For cardiovascular-related mortality, the hazard ratios favoured tafamidis over placebo, but the differences were not	Comments noted. The FAD has been updated to accordingly. (see FAD section 3.11).

Consultee	Comment [sic]	Response
	statistically significant in either wild-type (hazard ratio 0.71 [95% confidence interval 0.47 to 1.05]) or hereditary ATTR-CM (hazard ratio 0.69 [95% confidence interval 0.41 to 1.17]).” (Section 3.10; Page 12) This statement is incorrect, the hazard ratios reported are for all-cause mortality not cardiovascular related mortality.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
British Cardiovascular Society	The BCS feels that Tafamidis is associated with clinical benefit in treating transthyretin amyloid cardiomyopathy by slowing disease progression, but acknowledges NICE’s conclusion that this comes at an unacceptably high cost.	Comment noted. The committee took the clinical- and cost-effectiveness of tafamidis into consideration when making its recommendations (see FAD section 3.27).

British Society for Heart Failure	We have concern over the finding in Section 1, Recommendations: 'Inconsistent results on how effective tafamidis is for different types and stages of ATTR-CM mean that the evidence is uncertain. (Repeated in Section 3.10: 'the subgroup analyses raised concerns and uncertainty about clinical effectiveness of tafamidis.) The two subgroups of concern are amyloid subtype (variant or wild type) and NYHA class. a. Amyloid subtype. Although the reduction in combined primary end point of all-cause mortality and annual cardiovascular admissions was significant, and effect remained favourable it failed to achieve significance when amyloid subgroups were analysed individually. We are surprised at the weight that this finding has had in effectiveness assessment, as this was a trial of under 500 patients and the variant subgroup contained only 106 patients. We would urge the committee to avoid over emphasis on subgroup analysis as a basis for decision making particularly when cohort numbers are small and when both all-cause mortality and cardiovascular hospitalisation rate were lower albeit non-significant in the treatment group. b. NYHA Class. In NYHA class III, with more advanced symptoms, a non-significant reduction in all-cause mortality was seen but there was also an increase in cardiovascular admission rate. The addition of a heart failure expert at the committee meeting would have been beneficial as lack of significance is a common effect seen in advanced NYHA subgroups in heart failure trials. For example, subgroup analysis of the PARADIGM-HF Trial for sacubitril valsartan showed no significant benefit in the primary end point for NYHA classes III and IV. The CARE-HF Trial for cardiac resynchronisation therapy showed no significant benefit for NYHA class IV. Both treatments are approved by NICE. Common to all these trials are the small numbers of patients in the advanced heart failure NYHA subgroups – in ATTR-ACT there were only 141 patients in the NYHA class III subgroup. Advanced heart failure is associated with other important factors such as worsening renal function and increasing frailty and it is likely that the increase in co-morbid factors and smaller subgroup size has a bearing on the lack of effect significance seen recurrently in heart failure trials.	Comments noted. The committee agreed that although the subgroup results added a degree of uncertainty around the clinical effectiveness results for tafamidis it accepted that they were underpowered. So, it concluded they would not be considered in its decision making (see FAD section 3.11).

Nominating organisation	Comment [sic]	Response
British Society for Heart Failure	Section 3.3. Accurately diagnosing ATTR-CM is challenging and can take a long time. This title/statement is no longer correct. Although this was the case in the past, access to cardiac magnetic resonance and DPD scanning has improved detection enormously and this is reflected in the rapid increase in referrals for ATTR-CM to the National Amyloidosis Centre. The BSH agree with the committee's expert, Prof Hawkins' statement where he notes as his first key comment that this is now an easily diagnosed disorder.	Comment noted. The company highlighted NAC data showing that, on average, it took 3 years or more for a person to be accurately diagnosed with ATTR-CM. Two of the clinical experts agreed that there had been developments in recent years, but noted that there were challenges in diagnosing ATTR CM accurately (see FAD section 3.3). The committee agreed that even with the availability of DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM (see FAD section 3.4).
British Society for Heart Failure	Section 3.6. It is not appropriate to define starting and stopping rules for tafamidis based only on the NYHA classification. NYHA status is a subjective classification with well recognised limitations, however NYHA functional class remains the most commonly used method for stratification of patients in heart failure trials However, the NYHA classification is already employed in this setting in many other treatments for heart failure. For instance, an implantable cardioverter defibrillator (ICD) is NICE indicated in NYHA I, II, and III but not in NYHA IV. Similarly, cardiac resynchronisation therapy (CRT) is indicated in NYHA II, III and IV but not in NYHA I unless ECG shows a very prolonged QRS (≥150ms). Sacubitril valsartan is approved for NYHA classes II-IV (symptomatic heart failure) but not NYHA class I. Again, the addition of a heart failure clinician to give expert advice would be useful at further meetings.	Comments noted. The committee heard that although the NYHA classification was widely used in heart failure, because it was a subjective measure, it had limitations in terms of variability from day to day. It recognised this, but acknowledged that there was insufficient trial evidence available to consider an alternative objective measure (see FAD section 3.6). It agreed that using the NYHA classification to accurately identify people who need treatment and those who should stop treatment had limitations. So, it concluded not to consider starting and stopping rules for tafamidis based on the NYHA classification system in its decision making (see FAD sections 3.7 and 3.15).

Nominating organisation	Comment [sic]	Response
British Society for Heart Failure	Section 3.9 regarding annual cardiovascular-related hospitalisations. The committee considered this measure was not used in clinical practice so it was unclear what the relevance of these results was to people with ATTR-CM who would be seen in clinical practice. Cardiovascular hospitalisations are a standard measure in heart failure trials and given the long duration of the trial and subject group with high admission and mortality rate it is understandable that the hospitalisation rate was chosen as an end point as prolonged life expectancy may not translate into reduced admissions due to longer survival with a condition with high admission risk. The BSH considers that the number of times a heart failure patient needs to be admitted per year is a highly relevant outcome measure for heart failure patients.	Comments noted. The committee considered that although the components which made up the primary outcome were clinically relevant to patients and clinicians, it questioned whether the combined measure would be considered in clinical practice (see FAD section 3.10).
British Society for Heart Failure	Section 3.25. There are no equality issues that can be addressed in the guidance. ATTR-CM disproportionately affects people of African and Caribbean family origin. The current guidance will promote inequality for this minority group in terms of i) access to treatment to improve mortality and hospitalisations for a condition with no other available therapies and ii) access to appropriate investigations. Although detection rates have improved enormously in wild type ATTR due to ready access to cardiac MRI and DPD scanning, this benefit has not been seen in V122I ATTR where detection rates have been unaffected and remain unacceptably low (Lane et al, Circulation 2019; 140:16-26). Availability of an effective treatment has the potential to improve this situation as there will be an onus on clinicians not to miss a condition where an approved treatment is available. This could in turn enable equitable access for patients of African and Caribbean ethnicity to appropriate investigations that they are not able to access at present.	Comment noted. The committee acknowledged that ATTR-CM disproportionally affected people from certain ethnic groups (see FAD section 3.25). But, given that tafamidis was considered not to be a cost-effective use of NHS resources (see FAD section 3.24) it agreed it was not something that could be addressed in its recommendations.

Nominating organisation	Comment [sic]	Response
British Society for Heart Failure	Response to NICE questions above. • has all of the relevant evidence been taken into account? Yes, the BSH agrees all relevant evidence has been considered. • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Clinical effectiveness: No, the BSH considers that the emphasis on subgroup analysis of a trial with small numbers is not appropriate and considers that the pre-specified endpoints of the trial were appropriate (all-cause mortality and cardiovascular hospitalisation rate) and concur with the slowed reduction in quality of life as measured by KCCQ-OS seen in the ATTR-act trial. • are the provisional recommendations sound and a suitable basis for guidance to the NHS? No. This is a condition with very high morbidity and poor quality of life, even for heart failure, with relentless progression to death. This is the first effective treatment to reduce mortality and cardiovascular admission rate. On behalf of patients the BSH hopes that a further negotiation on cost can take place in order to enable patients in the UK to benefit from this therapy within the standard NICE ICER of £30,000 per QALY. The British Society for Heart Failure response to this recommendation has been endorsed by the patient charities Cardiomyopathy UK and Pumping Marvellous.	Comment noted. No action required. Comment noted. The committee agreed that although the subgroup results added a degree of uncertainty around the clinical effectiveness results for tafamidis it accepted that they were underpowered. So, it concluded they would not be considered in its decision making (see FAD section 3.11). Comment noted. The committee acknowledged that ATTR-CM was a debilitating disease which severely affects mental and physical health (see FAD section 3.2) It also acknowledged the benefits of tafamidis over placebo as seen in ATTR-ACT (see FAD section 3.10). However, the committee's most plausible ICER for tafamidis compared with best supportive care was substantially above the range that NICE usually considers an acceptable use of NHS resources (see FAD section 3.24). So, the committee did not recommend using tafamidis in the NHS for treating ATTR-CM (see FAD section 3.27).

Nominating organisation	Comment [sic]	Response
Cardiomyopathy UK	Are the recommendations sound and a suitable basis for guidance to the NHS? No. Tafamidis is the only treatment for people with ATTR-CM, there are no other options. We ask the NICE committee to reconsider their recommendation and, if needed, work with Pfizer to overcome any obstacles to making this treatment available.	Comment noted. The committee acknowledged the benefits of tafamidis over placebo for treating ATTR-CM (see FAD section 3.10). However, the committee's most plausible ICER for tafamidis compared with best supportive care was substantially above the range that NICE usually considers an acceptable use of NHS resources (see FAD section 3.24). So, the committee did not recommend using tafamidis in the NHS for treating ATTR-CM (see FAD section 3.27).
Cardiomyopathy UK	Accurately diagnosing ATTR-CM is challenging and can take a long time. The challenges of early diagnosis is already being overcome through wider clinical education, improved access to DPD scanning and patient awareness programmes. The committee acknowledges that diagnosis is already improving and this trend is set to continue with the lunch of amyloidosis online learning opportunities and online clinical education events planned but Cardiomyopathy UK and other partners in 2020 and 2021.	Comment noted. The company NAC data showing that, on average, it took 3 years or more for a person to be accurately diagnosed with ATTR-CM. Two of the clinical experts agreed that there had been developments in recent years, but noted that there were challenges in diagnosing ATTR CM accurately . The committee acknowledged the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM, but recognised that diagnosis can still take a long time (see FAD section 3.3).

Nominating organisation	Comment [sic]	Response
Cardiomyopathy UK	It is not appropriate to define starting and stopping rules for tafamidis based only on the NYHA classification system. The charity accepts that NYHA scale is subjective and not a precise tool but it is a good indicator of disease progress when uses as part of the usual dialogue between patient and clinician. Both clinicians and patients are perfectly used to starting and stopping medication not only in cardiac disease but in all disease areas. The committee acknowledges that tafamidis slows down decline in health (3.11) therefore it would be logical to give treatment to people at NYHA 1 with a confirmed diagnosis of ATTR-CM given the likely decline in health caused by the disease if left untreated. Amyloidosis seems to accelerate as it progresses and treatments are more effective in early stages, therefore early diagnosis and access to treatment is critical for patients.	Comments noted. The committee heard that although NYHA was widely used in trials of heart failure, because it was a subjective measure, it had limitations in terms of variability. It recognised this, but acknowledged that there was insufficient trial evidence available to consider an alternative objective measure (see FAD section 3.6). The committee acknowledged that tafamidis' marketing authorisation states that treatment should be started as early as possible. But, it was aware that tafamidis' marketing authorisation does not specify a treatment starting rule based on the NYHA classification system (see FAD section 3.6). The committee was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NHYA class 1, particularly if they do not have heart failure. It also states that an accurate diagnosis cannot be formally established without a number of procedures (such as biopsy and scintigraphy (See FAD section 3.4). Also, it agreed that, using the NYHA classification alone to accurately define the population who were eligible to receive tafamidis identify people who need treatment had limitations (see FAD section 3.6). So, it concluded not to considered treatment starting or stopping rules based on the NYHA classification system in its decision making (see FAD section 3.7).

Nominating organisation	Comment [sic]	Response
Cardiomyopathy UK	It is unclear if introducing tafamidis would reduce delays in diagnosis times. The committee recognises that the introduction of a new treatment, and one that has proven to be effective, on a rare disease area has a positive impact on time to diagnosis. This is our experience and also that of the committee in relation to patisiran and inotersen. It does not follow that because patisiran and inotersen have improved diagnosis time that tafamidis would not improve times further. It also has to be noted (as the committee has done elsewhere) that tafamidis is targeting a different form of the disease in a different population.	Comments noted. The committee noted that the availability of improved diagnostic tools and treatments in the disease area had increased awareness of ATTR-CM (see FAD section 3.3). But, it questioned whether recommending tafamidis would further increase awareness and reduce diagnosis times. The committee concluded that there was not enough evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD section 3.8).
Cardiomyopathy UK	The subgroup analyses raise concerns about the clinical effectiveness of tafamidis but are not robust. It is clear however that the tafamidis is effective overall. An ongoing study to monitor efficacy of tafamidis in practice could be undertaken once approval is given. This would clarify the points of uncertainty regarding efficacy in sub groups with small populations.	Comments noted. The committee agreed that although the subgroup results added a degree of uncertainty around the clinical effectiveness results for tafamidis it accepted that they were underpowered. It concluded that the subgroup results would not be considered in its decision making (see FAD section 3.11).
Cardiomyopathy UK	Tafamidis is more effective than placebo in slowing the decline in quality of life. The charity recognises that KCCQ is a good measure of quality of life but it does not include “living longer” and “few hospital visits” which are clearly patient priorities.	Comments noted. In addition to considering KCCQ (see FAD section 3.12), the committee considered the primary and secondary outcome results from ATTR-ACT, and noted that tafamidis was associated with statistically significant reductions in: cardiovascular-related mortality, and cardiovascular-related hospitalisations (see FAD section 3.10).

Nominating organisation	Comment [sic]	Response
Cardiomyopathy UK	A stopping rule for tafamidis based on NYHA classification should not be included in the economic model. As noted in 3.6 patients are used to starting and stopping treatment in consultation with clinicians based on self-assessment and discussion using NHYA. Making such decisions would not be challenging but normal practice.	Comments noted. The committee considered the comments from the patient organisation which explained that making decisions about stopping treatment in advanced disease stages were not uncommon. It also acknowledged comments from a clinical expert suggesting that people whose disease was classed NYHA 4 would be very unwell and likely moved onto best supportive care. However, it noted that tafamidis' marketing authorisation did not include stopping rule based on NYHA. It also noted the limitations of using the NYHA classification to accurately identify people who need treatment. So, it concluded that it would not consider starting and stopping rules for tafamidis based only on the NYHA classification system in its decision making (see FAD sections 3.6, 3.7 and 3.15)
Cardiomyopathy UK	There are no equalities issues that can be addressed in the guidance. ATTR-CM disproportionately affects people with African or Caribbean ancestry. It is not clear why the committee does not feel that it is appropriate to consider the disproportionate impact of the condition on minority communities and to include this in their decision making. The charity believes that ensuring fair accesses to treatment for all communities is a fundamental goal of NICE.	Comments noted. The committee acknowledged that ATTR-CM disproportionally affected people from certain ethnic groups (see FAD section 3.25). But, given that tafamidis was considered not to be a cost-effective use of NHS resources (see FAD section 3.24) it agreed it was not something that could be addressed in its recommendations.
NHS England	We consider that all of the relevant evidence been taken into account.	Comment noted. No action required.
NHS England	The summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	Comment noted. No action required.
NHS England	The provisional recommendations do provide a sound and a suitable basis for guidance to the NHS.	Comment noted. No action required.

Nominating organisation	Comment [sic]	Response
UK ATTR Amyloidosis Patients' Association	3.3 Diagnosis The challenges of early diagnosis can be overcome through wider clinical education of clinicians and patients. This is becoming evident with improvements in diagnosis (which the committee acknowledged) as a result in the increase of clinical education in this area. This trend is set to continue with the launch of amyloidosis online learning opportunities and online clinical education events planned this year. In the past, there has been a nihilistic attitude amongst clinicians due to the lack of specific treatments but this has already changed in specialist centres. In the centres involved in EAMS programme the time the diagnosis has been reduced from years to months.	Comments noted. The committee acknowledged that diagnosis times and awareness of ATTR-CM had improved, but questioned whether introducing tafamidis would improve them further (see FAD section 3.3). The committee understood that the short-term observational EAMS data were presented to support the assumption that introducing tafamidis could reduce diagnosis delays. It acknowledged that although this data was informative, the EAMS data can only demonstrate that diagnosis delay was reducing when tafamidis was available through EAMS, and not that tafamidis was the cause for this reduction. It noted that the trend of earlier diagnosis seen in the EAMS could be explained by improvements in diagnostic tools since the ATTR-ACT trial. It acknowledged that when ATTR-CM is suspected, implementing the diagnostic pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur. The committee agreed it was not possible to attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis. So, the committee concluded that there was not enough evidence introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD sections 3.3 and 3.8).

Nominating organisation	Comment [sic]	Response
UK ATTR Amyloidosis Patients' Association	3.6 Starting and stopping We accept that the NYHA scale is subjective and not precise but it is a good indicator of patient stage and part of the usual dialogue between patient and clinician. Both clinicians and patients are perfectly used to starting and stopping medication not only in cardiac disease but in all disease areas. The committee acknowledges that tafamidis slows down decline in health (3.11) therefore it would be logical to give treatment to people at NYHA 1 with a confirmed diagnosis of ATTR-CM given the likely decline in health caused by the disease if left untreated. Amyloidosis seems to accelerate as it progresses and treatments are more effective in early stages, therefore early diagnosis and access to treatment is critical for patients.	Comments noted. The committee acknowledged that tafamidis' marketing authorisation states that treatment should be started as early as possible. But, it was aware that tafamidis' marketing authorisation does not specify a treatment starting rule based on the NYHA classification system (see FAD section 3.7). The committee was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NHYA class 1, particularly if they do not have heart failure. It also states that an accurate diagnosis cannot be formally established without a number of procedures (such as biopsy and scintigraphy (See FAD section 3.4). The clinical experts noted that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment (See FAD section 3.7). The committee agreed that, using the NYHA classification in ATTR-CM had limitations (see FAD section 3.6). So, it concluded that using the NYHA classification alone to accurately define the population who were eligible to receive tafamidis also had limitations. It also concluded that it would not consider treatment starting or stopping rules based on the NYHA classification system in its decision making (see FAD sections 3.7 and 3.15).

Nominating organisation	Comment [sic]	Response
UK ATTR Amyloidosis Patients' Association	3.7 Impact of introduction of tafamidis on time to diagnosis The committee recognises that the introduction of a new treatment, and one that has proven to be effective, on a rare disease area has a positive impact on time to diagnosis. This is our experience and also that of the committee in relation to patisiran and Inotersen. It does not follow that because patisiran and Inotersen have improved diagnosis time that tafamidis would not improve times for this group of patients. It is of note that tafamidis is targeting a different form of the disease in a different population	Comments noted. The committee agreed that the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM, but recognised that diagnosis can still take a long time (see FAD section 3.3). It questioned whether recommending tafamidis would further increase awareness and reduce diagnosis times. It understood that the short-term observational EAMS data were presented to support the assumption that introducing tafamidis could reduce diagnosis delays. It acknowledged that although this data was informative, the EAMS data can only demonstrate that diagnosis delay was reducing when tafamidis was available through EAMS, and not that tafamidis was the cause for this reduction. It noted that the trend of earlier diagnosis seen in the EAMS could be explained by improvements in diagnostic tools since the ATTR-ACT trial. It acknowledged that when ATTR-CM is suspected, implementing the diagnostic pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur. The committee agreed it was not possible to attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis. So, it concluded that there was not enough evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD section 3.8).
UK ATTR Amyloidosis Patients' Association	3.10 Subgroups Subgroups are necessarily going to be smaller populations. The analysis model needs to accommodate this. The data should also be taken as a whole, that is that the treatment is effective. If Tafamidis was recommended and made available through the NHS, we would ask for an ongoing study to monitor efficacy of tafamidis in the real world, with a national register and prospective data collection in order to clarify the points of uncertainty.	Comments noted. The committee agreed that although the subgroup results added a degree of uncertainty around the clinical effectiveness results for tafamidis it accepted that they were underpowered. It concluded that the subgroup results would not be considered in its decision making (see FAD section 3.11).

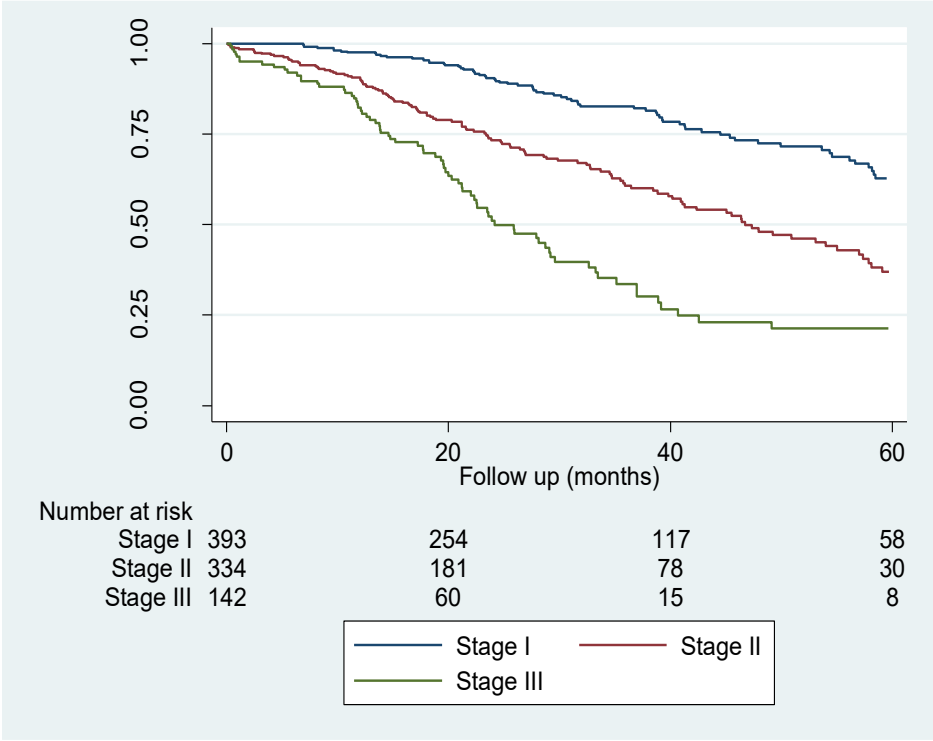
Nominating organisation	Comment [sic]	Response
UK ATTR Amyloidosis Patients' Association	3.11 Quality of Life KCCQ is a good measure of quality of life but does not include "living longer" and "few hospital visits" which are patient priorities and important outcomes.	Comments noted. In addition to considering KCCQ (see FAD section 3.12), the committee considered the primary and secondary outcome results from ATTR-ACT, and noted that tafamidis was associated with statistically significant reductions in: cardiovascular-related mortality, and cardiovascular-related hospitalisations (see FAD section 3.10).

Nominating organisation	Comment [sic]	Response
UK ATTR Amyloidosis Patients' Association	3.14 Stopping Rules As noted in 3.6 patients are used to starting and stopping treatment in consultation with clinicians based on self-assessment and discussion. We feel that it would be reasonable to include a stopping rule for patients with significant disease progression. This could be transition from NHYA 3 to NYHA 4, or if this is considered not practical, the use of more objective measurements by clinicians.	Comments noted. The committee considered the comments from the patient organisation which explained that making decisions about stopping treatment in advanced disease stages were not uncommon. It also acknowledged comments from a clinical expert suggesting that people whose disease was classed NYHA 4 would be very unwell and likely moved onto best supportive care. However, it noted that tafamidis' marketing authorisation did not include stopping rule based on NYHA. It also noted the limitations of using the NYHA classification to accurately identify people who need treatment. So, it concluded that it would not consider starting and stopping rules for tafamidis based only on the NYHA classification system in its decision making (see FAD sections 3.6, 3.7 and 3.15) See above response relating to the committee's considerations about defining starting and stopping rules for tafamidis based only on the NYHA classification. The committee also understood the merits of using objective measures to assess disease severity and progression. However, it accepted ATTR-ACT did not measure the necessary cardiac markers frequently enough to accurately characterise the disease using alternative objective measures (see FAD section 3.6). So, it was not possible for the committee to define treatment stopping rules based on alternative objective measures.

Nominating organisation	Comment [sic]	Response
UK ATTR Amyloidosis Patients' Association	3.25 Equality Issues It is not clear why the committee does not feel that it is appropriate to consider the disproportionate impact of the condition on minority communities and to include this in their decision making. Patients with mutation Val122Ile are mostly from African or Caribbean origin and develop ATTR-CM, but not usually neuropathy. At present, they do not have access to any specific treatment for ATTR while, for example, patients with the mutation Thr60Ala, also known as the Irish mutation, usually present with cardiac symptoms, but they also develop ATTR neuropathy, therefore being candidates for treatment with Inotersen or Patisiran. This creates, indirectly, inequality in access to drugs.	Comments noted. The committee acknowledged that ATTR-CM disproportionally affected people from certain ethnic groups (see FAD section 3.25). But, given that tafamidis was considered not to be a cost-effective use of NHS resources (see FAD section 3.24) it agreed it was not something that could be addressed in its recommendations.
UK ATTR Amyloidosis Patients' Association	3.27 Conclusions The committee acknowledges the safety and effectiveness of Tafamidis and the need for the treatment. There is no treatment available for ATTR-CM in the UK and many patients are deteriorating and dying while they could benefit from having access to Tafamidis. We would ask Pfizer and NHS commissioners to negotiate a feasible commercial agreement that makes this possible, and the NICE committee to reconsider their recommendation. It would be a tragedy if we leave our patient community in this situation any longer.	Comments noted. The committee acknowledged that ATTR-CM was a debilitating disease which severely affects mental and physical health (see FAD section 3.2). It also acknowledged the benefits of tafamidis over placebo as seen in ATTR-ACT (see FAD section 3.10). However, the committee's most plausible ICER for tafamidis compared with best supportive care was substantially above the range that NICE usually considers an acceptable use of NHS resources (see FAD section 3.24).

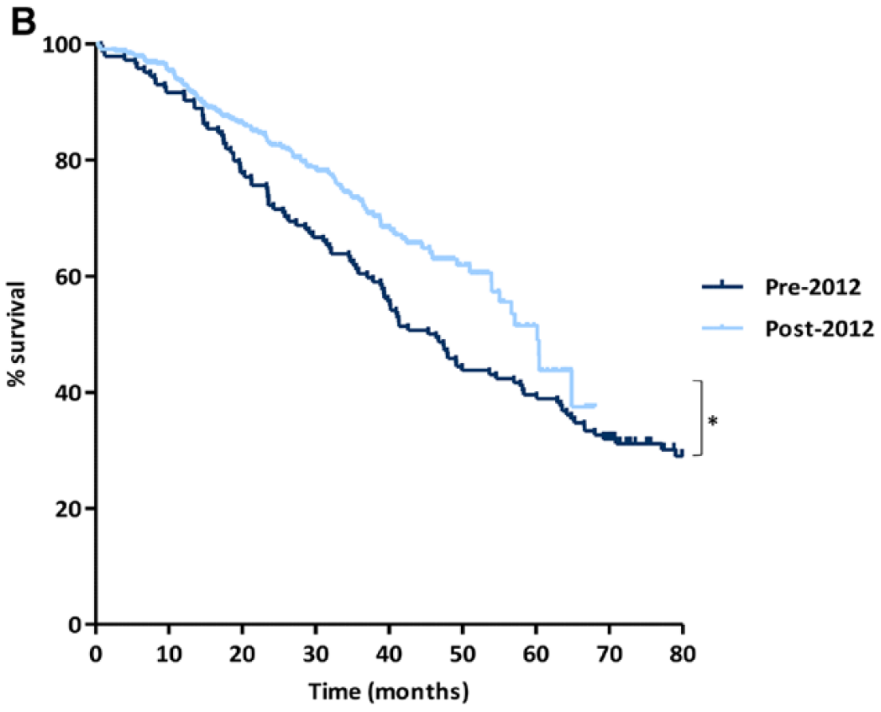
Comments received from commentators

Commentator	Comment [sic]	Response
National Amyloidosis Centre	3.5 Measuring the severity of ATTR-CM using the NYHA class has limitations I would agree with the above statement, noting that NYHA heart failure status can vary day to day in this disease since patients are exquisitely sensitive to fluid balance changes. By contrast, the prognosis of ATTR-CM (effectively the severity in terms of disease progression) can be very clearly defined by the NAC ATTR Staging system (Gillmore et al, EHJ 2018;39:2799–2806; see figure below). This staging system has been adopted worldwide (Capelli F et al, Can J Cardiol 2020;36(3):424-431.). Whilst the NAC ATTR Staging system did not exist at the time that the ATTR-ACT study was designed, the company have been asked on several occasions for a comparison of the numbers of participants in each treatment group by NAC ATTR Stage at enrolment, but they have not provided these data. NAC Stage is robustly	Comments noted. Although the committee acknowledged the views from clinical experts that NYHA is a used widely in heart failure trials, it maintained its view that its use for measuring the severity of ATTR-CM had limitations. However, it accepted ATTR-ACT did not measure the necessary cardiac markers frequently enough to accurately characterise the disease using an alternative objective measure. So, it acknowledged there was insufficient evidence available from the

Commentator	Comment [sic]	Response
	and simply based on serum eGFR and NT-proBNP measurements, which were recorded in the ATTR-ACT trial. Indeed, on page 17, ''Model Health Structure'', the company acknowledge that eGFR and NT-proBNP were measured at baseline. All of the benefits attributed to tafamidis in the ATTR-ACT trial (i.e., survival, QoL, functional status) could conceivably be explained by disease natural history alone if there was an imbalance in NAC ATTR stage at the time of enrolment. The NT-proBNP cutoff defining NAC ATTR Stage is 3000 ng/L, and very notably the median NT-proBNP in ATTR-ACT placebo group was >3000 ng/L whilst it was <3000 ng/L in the ATTR-ACT treatment group. I would strongly suggest that a post-hoc analysis of these data is made available to the committee to provide reassurance of true efficacy from tafamidis.  	trial to consider an alternative measure to the NYHA classification (see FAD section 3.6).
National Amyloidosis Centre	3.6 It is not appropriate to define starting and stopping rules for tafamidis based only on NYHA classification system	Comments noted. The committee acknowledged tafamidis' marketing authorisation states that

Commentator	Comment [sic]	Response
	‘’The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment’’ The use of tafamidis in NYHA class I is a data free zone. The ATTR-ACT study was undertaken in patients with heart failure and/or prior hospitalisation due to HF. There is currently no evidence to support use of tafamidis in NYHA class I patients with cardiac amyloid deposits which undoubtedly comprises a huge number of individuals; historical autopsy studies have shown presence of cardiac ATTR amyloid deposits in 25% of males over 80 years of age (Tanskanen et al, 2008;40:232-239) (~375,000 individuals in UK) and a recent study in Spain showed that 3.9% of males over 75 years of age (equivalent to >100,000 individuals in UK) had a positive DPD scan (Mohamed-Salem et al, 2018;270:192-196). This is a really important issue, since the ever increasing adoption of DPD scintigraphy as a diagnostic tool in cardiology will identify vast numbers of patients with incidental amyloid deposits that are of no clinical significance. The distinction between the mere finding of amyloid protein in the heart versus the heart failure syndrome of cardiac amyloidosis is incredibly important and remains widely misunderstood. A rough estimate of the potential cost of tafamidis to the NHS were all these individuals to be diagnosed with ATTR-CM rather than ‘cardiac amyloid deposits’ on the basis of a positive DPD scan would be >£1 billion.	treatment should be started as early as possible. But, it was aware that tafamidis’ marketing authorisation does not specify a treatment starting rule based on the NYHA classification system (see FAD section 3.7). The committee was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NHYA class 1, particularly if they do not have heart failure. It also states that an accurate diagnosis cannot be formally established without a number of procedures (such as biopsy and scintigraphy (See FAD section 3.4). The clinical experts noted that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment (See FAD section 3.7). The committee agreed that, using the NYHA classification in ATTR-CM had limitations (see FAD section 3.6). So, it concluded that using the NYHA classification alone to accurately define the population who were eligible to receive tafamidis also had limitations. It also concluded that it would not consider treatment starting or stopping rules based on the NYHA classification system in its decision making (see FAD sections 3.7 and 3.15). The committee understood that there was limited evidence to support the use of tafamidis in NYHA class 4 because ATTR-ACT did not recruit people whose disease was classed as NYHA class 4. It acknowledged the company’s view that the proposed stopping rule reflected treatment stopping in ATTR-ACT, in which most people stopped tafamidis quickly after progressing to NYHA class 4. It also acknowledged comments from the clinical experts suggesting that people whose disease was classed NYHA 4 would be very unwell and likely

Commentator	Comment [sic]	Response
	I do agree with the committee that it would be extraordinarily difficult in clinical practice to discontinue tafamidis in patients who progressed to NYHA class 4.	moved onto best supportive care. However, it noted that tafamidis' marketing authorisation did not include a treatment stopping rule based on NYHA classes. It also considered that using the NYHA classification to accurately identify people who need treatment had limitations. So, it concluded that it would not consider starting and stopping rules for tafamidis based only on the NYHA classification system in its decision making (see FAD sections 3.7 and 3.15)
National Amyloidosis Centre	3.7 It is unclear if introducing tafamidis would reduce delays in diagnosis times I agree. There are no compelling data to either support or indeed refute any assertion regarding improvement in diagnostic delays in relation to tafamidis. The increase in diagnoses in the UK and indeed worldwide, started to occur long before ATTR-ACT was published and long before DPD scintigraphy was adopted in many UK centres. This is highlighted in Lane et al, Circulation 2019;140:16–26 and is far more likely due to more widespread use of cardiac MRI to investigate HF and increased disease awareness than tafamidis or DPD availability. The figure below shows improvement in patient survival (from diagnosis) in patients diagnosed after 2012 compared to before 2012. None of these patients received tafamidis or any other disease-modifying therapy and supportive management has remained unchanged throughout the period. The only conceivable explanation for this improvement in survival therefore, is earlier diagnosis which can only be as a result of increased awareness and more widespread use of cardiac MRI since the DPD scans in >98% of these patients were performed only once the patient had been referred to NAC.	Comments noted. The committee agreed that the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM, but recognised that diagnosis can still take a long time (see FAD section 3.4). It questioned whether recommending tafamidis would further increase awareness and reduce diagnosis times. It understood that the short-term observational EAMS data were presented to support the assumption that introducing tafamidis could reduce diagnosis delays. It acknowledged that although this data was informative, the EAMS data can only demonstrate that diagnosis delay was reducing when tafamidis was available through EAMS, and not that tafamidis was the cause for this reduction. It noted that the trend of earlier diagnosis seen in the EAMS could be explained by improvements in diagnostic tools since the ATTR-ACT trial. It acknowledged that when ATTR-CM is suspected, implementing the diagnostic pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur. The committee agreed it was not possible to attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis. So, it concluded that there was not enough

Commentator	Comment [sic]	Response
	 **Numbers at risk** Pre-2012 144 133 112 97 80 64 57 44 23 Post-2012 555 454 301 193 107 52 20 0 0	evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD section 3.8).
National Amyloidosis Centre	B11 - The benefits of tafamidis (reflected in the transition matrices, survival functions and health-related quality of life parameters) will all continue to apply after a patients has discontinued tafamidis There is no evidence for a sustained benefit in any of these parameters after discontinuation of tafamidis. The ATTR-ACT trial did not shed any light on mechanism of action and work from Bellotti (Verona G et al, Sci Rep. 2017;7(1):182)	Comments noted. The committee considered that the company's approach of assuming continued treatment benefits. It acknowledged comments received at consultation from the NAC which suggested that ATTR-ACT had not revealed anything about how tafamidis works. The group stated that a recent publication had shown that

Commentator	Comment [sic]	Response
	has lately shown that 'stabilization' does not necessarily inhibit amyloid formation, such that the mechanism underlying the apparent benefit of tafamidis is unclear. Furthermore, if the mechanism of benefit is due to inhibition of amyloid formation, amyloid is overwhelmingly likely to re-accumulate after treatment has been discontinued.	disease stabilisation does not necessarily inhibit amyloid formation, so the mechanism underlying tafamidis' proposed benefit is unclear. The committee concluded that assuming continued treatment benefits without a cost was overly optimistic and would lead to an underestimated incremental cost-effectiveness ratio (ICER) (see FAD section 3.16).

Summary of comments received from members of the public

Theme	Response
The recommendation: • Tafamidis is the first proven effective treatment to reduce mortality and cardiovascular admissions. Further negotiation should take place to enable patients in the UK to benefit from this therapy. • A positive recommendation would ensure better outcomes and provide uniform access for people who currently have no options. • It is frustrating not being able to offer an effective treatment when no alternatives are currently available.	Comments noted. The committee acknowledged that ATTR-CM was a debilitating disease which severely affects mental and physical health (see FAD section 3.2) It also acknowledged the benefits of tafamidis over placebo as seen in ATTR-ACT (see FAD section 3.10). However, the committee's most plausible ICER for tafamidis compared with best supportive care was substantially above the range that NICE usually considers an acceptable use of NHS resources (see FAD section 3.24). So, the committee did not recommend using tafamidis in the NHS for treating ATTR-CM (see FAD section 3.27).
The condition; Transthyretin Amyloid Cardiomyopathy (ATTR-CM): • ATTR-CM is unresponsive to standard heart failure therapies • The condition has the most dire prognosis of all the heart failure causes	Comments noted. The committee acknowledged that ATTR-CM was a debilitating disease which severely affects mental and physical health (see FAD section 3.2).
Diagnosis: • ATTR-CM is an easily diagnosed disorder with increasing understanding and awareness • Tafamidis has improved ATTR-CM awareness. It is unclear if recommending it would further reduce diagnosis delays • Most diagnoses are (or can be) made using locally available tests • Diagnostic algorithm will reduce delays	Comments noted. The committee agreed that the availability of new diagnostic tests and treatment options in the disease area had improved awareness of ATTR-CM, but recognised that diagnosis can still take a long time (see FAD section 3.3). The committee heard conflicting views from the company and clinical experts present at the appraisal committee meeting regarding the interpretation and implications from an increased availability of DPD scans. So, it concluded that it was unclear if the availability of improved tests for diagnosing ATTR-CM would lead to an overdiagnosis of amyloidosis (see FAD section 3.4).

Theme	Response
• Challenging to managing increasing numbers of diagnoses • A network hub and spoke centres is proposed to handle high volume of diagnoses • Biomarker measurement combined with NYHA class is accepted in heart failure • DPD scans are a sensitive tool for early ATTR-CM detection • UK centres are increasingly capable of diagnosing ATTR-CM. More DPD kits are being supplied. • Highlighting incidental amyloid deposit findings from DPD scans as a barrier to diagnosis is questionable.	It questioned whether recommending tafamidis would further improve awareness and reduce diagnosis times. It understood that the short-term observational EAMS data were presented to support the assumption that introducing tafamidis could reduce diagnosis delays. It acknowledged that although this data was informative, the EAMS data can only demonstrate that diagnosis delay was reducing when tafamidis was available through EAMS, and not that tafamidis was the cause for this reduction. It also noted that these diagnoses were made at a specialist centre and questioned if the reduced delays to diagnosis achieved at the NAC could be achieved at other centres in clinical practice. It noted that the trend of earlier diagnosis seen in the EAMS could be explained by improvements in diagnostic tools since the ATTR-ACT trial. It acknowledged that when ATTR-CM is suspected, implementing the diagnostic pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur. The committee agreed it was not possible to attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis. So, it concluded that there was not enough evidence that introducing tafamidis would reduce ATTR-CM diagnosis delays (see FAD section 3.8).
Considerations of the evidence: • All of the relevant evidence has been considered • Too much emphasis placed on subgroups results. However, because the subgroups contain small numbers they are not robust. • Robust clinical trial evidence demonstrates tafamidis benefit • Observational data from the French Amyloidosis Centre support ATTR-ACT findings with respect to mortality benefits in NYHA 1-3.	Comment noted. No action required. Comment noted. The committee agreed that although the subgroup results added a degree of uncertainty around the clinical effectiveness results for tafamidis it accepted that they were underpowered. It concluded that the subgroup results would not be considered in its decision making (see FAD section 3.11). Comments noted. The committee considered the primary and secondary outcome results from ATTR-ACT, and noted that tafamidis was associated with statistically significant reductions in: the primary outcome, cardiovascular-related mortality, and cardiovascular-related hospitalisations (see FAD section 3.10).
New York Health Association (NYHA) functional classification system:	

Theme	Response
• A lack of familiarity with the NHYA classification scale is clear in the ACD • Despite limitations in terms of variability and reproducibility NYHA is used in clinical research because of its simplicity • NAC and French Amyloidosis centre data show NYHA class can predict prognosis in untreated people • NYHA is used to guide many recommendations in heart failure	Comments noted. Although the committee acknowledged the views from clinical experts that NYHA is used widely in heart failure trials, it maintained its view that its use for measuring the severity of ATTR-CM had limitations. Despite this it acknowledged there was insufficient evidence available from the trial to consider an alternative measure (see FAD section 3.6).
Tafamidis treatment starting and stopping rules: • No evidence of benefit in NYHA 4, so it would be uncomplicated to stop treatment. • A stopping rule should be modelled to reflect discontinuation observed in ATTR-ACT.	Comments noted. The committee understood that there was limited evidence to support the use of tafamidis in NYHA class 4 because ATTR-ACT did not recruit people whose disease was classed as NYHA class 4. It acknowledged the company's view that the proposed stopping rule reflected treatment stopping in ATTR-ACT, in which most people stopped tafamidis quickly after progressing to NYHA class 4. It considered comments from the patient organisation which explained that making decisions about stopping treatment in advanced disease stages were not uncommon. It also acknowledged comments from a clinical expert suggesting that people whose disease was classed NYHA 4 would be very unwell and likely moved onto best supportive care. However, it noted that tafamidis' marketing authorisation did not include stopping rule based on NYHA. It also noted the limitations of using the NYHA classification to accurately identify people who need treatment. So, it concluded that it would not consider starting and stopping rules for tafamidis based only on the NYHA classification system in its decision making (see FAD sections 3.6, 3.7 and 3.15)
The cost-effectiveness estimates: • Accepting an ICER of £20,000 per QALY gained ICER because of "high levels of uncertainty" is inappropriate given the evidence of clear benefit demonstrated in ATTR-ACT. Also, uncertainty is not unusual in the context of treatments for rare diseases.	Comments noted. The FAD has been updated and not longer highlights "high levels of uncertainty" as a rationale for accepting an ICER of £20,000 per QALY gained. However, the committee's most plausible ICER for tafamidis compared with best supportive care was substantially above the range that NICE usually considers an acceptable use of NHS resources (see FAD section 3.24). So, the committee did not recommend using tafamidis in the NHS for treating ATTR-CM (see FAD section 3.27).
Equality considerations: • This recommendation will disproportionately affect people of afro-Caribbean ethnicity	Comments noted. The committee acknowledged that ATTR-CM disproportionally affected people from certain ethnic groups (see FAD section 3.25). But, given that tafamidis was considered not to be a cost-effective use of NHS resources (see FAD section 3.24) it agreed it was not something that could be addressed in its recommendations.

Theme	Response
• Elderly people not enrolled in EAMS will be denied a treatment that could maintain a state of health and reduce morbidity, while those in EAMS receive life saving therapy • Penalising uncertainty by accepting a lower ICER penalises those with rare diseases	Comment noted. The committee considered that their recommendations did not disproportionately disadvantage certain age groups, and that access to tafamidis through EAMS was not in the scope of their recommendation (see FAD section 3.24).

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Pfizer Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**
Name of commentator person completing form:	**NA**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

Dear Appraisal Committee members,

Pfizer welcomes the opportunity to comment on the NICE Appraisal Consultation Document (ACD) for tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531].

Pfizer are disappointed with the draft decision; however, we remain committed to working with NICE to achieve access to tafamidis for patients with ATTR-CM in England and Wales. We have summarised our key concerns with the conclusions from the committee below.

- Accurate diagnosis of patients with ATTR-CM in the UK – we do not agree with these conclusions as they are not aligned with a validated approach to accurate diagnosis or the supportive evidence of its deployment in NHS clinical practice.
- Clinical interpretation of the ATTR-ACT data
    - Primary outcome measure – in contrary to the committee conclusions, we consider survival and hospitalisation to be highly relevant in clinical practice.
    - Efficacy of the overall population and subgroups – conclusions from the committee appear to contradict each another and suggest that tafamidis does not offer benefit in any subgroup, which is contrary to the clinical trial results.
- Utilisation of NYHA classification in clinical practice and the application of a stopping rule – NYHA is extensively validated and widely used in clinical practice. Therefore, given the evidence from the trial, a stopping rule based on NYHA is appropriate.
- Impact of tafamidis on early diagnosis and the subsequent effect on patients and the system – we are concerned that the dismissal of the NHS data generated through EAMS calls into question the merit of early treatment experience obtained in future EAMS programmes. The company has presented real-world UK data that directly demonstrates the impact of tafamidis on time to diagnosis and disease stage at diagnosis. Based on the evidence we believe it would be appropriate to recognise that a significant reduction in time to diagnosis would have a positive impact on both patients and the system.
- Treatment effect of tafamidis – the ERG analysis has been accepted by the committee as the most plausible without full consideration of the breadth of its limitations or the extent of evidence behind the company analysis.

Following your review of the evidence addressing each of our concerns in the table below, we believe the committee may want to revise their position on the degree of uncertainty and the need for the ICER threshold to be less than £30,000 per QALY. In addition, as seen through the trial data, the orphan

designation and the EAMs program, tafamidis represents a paradigm shift being the first ever treatment in the management of a rare, progressive and fatal orphan cardiovascular disease with a significant unmet need. However, it appears these elements have not been taken into consideration by the committee when determining an appropriate tolerance for the level of uncertainty or the most appropriate threshold. Yours sincerely,

[redacted]

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

Comment number	Comments
1 **Accuracy and speed of diagnosis**	**The committee concluded that *"Accurately diagnosing ATTR-CM is challenging and can take a long time."* (Section 1; Page 3) and "*Without validated and objective measures for assessing ATTR-CM, identifying people who need treatment and those who are benefiting from treatment will continue to be a challenge" (Section 3.27; Page 25)*. The company suggests that these conclusions are not supported by the evidence.** In 2016, a group of amyloid experts published a non-invasive diagnostic algorithm for ATTR-CM which was validated and found to have a specificity and positive predictive value for ATTR-CM of 100%.[1] This algorithm has been implemented at 17 EAMS sites across the UK using diagnostic equipment for nuclear scintigraphy and laboratory tests that are standard at most NHS hospitals. The aforementioned diagnostic algorithm is now supplemented by comprehensive international expert recommendations on diagnosis that are endorsed by multiple professional societies from across Europe and the United States.[2] The confirmatory tests in the diagnostic algorithm for ATTR-CM (nuclear scintigraphy, blood and urine tests for monoclonal protein)[1] can be performed in a single day. The huge delays in establishing the diagnosis of ATTR-CM following presentation with cardiac symptoms (prior to 2019 the average delay in the UK was >3 years with 40% waiting >4 years[3]), is likely the result of a low index of suspicion for the condition among cardiologists interacting with undiagnosed ATTR-CM patients in their daily practice and/ or clinical inertia in diagnosing ATTR-CM because of the lack of available treatment options. Historical UK data demonstrate the feasibility of rapid diagnosis as one third of patients received a diagnosis within 6 months from the onset of symptoms.[3] Rapid diagnosis could be expanded to most patients providing the equity of access to confirmatory diagnostic tests achieved through EAMS could be replicated going forwards (reducing the requirement for every patient to travel to a single centre). Data from the EAMS support the positive impact of tafamidis on early diagnosis in terms of both reducing the delay to diagnosis and identifying patients earlier in their disease course.
2 **Treatment benefits across subgroups defined by NYHA classification and genotype**	**The ACD contains the following statements which highlight uncertainty around the effectiveness of tafamidis in subgroups of the ATTR-ACT study. The conclusions of the committee within themselves are not consistent and are also not consistent with the observed results in either the subgroups or the overall trial population.** These statements (see Footnote) call into question the efficacy of the medicine. The positive benefit risk profile of tafamidis has already been determined by the EMA. As acknowledged by the committee, subgroup analyses were not powered to assess efficacy but rather are evaluated for consistency of the treatment benefit. We do not believe it is appropriate to use subgroup analyses to undermine results observed in the

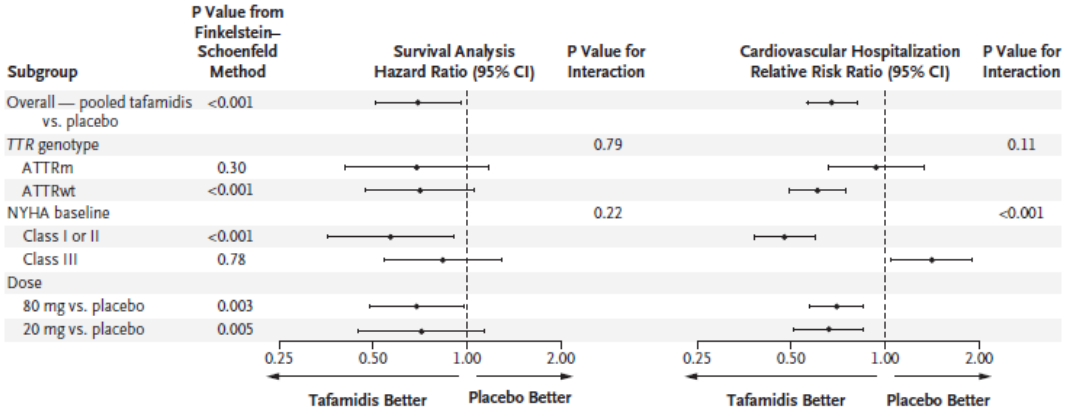
overall population or draw conclusions on subgroups when consistent results were observed.

Taken together the following statements (see Footnote) from the committee are inconsistent and raise concerns about the effectiveness of tafamidis in NYHA class 1, 2 and 3. The ATTR-ACT study only enrolled patients in NYHA Class 1, 2 and 3 and showed a 30% reduction in mortality (p=0.0259) and a 32% reduction in CV-related hospitalisation (p<0.0001) compared with placebo in the overall population. Despite these findings of a significant and clinically meaningful treatment benefit among patients treated with tafamidis, the committee have suggested the benefits are unclear in patients across the spectrum of NYHA classes that make up the totality of the enrolled trial population.

There is no scientific basis to support the committee's conclusion that there is a high level of uncertainty in the clinical effectiveness of tafamidis in patients with hereditary ATTR-CM. When testing for statistical interactions between subgroups, no significant interactions were observed between hereditary and wild-type ATTR-CM for all-cause mortality and CV-related hospitalisation (both components of the primary endpoint). The magnitude of reduction in all-cause mortality was in fact higher among patients with hereditary ATTR-CM (31.0%) than observed in those with wild-type ATTR-CM (29.4%).

Similarly, no significant interaction was observed between NYHA I/II and NYHA III for all-cause mortality supporting a consistent treatment effect across NYHA classes. The P value for interaction was significant between NYHA I/II and NYHA III for CV-related hospitalisation. This is thought to be attributable to patients living longer in a more advanced health state in the tafamidis treatment arm (as a consequence of the reduced mortality).[4]

Figure 1. Overall and subgroup results for all-cause mortality and cardiovascular related hospitalisations



Footnote

Section 1; Page 3: "*Evidence from clinical trials shows that it reduces deaths and hospitalisation from conditions affecting the heart and blood vessels compared with placebo. But inconsistent results on how effective tafamidis is for different types and stages of ATTR-CM mean that the*

	evidence is uncertain." Section 3.10; Page 13: "*The clinical experts suggested that the subgroup results could mean that a **large proportion of people with ATTR-CM would not benefit from tafamidis**"* Section 3.23; Page 22: "*The committee noted the high level of uncertainty, specifically: …. the effectiveness of tafamidis in people with hereditary ATTR-CM and in people with ATTR-CM classed as NYHA 3*" Section 3.6; Page 9: "*The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as **NYHA 1 because they have no functional limitations and might not benefit from treatment**."* Section 3.9; Page 12: "*The committee concluded that tafamidis could be **considered more effective than placebo based on the evidence presented**"* Section 3.10; Page 13: "*The committee accepted the company's point about a lack of statistical power in the subgroup analyses. But, it agreed that the subgroup results added to the uncertainty about the effectiveness of tafamidis in people with hereditary ATTR-CM and in people with ATTR-CM classed as NYHA 3…. So, it agreed that it was **unclear if there were any additional benefits to starting tafamidis when ATTR-CM is less severe and classed as NYHA 1 or 2**."* Section 3.14; Page 15: "*The committee noted the limitations of using the NYHA classification system in clinical practice and the **lack of evidence about tafamidis' effectiveness beyond NYHA class 1 and 2**."* Section 3.18; Page 19: "*The committee…. recalled that it was unclear if there were any additional benefits to starting tafamidis when ATTR-CM is classed as NYHA 1 or 2 (see section 3.10)."*
3 **NYHA classification and stopping rule**	**The committee has concluded that the NYHA classification system has limitations, therefore, those that benefit most cannot be accurately identified and a stopping rule based on NYHA classification is not appropriate. The company disagrees with this conclusion. NYHA classification is suitable to define a stopping rule because it is widely used in clinical practice, has been extensively validated and has been used in previous NICE recommendations. Furthermore, data from ATTR-ACT supports the use of the stopping rule and the EMA guidance is supportive, to some extent, of a stopping rule in NYHA IV.** NYHA classification is the most widely used functional classification in heart failure. It has been extensively validated and has been shown to correlate with quality of life,[5] quantitative assessment of cardiopulmonary performance such as peak VO2,[6] and prognosis.[7] Furthermore, NYHA classification is repeatedly used in NICE guidelines to describe the severity of heart failure and to define populations eligible for treatment with heart failure therapies.[8] There is clear biological rationale for expecting that the treatment effect size of tafamidis may differ by severity of disease in ATTR-CM. NYHA classification is the most widely

	used measure of severity in ATTR-CM. Therefore, as agreed with the EMA based on scientific advice, it was deemed appropriate to pre-specify a subgroup analysis by severity using NYHA classification. The limitations of the NYHA classification system do not introduce difficulty in identifying who benefits from tafamidis treatment. The ATTR-ACT study results are applicable to a broad population diagnosed with ATTR-CM by established criteria in whom tafamidis reduces all-cause mortality by 30% and reduced CV-related hospitalisation by 32%. There are no data to support the use of tafamidis in patients in NYHA IV, who have symptoms at rest, because this group were not enrolled in the ATTR-ACT study. When patients did progress to this advanced stage of disease, they discontinued treatment at a median of [redacted] days after entering NYHA IV classification. This observation suggests that discontinuations in practice mirror an NYHA IV stopping rule, confirming feasibility in clinical practice. The trial evidence showing very high and rapid discontinuation of tafamidis in NYHA IV reflects published guidance around management of end stage heart failure, which suggests medicines optimisation is recommended once reversible causes of heart failure are excluded.[9] Stopping unnecessary medicines that do not contribute to symptomatic improvement is recommended. Given that tafamidis is such a treatment, i.e. it offers no short-term symptomatic relief but addresses the underlying disease mechanism in reducing cumulative exposure to transthyretin amyloid over time, it is felt that a stopping rule at NYHA IV would be clinically appropriate. The randomised controlled trial evidence for tafamidis supports the effectiveness of the medicine in NYHA classes I-III. As the committee highlight, the European Medicines Agency Summary of Product Characteristics supports starting tafamidis as early as possible in NYHA I/II and recommends a physician decision on starting and maintenance in NYHA III. Therefore, it should be appropriate to specify a stopping rule in NYHA IV where there is no evidence of treatment benefit. **Footnote** Section 1.2; Page 3: "*Also, the measure used to assess how severe ATTR-CM is has limitations, so it is difficult to identify who benefits from treatment and decide who should stop."* Section 3.5; Page 8: "*The NYHA functional classification system is commonly used in clinical practice to assess heart failure…..The clinical experts explained that although NYHA classification is used in clinical practice, it has limitations……The committee concluded that using NYHA classification in ATTR-CM had limitations*." Section 3.6; Page 8: "*The committee considered that the NYHA classification could not be used to accurately identify people who need treatment. So, it concluded that defining starting and stopping rules for tafamidis based only on the NYHA classification system was not appropriate."* Section 3.6; Page 8: **"***The committee noted that the marketing authorisation for tafamidis did not*

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

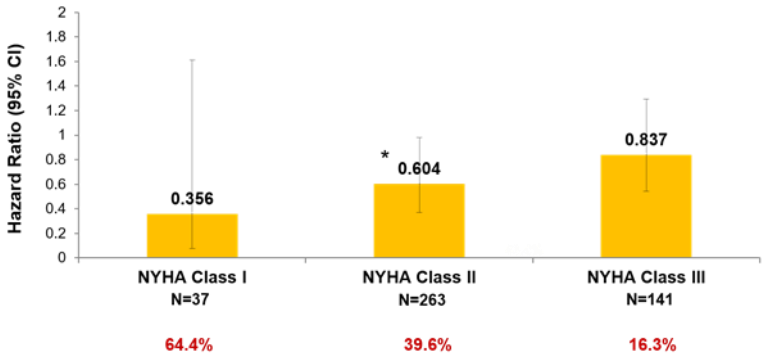
	specify starting and stopping rules for tafamidis based only on the NYHA classification system. It noted that the marketing authorisation states that tafamidis should be 'started as early as possible in the disease course when the clinical benefit on disease progression could be more evident. Conversely, when amyloid-related cardiac damage is more advanced, such as in NYHA class 3, the decision to start or maintain treatment should be taken at the discretion of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy" Section 3.14; Page 15: "*The committee noted the limitations of using the NYHA classification system in clinical practice …. It also noted that the marketing authorisation for tafamidis stated that there were limited clinical data in patients whose disease was classed NYHA 4 but did not specify that it should be stopped. The committee concluded that although there were limited clinical data in patients whose disease was classed as NYHA 4, it was not appropriate to model a stopping rule based on the NYHA classification. This was because it was not specified in the marketing authorisation and would be challenging to do in clinical practice."* Section 3.23; Page 22: "*The committee noted the high level of uncertainty, specifically: ….starting and stopping rules based on the NYHA classification system (see sections 3.6 and 3.14)"*
4 **NYHA classification as a measure of clinical effectiveness**	**We are concerned by the following statement which does not reflect the evidence submitted by the company: "*The committee noted the high level of uncertainty, specifically: measuring the clinical effectiveness of tafamidis using the NYHA classification system (Section 3.23; Page 22)"*** This statement is factually incorrect, the clinical effectiveness of tafamidis was not measured using the NYHA classification system in the clinical evidence package. NYHA classification was an exploratory endpoint in the ATTR-ACT study and it was a stratification factor used for the primary analyses. The clinical effectiveness of tafamidis was measured using a combination of all-cause mortality and CV-related hospitalisation.
5 **Differentiating amyloid deposits from amyloidosis**	**The following statement in the ACD is misleading as it is not aligned with clinical practice: "*The clinical experts……noted that transthyretin amyloid deposits are often an incidental finding in people having DPD scans. They explained that the population they see in practice had a range of amyloid deposits, sometimes because of older age, for example. Also, there is no defined point at which amyloid deposits become amyloidosis. So, it is unclear why some amyloid deposits progress to amyloidosis and others do not. Also, because other common comorbidities can lead to increased breathlessness and decreased mobility, a definitive ATTR-CM diagnosis is challenging." (Section 3.3; Page 6)*** It is misleading to suggest that ATTR deposits are often an incidental finding in patients undergoing DPD scans. Based on the validated diagnostic algorithm developed by the NAC and other centres,[1] patients are only eligible for a DPD scan if they meet the following criteria: "Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/ or cardiac magnetic resonance imaging suggesting/ indicating cardiac amyloid". Therefore, by definition, if patients are investigated according to this algorithm, DPD scans are only undertaken in symptomatic individuals with a clinical phenotype,

	consequently identification of amyloid deposits cannot be incidental. This algorithm has been safely and effectively implemented at 17 UK cardiology centres in EAMS, to identify patients aligned with the EMA indication, and without any evidence of misdiagnosis or misclassification. The suggestion that cardiologists specialising in heart failure or cardiomyopathy are not able to identify patients with a clinical phenotype on the basis of structural changes on imaging or cardiac signs/ symptoms undermines a core component of their routine practice. If a DPD scan is performed for another indication, for example the investigation of bone disease, a patient may have an incidental finding of cardiac amyloid deposits. However, this would never equate to a diagnosis of amyloidosis in the absence of the clinical phenotype described in the algorithm (Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/ or cardiac magnetic resonance imaging suggesting/ indicating cardiac amyloid).[1] While common comorbidities can lead to breathlessness, the diagnostic algorithm restricts DPD scans to patients with the clinical phenotype of cardiac amyloidosis that must be evident on echocardiogram and/ or cardiac magnetic resonance imaging. This statement has therefore introduced unfounded uncertainty as to the ability of clinicians to correctly identify the disease that is not supported by evidence.

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

6 **Treatment benefits in NYHA I**	**The ACD states: "*The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment"* (Section 3.6; Page 9). This statement is directly contradicting the conclusion from the EMA and is not aligned with published data from ATTR-ACT.** This statement directly contradicts the European Medicines Agency Summary of Product Characteristics which states, "Vyndaqel should be started as early as possible in the disease course when the clinical benefit on disease progression could be more evident." The evidence from the ATTR-ACT study suggests the medicine offers the greatest magnitude of benefit for the primary outcome measure in patients with NYHA I classification (Figure 2).[4] A diagnosis of ATTR-CM in NYHA class I is not a benign condition, in ATTR-ACT, [redacted] NYHA I patients in the placebo arm died and [redacted] underwent heart transplantation during the 30-month trial period. Patients with NYHA Class 1 are also not asymptomatic- they must have a clinical phenotype for a diagnosis, this would include cardiac remodelling on echocardiogram or magnetic resonance, they may have clinical signs of heart failure or a previous hospitalisation for heart failure- treatment with diuretics may reduce the functional limitation for a time limited period before progression of disease. Delaying treatment while patients progress to a functional limitation is counter to international clinical consensus and deprives patients of an opportunity to halt progression of their disease in an early stage and reduce mortality. **Figure 2. All-cause mortality by NYHA class** 
7 **The impact of tafamidis on early diagnosis**	**The ERG and subsequently the committee concluded that diagnosis times are unlikely to change if tafamidis were approved: "*The ERG highlighted that the trend of earlier diagnosis seen during the EAMS period could be explained by improvements in diagnostic tools since the ATTR-ACT trial (see section 3.3). Also, it noted that awareness of ATTR-CM had increased after patisiran and inotersen were introduced (see section 3.4). So, diagnosis times are unlikely to substantially change if tafamidis was to be recommended by NICE" (Page 10).* The company are concerned that this is not a reasonable conclusion, given past trends, current licensed treatments and the evidence submitted by the company from the EAMS programme.**

Please return to: **NICE DOCS**

	Nuclear scintigraphy is the diagnostic tool referred to in the ACD; this tool was introduced into routine practice at the NAC in 2012. Average delays to diagnosis remained >3 years despite the introduction of scintigraphy at the NAC. The company presented NHS evidence to NICE in order to support the impact of tafamidis during EAMS on early diagnosis. We compared the proportion of patients diagnosed in NYHA I/II classes at the NAC (since the introduction of nuclear scintigraphy)[3] and those treated during EAMS. A greater proportion of patients treated in EAMS were NYHA I/II compared with NAC diagnoses before EAMS (86% versus 75%, respectively).[3] Patisiran and inotersen are unlicensed for ATTR-CM so cannot be linked to an increased awareness of ATTR-CM or a change in the time to diagnosis. They have not been introduced in ATTR-CM beyond a clinical trial setting at the NAC and remain investigational treatments in this setting. Any disease awareness activities suggesting these medicines are applicable in ATTR-CM would constitute promotion outside of a license.
8 **Misinterpretation of published data**	**The committee *"noted that data from the National Amyloidosis Centre suggested that a third of people had an accurate ATTR-CM diagnosis within 6 months. It acknowledged this was an improvement on current diagnosis delays, but recognised these diagnoses were made at a specialist centre and questioned if this could be done in clinical practice."* (Section 3.7; Page 10). This is a misinterpretation of the data published by the National Amyloidosis Centre (NAC) and suggests the opposite, that reducing delays to diagnosis below 6 months is feasible in clinical practice.** This is a misinterpretation of the data published by the National Amyloidosis Centre (NAC). The data from the NAC showed that the observed mean delay to diagnosis was >3 years and one third of these patients were diagnosed in less than 6 months. This one third of patients is from the same groups of patients that the significant delays to diagnosis were calculated from, therefore they do not represent an improvement on current delays in diagnosis. The third of patients that were diagnosed in less than 6 months does, however, demonstrate that with greater suspicion of disease and local access to diagnostic tests (referral into a single national centre no longer being required), that the average diagnosis could be less than 6 months in the future due to the introduction of tafamidis. These data informed the company assumption that the expected reduction in time to diagnosis could be reduced from greater than 3 years to less than 6 months (ACD Section 3.18 page 18-19). This reduction in time to diagnosis is further supported by institutional data from the EAMS centres showing reductions in diagnostic delays to <6 months. In EAMS we also observed a greater proportion of patients diagnosed in early stage disease (NYHA I/II) compared with NAC diagnoses before EAMS (86% versus 75%, respectively).[3]

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

9 **Clinical relevance of the primary outcome measure in ATTR-ACT**	**The committees' concerns regarding the trial outcomes are unclear, all-cause mortality and cardiovascular-related hospitalisation are highly relevant, hard clinical endpoints and are considered as composite primary endpoints in other cardiovascular related trials.** In these statements (see Footnote) the committee are suggesting that all-cause mortality and cardiovascular-related hospitalisation are measures not used in clinical practice. The company considers these endpoints to be highly relevant in clinical practice. If the concern is the combination of these endpoints using the Finkelstein-Schoenfeld method, we would respectfully highlight the company submission data where we presented components of the primary outcome measure separately. These results mirror those of the combined endpoint- i.e. patients treated in the pooled tafamidis arm experienced significant reductions in both all-cause mortality (HR 0.698, 95% CI 0.508, 0.958, p=0.0259) and CV-related hospitalisations (RR 0.68, 95% CI 0.56, 0.81, p<0.0001) when considered separately. Combining endpoints in commonly known methods such as major adverse cardiovascular events (MACE) use a time to event function. The Finkelstein-Schoenfeld method does exactly the same but prioritises mortality in a hierarchical fashion.[10] The ATTR-ACT study underwent scientific advice with the EMA where this validated measure was agreed. In addition, both heart failure treatments previous appraised by NICE included primary composite endpoints with both survival and hospitalisation.[11,12] **Footnote** Section 3.9; Page 11: "*The primary outcome measured differences in all-cause mortality and the frequency of cardiovascular-related hospitalisations between tafamidis and placebo. Of those alive at month 30, people who had tafamidis had fewer annual cardiovascular-related hospitalisations (0.297) on average than those who had placebo (0.455) and differences were statistically significant. The committee considered that this measure was not used in clinical practice, so it was unclear what the relevance of these results was to people with ATTR-CM who would be seen in clinical practice*." Section 3.23; Page 22: "The committee noted the high level of uncertainty, specifically: *the relevance of trial outcomes to people in clinical practice ….."* Section 3.27; Page 25: "*It acknowledged that tafamidis was more effective than placebo in the outcomes assessed in ATTR-ACT, but it had some concerns about the measure assessed as the primary outcome (see section 3.9)."*
10 **Hierarchy of submitted clinical evidence**	**The company is concerned that the data from the RCT has been dismissed by the committee and the absence of a specific findings in EAMS prioritised (see footnote).** The EAMS was not intended to provide evidence to support the efficacy of tafamidis, the purpose was to provide access to a medicine that did not yet have a marketing

	authorisation. The longest duration of treatment when the scheme closed on 17th February 2020 was 6 months. The evidence supporting the additional benefits of tafamidis when started in patients with NYHA I/II classification comes from the ATTR-ACT study and is represented in Figure 1. In a hierarchy of evidence, we suggest this randomised controlled trial data should be prioritised for consideration over the absence of real-world efficacy data in the EAMS that was not designed for this purpose. **Footnote** Section 3.10; Page 13: "*The company also presented data from EAMS which suggested a trend towards earlier diagnosis and treatment in greater proportion of people with less severe disease (NYHA 1 or 2; see section 3.7). The committee acknowledged the trend, but noted that there was no evidence from EAMS that showed a different effect of tafamidis when it was started in the less severe NYHA classes. So, it agreed that it was unclear if there were any additional benefits to starting tafamidis when ATTR-CM is less severe and classed as NYHA 1 or 2*."
11 **Continuation of treatment benefit**	**The committee concluded that despite the ERG analyses "*had limitations….they provided realistic alternatives to the company's overly optimistic analyses" and "that the ERG's analyses were appropriate for decision making"* (Section 3.16; Page 16-17). The company believes the relevant merits of the company analyses have not been taken into consideration compared to the extensive limitations associated with the ERG analyses.** The committee has acknowledged that ATTR-ACT was unique in that it had complete follow-up, by which we mean there was no censoring or loss to follow-up within the trial period. As a result, the impact of tafamidis discontinuation on efficacy was accounted for within the predicted OS curves which were aligned with the observed data. However, this has only been reflected in the consideration of the limitations of the ERG analysis and not when considering the company analysis. Tafamidis works by reducing cumulative exposure to amyloid, therefore, if patients discontinue in earlier NYHA stages they would have a better prognosis than a patient that had been on BSC. This impact would become greater the longer a patient has been on tafamidis, as an equivalent patient on BSC would have experienced continued disease progression, as opposed to the tafamidis patient who had controlled disease whilst on treatment and discontinued in NYHA I-III for a reason other than progression of disease. This expected separation of overall survival and treatment discontinuation was observed within ATTR-ACT and the long-term extension, which provides a clear rationale for a separation of overall survival and treatment duration in the extrapolated curves. Therefore, given the complete follow-up in the data, the clinical rationale that patients discontinuing tafamidis cannot be considered equal to patients who have never received tafamidis, and the trend observed in the long-term data, the company analysis provides the most accurate modelling of the observed data without the introduction of arbitrary assumptions. A constant rate of discontinuation in NYHA I-III was observed in ATTR-ACT which is

	contrary to the conclusion from the clinical expert comment in Section 3.15 of the ACD. Observed data from the trial should be considered the most appropriate evidence to inform any modelling assumptions. This constant rate of discontinuation observed in the 30-month data was consistent with the extension study beyond the 30-month trial period (Technical Engagement Response Appendix Figure 1) and was supported by exponential having the best statistical fit. Therefore, in the absence of any clear explanation on why this long-term trend would suddenly change after the observation period, a constant rate of discontinuation is appropriate. This demonstrates that the first ERG analysis is unrealistic and not reflective of the observed data from the RCT. It should be noted, that the plateau observed in the end of the extension data is not informative given the low number of patients at risk. The significant limitations associated with the second ERG analysis were acknowledged by the ERG in their report "i) upon discontinuation, tafamidis patients immediately experience the same events and accrue QALYs in the same way as BSC patients, with no transition period; ii) that the prognosis of each patient upon discontinuation is equivalent to the mixture of patients in BSC (NYHA classification mix) at each respective time of discontinuation; iii) despite the complete follow-up (no censoring) up to 30 months in ATTR-ACT, the impact of the observed discontinuation is not reflected in any capacity in the extrapolation". Considering these limitations, the ERG included their first analysis where treatment discontinuation was assumed to plateau in their preferred analysis. However, the extent of these limitations does not appear to have been fully reflected in the committee conclusions and therefore cannot be considered appropriate for decision making compared to the company analysis.
12 **Overall survival extrapolation**	**The committee *"concluded that the reason for using generalised gamma functions to model overall survival was unclear and agreed to consider only the log-normal extrapolation functions in its decision making."* Section 3.17; Page 17. The company acknowledges the rationale for the change in survival model following the submission of the updated data cut was potentially unclear, please see further rationale below.** The company acknowledges the rationale for the change in survival model following the submission of the updated data cut was potentially unclear. Please see further rationale below. Despite all placebo patients crossing over to tafamidis at 30 months, there has been a continued separation in the survival curves observed within the long-term extension, with the initial long-term extension data cut observing a HR of 0.64 (0.47 - 0.85); 36% reduction in risk of death compared to 0.70 (0.51 – 0.96) in the initial trial period. This observed increase in efficacy is expected to increase further over time given those with NYHA III are associated with higher risk of mortality, therefore, in the long term there will be a shift in the population to a greater proportion of those that were NYHA I/II at baseline (who derive the greatest benefit from tafamidis). These long-term trends and clinical rationale suggest that the curves most likely do not

	reflect the full survival gains expected from tafamidis. Therefore, given the minimal difference between the log-normal and generalised gamma both in terms of visual and statistical fit to the observed data, the more 'optimistic' curve was felt to be the most appropriate.
13 **Improvements in diagnosis delay and impact on costs**	**'*The ERG highlighted that it was unclear how the company had estimated that diagnosis delays could be reduced by 2.5 years and how potential cost savings of £20,000 had been estimated'* (Section 3.18; Page 18-19). The committee subsequently concluded "that the company's early diagnosis assumptions were not appropriate for decision making because there was not enough evidence to support them." (Section 3.18; Page 19). The company acknowledged it would not be possible to provide hard empirical estimates for the assumptions related to early diagnosis, however there is rationale for the estimates proposed by the company, and it is not appropriate to conclude there would be no impact.** The NAC data demonstrate huge delays in establishing the diagnosis of ATTR-CM following presentation with cardiac symptoms, with this taking >4 years in >40% of patients (average >3 years) on a background of a median 17 hospital attendances during the 3 years before diagnosis.[3] Encouragingly, one third of patients in the same report were diagnosed rapidly within 6 months from the onset of cardiac symptoms. This rapid diagnosis in one third of patients before the availability of tafamidis demonstrates the feasibility of early diagnosis. In the tafamidis EAMS scheme, we observed an 18% increase in the diagnosis of patients in early stage disease (NYHA I/II) versus ATTR-ACT and an 11% increase versus the NAC.[3] In some EAMS centres, initial anecdotal data suggest that the average delay to diagnosis was reduced to <6 months. Compared with the historical average of >3 years at the NAC,[3] these data support at least a 2.5 year reduction in the average delay to diagnosis. This reduction is likely to result from the availability of the first treatment for ATTR-CM which is no longer an academic diagnosis, a greater index of suspicion of the disease coupled with equitable access to confirmatory diagnostic tests across the UK. In terms of costs, the 3-years prior to diagnosis involves 17 hospital attendances across inpatient admissions, outpatient and emergency department visits,[3] with further touch points in the 4th and other years prior to diagnosis. In addition to these attendances, many of which are avoidable, healthcare resource utilisation during the period also includes procedures and investigations. Some examples of unnecessary procedural/ investigation costs incurred during the diagnostic odyssey are coronary angiograms (one of the patient experts during the ACM described his experience of this test), implantation of cardiac defibrillators and repeated imaging investigations when cycling through secondary care specialist clinics (cardiac MRI, cardiac CT). Cost savings submitted by the company were estimated on the basis of these avoidable costs that have been quantified in terms of the proportion of patients they apply to and their reference costs. There are also the cost implications of misdiagnosis during this delay. Data from outside

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

	the UK suggests as many as 45% of patients received ≥1 misdiagnosis, of which 77% received treatment for these misdiagnoses, which demonstrate avoidable treatment costs during the delay to diagnosis.[13,14] The range of scenarios provided in Technical Engagement Response Appendix C and D demonstrate the direction and impact of a reduction in the delay to diagnosis by 2.5 years, which may be conservative given the historical data from the NAC and comparisons with the findings from EAMS.
14 **Adverse impact of diagnosis delay on QoL**	**The committee concluded that the QALY *"gain for reduced anxiety or depression for all patients was not a reasonable approach because it was not supported by any evidence'* Section 3.18; Page 18-19. The company acknowledges the lack of supporting evidence for the assumption. However, it cannot be concluded that a delayed diagnosis has no impact on patient quality-of-life.** It should be acknowledged by the committee that a patient experiencing symptoms such as breathlessness, fatigue and pain whilst having multiple touch points with different specialities over an extended period of time with no diagnosis would clearly have a negative impact on a patients' quality-of-life.
15 **Mechanism of action**	**The following statement in the ACD is not evidence based *"The clinical expert explained that new research had changed their understanding of the way that tafamidis treats ATTR-CM. They suggested that the mechanism by which it works may not be as innovative as was originally thought."* (Section 3.26; Page 24)** There is no peer-reviewed, published evidence to contradict the mechanism of action of tafamidis established over a decade of clinical development activity in ATTR-CM and in 9 years post-marketing data in ATTR polyneuropathy. The clinical experts stated in the ACM that they have conducted a "test tube experiment" at the NAC that casts doubt over the mechanism of action of tafamidis. These data have neither been peer-reviewed or published and should not have been considered by the committee. We respectfully cannot see any plausible link between this clinical input around the mechanism of action and the innovative nature of tafamidis and request it is withdrawn from the committee's conclusion. Within the ATTR-ACT clinical trial there is robust direct evidence of target engagement supporting the mechanism of action; stabilisation of the TTR protein was observed in 86% of patients in the pooled tafamidis group and 3.5% of those in the placebo group ($p<0.0001$).
16 **Factual inaccuracy**	**The following statement is factually inaccurate: "*The company estimated that it took 3 years or more for a person to be accurately diagnosed with ATTR-CM."* (Section 3.3; Page 6)** The 3-year average delay to diagnosis was not an estimate and was not provided by the company. These data are from a cohort study of patients diagnosed with ATTR-CM at the NAC.[3] In that study, the average delay to diagnosis was >3 years, one third of patients were diagnosed in less than 6 months demonstrating the feasibility of early diagnosis,

	however 40% waited for >4 years. Data from the tafamidis EAMS supports the positive impact of tafamidis on early diagnosis in terms of both reducing the delay to diagnosis and identifying patients earlier in their disease course.
17 **Factual inaccuracy**	**The company has not suggested that patients should start in NYHA I/II and discontinue in NYHA III. As stated in Section 3.6; Page 8: "*The company submission included analyses with these starting and stopping rules:*** ***• people whose disease is classed as NYHA 1 or 2 can start tafamidis*** ***• people whose disease is classed as NYHA 1, 2 or 3 can keep taking tafamidis and*** ***• people should stop tafamidis if their disease progresses to NYHA 4.*** ***The ERG explained that it had concerns about the clinical relevance of only allowing people whose disease is classed as NYHA 1 or 2 to start treatment."*** This statement is a misrepresentation of the company submission. This issue was raised at technical engagement where the company agreed 'that it would not be clinically appropriate for patients in NYHA III to not be eligible to start treatment but for NYHA I/II patients to remain on treatment upon progression to NYHA III'. The company also reiterated that 'the NYHA I/II subgroup was presented in the manufacturers submission (MS) to demonstrate the additional health gains expected in the overall population once tafamidis becomes available'. It is unclear why, when this issue was clarified and effectively resolved that is has still been included in discussion within the ACD in this context.
18 **Factual inaccuracy**	**The following statement is factually inaccurate *"For cardiovascular-related mortality, the hazard ratios favoured tafamidis over placebo, but the differences were not statistically significant in either wild-type (hazard ratio 0.71 [95% confidence interval 0.47 to 1.05]) or hereditary ATTR-CM (hazard ratio 0.69 [95% confidence interval 0.41 to 1.17])."* (Section 3.10; Page 12)** This statement is incorrect, the hazard ratios reported are for all-cause mortality not cardiovascular related mortality.

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14. Lousada I, Maurer MS, Warner M, Guthrie S, Hsu K, Grogan M. Amyloidosis Research Consortium Cardiac Amyloidosis Survey: Results from Patients with AL and ATTR Amyloidosis and Their Caregivers. *Imaging.* 2018;50:60.

Name	[redacted]
Organisation	Cardiomyopathy UK
Comments on the ACD:	

Are the recommendations sound and a suitable basis for guidance to the NHS?
No.
Tafamidis is the only treatment for people with ATTR-CM, there are no other options. We ask the NICE committee to reconsider their recommendation and, if needed, work with Pfizer to overcome any obstacles to making this treatment available.

Accurately diagnosing ATTR-CM is challenging and can take a long time.
The challenges of early diagnosis is already being overcome through wider clinical education, improved access to DPD scanning and patient awareness programmes. The committee acknowledges that diagnosis is already improving and this trend is set to continue with the lunch of amyloidosis online learning opportunities and online clinical education events planned but Cardiomyopathy UK and other partners in 2020 and 2021.

It is not appropriate to define starting and stopping rules for tafamidis based only on the NYHA classification system.

The charity accepts that NYHA scale is subjective and not a precise tool but it is a good indicator of disease progress when uses as part of the usual dialogue between patient and clinician. Both clinicians and patients are perfectly used to starting and stopping medication not only in cardiac disease but in all disease areas.
The committee acknowledges that Tafamidis slows down decline in health (3.11) therefore it would be logical to give treatment to people at NYHA 1 with a confirmed diagnosis of ATTR-CM given the likely decline in health caused by the disease if left untreated. Amyloidosis seems to accelerate as it progresses and treatments are more effective in early stages, therefore early diagnosis and access to treatment is critical for patients.

It is unclear if introducing tafamidis would reduce delays in diagnosis times.

The committee recognises that the introduction of a new treatment, and one that has proven to be effective, on a rare disease area has a positive impact on time to diagnosis. This is our experience and also that of the committee in relation to Patisiran and Inotersen. It does not follow that because Patisiran and Inotersen have improved diagnosis time that Tafamidis would not improve times further. It also has to be noted (as the committee has done elsewhere) that Tafamidis is targeting a different form of the disease in a different population.

The subgroup analyses raise concerns about the clinical effectiveness of tafamidis but are not robust.
It is clear however that the Tafamidis is effective overall. An ongoing study to monitor efficacy of Tafamidis in practice could be undertaken once approval is given. This would clarify the points of uncertainty regarding efficacy in sub groups with small populations.

Tafamidis is more effective than placebo in slowing the decline in quality of life.

The charity recognises that KCCQ is a good measure of quality of life but it does not include “living longer” and “few hospital visits” which are clearly patient priorities.

A stopping rule for tafamidis based on NYHA classification should not be included in the economic model.
As noted in 3.6 patients are used to starting and stopping treatment in consultation with clinicians based on self-assessment and discussion using NHYA. Making such decisions would not be challenging but normal practice.

There are no equalities issues that can be addressed in the guidance.
ATTR-CM disproportionately affects people with African or Caribbean ancestry. It is not clear why the committee does not feel that it is appropriate to consider the disproportionate impact of the condition on minority communities and to include this in their decision making. The charity believes that ensuring fair accesses to treatment for all communities is a fundamental goal of NICE.

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 2 July 2020 through NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK ATTR AMYLOIDOSIS PATIENTS' ASSOCIATION (UKATPA)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I can confirm that the UK ATTR Amyloidosis Patients' Association (UKATPA) has never past or present had direct or indirect links to, or funding from, the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	We the UK ATTR Amyloidosis Patients' Association (UKATPA) would like to submit the following comments in response to the Consultation on the appraisal consultation document for ID1531 Tafamidis:
1	**3.3 Diagnosis** The challenges of early diagnosis can be overcome through wider clinical education of clinicians and patients. This is becoming evident with improvements in diagnosis (which the committee acknowledged) as a result in the increase of clinical education in this area. This trend is set to continue with the launch of amyloidosis online learning opportunities and online clinical education events planned this year. In the past, there has been a nihilistic attitude amongst clinicians due to the lack of specific treatments but this has already changed in specialist centres. In the centres involved in EAMS programme the time the diagnosis has been reduced from years to months.
2	**3.6 Starting and stopping** We accept that the NYHA scale is subjective and not precise but it is a good indicator of patient stage and part of the usual dialogue between patient and clinician. Both clinicians and patients are perfectly used to starting and stopping medication not only in cardiac disease but in all disease areas. The committee acknowledges that Tafamidis slows down decline in health (3.11) therefore it would be logical to give treatment to people at NYHA 1 with a confirmed diagnosis of ATTR-CM given the likely decline in health caused by the disease if left untreated. Amyloidosis

	seems to accelerate as it progresses and treatments are more effective in early stages, therefore early diagnosis and access to treatment is critical for patients.
3	**3.7 Impact of introduction of Tafamidis on time to diagnosis** The committee recognises that the introduction of a new treatment, and one that has proven to be effective, on a rare disease area has a positive impact on time to diagnosis. This is our experience and also that of the committee in relation to Patisiran and Inotersen. It does not follow that because Patisiran and Inotersen have improved diagnosis time that Tafamidis would not improve times for this group of patients. It is of note that Tafamidis is targeting a different form of the disease in a different population
4	**3.10 Subgroups** Subgroups are necessarily going to be smaller populations. The analysis model needs to accommodate this. The data should also be taken as a whole, that is that the treatment is effective. If Tafamidis was recommended and made available through the NHS, we would ask for an ongoing study to monitor efficacy of Tafamidis in the real world, with a national register and prospective data collection in order to clarify the points of uncertainty.
5	**3.11 Quality of Life** KCCQ is a good measure of quality of life but does not include “living longer” and “few hospital visits” which are patient priorities and important outcomes.
6	**3.14 Stopping Rules** As noted in 3.6 patients are used to starting and stopping treatment in consultation with clinicians based on self-assessment and discussion. We feel that it would be reasonable to include a stopping rule for patients with significant disease progression. This could be transition from NHYA 3 to NYHA 4, or if this is considered not practical, the use of more objective measurements by clinicians.
7	**3.25 Equality Issues** It is not clear why the committee does not feel that it is appropriate to consider the disproportionate impact of the condition on minority communities and to include this in their decision making. Patients with mutation Val122Ile are mostly from African or Caribbean origin and develop ATTR-CM, but not usually neuropathy. At present, they do not have access to any specific treatment for ATTR while, for example, patients with the mutation Thr60Ala, also known as the Irish mutation, usually present with cardiac symptoms, but they also develop ATTR neuropathy, therefore being candidates for treatment with Inotersen or Patisiran. This creates, indirectly, inequality in access to drugs.
8	**3.27 Conclusions** **The committee acknowledges the safety and effectiveness of Tafamidis and the need for the treatment.** **There is no treatment available for ATTR-CM in the UK and many patients are deteriorating and dying while they could benefit from having access to Tafamidis. We would ask Pfizer and NHS commissioners to negotiate a feasible commercial agreement that makes this possible, and the NICE committee to reconsider their recommendation. It would be a tragedy if we leave our patient community in this situation any longer.**

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 2 July 2020 through NICE DOCS

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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Cardiovascular Society (BCS)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures**
Name of commentator person completing form:	[redacted]

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Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 June 2020 through NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The BCS feels that Tafamidis is associated with clinical benefit in treating transthyretin amyloid cardiomyopathy by slowing disease progression, but acknowledges NICE's conclusion that this comes at an unacceptably high cost.
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Insert extra rows as needed

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- Do not use abbreviations
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Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Society for Heart Failure**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No disclosures to declare**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Consultation on the appraisal consultation document – deadline for comments 5pm on 2 July 2020 through NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We have concern over the finding in Section 1, Recommendations: 'Inconsistent results on how effective tafamidis is for different types and stages of ATTR-CM mean that the evidence is uncertain. (Repeated in Section 3.10: 'the subgroup analyses raised concerns and uncertainty about clinical effectiveness of tafamidis.)** The two subgroups of concern are amyloid subtype (variant or wild type) and NYHA class. a. Amyloid subtype. Although the reduction in combined primary end point of all-cause mortality and annual cardiovascular admissions was significant, and effect remained favourable it failed to achieve significance when amyloid subgroups were analysed individually. We are surprised at the weight that this finding has had in effectiveness assessment, as this was a trial of under 500 patients and the variant subgroup contained only 106 patients. We would urge the committee to avoid over emphasis on subgroup analysis as a basis for decision making particularly when cohort numbers are small and when both all-cause mortality and cardiovascular hospitalisation rate were lower albeit non-significant in the treatment group. b. NYHA Class. In NYHA class III, with more advanced symptoms, a non-significant reduction in all-cause mortality was seen but there was also an increase in cardiovascular admission rate. The addition of a heart failure expert at the committee meeting would have been beneficial as lack of significance is a common effect seen in advanced NYHA subgroups in heart failure trials. For example, subgroup analysis of the PARADIGM-HF Trial for sacubitril valsartan showed no significant benefit in the primary end point for NYHA classes III and IV. The CARE-HF Trial for cardiac resynchronisation therapy showed no significant benefit for NYHA class IV. Both treatments are approved by NICE. Common to all these trials are the small numbers of patients in the advanced heart failure NYHA subgroups – in ATTR-ACT there were only 141 patients in the NYHA class III subgroup. Advanced heart failure is associated with other important factors such as worsening renal function and increasing frailty and it is likely that the increase in co-morbid factors and smaller subgroup size has a bearing on the lack of effect significance seen recurrently in heart failure trials.
2	**Section 3.3. Accurately diagnosing ATTR-CM is challenging and can take a long time**. This title/statement is no longer correct. Although this was the case in the past, access to cardiac magnetic resonance and DPD scanning has improved detection enormously and this is reflected in the rapid increase in referrals for ATTR-CM to the National Amyloidosis Centre. The BSH agree with the committee's expert, Prof Hawkins' statement where he notes as his first key comment that this is now an easily diagnosed disorder.
3	**Section 3.6. It is not appropriate to define starting and stopping rules for tafamidis based only on the NYHA classification**. NYHA status is a subjective classification with well recognised limitations, however NYHA functional class remains the most commonly used method for stratification of patients in heart failure trials However, the NYHA classification is already employed in this setting in many other treatments for heart failure. For instance, an implantable cardioverter defibrillator (ICD) is NICE indicated in NYHA I, II, and III but not in NYHA IV. Similarly, cardiac resynchronisation therapy (CRT) is indicated in NYHA II, III and IV but not in NYHA I unless ECG shows a very prolonged QRS (≥150ms). Sacubitril valsartan is approved for NYHA classes II-IV (symptomatic heart failure) but not NYHA class I. Again, the addition of a heart failure clinician to give expert advice would be useful at further meetings.

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4	**Section 3.9 regarding annual cardiovascular-related hospitalisations. The committee considered this measure was not used in clinical practice so it was unclear what the relevance of these results was to people with ATTR-CM who would be seen in clinical practice.** Cardiovascular hospitalisations are a standard measure in heart failure trials and given the long duration of the trial and subject group with high admission and mortality rate it is understandable that the hospitalisation rate was chosen as an end point as prolonged life expectancy may not translate into reduced admissions due to longer survival with a condition with high admission risk. The BSH considers that the number of times a heart failure patient needs to be admitted per year is a highly relevant outcome measure for heart failure patients.
5	**Section 3.25. There are no equality issues that can be addressed in the guidance.** ATTR-CM disproportionately affects people of African and Caribbean family origin. The current guidance will promote inequality for this minority group in terms of i) access to treatment to improve mortality and hospitalisations for a condition with no other available therapies and ii) access to appropriate investigations. Although detection rates have improved enormously in wild type ATTR due to ready access to cardiac MRI and DPD scanning, this benefit has not been seen in V122I ATTR where detection rates have been unaffected and remain unacceptably low (Lane et al, Circulation 2019; 140:16-26). Availability of an effective treatment has the potential to improve this situation as there will be an onus on clinicians not to miss a condition where an approved treatment is available. This could in turn enable equitable access for patients of African and Caribbean ethnicity to appropriate investigations that they are not able to access at present.
6	Response to NICE questions above. • **has all of the relevant evidence been taken into account?** Yes, the BSH agrees all relevant evidence has been considered. • **are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Clinical effectiveness: No, the BSH considers that the emphasis on subgroup analysis of a trial with small numbers is not appropriate and considers that the pre-specified endpoints of the trial were appropriate (all-cause mortality and cardiovascular hospitalisation rate) and concur with the slowed reduction in quality of life as measured by KCCQ-OS seen in the ATTR-act trial. • **are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. This is a condition with very high morbidity and poor quality of life, even for heart failure, with relentless progression to death. This is the first effective treatment to reduce mortality and cardiovascular admission rate. On behalf of patients the BSH hopes that a further negotiation on cost can take place in order to enable patients in the UK to benefit from this therapy within the standard NICE ICER of £30,000 per QALY. The British Society for Heart Failure response to this recommendation has been endorsed by the patient charities Cardiomyopathy UK and Pumping Marvellous.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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1	We consider that all of the relevant evidence been taken into account.
2	The summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.
3	The provisional recommendations do provide a sound and a suitable basis for guidance to the NHS.
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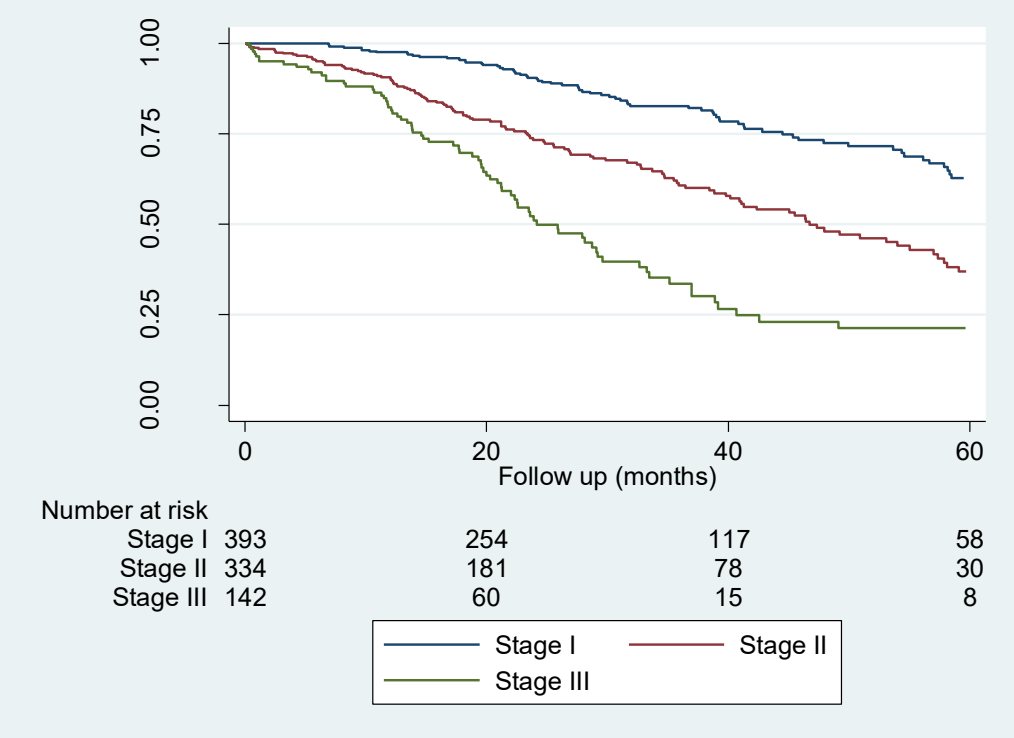
Response to the NICE Institute for Health and Care Excellence (NICE) Appraisal Consultation Document: Tafamidis for treating transthyretin amyloidosis with cardiomyopathy

Submitted by

[redacted]
National Amyloidosis Centre, UK

3.5 Measuring the severity of ATTR-CM using the NYHA class has limitations

I would agree with the above statement, noting that NYHA heart failure status can vary day to day in this disease since patients are exquisitely sensitive to fluid balance changes. By contrast, the prognosis of ATTR-CM (effectively the severity in terms of disease progression) can be very clearly defined by the NAC ATTR Staging system (Gillmore et al, EHJ 2018;39:2799–2806; see figure below). This staging system has been adopted worldwide (Capelli F et al, Can J Cardiol 2020;36(3):424-431.) Whilst the NAC ATTR Staging system did not exist at the time that the ATTR-ACT study was designed, the company have been asked on several occasions for a comparison of the numbers of participants in each treatment group by NAC ATTR Stage at enrolment, but they have not provided these data. NAC Stage is robustly and simply based on serum eGFR and NT-proBNP measurements, which were recorded in the ATTR-ACT trial. Indeed, on page 17, ''Model Health Structure'', the company acknowledge that eGFR and NT-proBNP were measured at baseline. **All of the benefits attributed to tafamidis in the ATTR-ACT trial (i.e., survival, QoL, functional status) could conceivably be explained by disease natural history alone if there was an imbalance in NAC ATTR stage at the time of enrolment. The NT-proBNP cutoff defining NAC ATTR Stage is 3000 ng/L, and very notably the median NT-proBNP in ATTR-ACT placebo group was >3000 ng/L whilst it was <3000 ng/L in the ATTR-ACT treatment group.** I would strongly suggest that a post-hoc analysis of these data is made available to the committee to provide reassurance of true efficacy from tafamidis.



From Gillmore et al, Eur Heart J 2018;39, 2799–2806. Kaplan–Meier curves showing survival probabilities in 869 patients with cardiac transthyretin amyloidosis stratified by disease stage (log-rank test; Stage I vs. Stage II, P<0.0001; Stage II vs. Stage III, P<0.0001). Stage I patients had a median survival of 69.2months (95% CI lower limit 62.9months, upper limit indeterminable), Stage II patients had a median survival of 46.7months (95% CI 40.2–57.0months), and Stage III patients had a median survival of 24.1months (95% CI 21.2–29.6 months (P<0.0001 for Stage I vs. II and P<0.0001 for Stage II vs. III). By Cox proportional hazards regression analysis, compared with Stage I, the HR for death was 2.05 (95% CI 1.54–2.72, P<0.001) for Stage II and 3.80 (95% CI 2.73–5.28, P< 0.001) for Stage III patients. The HR for death in patients with Stage III cardiac ATTR amyloidosis compared with Stage II was 1.86 (95% CI 1.38–2.48, P< 0.001). Harrell's c-statistic was 0.69.

3.6 It is not appropriate to define starting and stopping rules for tafamidis based only on NYHA classification system

''The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment''

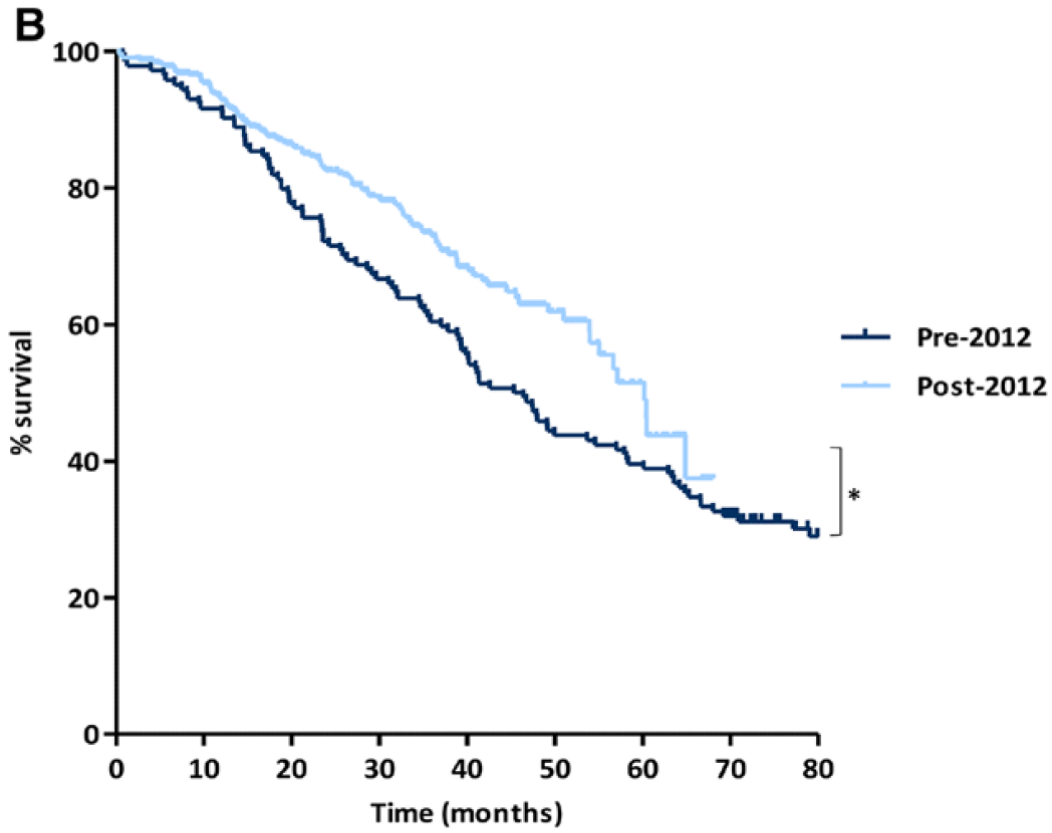
The use of tafamidis in NYHA class I is a **data free zone**. The ATTR-ACT study was undertaken in patients with heart failure and/or prior hospitalisation due to HF. There is currently no evidence to support use of tafamidis in NYHA class I patients with cardiac amyloid deposits which undoubtedly comprises a huge number of individuals; historical autopsy studies have shown presence of cardiac ATTR amyloid deposits in 25% of males over 80 years of age (Tanskanen et al, 2008;40:232-239) (~375,000 individuals in UK) and a recent study in Spain showed that 3.9% of males over 75 years of age (equivalent to >100,000 individuals in UK) had a positive DPD scan (Mohamed-Salem et al, 2018;270:192-196). This is a really important issue, since the ever increasing adoption of DPD scintigraphy as a diagnostic tool in cardiology will identify vast numbers of patients with incidental amyloid deposits that are of no clinical significance. The distinction between the mere finding of amyloid protein in the heart versus the heart failure syndrome of cardiac amyloid**osis** is incredibly important and remains widely misunderstood. **A rough estimate of the potential cost of tafamidis to the NHS were all these individuals to be diagnosed with ATTR-CM rather than 'cardiac amyloid deposits' on the basis of a positive DPD scan would be >£1 billion.**

I do agree with the committee that it would be extraordinarily difficult in clinical practice to discontinue tafamidis in patients who progressed to NYHA class 4.

3.7 It is unclear if introducing tafamidis would reduce delays in diagnosis times

I agree. There are **no compelling data** to either support or indeed refute any assertion regarding improvement in diagnostic delays in relation to tafamidis.

The increase in diagnoses in the UK and indeed worldwide, started to occur long before ATTR-ACT was published and long before DPD scintigraphy was adopted in many UK centres. This is highlighted in Lane et al, Circulation 2019;140:16–26 and is far more likely due to more widespread use of cardiac MRI to investigate HF and increased disease awareness than tafamidis or DPD availability. The figure below shows improvement in patient survival (from diagnosis) in patients diagnosed after 2012 compared to before 2012. None of these patients received tafamidis or any other disease-modifying therapy and supportive management has remained unchanged throughout the period. The only conceivable explanation for this improvement in survival therefore, is earlier diagnosis which can only be as a result of increased awareness and more widespread use of cardiac MRI since the DPD scans in >98% of these patients were performed only once the patient had been referred to NAC.



Numbers at risk

Pre-2012	144	133	112	97	80	64	57	44	23
Post-2012	555	454	301	193	107	52	20	0	0

From Lane *et al,* Circulation 2019;140:16-26. Survival of patients with wild-type ATTR amyloidosis stratified by year of diagnosis (*P=0.009).

B11 - The benefits of tafamidis (reflected in the transition matrices, survival functions and health-related quality of life parameters) will all continue to apply after a patients has discontinued tafamidis

There is **no evidence** for a sustained benefit in any of these parameters after discontinuation of tafamidis. The ATTR-ACT trial did not shed any light on mechanism of action and work from Bellotti (Verona G *et al*, Sci Rep. 2017;7(1):182) has lately shown that 'stabilization' does not necessarily inhibit amyloid formation, such that the mechanism underlying the apparent benefit of tafamidis is unclear. Furthermore, if the mechanism of benefit is due to inhibition of amyloid formation, amyloid is overwhelmingly likely to re-accumulate after treatment has been discontinued.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	

The increasing number of patients being diagnosed with ATTR-CM is already a challenge and a network of hub and spoke centres is proposed with virtual MDT assessment to overcome this issue.

This is a well recognised effect in heart failure trials - see Paradigm (sacubitril valsartan), CareHF (cardiac resynchronisation therapy) and most recently DAPA-HF (dapagliflozin, currently under review at NICE) as key examples.

Has all of the relevant evidence been taken into account?
Yes, all the relevant scientific evidence has been included.
Interpretation of the trial evidence appears to have been distracted by lack of clinical familiarity with the NYHA classification system. The input of a heart failure expert should be sought at future meetings.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The summary of clinical effectiveness has placed too much emphasis on subgroup analysis. The ATTR-act trial was designed with clinically relevant pre-specified end points of all-cause mortality, rate of hospital admissions and quality of life and was shown to be effective in both the combined primary end point and separate analysis of mortality, cardiovascular admissions and KCCQ-OS.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No. This is a condition with high morbidity, poor quality of life and relentless progression to death with current supportive therapy. This is the first proven effective treatment to reduce mortality and cardiovascular admissions. Clinical effectiveness is apparent from trial and extension trial evidence. Cost effectiveness should be a matter of further negotiation to enable patients in the UK to benefit from this therapy.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Yes. ATTR-CM preferentially affects those of Black African heritage who are affected by V122I ATTR hereditary cardiomyopathy. The V122I gene is carried by 4% of those of black African descent. Detection rates are poor and although there has been a significant improvement in diagnosis rates for wild type ATTR CM in recent years due to better access to cardiac MRI, detection rates for V122I ATTR remain very low and 25% of the entire UK cohort is detected in a single UK centre, where V122I ATTR has been shown to be the cause of 10% of heart failure cases in Afro-Caribbeans. This decision will therefore have a disproportionate affect on heart failure patients of Afro-Caribbean ethnicity and the improved detection rate that may have been expected with an approved treatment will not be achieved.

Under section 'recommendations'

This is incorrect. I agree with your clinical expert, Prof Hawkin's expert statement where he notes as his first key comment that this is now an easily diagnosed disorder. Previously delay in diagnosis resulted from poor clinician awareness and lack of access to CMR and DPD scanning.

In heart failure trials, it is usual that less benefit will be seen in advanced disease. For example subgroup analysis of the Paradigm Trial for sacubitril valsartan showed no significant benefit in the primary end point for NYHA classes III and IV. The Care HF Trial for cardiac resynchronisation therapy showed no significant benefit for NYHA class IV. Both of these treatments are approved by NICE.

Under section 'committee-discussion'
Accurately diagnosing ATTR-CM is challenging and can take a long time. The patient experts explained that getting an accurate diagnosis for ATTR-CM could be challenging. This is incorrect. The clinical expert statement from Prof Hawkins states that ATTR cardiac amyloidosis is an easily diagnosed disorder. (see point 25, key messages, item number 1).

This observation is not correct. As noted by Professor Hawkins, the committee expert, ATTR-CM is now an easily diagnosed condition (since cardiac MRI became widely available and DPD scanning was introduced.)

NYHA class is combined with clinical examination and biomarker measurement in the assessment of the heart failure patient. Although there are limitations, it is a universally accepted and understood scoring system and of great value in the assessment and follow-up of patients. It would be useful to ensure that at least one of the clinical experts is a heart failure specialist as the issues with NYHA measurement have been overestimated. NYHA classification has been used in the majority of international heart failure trials to date.

The ATTR-act Trial showed that it was the case that most patients stopped treatment before disease progression to NYHA 4. Care of the heart failure patient involves every stage of the disease from diagnosis to end stage deterioration and end of life care. Heart failure specialists are responsible for the palliative care needs of our patients so it is routine for us to stop medications that are not providing symptomatic benefit in the final stages of disease. As an ATTR-act investigator, and after discussions with the patient and their family elected to stop medication in the later stages of the disease. There is no proven benefit for Tafamidis in NYHA 4 so patient discussion would be uncomplicated, particularly as care focus changes to symptom control and away from simply extending duration of life in the later stages of heart failure management. Discontinuation of Tafamidis would be only one of the changes introduced to better support the patient and family at this time (including other discussions such as ICD deactivation, stopping or reducing renal function testing etc).

It is unclear if introducing tafamidis would reduce delays in diagnosis times. At technical engagement, the company highlighted that introducing tafamidis reduced delays to ATTR-CM diagnoses.

The positive results of the ATTR-act trial has led to much greater awareness of the condition among cardiologists, particularly because this trial was the only positive large trial in cardiology in 2018. An effective treatment means that clinicians would be obliged to investigate for the condition so that patients do not miss out of potentially life-prolonging therapy.

The subgroup analyses raise concerns about the clinical effectiveness of tafamidis but are not robust. The subgroup analyses raise concerns about the clinical effectiveness of tafamidis but are not robust.

A surprising weight has been put on subgroup analysis in this document and is not appropriate given the well recognised caveats particularly when the subgroups contain small numbers.
Please note that subgroup analysis of the Paradigm trial showed no significant effect in patients from Europe but Sacubitril Valsartan is a NICE and EMA approved therapy.

Hereditary ATTR-CM made up less than 25% of trial participants and this is the most important factor in the lack of subgroup significance. Both all-cause mortality and cardiovascular admissions were favoured by treatment with tafamidis despite lack of significance.

A stopping rule for tafamidis based on NYHA classification should not be included in the economic model. A stopping rule for tafamidis based on NYHA classification should not be included in the economic model.

"I disagree with this decision on two counts. 1. The evidence from the ATTR-CM trial shows that treatment was stopped in most patients before progression to NYHA IV.
2. ATTR-CM patients are under the long term care of heart failure specialist multi-disciplinary teams with extensive experience in management of the condition and heart failure end of life care. It is not routine practice to discontinue therapies that are not adding symptomatic benefit at this stage of the disease. As well as rationalising medications this also involves discussions with the patient and family for the deactivation of ICDs (Internal Cardiac Defibrillators) in the later stages of disease."

Because of the high levels of uncertainty an acceptable ICER is around £20,000 per QALY gained. Because of the high levels of uncertainty an acceptable ICER is around £20,000 per QALY gained.

The trial and extension trial evidence shows a clear benefit in both all cause mortality and hospital admissions from tafamidis. This is the only treatment option available for a condition with a very high morbidity and relentless progression to death with supportive care only. Like most other heart failure trials, benefit is non-significant when subgroup analysis of later disease stages is performed. Effectiveness should be judged on trial results of the pre-specified primary outcome measure rather than subgroup analysis, particularly when the trial numbers are small.

Name	[redacted]
Organisation	The Pumping Marvellous Foundation
Comments on the ACD:	
Has all of the relevant evidence been taken into account? It can't have been taken into account, it may have been read but not acted on. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* Read our comment	

Are the recommendations sound and a suitable basis for guidance to the NHS?
We fundamentally disagree with the NICE recommendations

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

"Tafamidis has a clear mortality benefit to the patient and reduces hospital readmissions as demonstrated by an RCT. These are the two current metrics which NICE bases its decision making on, e.g. NG106 Guidelines, STA TA388. Therefore I cannot understand why Tafamidis has not been recommended based on the evidence of benefit from these two measurements. As a patient group submission, I also have to say whether the committee has been fully furnished with the entirety of the dilemma pushing past the individual challenges of the condition which are extremely debilitating along with a poor prognosis which impacts not only the physical ability but also mental health.
We need to understand we have the opportunity to treat people with HFpEF with a prognostically beneficial treatment, where they have no other treatment. Based on the clinical evidence and expert commentary, there is no reason to not recommend Tafamidis for the treatment of wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults. It is essential to re-examine the impact of this decision to the point that the condition impacts a significant subpopulation of people with HFpEF. If this technology were made available across the NICE domain, it would ensure better outcomes for people who currently have no options. It is vital to have a centre of excellence for treatments however with the fragility of patients in this sub-set of HFpEF patients, reconsidering the recommendation to ensure market access to the broader NHS will provide uniform access to patients who need it. Also, a negative recommendation, based on what it seems is robust clinical evidence is a real ""kick in the teeth"" for people living with HFpEF and specifically those with the disease. We need to make HFpEF treatable, and this would have been a step in the right direction."

Name	[redacted]
Organisation	EAMS Cardiac Group
Comments on the ACD:	
Has all of the relevant evidence been taken into account? "On behalf of the NHS centres designated for assessment and treatment of patients with transthyretin (TTR) amyloidosis by the EAMS programme (herein referred to as the EAMS Cardiac Group), we write to express our disappointment and concern about the NICE decision not to approve tafamidis for the treatment of patients with TTR related cardiomyopathy. In our opinion, the clinical arguments against its use are flawed and we are of the opinion that patients with this hitherto untreatable disease will be disadvantaged by this decision. We provide a response to the NICE appraisal committee in which we specifically address what we believe to be incorrect interpretation of data and provide additional real World (confidential) data from a similar economy and demography–France–which demonstrate the feasibility of early diagnosis of ATTR cardiomyopathy and provide supportive evidence for the beneficial effect of the drug.	

Statements from members of the EAMS Cardiac Group:
As part of our response to the NICE committee's decision, we provide individual short statements from the clinical leads at the EAMS centres (see appendix 1).

EAMS Cardiac Group assert that additional evidence show the impact of tafamidis in patients with ATTR-CM. Our specific responses to the report are as follows:

Is the diagnosis of ATTR-CM difficult? :

Difficulty in diagnosing a condition is a problem which is routinely overcome by education, awareness and experience. Indeed, education is mandated as continuous professional development for medical practitioners.

The EAMS sites have been set up by clinicians with an interest in amyloidosis to improve local understanding and referral pathways for the condition. The large number of patients recruited into EAMS reflects improvement in diagnosis and understanding of ATTR amyloidosis. This is testament not only to the aspiration of cardiologists to learn more about the condition, but reflects the benefits of education delivered by the National Amyloidosis Centre and other experts.

Reference is made in the NICE appraisal committee report to the confusion of incidental amyloid deposits versus amyloidosis as a barrier to correct diagnosis. Autopsy data show that among adults more than 80 years of age, 25% have TTR amyloid deposits in the myocardium , but the relevance of this to patients presenting with heart failure or other clinical scenarios is highly questionable. More relevant, are data showing that among patients with heart failure and preserved ejection fraction (HFpEF), at least 5% have significant amyloid deposits that can be reasonably attributed to the observed phenotype. These data are consistent with studies using nuclear scintigraphy which demonstrate that 13% (95% CI 7.2-19.5%) of patients hospitalized with HFpEF have ATTRwt cardiomyopathy.

Historically, AL cardiac amyloidosis has been misdiagnosed and the diagnosis delayed with significant consequences for patients. In a survey of more than 500 patients with AL amyloidosis (37% of whom had cardiac involvement) the average time from initial symptoms to diagnosis was 2 years. A substantial proportion of patients (31.8%) reported seeing a minimum of 5 physicians before receiving a diagnosis of amyloidosis. Cardiologists were consulted more often than haematologists, oncologists and nephrologists, but were responsible for making the diagnosis in only 18.7% of cases.

Data for TTR-CA differ considerably in that almost half of patients are diagnosed within 6 months, mainly by cardiologists.4 The experience from individual EAMS centres indicates that delay to diagnosis has substantially shortened. A major contributor to reduced time to diagnosis is the use of bone scintigraphy for non-invasive diagnosis of cardiac amyloidosis. This practice is based on an algorithm developed and promulgated by the UK National Amyloidosis Centre.

If ATTR-CM is suspected, blood and urine should be analysed for evidence of a plasma cell dyscrasia and imaging with bone tracer considered if ATTR-CM is likely. If these tests are negative, then the evidence suggests that CA is very unlikely.5 Cardiac Magnetic Resonance Imaging (CMRI) may be used prior to nuclear scintigraphy and may be a prompt to the diagnosis of cardiac amyloidosis, but a 10-20% false negative and false-positive rate (possibly more so in people of

Afro-Caribbean ancestry) for conventional contrast enhanced scans means that it does not substitute for other tests.

Until very recently, a tissue diagnosis was considered essential in all cases of suspected cardiac amyloidosis, but there is now consensus that in the setting of a positive 99mTc-phosphate scan without evidence for plasma clone on blood and urine testing, a diagnosis of ATTR-CA can be made without a biopsy. For patients with evidence for a plasma cell dyscrasia, a histological diagnosis is still required.

National promotion of the diagnostic algorithm developed by the UK National Amyloidosis Centre has been paralleled by increasing numbers of referrals (figure 1). Data supplied courtesy of Dr T. Damy summarising the experience of the French National Amyloidosis Centre show a similar trend (figure 2). Almost 100% of ATTR-CM patients in France are diagnosed with bone scintigraphy.

Figure 1 (see full report)

Figure 2 (CONFIDENTIAL)-see full report

Data on the number of French centres, and specifically cardiologists, who are prescribing tafamidis to patients with a definite diagnosis of ATTR-CM are shown in figure 3. This number has also increased substantially in France.

Figure 3: (CONFIDENTIAL)-see full report

Keypoint 1: Times to diagnosis of ATTR-CM have reduced substantially and most diagnoses are (or can be) made by cardiologists using locally available tests.

Are the results from the double blind randomised clinical trial, ATTRACT, inconsistent with respect to different types and stages of ATTR-CM?

We believe there is a conflation of several issues relating to NYHA functional class which distract from the primary evidence that tafamidis reduces death and hospitalisation in patients with ATTR-CM; namely, (1) the use of NYHA class to select patients for the trial; (2) the value of NYHA class as a measure of tafamidis efficacy; and (3) the validity of NYHA class as a prognostic marker in cardiac amyloidosis. We believe that (1) is the only relevant issue to this application.

(1) Selection of patients for ATTR-ACT trial

It is acknowledged that the NYHA classification was originally designed as a clinical and not a research tool and that much has been written regarding its limitations with respect to its variability and reproducibility. Nevertheless, investigators continue to use it in clinical research because of its simplicity and because any system that might replace it needs to be more accurate without being more complex.

NYHA functional class remains the most commonly used method for stratification of patients in heart failure trials . Consequently, it has informed previous decisions by NICE (and other regulators) in the approval of drugs and devices and is part of current NICE guidance on the selection of patients for therapy . It is also a primary determinant for the need for cardiac transplantation and ventricular assist devices.

The NICE appraisal committee recognised that patients with ATTR CM who were selected on the basis of NYHA functional class (I-III) had a significant reduction in

death and hospitalisation. The decision to disregard this finding because of a debatable analysis of subgroups in the trial is to our mind mistaken for the following reasons:

- Although prespecified, the subgroup analysis for NYHA class is underpowered and therefore statistically unreliable.

- The data from ATTR-ACT show that across NYHA classes (I or II vs. III) the difference in all-cause mortality and frequency of cardiovascular-related hospitalizations favoured tafamidis over placebo, except in patients in NYHA class III at baseline among whom the rates of cardiovascular-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo. However, the trends towards improvement in mortality are the same across all three NYHA functional classes. Data are provided by Pfizer that show the p value for mortality is <0.05 for NYHA 1 and 2 but not for 3, again probably reflecting small numbers.

The explanation for the increased hospitalization in NYHA class 3 patients is entirely speculative and to dismiss the trial on the basis of a single statistic in a subgroup analysis is unacceptable. To disregard the very clear results of the trial on such dubious statistical arguments exposes the majority of patients to a risk of death and poor quality of life.

- Further support for the effect of tafamidis is seen in data from the French Amyloidosis Centre (figure 3). Tafamidis has been approved for the treatment of ATTRv with neuropathy since 2012 in France, meaning that ATTRv patients with cardiac involvement can only be treated if they present with mixed cardiac and neurological impairment. For 631 patients with ATTR-CM, median survival time increased with tafamidis treatment (N=98): 1565 (1010-2400) days vs. 771 (686-895) days without treatment (log-rank p<0.001) (figure 4). The beneficial effect persisted after correcting for age at inclusion, NT-proBNP and amyloidosis type.

Figure 4 (CONFIDENTIAL)-see full report

(2) Improvement in NYHA class as a measure of tafamidis efficacy:

NYHA class was not a prespecified primary or secondary end-point (as stated in the report). Indeed, the goal of therapy, based on the known mechanism of action of tafamidis, is to stabilise and prevent deterioration in functional status rather than improve it. Evidence that tafamidis has this effect comes from the demonstration of a slower decline in six minute walk time and the KCCQ score in the ATTR-ACT trial.

(3) NYHA class as a measure of prognosis in ATTR-CM:
The EAMS Cardiac Group believe that the NICE appraisal committee's assertion that NYHA class is unreliable predictor of prognosis is mistaken. There are data showing that NYHA class predicts prognosis in untreated patients; for example, in a study of biopsy proven ATTR-CM from the National Amyloidosis Centre, median survival for each class was: class I, 4.58 years; class II, 4.06 years; class III, 2.08 years; and class IV, 1.31 years; log-rank test for trend P<0.001). This relationship remained significant in a Cox proportional hazards multivariable analysis. Data from the French Amyloidosis centre corroborate this finding (figure 5):

Figure 5 (CONFIDENTIAL)- -see full report

Keypoints 2:

(a) The ATTRACT trial shows that when selected on the basis of an NYHA functional class 1-3, patients that receive tafamidis have a statistically significant reduction in the combined end-point of death and hospitalisation.

(b) Observational data from the French Amyloidosis Centre corroborate the ATTR-ACT trial's main finding with respect to mortality in patients classified as class 1-3 at baseline.

(c) Subgroup analysis based on NYHA class in the ATTR-ACT trial is unreliable and thus should be a secondary consideration in the decision to license tafamidis for clinical use.

Wild type versus variant TTR:

In ATTR-ACT, the difference in all-cause mortality and frequency of cardiovascular-
related hospitalisations favoured tafamidis over placebo for both ATTRv and ATTRwt related cardiomyopathy. In the subgroup analysis, the combined endpoint was significant ($p<0.05$) for ATTRwt.

Additional data from Pfizer are partially redacted in the publicly available report, but are reported as follows:
When analysed separately, differences in all-cause mortality and CV-related hospitalisation favoured tafamidis over placebo in all subgroups by TTR genotype. The hazards ratios from the all-cause mortality Cox-proportional hazard model for variant and wild-type TTR genotype participants in the pooled tafamidis group were 0.690 (95% CI 0.408, 1.167) and 0.706 (95% CI 0.474, 1.052), respectively (p=xxxxxx and xxxxxx, respectively).

The argument against the emphasis on subgroups is the same as for NYHA class. In addition, there were fewer patients with the variant type enrolled in ATTR-ACT (335 patients with ATTRwt (201 tafamidis, 134 placebo) and 106 with ATTRv (63 tafamidis, 43 placebo) enrolled in ATTR-ACT. Moreover, patients with ATTRwt (vs. ATTRv) had less advanced disease at baseline and a lower rate of disease progression over the study.

Keypoints 3:
Given that the hazard ratios show a similar absolute reduction for the combined end-point, the findings of the ATTR-ACT are consistent with a beneficial effect of tafamidis in both major subtypes of ATTR-cardiomyopathy.

Appendix 1
individual statements from EAMS site lead clinicians

[redacted], Consultant Cardiologist
Queen Elizabeth University Hospital Glasgow

In Scotland, like other centres, we have growing awareness and experience in the non-invasive diagnosis and subsequent management of amyloid cardiomyopathy. Due to our geography and their symptom burden, some patients struggle to physically attend NAC for assessment and follow-up. Although we still await the SMC decision on tafamdis, the NICE appraisal is disappointing. The NYHA

classification is used to guide many treatment recommendations in heart failure. The early improvement in quality of life and walking distance reported in the ARRT-ACT study reflects my own experience using tafamidis through the EAMS scheme.

[redacted], Consultant Cardiologist
St Georges Hospital

Since my appointment as a consultant for Heart Failure in London I have treated over 100 Afro-Caribbean patients with ATTR cardiomyopathy. The condition carries the most dire prognosis of all the heart failure aetiologies, is unresponsive to standard heart failure therapies and progresses to death within 28 months. The condition is also little known about and underdiagnosed - in fact 25% of all V122I ATTRs in the UK have been detected at our unit, indicating significant under-detection elsewhere. The introduction of the first available therapy for this condition offers not only improved outlook in terms of life expectancy and hospital admission but as importantly will act to raise awareness of this overlooked and misdiagnosed condition.
Although other treatments are in development , life expectancy is so short that the current patients under my care will not survive to see the outcomes of any ongoing trials translated into clinically available therapies. A positive outcome from the NICE appraisal process would enable us to delay disease progression in these patients so that they may in the future benefit from other therapies in development.

[redacted], Consultant Cardiologist
Queen Elizabeth Hospital Birmingham – University Hospitals Birmingham

Having established regular clinical services, with multidisciplinary input and communication with external centres, backed by the knowledge that we could provide a potentially life-modifying treatment, this is extremely disappointing. There is not only a large Afro-Caribbean population in Birmingham but a large cohort of native origin Irish, both with a significant rate of cardiac infiltration. There are plenty of patients but having looked after several with cardiac amyloid over the years and observed their decline with little to offer but supportive care, to return the service to that will be frustrating.

[redacted], Consultant Cardiologist
St Thomas' Hospital

We have access to DPD, CMR and genetics on site and have successfully used tafamidis through EAMS and found it to be very well tolerated indeed. Since EAMS ended, we have identified several patients who would benefit from treatment. The only thing more frustrating than having no treatment for a condition is having a drug available but not being able to prescribe it. This will be generating a lot of anxiety for patients who know they have a progressive but now treatable condition for which they cannot access treatment. The COVID19 outbreak and the impact on the health system has only added to this. Locally we have a very large Afrocarribean population and so possibly have a higher than average prevalence of ATTR amyloid. Having access to effective treatment will help contribute to local efforts to try and address health inequalities.

[redacted], Consultant Cardiologist
Leeds General Infirmary

In Leeds the development of medical therapy for ATTR has driven the development of local expertise and we now have a number of interested cardiologists, in addition to access to a full MDT where required. A knock on effect of treatment being available for this condition has been the delivery of enhanced local care for those with other forms of cardiac amyloidosis and a more cohesive working environment with our haematology, pathology, neurology and renal colleagues to manage this multisystem disease. We also have also become the local referral centre for patients with suspected cardiac amyloidosis, an area we expect to be expanding. We have a number of patients who have accessed Tafamidis via the EAMS scheme. We also have easy access to DPD scans and have not found the diagnosis particularly challenging to make.

[redacted], Consultant Cardiologist
Castle Hill Hospital – Hull and East Yorkshire Hospitals

Hull University Teaching Hospitals NHS Trust provide tertiary cardiology services to the population of Hull, the East Riding of Yorkshire and North and East Lincolnshire. The institution ready access to DPD scans and a group of interested clinicians who actively seek out the diagnosis of ATTR. We have performed 159 DPD scans in the last 3 years, making the diagnosis of ATTR in 52 patients. We have become the local referral centre for the diagnosis and management patients with potential ATTR. We have started treatment with tafamidis in patients with a confirmed diagnosis with NYHA class II and II symptoms through EAMS. Far from finding ATTR to be a complex condition, difficult to diagnose, we have found the diagnosis straightforward to make, and we were greatly anticipating being able to treat patients more widely.

[redacted], Consultant Cardiologist
Southampton General Hospital

I joined the EAMS with only 2 weeks left to run. I was able to start 5 patients on tafamadis in that time and my patients have all enjoyed taking it. We have this week gained the license for DPD scanning at UHS and I am sure that Southampton will be the local/regional referral centre for amyloid. It is most frustrating for me and for my patients to know that there is a treatment available with good evidence of efficacy and safety and be unable to offer it.

[redacted], Consultant Cardiologist
St Thomas' Hospital

We have diagnosed 60 patients across SE London and are very happy with making the diagnosis and also understand NYHA class reasonably well.

[redacted] Consultant Cardiologist
Royal Stoke University Hospital

The historic understanding of wttr amyloidosis is usually from the perspective of quaternary national centres – whereas the majority of wttr is as yet undiagnosed in our local hospitals. Predictive models of prevalence, presentation and progression of wttr based on quaternary experience are therefore likely to be inaccurate. This

is a condition likely to affect far more people than are either likely to travel to or can be accommodated by the National Amyloid centre.

All of the work and impetus in promoting awareness of amyloidosis and pathways to diagnose and treat people with amyloid cardiomyopathy sooner will be lost if treatments are denied to this vulnerable and often elderly group.

As with many other centres we had prepared multi-disciplinary pathways for people with suspected cardiac or neurological amyloidosis to be fast tracked to cardiac services.
We have set up multiple education and engagement sessions for clinicians to familiarise themselves with the multi-faceted presentations of amyloidosis and AL and ttr in particular. This is on the background of multiple review and best practice articles about the diagnosis and management of cardiac amyloidosis in all major cardiovascular journals within the last year.
We have set up close links with our nuclear medicine department and are using DPD SPECT as recommended by the NAC. We have set up e mail MDTs with Prof Gilmore with regards to suitable patients for Tafamidis.

All of our progress to date to ensure we:
- diagnose amyloid cardiomyopathy in a much quicker time frame than normal,
- provide local multi-disciplinary pathways to support our patients
- offer treatment locally without hundreds of miles of travel for vulnerable, elderly patients with multiple co-morbidities

will be wasted.
Our opportunities are not just for Tafamidis but for the multiple potential treatments in the pipeline and the greater multi-centre opportunities for our patients to be involved in future trials.

[redacted], Consultant Cardiologist
St Bartholomew Hospital

St. Bartholomew's Hospital is a national referral centre for heart muscle disease with an annual new patient caseload of > 2000 patients. Over the past decade, we have established diagnostic pathways for patients with suspected cardiac amyloidosis based on cardiac imaging with echocardiography, cardiac magnetic resonance imaging, DPD scintigraphy and cardiac biopsy. Between 2015 and 2019, 591 DPD scans were performed; 22% were positive. Pre 2018, the time from presentation to diagnosis was 16.1 months; from 2018 onwards, it was 4.7 months. With our participation in EAMS, we created a dedicated TTR clinic funded by the Trust and staffed by volunteers. 21 patients were reviewed, 11 patients were started on tafamidis; 38 patients with positive DPD scans are awaiting review. The decision by the NICE appraisal committee not to approve tafamidis puts clinicians and patients in an invidious position. We have the tools to make a rapid diagnosis and have offered treatment to a cohort of patients. Now we face the task of informing patients waiting for assessment that treatment is no longer available in the UK and that they are condemned to rapid deterioration and death.

[redacted], Consultant Cardiologist
University Hospitals of Leicester

University Hospitals of Leicester (UHL) provides specialist cardiology service to the population of Leicestershire. We also have close links with a number of other trusts in the East Midlands. UHL has a well-established heart failure team which has anticipated treating the aTTR amyloid patient in a number of ways:

- Regular specialist MDT – including close liaison with the haematology and imaging departments. This is overseen by the Amyloid MDT co-ordinator.
- A 2 week wait for cardiac MRI for suspected amyloid patients
- A cardiac biopsy service
- A rapid access specialist heart failure service (72hr wait)
- Close liaison with NAC, particularly as regards genetic testing, although we also have a local genetic service
- DPD scan capability – almost ready to start locally
- Early engagement with EAMS programme. Stakeholder meeting in September 2019 with all relevant specialities to consider future expansion of service.
- To date, over 40 patients have been discussed at the MDT and subsequently 3 patients considered appropriate on clinical grounds to fit criteria for treatment and now established on Tafamidis without ill effects.

In short, despite the relatively short timescale, we have demonstrated that we understand the complexities of a setting up a service to treat a complex multisystem disease that requires the input of several specialities. Furthermore, a cursory inspection of our data suggests that we have been careful in selecting the "right" patient that would be more likely to benefit from treatment.

The process of setting up such a service has taken months of hard work and we are now at the threshold of being able to offer a fully functioning and capable service for the patients of Leicestershire and the wider East Midlands. Patients with a previously terminal disease have had the hope of effective treatment abruptly put on hold. Whilst the issue of cost vs benefit has to be addressed, we do not believe that the current NICE position is appropriate and will lead to more inequality, longer waits for diagnosis and outcomes and ultimately, poorer patient outcomes.

[redacted]
Consultant Cardiologist,
[redacted] University Hospitals Coventry & Warwickshire NHS Trust
Honorary Professor of Cardiology
Warwick Medical School & Coventry University

Cardiovascular Lead West Midlands NIHR Clinical Research Network Chair, Midlands Heart Failure Group In my capacity as Chair of the Midlands Heart Failure Group, I would like to support the bid to
facilitate the use of Tafamidis in patients with Transthyretin Amyloidosis with cardiomyopathy
(ATTR-CM). The outcome of NICE'S appraisal consultation to not recommend Tafamidis for ATTR-CM is disappointing and I feel that this decision should be reconsidered after a second look at the evidence of the benefits of the drug in this population that has had no treatment options prior to the arrival of the drug. I will be hoping for a favourable outcome from the NICE Appraisal Committee."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We accept that cost efficacy is an important consideration, but argue that decisions on therapy in patients with advanced disease are common to many conditions where the same considerations apply. Reference if made to “a commercial arrangement, which would have applied if the technology had been recommended”. This seems a critical consideration in establishing the cost efficacy.

Are the recommendations sound and a suitable basis for guidance to the NHS?
"No.

1. We refute the notion that accurate diagnosis of ATTR-CM is challenging and that it should necessarily take a long time.

2. We believe the recommendations are contradictory. They acknowledge the primacy of data derived from The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) but then dismisse the result on the basis of an unsupportable interpretation of sub-studies. We assert that the results of ATTR-ACT and the additional data presented by Pfizer are internally consistent and in line with additional confidential data obtained from France in support of this application.

3. We accept that measures used to determine disease severity in patients with heart failure (the most appropriate analogy for this application) are imperfect, but they are validated in trials and underpin NICE guidance for other interventions. We provide additional data to show that they predict outcomes in ATTR Cardiomyopathy. Again, we assert that the primary outcome of ATTR-ACT trial supports use of tafamidis in all but the most severely affected patients who were excluded from the trial."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"The EAMS network believe that the NICE Appraisal Committee’s decision and its justification is discriminatory to the following groups:

- *Elderly patients –the population at risk–will be denied a treatment that, if started early enough, maintains a state of healthy aging in a condition that otherwise progresses rapidly with considerable morbidity if managed conventionally.*
- *The fact that patients enrolled in EAMS will continue to receive therapy means that there will be two disease populations; one with receiving a life-saving therapy and the other not. This poses an unacceptable ethical dilemma for clinical teams who diagnose and manage patients with ATTR.*

- *Afro-Caribbean and Celtic patients who are at greater risk of developing ATTR will be denied a therapy that has the potential to improve lifespan.*

- *Patients with heart failure with preserved ejection fraction. The incentive created by the positive clinical trial and the EAMS programme to identify*

patients with heart failure with preserved ejection fraction amyloidosis will be lost, to the detriment of many patients."

Name	[redacted]
Organisation	British Nuclear Cardiology Society
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
"BNCS would suggest not.

The promotion of DPD scintigraphy in the UK facilitates the provision of this non-invasive diagnostic test for ATTR-CM, using existing and widely available scanning infrastructure. As was acknowledged in the initial consultation, it is also our experience that DPD imaging provides a very sensitive tool for the early detection of ATTR-CM, maximising the impact of the proposed novel treatment. We note that a major objection to the approval of tafamidis was that: The committee concluded that accurately diagnosing ATTR-CM is challenging, and can take a long time.

This statement is based on historic experience at the National Amyloidosis Centre, summing activity over time (Lane et al. 2019). This prospective analysis of >1000 ATTR-CM also found that the patient made a median of 17 hospital visits and there was a lag of 3 years before diagnosis. Yet the same paper demonstrated a huge increase in the diagnosis of ATTR in the mid 2010s as awareness and use of DPD increased.

Gilmore et al presenting data in 2015 in the Orphanet of rare disease revealed 47% patients are NYHA Class II and 22% NYHA class III at diagnosis and results for 6MWD reduced by an average of 89m at 18 months.
Figure taken from 'Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis' Circulation. Lane et al. 2019;140:16–26.

In response to the NICE appraisal document, we have undertaken a survey (mid June 2020) of our membership. We believe the results provide current evidence that needs to be taken into account in this consultation. We can report that:

- 24 centres undertaking nuclear cardiology procedures responded.
- 87.5% of the centres are already performing DPD scans for TTR amyloid.
- 7 of the 24 centres had not undertaken any cardiac DPD scans before 2018, confirming recently increased local understanding and interest from referring clinicians.
- A mean of 37% of the DPD scans are grade 2 or 3 on the Perugini scale (positive for ATTR amyloid), suggesting that clinicians are actively considering and detecting a diagnosis of ATTR amyloid.
- The mean wait for a DPD scan is only 2.6 weeks.

We have also consulted with Curium Pharma UK Ltd who distribute DPD radiotracer kits in the UK. Up to 15 patients can be scanned with each kit. They confirm that there has been a significant increase in DPD sales in the UK in the last few years. In 2018 they supplied 15 NHS Trusts with 85 kits, in 2019 25 NHS Trusts were supplied with 145 kits. Again, this confirms an increasing number of centres and numbers of patients undergoing DPD scans looking for ATTR cardiac amyloidosis."

Are the recommendations sound and a suitable basis for guidance to the NHS?
To request further study of clinical efficiency on patients who are earlier in their disease trajectory would seem the logical next step. Use of DPD to improve the time to diagnosis is a key element of this which is the reason the BNCS wish to respond.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The condition has an increased prevalence in the elderly, Irish and Afro-Carribbean populations due consideration and efforts to ensure the recommendation does not result in unintended widening of health inequalities should be made.

Please see the letter from the British Nuclear Cardiology Society. We respectively question the decision not to recommend the use of tafamadis.

The company's early diagnosis assumptions are not appropriate for decision making

Given the average number of hospital attendances prior to diagnosis are 17 and £3,796 is the typical cost per hospital admission episode for heart failure how is the figure of £20,000 calculated?

Name	[redacted]
Organisation	Welsh Cardiovascular Society
Comments on the ACD:	

"On behalf of the heart failure working group of the Welsh Cardiovascular Society we wish to express our disappointment and concern over the NICE decision not to approve the use of Tafamidis for our patients with TTR-related cardiac amyloid diseases (TTR-CA). In particular we disagree with NICE's views that diagnostic pathways to reach a diagnosis of TTR-CA and clinical staging of disease severity and response to treatment are sufficiently problematic to dilute the cost effectiveness of this (and currently only) life-extending treatment.

Since the publication of bone scintigraphy techniques to facilitate swifter diagnosis of TTR-CA (2016) and a randomised clinical trial demonstrating the first effective treatment for TTR-CA (2018), interest in this condition has increased within our community. The HF working group of the Welsh Cardiovascular Society has developed a referral pathway involving multi-disciplinary meetings with the National Amyloid Centre for patients with suspected TTR-CA and the all-Wales HF Forum meeting (Dec 2019) focused specifically on the education and training in cardiac amyloid with guest lectures from the National Amyloid Centre.

The two tertiary cardiac centres in Wales at Cardiff and Swansea, as well as some larger District General Hospitals have an appropriate set up for investigation, treatment and management of patients with suspected amyloidosis with advice provided by the National Amyloid Centre when appropriate. Both tertiary centres have entered patients into the EAMS scheme for Tafamidis and there are at least

10 additional patients in Wales who have been fully worked up and are awaiting treatment with Tafamidis once approved.

Clinical comments
Sec 3.3 – Accurate diagnosis of ATTR-CM is actually relatively straightforward and does not require referral to the National Amyloid Centre in the vast majority of cases. Awareness of the condition is increasing, and now that there's an effective treatment clinicians have started looking for it more readily. There should not be any delays in diagnosis. DPD bone scans, echocardiography, MRI, and blood/urine tests to exclude light chain disease are widely available throughout Wales.
Sec 3.5 The NYHA functional classification is a measure of subjective symptoms and does not always correlate to severity of disease – some people have relatively mild disease and severe symptoms and the converse is also true. This is however one of the best functional measures of disease severity and is widely used in clinical trials as an outcome measure and by NICE in its guidance on HF treatments; e.g. biventricular pacemakers, defibrillators, and neuro-hormonal medical therapies.
3.10 The ATTR-ACT study looked at the combined group of hereditary and wild type ATTR-CM and not at the subgroups. It was not set up or powered to look at statistical significance in the subgroups and comments on statistical significance of subgroups are not appropriate.

We would be most grateful if the NICE committee could reconsider their decision not to approve Tafamidis for the treatment of TTR-CM.

Submitted on behalf of the Heart failure working group of the Welsh Cardiovascular Society.

[redacted] ([redacted]: HF working group of the WCGS)
[redacted]: (HF working group of the WCVS; SE Wales)
[redacted]: (HF working group of the WCVS; SW Wales)
[redacted]: (HF working group of the WCVS; North Wales)
[redacted]: (Wales Cardiac Network)
[redacted]: ([redacted]: WCVS)"

Name	[redacted]
Organisation	Genetic Alliance UK
Comments on the ACD	

Comment on "Because of the high levels of uncertainty an acceptable ICER is around £20,000 per QALY gained"

If Single Technology Appraisals are to be an effective form of cost benefit decision-making for rare disease medicines, we believe section 6.3.3 of the guide to the methods of technology appraisal will need to be interpreted differently from the approach taken here. Treatments for rare conditions arrive at the HTA stage of their access pathway with a relatively high degree uncertainty in comparison with treatments for common conditions. This is for two major reasons. The first is that the populations are small, which makes statistical analysis more challenging with less significant results. The second is that the high degree of unmet need for treatment for rare conditions is taken as a basis for the European Medicines Agency (and other regulators) to accelerate their decision-making process. This means there is less scope for the generation of long and medium term evidence (though evidently the amount generated is sufficient for a risk benefit decision).

The two circumstances described are usual for rare disease treatments. Almost all would be affected by one or both of these challenges. The uncertainty discussed in this consultation document does not appear to be unusual in the context of a treatment for a rare disease.

We are therefore concerned that without a different approach to interpreting section 6.3.3 of the guide, rare disease treatments will be appraised against a lower bar for cost per QALY gained against other treatments. This will lead to discrimination against those affected by rare conditions.

The uncertainty here does not appear to be unusual for a treatment for a rare condition. On that basis, we believe the committee should exercise a degree of flexibility to allow for the fact this is a treatment for a rare condition.

Tafamidis for treating transthyretin amyloid cardiomyopathy: A Single Technology Appraisal

Addendum: ERG comments on company's response to the ACD

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Kate Ennis, Research Associate in Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	6th August 2020

Introduction

In May 2020, NICE issued its Appraisal Consultation Document (ACD) on the use of tafamidis for the treatment of transthyretin amyloidosis with cardiomyopathy (ATTR-CM).[1] The ACD makes the following recommendation:

"Tafamidis is not recommended, within its marketing authorisation, for treating wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults" (NICE ACD,[1] page 2)

The ACD[1] states that the evidence from the ATTR-ACT trial[2] demonstrates that tafamidis reduces deaths and hospitalisation compared to placebo. However, the ACD highlights a number of issues relating to the evidence supporting its use on the NHS, including: inconsistent clinical results for different types and stages of ATTR-CM; limitations in the measure of the disease severity (NYHA) and difficulties in identifying who benefits from treatment and who should stop treatment; uncertainty surrounding assumptions of early diagnosis; uncertainty surrounding treatment effects following discontinuation, and uncertain cost-effectiveness estimates which are higher than what NICE normally considers to reflect an acceptable use of NHS resources.

This addendum presents the ERG's comments on the company's response to the ACD.[3] For the sake of brevity, the company's comments are not reproduced in full; hence, this addendum should be read in conjunction with the company's ACD response. It should also be noted that the company's ACD comments do not include any new data, analyses or pricing proposals; as such, the ERG's responses focus on only matters of misunderstanding, clarification and factual inaccuracy.

Table 1: ERG comments on company's ACD response

Issue	Company's issue (headline points)	ERG response
1.Accuracy and speed of diagnosis	The committee concluded that *"Accurately diagnosing ATTR-CM is challenging and can take a long time."* (Section 1; Page 3) and "*Without validated and objective measures for assessing ATTR-CM, identifying people who need treatment and those who are benefiting from treatment will continue to be a challenge"* (Section 3.27; Page 25). The company suggests that these conclusions are not supported by the evidence.	The ERG believes that the statements made in the ACD[1] are generally reasonable. The expert statement from the National Amyloid Centre (NAC)[4] draws a distinction between patients who have ATTR-CM with heart failure (HF) and previous hospitalisation for HF who might benefit from treatment with tafamidis (i.e. reflecting the trial population in ATTR-ACT[2]), and a larger group of patients with incidental cardiac amyloid deposits which are of no clinical significance. Whilst the ERG agrees that for a patient in whom ATTR-CM is suspected, the current diagnostic pathway may achieve a diagnosis quickly, this is not the case for many patients who instead suffer significant delays before reaching a diagnosis of ATTR-CM.[5] The company's economic analyses, which postulate that a future positive NICE recommendation for tafamidis will lead to additional benefits due to earlier diagnosis, are hinged on this argument. The ERG notes that the company's ACD response[3] contests the NAC's view that amyloid deposits are often incidental findings on DPD scans (see Issue 6); the ERG considers this to be a matter for the company to take up with the NAC directly. The lack of *"validated and objective measures for assessing ATTR-CM"* mentioned in Section 3.27 of the ACD is referring to the use of the New York Heart Association (NYHA) classification system rather than the NAC diagnostic algorithm (as suggested by the arguments made in the company's ACD response[3]). The problems associated with the NYHA classification system are described in Section 5.3.3 of the ERG report;[6] these are not repeated here.
2.Treatment benefits across subgroups defined by NYHA classification and genotype	The ACD contains the following statements which highlight uncertainty around the effectiveness of tafamidis in subgroups of the ATTR-ACT study. The conclusions of the committee within themselves are not consistent and are also not consistent with the observed results in either the subgroups or the overall trial population.	The ERG agrees with the company that, taken together, some of the statements in the ACD[1] appear to be inconsistent. Overall, the ATTR-ACT trial[2] found that tafamidis significantly reduced all-cause mortality and cardiovascular (CV)-related hospitalisations and reduced the decline in functional capacity and quality of life compared with placebo. This general statement is reflected in the ACD (page 3 and Section 3.9, page 12). The ERG considers this statement to be appropriate. The ERG considers the statements in the ACD about uncertainty regarding the effectiveness of tafamidis in certain subgroups to also be appropriate (ACD Sections 3.10 and 3.23). The ERG believes it is reasonable to be uncertain regarding the benefits of

Issue	Company's issue (headline points)	ERG response
		tafamidis in patients with NYHA baseline class III and in patients with hATTR on the basis of the subgroup analyses presented in the CS.[7] However, as noted in the ERG report[6] (Section 4.5.1), the subgroups were not powered to assess effect of each subgroup on the study endpoints and, therefore, all analyses undertaken were exploratory and did not control for Type 1 errors. The statements in the ACD relating to whether there are additional benefits in treating patients in NYHA I/II may be inconsistent with the committee's concerns regarding the results for the NYHA III subgroup. As noted in the company's ACD response,[3] the Summary of Product Characteristics (SmPC) for tafamidis[8] recommends starting treatment *"as early as possible in the disease course when the clinical benefit on disease progression could be more evident."* The ERG believes that the experts' statements relating to reservations about treating patients with NYHA I and no functional limitations may relate to the distinction raised by the NAC[4] between the population of the ATTR-ACT trial (patients with ATTR-CM with HF and prior hospitalisation) and patients with incidental cardiac amyloid deposits. As discussed in the ERG's response to Issue 1, this matter should be taken up by the company and the NAC directly.
3. NYHA classification and stopping rule	The committee has concluded that the NYHA classification system has limitations, therefore, those that benefit most cannot be accurately identified and a stopping rule based on NYHA classification is not appropriate. The company disagrees with this conclusion. NYHA classification is suitable to define a stopping rule because it is widely used in clinical practice, has been extensively validated and has been used in previous NICE recommendations. Furthermore, data from ATTR-ACT supports the use of the stopping rule and the EMA guidance is supportive, to	The company's ACD response[3] highlights that in ATTR-ACT,[2] patients reaching NYHA IV discontinued rapidly, and that this suggests that a stopping rule is feasible in practice. The ERG believes that defining a stopping rule solely on the basis of NYHA may be problematic for several reasons: • The problems associated with the NYHA classification system (e.g. reproducibility and subjective assessments, see ERG report,[6] Section 5.3.3) • Patients may reach NYHA IV and subsequently improve, as observed in both groups in ATTR-ACT. It is unclear whether these patients would be considered eligible for re-treatment with tafamidis. • The marketing authorisation for tafamidis[8] does not require patients to discontinue treatment upon reaching NYHA IV. • Clinicians and patients may be reluctant to withdraw treatment if they perceive that the patient is benefitting it, particularly given that no other effective treatment options exist. Some of the ACD respondents suggest that this would be a problem, whilst others suggest that it would not.

Issue	Company's issue (headline points)	ERG response
	some extent, of a stopping rule in NYHA IV.	The ERG notes that the NYHA IV stopping rule is already included in the ERG's, the NICE Technical Team's and the company's preferred analyses.[6, 7, 9, 10] Removing the NYHA IV stopping rule increases the ICER for tafamidis.
4. NYHA classification as a measure of clinical effectiveness	We are concerned by the following statement which does not reflect the evidence submitted by the company: "*The committee noted the high level of uncertainty, specifically: measuring the clinical effectiveness of tafamidis using the NYHA classification system (Section 3.23; Page 22)"*	The ERG disagrees with the company's ACD response.[3] This section of the ACD[1] is referring to uncertainty around the ICER for tafamidis. The company's economic model captures the clinical benefit of tafamidis through its predicted impacts on NYHA classification, CV-related hospitalisations and mortality. Therefore, the statement in the ACD is not factually incorrect.
5. Differentiating amyloid deposits from amyloidosis	The following statement in the ACD is misleading as it is not aligned with clinical practice: "*The clinical experts……noted that transthyretin amyloid deposits are often an incidental finding in people having DPD scans. They explained that the population they see in practice had a range of amyloid deposits, sometimes because of older age, for example. Also, there is no defined point at which amyloid deposits become amyloidosis. So, it is unclear why some amyloid deposits progress to amyloidosis and others do not. Also, because other common comorbidities can lead to increased breathlessness and decreased mobility, a definitive ATTR-CM diagnosis is challenging." (Section 3.3; Page 6)*	The ERG believes that the ACD[1] reflects the view expressed by the clinical experts during the Appraisal Committee meeting, which is reiterated in the NAC's response to the ACD.[4] This is a matter for the company to take up with the NAC directly.
6. Treatment benefits in NYHA I	The ACD states: "*The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as*	The ERG agrees with the company that the ACD comment appears to contradict the SmPC,[8] which states that treatment with tafamidis should be started as early as possible. Again, the ERG refers to the response to the ACD from the NAC[4] regarding the distinction between patients who have ATTR-CM with HF and prior hospitalisation who

Issue	Company's issue (headline points)	ERG response
	NYHA 1 because they have no functional limitations and might not benefit from treatment" (Section 3.6; Page 9). This statement is directly contradicting the conclusion from the EMA and is not aligned with published data from ATTR-ACT.	might benefit from treatment with tafamidis (i.e. reflecting the trial population in ATTR-ACT[2]), and a patients with incidental cardiac amyloid deposits which are of no clinical significance.
7. The impact of tafamidis on early diagnosis	The ERG and subsequently the committee concluded that diagnosis times are unlikely to change if tafamidis were approved: "*The ERG highlighted that the trend of earlier diagnosis seen during the EAMS period could be explained by improvements in diagnostic tools since the ATTR-ACT trial (see section 3.3). Also, it noted that awareness of ATTR-CM had increased after patisiran and inotersen were introduced (see section 3.4). So, diagnosis times are unlikely to substantially change if tafamidis was to be recommended by NICE" (Page 10).* The company are concerned that this is not a reasonable conclusion, given past trends, current licensed treatments and the evidence submitted by the company from the EAMS programme.	The ERG did not conclude that diagnosis times are unlikely to change if tafamidis receives a positive recommendation from NICE. The ERG's technical engagement response[9] stated that it is unclear whether the differences in the proportion of patients with NYHA I/II in the EAMS programme and the NAC cohort is entirely a consequence of tafamidis being available through the EAMS, or whether other factors may have contributed to the apparent shift in stage at diagnosis, e.g. increased awareness of ATTR-CM and/or wider availability of nuclear scintigraphy. Responses to the ACD from Cardiomyopathy UK indicate that diagnosis has been improving over time and the trend is set to continue due to planned educational events aimed at increasing awareness.[11] This stakeholder highlighted that patisiran and inotersen have improved time to diagnosis and indicates that tafamidis may have a further positive impact. The response to the ACD from the British Nuclear Cardiology Society (BNCS)[12] highlights that diagnoses of ATTR have been increasing since the mid-2010s and that DPD scanning is now widely available, leading to increased numbers of patients being diagnosed. The response to the ACD from the NAC[4] also note that there are *"no compelling data to either support or indeed refute any assertion regarding improvement in diagnostic delays in relation to tafamidis."* The ERG notes the following: • There are two potential implications associated with earlier diagnosis: (i) patients may receive tafamidis at an earlier disease stage, and (ii) patients diagnosed earlier may avoid costs and QALY losses associated with diagnostic delays. • The company's and the ERG's economic subgroup analyses suggest that even if all patients begin treatment in NYHA I or II, the ICER for tafamidis is similar to that for the overall population (see ERG's technical engagement response[9] Tables 5 and 6: ERG's preferred analysis in all patients - ICER = [redacted] per QALY

Issue	Company's issue (headline points)	ERG response
		gained; ERG's preferred analysis in NYHA I/II – ICER = [redacted] per QALY gained). • With respect to potentially avoidable QALY losses and cost savings associated with reducing diagnostic delays, the company's analysis implies that all patients would achieve a diagnosis within 6-months and that this reduction in diagnostic delay, and the cost savings and health benefits arising from earlier diagnosis, are exclusively attributable to the future availability of tafamidis. The ERG has doubts regarding the robustness of the company's estimates of cost savings and QALY losses avoided and whether these should be considered attributable to tafamidis (see ERG's technical engagement response,[9] Table 1, final row). It may be the case that at least some of these benefits would accrue irrespective of whether NICE issues a positive recommendation for tafamidis. However, there is no evidence to support or refute this.
8. Misinterpretation of published data	The committee *"noted that data from the National Amyloidosis Centre suggested that a third of people had an accurate ATTR-CM diagnosis within 6 months. It acknowledged this was an improvement on current diagnosis delays, but recognised these diagnoses were made at a specialist centre and questioned if this could be done in clinical practice."* (Section 3.7; Page 10). This is a misinterpretation of the data published by the National Amyloidosis Centre (NAC) and suggests the opposite, that reducing delays to diagnosis below 6 months is feasible in clinical practice.	The ERG reiterates that there is no actual evidence to support the company's argument that a positive recommendation for tafamidis would reduce diagnostic delays to less than 6 months. The ERG believes that cited data from Lane *et al*[5] reflect a distribution of patients, some of whom achieved a diagnosis earlier (≤6 months) whilst others achieved a diagnosis later (>6 months). The ERG believes that the wording of the ACD could be amended to more clearly reflect this.
9. Clinical relevance of the primary outcome measure in ATTR-ACT	The committees' concerns regarding the trial outcomes are unclear, all-cause mortality and cardiovascular-related hospitalisation are highly relevant, hard clinical endpoints and are considered as	The ERG believes that the company's concerns most likely relate to the statement in Section 3.9 the ACD[1] that the primary outcome measure used in ATTR-ACT, a composite of mortality and CV-related hospitalisations, *"is not used in clinical practice."* The company's response also highlights two further statements in the ACD (Sections 3.23 and

Issue	Company's issue (headline points)	ERG response
	composite primary endpoints in other cardiovascular related trials.	3.27) which highlight the committee's concerns regarding the primary outcome of the trial and its relevance to clinical practice. The ERG agrees with the company that both mortality and hospitalisations are hard clinical endpoints which are relevant to the management of patients with ATTR-CM and which characterise the clinical benefit of tafamidis. However, the ERG notes that the text in Section 3.9 of the ACD - immediately after the text quoted in the company's comment - highlights that tafamidis improved CV-related mortality, hospitalisations and mobility decline, and that tafamidis is more effective than placebo. As such, the ERG believes that the Appraisal Committee's view regarding the clinical effectiveness of tafamidis, as stated in the ACD, is clear.
10. Hierarchy of submitted clinical evidence	The company is concerned that the data from the RCT has been dismissed by the committee and the absence of a specific findings in EAMS prioritised (see footnote).	Section 3.10 (page 13) of the ACD[1] discusses the information provided by the EAMS, stating that *"The committee acknowledged the trend, but noted that there was no evidence from EAMS that showed a different effect of tafamidis when it was started in the less severe NYHA classes. So, it agreed that it was unclear if there were any additional benefits to starting tafamidis when ATTR-CM is less severe and classed as NYHA 1 or 2."* The ERG believes that this statement is accurate – the EAMS does not provide evidence regarding improved outcomes for patients receiving tafamidis with earlier disease. The ERG agrees with the company that the EAMS was not designed to provide this information. However, the ERG does not agree with the company that this implies that the data from ATTR-ACT[2] has been dismissed by the Appraisal Committee.
11. Continuation of treatment benefit	The committee concluded that despite the ERG analyses *"had limitations….they provided realistic alternatives to the company's overly optimistic analyses"* and *"that the ERG's analyses were appropriate for decision making "* (Section 3.16; Page 16-17). The company believes the relevant merits of the company analyses have not been taken into consideration compared to the extensive limitations associated with the ERG analyses.	*Company's original model[7] and ERG critique[6]* The company's original model[7] assumed indefinite treatment effects for tafamidis (on survival, CV-related hospitalisations, NYHA transitions and health-related quality of life [HRQoL]) together with an assumption that the hazard of discontinuation will persist at a constant rate beyond the observed duration of the ATTR-ACT trial[2] (30 months). Therefore, an increasing proportion of surviving patients are assumed to discontinue tafamidis whilst continuing to accrue the benefits of treatment (based on the average level of exposure to tafamidis observed in ATTR-ACT), without incurring any further treatment costs. As discussed in the ERG report[6] (Section 5.3.3) and the ERG's technical engagement response[9] (Issue 2), this is unlikely to be a reasonable assumption which will underestimate the ICER for tafamidis versus BSC.

Issue	Company's issue (headline points)	ERG response
		The ERG report[6] and the ERG's technical engagement response[9] present the results of two exploratory scenarios, both of which assume that treatment effects persist whilst the patient remains on treatment: • ERG-preferred scenario – this assumes that time to treatment discontinuation (TTD, censored for death and progression to NYHA IV) plateaus at the end of the observed period (30 months in the ERG report based on the RCT, [redacted] months in the technical engagement response, based on the RCT plus the long-term extension [LTE] study), treatment effects apply indefinitely • Alternative ERG sensitivity analysis 1 – this assumes that the discontinuation rate continues beyond the observed period, outcomes for the tafamidis group are applied to patients remaining on treatment, outcomes for the BSC group are applied to tafamidis discontinuers. As discussed in the ERG report and the ERG's technical engagement response, neither of these analyses are ideal. The ERG-preferred scenario may not be externally valid if, in usual practice, patients have an ongoing risk of discontinuing treatment after 30 months ([redacted] months in the ERG's technical engagement response). The ERG's alternative sensitivity analysis is limited in that it assumes that the treatment effect is immediately lost at the time at which patients discontinue tafamidis, and because it does not account for discontinuation which occurred within the observed period of the trial. The ERG believes that the most appropriate analysis would involve formally adjusting for non-adherence using causal inference methods. *Company's technical engagement response[13]* In their technical engagement response[13] (Issue 2, page 4), the company stated *"if patients discontinued for any other reasons than death or transition to NYHA IV, [the] treatment effect would be maintained for an unknown duration. However, the company acknowledges this would not be indefinitely."* The company's technical engagement response also stated that the *"company acknowledges that discontinuation in the original base-case analysis may be overestimating discontinuation beyond the observed data."* Their technical engagement response also recognised the potential for a plateau in discontinuation and suggested that, based on additional data from the LTE study, this plateau might apply from [redacted] months. The company further stated that, except for progression to NYHA IV or death, there were limited additional reasons why a patient

Issue	Company's issue (headline points)	ERG response
		might discontinue tafamidis. Despite this, almost all of the company's additional analyses presented in their technical engagement response retained the company's original assumption of an ongoing tafamidis discontinuation rate, reduced costs and no loss of relative treatment effect. As such, the additional analyses presented in the company's response to technical engagement were not consistent with the statements made by the company within their technical engagement response. Because of this, the ERG did not consider the updated results presented in the company's technical engagement response to be appropriate. *Company's ACD response*[3] The company's ACD response[3] appears to revert back to the position suggested within the CS[7] and the company's original model i.e. that the hazard of discontinuation will persist at a constant rate with no loss of treatment effect and no further treatments costs for patients who discontinue tafamidis. *ERG's view on the company's ACD response* The ERG notes the following: • The ERG's concerns regarding the problems of the company's approach remain unchanged. • The company's view expressed in their ACD response[3] is inconsistent with the view expressed in their technical engagement response.[13] The company has previously acknowledged that their original analysis is likely to be optimistic and that treatment effects will be lost at some time point following discontinuation. The company also previously accepted the notion of a plateau for discontinuation. The company's ACD response suggests that they no longer agree with this previously expressed view. • The company's ACD response appears to simultaneously argue two contradictory standpoints: (i) that the observed data from ATTR-ACT[2] should be used to extrapolate future discontinuation rates, and (ii) that the observed data from the longer-term ATTR-ACT plus LTE study should not be used to extrapolate future discontinuation rates, because of the low number of patients at risk in the tail of the Kaplan-Meier function. The ERG considers the company's argument to be illogical.

Issue	Company's issue (headline points)	ERG response
		• As discussed in the ERG report,[9] the key issue relates not only to the rate of discontinuation over time, but also what happens to the relative treatment effect after patients discontinue treatment. Whilst both the ERG's preferred analysis and the additional sensitivity analyses are subject to limitations, these are explained the ERG report, the ERG's response to technical engagement and these were also communicated verbally by the ERG during the Appraisal Committee meeting. The ERG considered these exploratory analyses to be necessary in order to avoid the problematic assumptions underpinning the company's analysis. • The ERG notes that the NAC's response to the ACD[4] states that *"if the mechanism of benefit is due to inhibition of amyloid formation, amyloid is overwhelmingly likely to re-accumulate after treatment has been discontinued."* This appears to suggest that the company's assumption of an ongoing treatment effect following discontinuation is not clinically realistic.
12. Overall survival extrapolation	The committee *"concluded that the reason for using generalised gamma functions to model overall survival was unclear and agreed to consider only the log-normal extrapolation functions in its decision making."* Section 3.17; Page 17. The company acknowledges the rationale for the change in survival model following the submission of the updated data cut was potentially unclear, please see further rationale below.	The company's original model applied the log-normal model for OS for the tafamidis group. As described in the ERG report[7] (Section 5.2), this selection was made on the basis that together with the exponential distribution, the log-normal distribution was one of the best fitting models of excess hazards, and because all other models except for the exponential model appeared to underestimate all-cause OS based on a comparison of survival at 50 months in the ATTR-ACT extension study. The company's technical engagement response[13] included scenarios in which the generalised gamma model was applied instead of the log-normal model. The use of this alternative parametric model was described as an *"optimistic scenario."* No further explanation was given. The company's ACD response[3] argues that the fitted models *"most likely do not reflect the full survival gains expected from tafamidis"* and that *"given the minimal difference between the log-normal and generalised gamma both in terms of visual and statistical fit to the observed data, the more 'optimistic' curve was felt to be the most appropriate."* The ERG notes that the AIC values were similar for the log-normal and generalised gamma models. However, the generalised gamma was the worst-fitting model according to BIC values using the 30-month data-cut[7] and using the additional LTE dataset.[14] The

Issue	Company's issue (headline points)	ERG response
		ERG does not consider the company's explanation to provide a sufficient justification for selecting an alternative OS model.
13. Improvements in diagnosis delay and impact on costs	'The ERG highlighted that it was unclear how the company had estimated that diagnosis delays could be reduced by 2.5 years and how potential cost savings of £20,000 had been estimated' (Section 3.18; Page 18-19). The committee subsequently concluded *"that the company's early diagnosis assumptions were not appropriate for decision making because there was not enough evidence to support them."* (Section 3.18; Page 19). The company acknowledged it would not be possible to provide hard empirical estimates for the assumptions related to early diagnosis, however there is rationale for the estimates proposed by the company, and it is not appropriate to conclude there would be no impact.	The company's technical engagement response[13] included some examples of costs which might be avoided through earlier diagnosis. Similarly, the company's ACD response[3] lists examples of cost items incurred prior to diagnosis. However, the company has still not presented any clear calculations which support the assumed value of £20,000 saved per patient or the proportion of patients for whom this cost saving might accrue. The ACD[1] does not state that there would be no impact of earlier diagnosis on cost savings and avoidable QALY losses. The text of the ACD states *"The committee agreed that the extent that reducing diagnostic delays could lead to cost savings or reduced quality-of-life losses was unclear. It concluded that the company's early diagnosis assumptions were not appropriate for decision making because there was not enough evidence to support them."*
14. Adverse impact of diagnosis delay on QoL	The committee concluded that the QALY *"gain for reduced anxiety or depression for all patients was not a reasonable approach because it was not supported by any evidence'* Section 3.18; Page 18-19. The company acknowledges the lack of supporting evidence for the assumption. However, it cannot be concluded that a delayed diagnosis has no impact on patient quality-of-life.	The ACD does not state that a delayed diagnosis has no impact on patients' HRQoL. Rather, the ACD states that there is no evidence to support such an impact. The ERG agrees with this statement.

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15. Mechanism of action	The following statement in the ACD is not evidence based *"The clinical expert explained that new research had changed their understanding of the way that tafamidis treats ATTR-CM. They suggested that the mechanism by which it works may not be as innovative as was originally thought."* (Section 3.26; Page 24)	The ERG refers the reader to the response to the ACD from the NAC.[4]
16. Factual inaccuracy	The following statement is factually inaccurate: *"The company estimated that it took 3 years or more for a person to be accurately diagnosed with ATTR-CM." (Section 3.3; Page 6)*	The ERG agrees with the company. The ERG believes that this statement should be amended to read: *"the company estimated that, on average, it took 3 years or more for a person to be accurately diagnosed with ATTR-CM"*
17. Factual inaccuracy	The company has not suggested that patients should start in NYHA I/II and discontinue in NYHA III. As stated in Section 3.6; Page 8: "*The company submission included analyses with these starting and stopping rules:* *• people whose disease is classed as NYHA 1 or 2 can start tafamidis* *• people whose disease is classed as NYHA 1, 2 or 3 can keep taking tafamidis and* *• people should stop tafamidis if their disease progresses to NYHA 4.* *The ERG explained that it had concerns about the clinical relevance of only allowing people whose disease is classed as NYHA 1 or 2 to start treatment."*	The ERG agrees that this issue should be considered as resolved and that the economic analyses for the NYHA I/II subgroup should not be considered for decision-making.

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18. Factual inaccuracy	The following statement is factually inaccurate "For cardiovascular-related mortality, the hazard ratios favoured tafamidis over placebo, but the differences were not statistically significant in either wild-type (hazard ratio 0.71 [95% confidence interval 0.47 to 1.05]) or hereditary ATTR-CM (hazard ratio 0.69 [95% confidence interval 0.41 to 1.17])." (Section 3.10; Page 12)	The ERG agrees with the company – the reported hazard ratios relate to all-cause mortality rather than CV-related mortality.

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