NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# SINGLE TECHNOLOGY APPRAISAL

# APPEAL HEARING

## Advice on tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

### Decision of the panel

### Introduction

1. An appeal panel was convened on 4 and 5 March 2021 to consider an appeal against the final appraisal document (FAD), to the NHS, on tafamidis for treating transthyretin amyloid cardiomyopathy (ATTR-CM) [ID1531].
2. The appeal panel consisted of:

* Prof Alan Silman Chair
* Mr Tom Wright Non-executive director of NICE
* Mr Chris Rao Health Service representative
* Dr Mark Chakravarty Industry representative
* Mr Paddy Storrie Lay representative

1. None of the members of the appeal panel had any competing interests to declare.
2. Dr Mark Chakravarty declared that further to the panel member’s central register of interests his wife had started a communications consultancy, which was not in the commercial sector as defined by NICE’s policy on managing and declaring interests. This was not judged to be a conflict of interest.
3. The panel considered appeals submitted by Pfizer Ltd, The British Society for Heart Failure (BSH), and Cardiomyopathy UK.
4. Pfizer were represented by:

* Ms Emma Clifton-Brown Head of Health & Value, Pfizer UK
* Mr Sam Large Senior HTA Manager, Pfizer UK
* Mr Jack Brownrigg Rare Disease, UK Medical Director, Pfizer UK
* Prof Perry Elliott Research Lead of the Inherited Cardiovascular Disease Unit, Bart’s Heart Centre. Professor of Cardiovascular Medicine and Consultant Cardiologist, UCL
* Dr Adela Williams Legal representative, Partner, Arnold & Porter

1. BSH were represented by:

* Dr Lisa Anderson Heart Failure Consultant, St George’s University Hospitals NHS Foundation Trust, and deputy chair BSH
* Dr Carol Whelan Consultant Cardiologist, Royal Free Hospital
* Ms Louise Clayton Advanced Nurse Practitioner and Heart Failure Nurse Specialist, Leicester University Hospitals Trust, and board member BSH

1. Cardiomyopathy UK were represented by:

* Mr Joel Rose Chief Executive, Cardiomyopathy UK
* Mr Paul Pozzo Patient representative, Cardiomyopathy UK
* Mr Vince Nicholas Patient representative, Cardiomyopathy UK
* Mr David Gregory Patient representative, Cardiomyopathy UK

1. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

* Prof Stephen O’Brien TA Committee C Chair, NICE
* Mrs Helen Knight Programme Director, NICE
* Mr Jasdeep Hayre Associate Director, NICE
* Mr Thomas Paling Technical Analyst, NICE
* Prof Paul Tappenden Evidence Review Group (ERG) Member, School of Health and Related Research (ScHARR)
* Dr Alex Cale TA committee C Member, NICE

1. None of the individuals involved in the appraisal or appeal had any competing interests to declare.
2. Adela Williams, on behalf of Pfizer, raised concerns that Paul Tappenden’s role at ScHARR and membership of TA committee C potentially represented a conflict of interest, even though Paul Tappenden was clear that he attended the appeal as a member of the ERG and that he had recused himself from all discussion of tafamidis in TA committee C. Adela Williams was concerned that the ERGs were funded by NICE and that another member of ScHARR may have been present at meetings of TA committee C, during which tafamidis was discussed. Furthermore, she was concerned that minutes of the second meeting of TA committee C during which tafamidis had been discussed had still not been published. Helen Knight, on behalf of NICE, corrected Adela Williams’ statement that the ERGs were funded by NICE, stating that they were funded directly by the Department of Health and Social Care. Helen Knight, apologised on behalf of NICE that the minutes had not been published, explaining that this had occurred because of the prioritisation of work related to the SARS-CoV-2 pandemic, and undertook to ensure this was done as soon as possible.
3. Whilst Paul Tappenden’s potential conflict of interest was noted by the appeal panel, it was satisfied that it had been correctly managed and did not impact on the decision making of the appraisal committee in relation to its determination on tafamidis.
4. The panel believes that the other member of TA committee C with an affiliation to ScHARR is Professor Stevenson. The panel noted he is not an author of the ERG report and does not appear to have worked on it. The panel concluded that a reasonable person would not think there was a real possibility that Professor Stevenson’s judgement in this appraisal to have been affected by the fact that the ERG report was produced by ScHARR.
5. NICE’s legal adviser Mr Stephen Hocking, DAC Beachcroft LLP, was also present.
6. The following members of the NICE Appeal panel for highly specialised technologies and technology appraisals were present as silent observers throughout the hearing and panel discussions.

* Mr Adrian Griffin Appeal panel observer (Industry)
* Dr Paul Robinson Appeal panel observer (Industry)
* Prof Kiran Patel Appeal panel observer (Health Service)

1. Under NICE’s appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.
2. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

1. The Vice Chair of NICE, Mr Tim Irish, in preliminary correspondence had confirmed that:

* BSH potentially had valid grounds for appeal as follows: Ground 1(a), and Ground 2.
* Cardiomyopathy UK potentially had valid grounds for appeal as follows: Ground 1(a)
* Pfizer potentially had valid grounds for appeal as follows: Ground 1(a), and Ground 2.

1. The appraisal that is the subject of the current appeal provided advice to the NHS on tafamidis for treating transthyretin amyloid cardiomyopathy (ATTR-CM).
2. Tafamidis stabilises the correctly folded tetrameric form of the transthyretin protein, preventing the misfolded protein from causing damage to the heart as the misfolded protein aggregates in the heart muscle causing ATTR-CM. This results in progressive deterioration in the function of the heart significantly impairing health-related quality-of-life and predisposes to sudden death from heart arrhythmia.
3. Vince Nicholas was invited by the panel chair to describe his experience as a patient with ATTR-CM. The panel would like to thank Mr Nicholas and the other patient representatives for their insights into living with ATTR-CM. The Panel was left in no doubt that ATTR-CM is a serious, progressive, debilitating and ultimately fatal condition without disease modifying treatment options and that patients, their families and their clinicians would very much value tafamidis as a treatment option to slow disease progression.
4. Before the appeal panel inquired into the detailed appeal points the following made preliminary statements: Emma Clifton-Brown on behalf of Pfizer, Lisa Anderson on behalf of BSH, Joel Rose on behalf of Cardiomyopathy UK, and Stephen O’Brien on behalf of the appraisal committee.

## Appeal by Pfizer Ltd

### Appeal Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly.

### Appeal point Ground 1a.2 - The Committee’s conclusions regarding the diagnosis of ATTR-CM have misconstrued the European Public Assessment Report for tafamidis.

1. Jack Brownrigg, for Pfizer, stated that the multiple references to the European Public Assessment Report (EPAR) and its content in the Final Appraisal Document (FAD) suggested that the appraisal committee relied on the EPAR for its understanding of the diagnostic pathway for ATTR-CM. In many respects the EPAR is outdated and no longer relevant. For example, biopsy no longer play a role in the routine diagnosis of ATTR-CM. Furthermore, the EPAR refers to biopsy or DPD, and not biopsy and DPD, and calls for a diagnostic algorithm that now exists. Jack Brownrigg stated that whilst it was a narrow point, it was potentially fundamental. When asked why by the chair of the appeal panel, he stated that if the committee thought a biopsy was necessary then they misunderstood and overestimated the difficulty of making a diagnosis.
2. Adela Williams, for Pfizer, stated that the FAD must be considered a reflection of the panel’s thinking and the reference to the EPAR shows the committee are confusing the roles of technology appraisal and regulator.
3. Stephen O’Brien, for NICE, stated that it was appropriate to reference the EPAR and what is said in it. He said the appraisal committee understood the changes in thinking in respect to the diagnosis of ATTR-CM, and rejected the diagnostic pathway described in the EPAR. They understood DPD was the mainstay of diagnosis provided a clinician thought to refer the patient for a scan. He therefore did not think that the committee had been unduly influenced by the EPAR.
4. Thomas Paling, for NICE, suggested that it was for the committee to weigh up evidence from different sources, including the EPAR. In this case they put more weight on evidence from the company and experts.
5. The appeal panel concluded as follows:
6. The reference to the EPAR in the FAD was discursive and intended to provide background and context. The appeal panel are not convinced that the EPAR unduly influenced the committee’s understanding of the diagnosis of ATTR-CM based on the content of the FAD, written evidence, and the oral evidence heard in the appeal hearing.
7. In particular, the panel do not believe that the committee disregarded the National Amyloidosis Centre (NAC) diagnostic algorithm or the opinion of other clinical experts in favour of information contained in the EPAR when considering the diagnosis of ATTR-CM.
8. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 1a.3 - The Appraisal Committee’s reference to the fact that the marketing authorisation for tafamidis does not specify starting and stopping rules based on the NYHA classification, relies on an irrelevant consideration.

1. Adela Williams, for Pfizer, stated that no marketing authorisation (MA), contains stopping rules unless for reasons of safety, and therefore the marketing authorisation could not be expected to have contained NYHA (New York Heart Association Functional Classification) based stopping rules. She suggested that the committee were confusing the roles of medicines regulator, driven by safety and efficacy, and health technology approval, driven by cost efficacy. She suggested that it was up to NICE to decide which subgroups would benefit from treatment, and that there was no legal basis or precedent in NICE guidelines for a reliance on the marketing authorisation to define stopping rules.
2. Stephen O’Brien, for NICE, was clear in his response to Adela Williams that although the appraisal committee were aware of the content of the MA, they were not constrained by it. Considerations about whether to adopt a stopping rule in the economic model were informed by uncertainty about whether they could be applied in practice. It was informed by evidence from experts who stated that assessment of NYHA classification was subjective. They stated that there could be fluctuations in functional status. Finally, they stated that it would be difficult to stop a drug that improved prognosis.
3. This was supported by Alex Cale, for NICE, who also stated that the appraisal committee had concerns about whether a stopping rule could be applied in clinical practice based on expert opinion.
4. Stephen O’Brien, for NICE, in response to a question from the chair of the panel did not feel that the content of the MA was given undue prominence in the FAD. This was supported by Helen Knight, for NICE, who suggested that as the MA was the starting point for NICE technology appraisal it was entirely appropriate to refer to it in the FAD.
5. Paul Tappenden, for NICE, stated that, many marketing authorisations do include stopping rules, for example cancer drugs often include stopping rules in the context of disease progression. Adela Williams, for Pfizer, argued that these stopping rules were for reasons of safety and were therefore not relevant to this case. She pointed out that the concern was with the wording of the FAD and that that suggested the committee had given weight to the content of the marketing authorisation in deciding a stopping rule could not be used.
6. The appeal panel concluded as follows:
7. The panel accept Pfizer’s reasoning that the decision to adopt or reject stopping rules for a medication should not be driven on the content of the marketing authorisation. It is possible (indeed usual) to have a stopping rule for health economic reasons that is not to be found in the marketing authorisation.
8. The panel were not convinced, however, that the appraisal committee’s decision to reject stopping rules for tafamidis based on the NYHA classification was wrongly informed by the content of the marketing authorisation. Based on the content of the FAD, written and oral evidence to the panel, it was satisfied that the decision to reject NYHA stopping rules in the economic model was based on uncertainty about whether they could or would be applied in clinical practice and that there were several logically plausible reasons for that uncertainty that did not draw on the marketing authorisation.
9. The panel did not consider it inappropriate to refer to the marketing authorisation in the FAD. The panel felt that the reference to the absence of NYHA based stopping rules in paragraph 3.7 of the FAD was intended to provide context to the appraisal committee’s reasoning contained in the FAD and consequently could not be considered either unfair or unreasonable.
10. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 1a.4 - The Appraisal Committee’s conclusion that it would not consider starting and stopping rules for tafamidis based on the NYHA classification system even though the NYHA system has been used in previous NICE appraisals is unexplained and potentially discriminatory.

1. Perry Elliott, for Pfizer, stated that stopping rules are routinely used in clinical practice. He cited examples of stopping Angiotensin Converting Enzyme (ACE) inhibitors when renal function begins to decline and turning off implantable cardiac defibrillators in patients in end stage heart failure. He said the ATTR-ACT trial should not be viewed through the prism of a rare diseases trial, but as a conventional heart failure trial. He stated that whilst the NYHA classification was subjective it was routinely used in clinical practice. Perry Elliot stated that it was not difficult to define patients who were in NYHA class I and IV, in particular. He stated that whilst there was fluctuation between classes, NYHA was never evaluated in isolation or in the context of acute illness.
2. Adela Williams, for Pfizer, said the NYHA classification was routinely used in NICE guidelines. She cited examples of implantable cardioverter, cardiac resynchronisation therapy, valsartan, ivabradine, and dabigatran. She stated that ATTR-CM was more common in the elderly and some ethnic minority groups and therefore to reject the use of the NYHA in this case when it has been used in previous NICE guidelines was potentially discriminatory. Consequently, the appraisal committee needed to explain why tafamidis had been treated differently to previous technology appraisals.
3. Stephen O’Brien, for NICE, stated that not all the clinical experts agreed that NYHA based stopping rules could easily be applied in clinical practice. For example, patients in NYHA class IV could be improved to class III if fluid overload were treated. He stated that the limitations of the NYHA classification were the subject of several publications. Reservations about the NYHA classification led to the appraisal committee exploring if there was an alternative biomarker that could be used to define stopping rules, unfortunately there was little evidence to support this. He stated that there was no evidence that NYHA stopping rules could be applied in clinical practice as they were not included in the ATTR-ACT clinical trial and other clinical trials for medications such as ivabradine.
4. Adela Williams, for Pfizer, stated in response to Stephen O’Brien’s evidence that whilst NICE appraisals are not bound by the methodology of previous appraisals, they must be consistent to be considered fair. Adela Williams asked for clarification for why there was an unexplained difference in the appraisal committee’s treatment of the NYHA classification compared to previous technology appraisals. In response to questioning from the panel about whether previous NICE guidelines in which NYHA had been used to define starting rules were analogous to tafamidis where it was being used to define a stopping rule, Adela Williams cited the example of implantable defibrillators. Adela Williams stated that the question was not whether NYHA could be used as effectively for starting and stopping rules but whether it could be used for decision making in general. As NYHA had been used in other appraisals she felt that this was also true for tafamidis.
5. Adela Williams, in response to questioning from the panel, suggested that differences in expert opinion could be explained by an absence of appropriately qualified experts in the management of heart failure.
6. Stephen O’Brien, for NICE, when asked by the panel if stopping rules where impossible in any circumstance, stated that the appraisal committee did not believe that this was the case. He said that the reason that they could not be applied for tafamidis was the limitations of the NYHA classification system. He asserted that implantable defibrillators were not analogous technology to a drug, and that NYHA based stopping rules had never been applied in NICE guidance for any drug.
7. In response to questioning from the panel about why there was a difference in opinion between specialists and how this could be resolved, Alex Cale, for NICE stated the following: “We should not oversimplify heart failure. It is a myriad of diseases, some reversable, some not. This appraisal was only concerned with one form of heart failure and the question was whether starting and stopping rules could be defined for treatment for this form of heart failure. There was no lack of understanding of the NYHA classification. We could not understand from the experts how asymptomatic patients could be started on the medication, and how patients in NYHA Class IV could be stopped when there was potential for recovery”. Alex Cale stated that the appraisal committee wanted to accept the feasibility of NYHA stopping rules for tafamidis as it was an important drug, however based on expert evidence they could not be convinced that they were applicable in clinical practice.
8. Jack Brownrigg, for Pfizer, stated that NYHA is an independent predictor of outcomes. He stated that because of the nature of ATTR-CM, NYHA deterioration is progressive. This is consistent with the opinions of clinicians who treat patients with ATTR-CM daily.
9. The appeal panel concluded as follows:
10. The appeal panel are satisfied that the committee understood that the NYHA system is extensively used in clinical practice and the academic literature. It is also satisfied that the committee were aware of its extensive use in previous NICE guidelines and technology appraisals.
11. The committee had recognised the difficulty in defining a stopping rule based on the NYHA classification alone. The reasons for this included fluctuation in NYHA functional status determined by reversible factors such as systemic infection and fluid overload. Evidence heard by the panel from clinical experts such as Perry Elliott, who asserted that NYHA was not used in isolation when making this decision but in conjunction with other clinical and diagnostic tests appear to support the committee’s reservations about an NYHA based stopping rule.
12. The appeal panel recognise that appraisal committees are not bound by the methodological approaches adapted in previous appraisals, however, it understands that a broadly consistent approach is required to ensure fairness and transparency. The appeal panel accept that NHYA classification has been used to define inclusion and exclusion for the initiation of treatment in previous NICE guidance, however it has never been used to define a stopping rule.
13. The appeal panel did consider implantable cardiac defibrillators which was cited as an example where NYHA classification was used to define a stopping rule. The appeal panel noted that the NYHA classification was used in that appraisal to define treatment indication not a stopping rule such as in the case of tafamidis.
14. The panel recognise a subtle but important distinction in using NYHA to define the appropriate population to initiate treatment versus stopping rules. As the use of NYHA classification to define stopping rules is not widespread in NICE guidance it cannot accept that the appraisal committee’s actions in this instance were either inconsistent with the methodology used in previous NICE guidance or was unfair.
15. The appeal panel are satisfied based on the written evidence submitted that due consideration was given by the NICE appraisal committee to the impact of the guidance on patients with protected characteristics, and consequently were not persuaded that the FAD was discriminatory.
16. The appeal panel therefore dismissed the appeal on this point.

## Appeal by the British Society of Heart Failure (BSH)

### Appeal Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly.

### Appeal point Ground 1a.1 - Failures in engaging with the BSH as a consultee.

1. Lisa Anderson, on behalf of BSH, stated that the accidental exclusion of BSH as a consultee led to fundamental errors and misconceptions about the management of ATTR-CM remaining unchallenged due to the absence of appropriately qualified clinical experts in the appraisal committee meetings. These errors and misconceptions then informed the FAD, resulting in flawed conclusions. This included the following: that NYHA class could not inform stopping rules, that it was challenging to diagnose ATTR-CM, and that DPD scans could result in falsely diagnosing ATTR-CM because of the presence of incidental amyloid deposits.
2. Concerns relating to the absence of clinicians with appropriate expertise in the management of heart failure were also expressed by Carol Whelan, on behalf of BSH.
3. In response Stephen O’Brien, on behalf of NICE, stated that there were several clinicians at the table in both TA committee meetings. He stated that the appraisal committee had read and understood the written evidence of clinical experts including from the BSH. Stephen O’Brien also explained that whilst it is not the usual practice to invite clinical experts to the second committee meeting, in which the primary focus is often the discussion of the economic data, in this instance clinical experts including heart failure specialists were invited and did speak.
4. Jasdeep Hayre, on behalf of NICE, stated that BSH had been identified as a stakeholder following the scoping exercise. They were sent a confidentiality agreement to facilitate participation in the appraisal committee meeting in late 2019. As no reply was received from BSH, NICE did not engage further with BSH as a consultee. In May/ June 2020 it became apparent that BSH had been overlooked and the confidentiality agreement was again sent to BSH. After the confidentiality agreement was returned, BSH were included as a consultee. As a consequence of the delay in including BSH as a consultee, BSH did not have the opportunity to nominate experts and participate in the technical engagement phase of the review. Jasdeep Hayre suggested that the treatment of BSH was not unfair as their treatment by NICE was consistent with all other stakeholders. In response to questioning from the panel chair about whether in the case of rare diseases all stakeholders should be treated equally, Jasdeep Hayre, stated that there was strong input from clinical experts including from the NAC and the British Cardiovascular Society.
5. The panel were subsequently informed that Carol Whelan had filled in the relevant confidentiality agreement, however not as a representative of BSH.
6. The appeal panel concluded as follows:
7. NICE had made appropriate efforts to engage all relevant stakeholders identified during the scoping exercise including BSH. There appeared to be some confusion concerning the confidentiality agreement returned by Carol Whelan, who had been nominated as an expert by the Royal College of Physicians. NICE had understood she had returned a form in that capacity rather than on behalf of BSH, the panel felt this was a reasonable explanation and did not indicate a lack of diligence by NICE in engaging with BSH.
8. In the absence of a BSH representative, the NICE appraisal committee considered evidence from a range of clinical experts including heart failure specialists. This included both written evidence and the oral evidence of a heart failure specialist during the second committee meeting.
9. BSH had submitted aresponse to the ACD and so their input had informed the committee’s deliberations before the finalisation of the FAD.
10. The appeal panel did not think that NICE had failed to engage properly with BSH as a consultee. NICE had not appreciated BSH wished to engage actively with the appraisal and while the misunderstanding is regrettable the appeal panel did not feel that anyone was at fault. Furthermore, BSH has submitted comment on the ACD (and did not raise the issue of not attending the first committee meeting in those comments) so NICE would have reasonably considered that BSH had been engaged with appropriately.
11. The appeal panel therefore dismissed the appeal on this point.

## Appeal by Cardiomyopathy UK

### Appeal Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly.

### Appeal point Ground 1a.1 – Unfair conduct of second committee meeting at which FAD was developed.

1. Joel Rose, on behalf of Cardiomyopathy UK, stated that the technology appraisal system was unfair as it was impossible for patients to understand the impact of their statements in the decision-making process, in particular, to understand what weighting the patient’s experience had compared to the economic data.
2. Joel Rose expressed his concern that the conduct of the second meeting was such that he would feel uncomfortable asking patients to engage with the appraisal process in future. Joel Rose said that the ‘pseudo judicial’ nature of the appraisal process did not put patients at ease and allow them to feel that they were able to make their point, particularly as it was not evident what impact their statements would have relative to the economic data.
3. In response to questioning from the panel, Joel Rose stated that Cardiomyopathy UK was given very short notice to find a patient who had been on tafamidis before the second appraisal committee meeting, and that they had very limited opportunity to speak at the second appraisal committee meeting. He confirmed that Cardiomyopathy UK had also made written submissions.
4. David Gregory, patient representative from Cardiomyopathy UK, stated that in the first meeting, patient representatives were asked questions and had a good experience. He stated that Cardiomyopathy UK represented the only group of patients at the meeting and consequently had sufficient time to describe their experience of living with ATTR-CM. In the second meeting they were told that they would not be required to make any comment and then were subsequently asked to speak briefly.
5. Stephen O'Brien, on behalf of NICE, was asked what procedures existed to ensure that patient representatives were heard and what mechanisms were in place to ensure that their views were taken into consideration. He replied that the patient’s opinion on the disease impact and effect of treatment on quality of life was very important. He explained that patients’ representatives were always asked to speak in the first meeting, and a range of clinical experts were also usually invited. At the second meeting it was less common to invite patient representative as the discussion was usually primarily focused on the economic data. Stephen O’Brien stated that the committee invited and heard evidence from a patient in the second appraisal meeting in addition to inviting seven clinical experts. This was not usual practice, however the appraisal committee appreciated this was a difficult case. He acknowledged the difficulty in the second committee meeting given the necessary focus on the technical considerations of the economic modelling.
6. Stephen O'Brien stated that evidence from patient representatives was very important because it brought to life the numbers and explained the reality of the patient experience within the NHS. In response to questioning about whether patients could ever say anything that would change the decision, Stephen O'Brien stated that on occasions the committee had not fully understood the magnitude of the impact of a condition or treatment on patient health-related quality-of-life, and the evidence of patient representatives had resulted in committees asking for the submission of more quality-of-life data.
7. Helen Knight, on behalf of NICE, stated that patient involvement was very important to NICE and that there was a programme to support patients and charities to engage with the appraisal process. She said that the economic models were submitted by the company and then appraised by NICE, and that patient involvement was key to informing this process.
8. The appeal panel concluded as follows:
9. Patient experts from Cardiomyopathy UK had had the opportunity to speak in the first committee meeting and Cardiomyopathy UK had the opportunity to make written submissions.
10. Despite the usual focus of the second committee meeting on the technical aspects of the economic model, patient and clinical experts were invited to speak at this meeting. Whilst the time allowed for patient experts from Cardiomyopathy UK was very limited, the panel heard how another patient expert had spoken at this meeting.
11. The panel noted the evidence of Stephen O’Brien in which he said that he tried to make patient experts feel welcome, and during which he expressed his regret that the patient representatives had such a negative experience during the second committee meeting. The panel heard from Stephen O’Brien that he intended to reflect on how patient representatives could be made to feel more welcome.
12. Whilst the appeal panel regretted that the patient experts from Cardiomyopathy UK did not feel that their views were adequately heard in the second committee meeting, it was not convinced that the meeting was conducted unfairly. Notwithstanding that the meeting was not unfair, the appeal panel welcomed Stephen O’Brien’s regret at the impression created and that he would reflect on this, which it considered an appropriate and constructive response.
13. The appeal panel therefore dismissed the appeal on this point.

## Appeal by Pfizer Ltd

### Appeal Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.

1. There was no appeal under this ground.

## Appeal by the British Society of Heart Failure (BSH)

### Appeal Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.

1. There was no appeal under this ground.

## Appeal by Cardiomyopathy UK

### Appeal Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.

1. There was no appeal under this ground.

## Appeal by Pfizer Ltd

### Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

### Appeal point Ground 1a.1 - The Committee has failed to take into account relevant evidence or to explain why the diagnostic algorithm prepared by the National Amyloidosis Centre has not been accepted.

1. Whilst initially raised on Ground 1a in the appeal of Pfizer Ltd, Tim Irish, Vice-Chair of NICE, during initial scrutiny, considered this appeal point more appropriately related to whether the NICE appraisal committee had acted reasonably. Consequently, this appeal point was considered by the panel based on Ground 2.
2. Jack Brownrigg, for Pfizer, stated that there was strong evidence to suggest that whilst the diagnosis of ATTR-CM was historically difficult, following the advent of the NAC algorithm, which can diagnose ATTR-CM with 100% specificity, the diagnosis of ATTR-CM is not now difficult. This is supported by many clinicians in their evidence to NICE, in addition to clinicians from every single Early Access to Medicines Scheme (EAMS) centre. In response to evidence from clinical experts during the appraisal process, raising concerns about the incidental finding of cardiac amyloid deposits on DPD scintigraphy, Jack Brownrigg stated that this is addressed in the first line of the NAC diagnostic algorithm and therefore these patients with an incidental finding of cardiac amyloid on DPD scintigraphy would consequently not be falsely diagnosed with ATTR-CM.
3. Perry Elliot, for Pfizer, stated that incidental finding of cardiac amyloid deposits can be made in two contexts. Firstly, at post-mortem examination, although, in this circumstance we do not have any knowledge of patients premortem cardiac functional status. Secondly when DPD scintigraphy is performed for other indications. He suggested that the proportion of patients who have incidental findings of cardiac amyloid deposits on DPD scintigraphy, performed for other indications, who do not have ATTR-CM is less than 0.43% and therefore not of significant clinical relevance. Furthermore, in neither of these cases would the patients be entered into the NAC algorithm, as the algorithm is only applied to patients for whom there is a sufficiently high prior clinical suspicion of ATTR-CM, and consequently there would be no risk of a false diagnosis of ATTR-CM.
4. Perry Elliot, for Pfizer, was asked to clarify if a robust diagnosis, facilitated by the diagnostic algorithm was necessarily the same as an easier diagnosis. In response Perry Elliot stated that delayed diagnosis of ATTR-CM historically occurred because the cardiologist did not consider the diagnosis or because the appropriate diagnostic tests were not readily available. He said that the availability of tafamidis had improved awareness of ATTR-CM and that there was much easier access to DPD scintigraphy. Consequently, he was now seeing a different natural history and course of the disease as patients were diagnosed earlier.
5. In response Stephen O’Brien, for NICE, stated that while the diagnostic algorithm seemed like a reasonable algorithm it was not the committee’s job to accept or reject the algorithm. There were still delays in diagnosis, not to do with the algorithm but to do with delayed entry into the process that the algorithm describes. He was supported by Jasdeep Hayre, on behalf of NICE, who later stated that it was not in the appraisal committee’s remit to accept or reject the NAC algorithm. He did suggest, however that the ease of diagnosis had an impact on cost-effectiveness which was in the remit of the appraisal committee.
6. The committee felt that delays in diagnosis were not related to a failure to apply the algorithm but to awareness of the condition. Stephen O’Brien reminded the panel that Perry Elliot had stated that a condition for entry into the algorithm was a sufficiently high clinical suspicion of ATTR-CM. Stephen O’Brien suggested that the company’s argument was a little contradictory; if diagnosis of ATTR-CM was so easy how could tafamidis reduce the time to diagnosis further? Stephen O’Brien stated that the committee considered both the possibility that the diagnosis was easy and tafamidis would make no impact on the time to diagnosis. Stephen O’Brien admitted following questioning from the panel that it was difficult to determine how challenging a diagnosis is for a clinician working in the NHS based on the evidence of expert witnesses who by definition have specialist expertise. Stephen O’Brien however suggested that the committee’s primary concern about the challenges of making a diagnosis was related to awareness rather than the utility of the diagnostic algorithm.
7. In response to questions from the panel Stephen O’Brien, for NICE, stated that incidental finding of cardiac amyloid deposits on DPD scintigraphy was not really a significant fact in the decision making of the panel. Adela Williams, for Pfizer, stated that it was essential that the panel should judge if the appraisal committee had acted unreasonably based on the content of the FAD and not based on oral evidence given to the panel during the hearing when they were contradictory. The consistency of Stephen O’Brien’s statement about the importance of incidental amyloid deposits on DPD scintigraphy, with the content of the FAD was disputed, by Stephen O’Brien and Adella Williams.
8. Alex Cale, for NICE, stated that it was unclear how asymptomatic (NYHA Class I) patients came to be diagnosed with ATTR-CM. Perry Elliot, for Pfizer, clarified that these were either patients who had incidental ECG or Echo features of ATTR-CM or who were in NYHA Class II before treatments, such as diuretics, were administered. Perry Elliot cited evidence from the ATTR-ACT trial that patients in NYHA Class I with ATTR-CM could be identified.
9. In conclusion, Emma Clifton-Brown, for Pfizer stated that there was a difference between ease of diagnosis and willingness to diagnose. She also stated that there was a difference between awareness and ease of diagnosis.
10. The appeal panel concluded as follows:
11. The appraisal committee had heard differing opinions from a range of appropriately qualified clinical experts in written and oral submissions about the ease with which a diagnosis of ATTR-CM could be made.
12. It was not the opinion of the panel that the appraisal committee had unreasonably rejected the NAC diagnostic algorithm. In fact, the appraisal committee appeared to broadly accept that where a diagnosis of ATTR-CM was considered the algorithm and non-invasive diagnostic tests facilitated timely diagnosis.
13. The primary concerns of the appraisal committee appeared to relate to the effect that lack of awareness of ATTR-CM may have on the ease of diagnosis of ATTR-CM, because of the delay in considering ATTR-CM as a possible diagnosis rather than a difficulty in diagnosis ATTR-CM once suspected.
14. The presence of incidental amyloid deposits on DPD scintigraphy performed for other indications and uncertainty about how asymptomatic patients entered the NAC Algorithm appear to also have been considered by the committee. Written and oral evidence received by the panel appear to suggest that these factors did not have a significant impact on the appraisal committee’s decision making.
15. It is neither illogical or inconceivable that a diagnosis can be challenging despite the availability of accurate diagnostic tests and algorithms, specifically the diagnostic algorithm from the NAC. Consequently, the appraisal committee could not have been said to have acted unreasonably.
16. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 2.1 - The Committee’s approach to the economic modelling of patients who discontinue treatment with tafamidis during NYHA class 1,2 or 3 is internally inconsistent and disregards the trial data from the ATTR-ACT trial

1. Discussion of this appeal point was preceded by discussion about whether an additional document submitted by Pfizer could be considered as part of their appeal. It was argued by Sam Large, for Pfizer, that this did not constitute new information. Helen Knight and Jasdeep Hayre, for NICE, argued that this could be new information and should not be permitted. The panel permitted the additional document in the expectation that it would not contain new information, on this occasion, however NICE may consider that this does not constitute a precedent for future appeal hearings.
2. Sam Large, for Pfizer, stated that in most clinical trials patients were censored and this represented a form of selection bias, however, in the ATTR-ACT trial there was no censoring, as no patients were lost to follow-up. He stated that ordinarily when survival is modelled the selection bias caused by censoring is accounted for, however as there was no censoring in the ATTR-ACT trial then the modelling of survival was overly pessimistic.
3. Sam Large, for Pfizer, stated that the clinical outcomes for patients in the ATTR-ACT clinical trial were pooled for both patients who continued tafamidis and those who stopped tafamidis. Consequently, assuming that all patients continued to enjoy clinical benefit irrespective of whether they continued tafamidis or not in the economic model was not an optimistic assumption but a reflection of the real-world data from the ATTR-ACT clinical trial. NICE considered two alternative (models) analyses: Alternative Analysis 1 (Alt 1) in which it was assumed that patients who discontinued treatment reverted to the clinical outcomes and costs associated with best supportive management, and Alternative Analysis 2 (Alt 2) in which it was assumed that no patients discontinued treatment, with all the associated life-time costs. Sam Large stated that NICE’s two alternative analyses where flawed and resulted in an overly pessimistic assessment of the cost-effectiveness of tafamidis.
4. Stephen O’Brien, for NICE, stated that this was a key point for the economic analysis of tafamidis. Stephen O'Brien stated that if you stop a medication and it continues to have a clinical effect this favours a very good economic outcome. He stated that the key questions for the appraisal committee were: (1) what proportion of patients in NYHA Class I-III would discontinue the medication, and (2) what would happen to them? He stated it was not clear what the answers were to these questions. Therefore, the appraisal committee wanted to explore using alternative analysis, what were the plausible ranges in which the ICER may sit. Unfortunately, however, even considering all scenario analyses they could not find a situation in which the technology was plausibly cost-effective.
5. Paul Tappenden, for NICE, stated ~~t~~hat the appraisal committee had been clear that they considered a scenario where patients would default to the costs and benefits of best supportive care following discontinuation of treatment as their preferred scenario in every appraisal committee meeting and during the technical engagement phase. He stated that in technical engagement the company accepted that the treatment effect should not be indefinite after tafamidis is stopped. He also stated that the appraisal committee had reservations about the structure of the company’s state transition model, and that these were also accepted at the technical engagement phase by Pfizer. He stated that despite the consensus he felt had been reached at the technical engagement stage at the appraisal committee meeting the company reverted to its base case analysis as a plausible option. He stated that whilst all the models are flawed, the two alternative analyses represent bookends or plausible ranges for the cost-effectiveness of tafamidis.
6. Sam Large, for Pfizer, stated that the company’s base case analysis represented a pessimistic not the most optimistic analysis based on real-world data from the ATTR-ACT trial. He stated that the middle ground was not between Alt 1 and Alt 2. He also stated that some of the changes suggested by NICE were not feasible given the number of patients enrolled in the ATTR-ACT trial. Sam Large stated that NICE’s modelling of survival based on data from ATTR-ACT was also pessimistic. In response to questioning he accepted that the true ICER probably lay between the company’s base case and Alt 1.
7. Emma Clifton-Brown, for Pfizer, stated that 25% of patients in the ATTR-ACT trial discontinued medication so the assumption of continued effect was not flawed. Sam Large, for Pfizer, in response to questions from the panel clarified that this percentage emerged during the 64-month follow-up data from the ATTR-ACT continuation study.
8. In response to questioning from the panel Stephen O’Brien, for NICE, stated that if you considered the true ICER to be between Pfizer’s base case and Alt 1, tafamidis would still be substantially over NICE’s cost-effectiveness threshold.
9. In response to questioning from the panel Stephen O’Brien denied that at every opportunity they had adopted the most pessimistic modelling assumption. He stated that the implication is that appraisal committees are trying to say no to new technology. Stephen O’Brien stated that in contrast, in most of the cases the appraisal committees assess, the new technology is adopted. He stated that often appraisal committees adopt some and not all modelling assumptions. However, in the case of tafamidis the appraisal committee were being asked to accept a string of optimistic assumptions which even so would only just render tafamidis arguably cost effective.
10. Jack Brownrigg, for Pfizer, stated that the FAD suggested that the appraisal committee thought the ICER was bookended by Alt 1 and 2 and not the company’s base case. Stephen O’Brien, for NICE denied that this was the case, referencing paragraph 3.15 of the FAD.
11. Jasdeep Hayre, for NICE, stated that the process guide for NICE clearly states that the company should start the process with its best value proposition, and he was disappointed based on the evidence of Pfizer in the appeal hearing that they did not. In response Emma-Clifton Brown, for Pfizer stated that the company had made an excellent value proposition.
12. Helen Knight, for NICE, stated that NICE’s cost effectiveness threshold was in fact £20-30,000/QALY and that new technology should only be considered at the upper end of the spectrum if there is certainty about cost-effectiveness. This was supported by Stephen O’Brien, also for NICE, who said that the appraisal committee should also take into account technical innovation. Adela Williams, for Pfizer, suggested that in the case of rare diseases, they should be evaluated at the upper end of the spectrum. In response to questioning from the panel on what effect the rarity of the disease should have on the cost-effectiveness threshold, Stephen O’Brien said that technology related to rare diseases are evaluated by a different committee (the highly specialised technologies evaluation committee) using a modified process, and this technology was not referred to this committee. Adela Williams, for Pfizer, stated that if tafamidis was evaluated by any other threshold than £30,000/QALY the appraisal committee should have clearly laid out its reasons in the FAD.
13. In conclusion Emma-Clifton Brown, for Pfizer, stated that the issue before the panel was not whether tafamidis was cost-effective or not, but whether the appraisal committee had acted unreasonably in its modelling of patients who discontinued treatment.
14. The appeal panel concluded as follows:
15. The appeal panel did not feel that the designation of alternative analysis 1 as the appraisal committee’s preferred case was unreasonable given the uncertainty associated with model structure, assumptions, and parameters.
16. The appeal panel noted that there appeared to be consensus between Paul Tappenden (ERG) and Sam Large (Pfizer) that the base-case model, alternative analysis 1, and alternative analysis 2, were all based on flawed assumptions. The panel also noted the apparent agreement between Paul Tappenden and Sam Large that the true ICER may lie intermediate to the Pfizer’s base-case analysis and the appraisal committee’s preferred analysis (alternative analysis 1). This would make it unlikely to fall below the cost effectiveness threshold of £30,000/QALY.
17. The panel were convinced by Paul Tappenden’s explanation that the alternative analyses were attempts to understand ranges for where the ICER may plausibly lie using a structurally flawed model rather than being thought of as an attempt accurately to model use of the drug. This is supported by the written evidence submitted to the panel and consistent with the FAD. This approach and outcome are reasonable and consistent with the NICE guidelines for technology appraisal.
18. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 2.2 - The Committee’s conclusion that there are “challenges” in making the diagnosis of ATTR-CM are not reasonable in the light of the available evidence.

1. The appeal panel refer to the evidence given in response to the appeal by Pfizer point 1a.1 which is relevant to this appeal point.
2. Further to evidence given in relation to the appeal of Pfizer point 1.1a, Jack Brownrigg, for Pfizer, stated there was overwhelming evidence to support the use of the diagnostic algorithm. He stated that it was 100% specific with no false positive results. He stated that whilst he was not arguing that access to swift and accurate diagnosis was possible across the NHS it was clearly possible in EAMS centres.
3. Stephen O’Brien, for NICE, stated that beyond what was discussed in response to the appeal of Pfizer point 1.1a NICE had no further evidence to give in response to the appeal of Pfizer point 2.2.
4. The appeal panel concluded as follows:
5. The appraisal committee heard differing opinions from a range of appropriately qualified clinical experts in written and oral submissions about the ease with which a diagnosis of ATTR-CM could be made.
6. It was the opinion of the panel that the appraisal committee had accepted the effectiveness of the NAC diagnostic algorithm and the accuracy of diagnostic tests for ATTR-CM.
7. The primary concerns of the appraisal committee appeared to relate to the effect that lack of awareness of ATTR-CM may have on the ease of diagnosis of ATTR-CM because of the delay in considering ATTR-CM as a possible diagnosis rather than a difficulty in diagnosis ATTR-CM once suspected.
8. The presence of incidental amyloid deposits on DPD scintigraphy performed for other indications and uncertainty about how asymptomatic patients entered the NAC Algorithm appear to also have been considered by the committee. Written and oral evidence received by the panel appear to suggest that these factors did not have a significant impact on the appraisal committee’s decision making.
9. It is neither illogical or inconceivable that a diagnosis can be challenging despite the availability of accurate diagnostic tests and algorithms. Consequently, the appraisal committee could not have been said to have acted unreasonably.
10. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 2.5 - The Committee’s conclusion that it would be difficult for clinicians to implement a stopping rule for tafamidis does not reflect the available evidence.

1. The appeal panel refer to the evidence given in response to the appeal by Pfizer point 1a.4 which is relevant to this appeal point.
2. Jack Brownrigg, for Pfizer, stated that NICE had disregarded the evidence. Stopping rules had been implemented in numerous national clinical guidelines and the heart failure guidelines of NICE. He stated that the appraisal committee had not listened to the evidence from the second appraisal committee meeting, and from the BSH and other consultees, all of whom were experts in the management of heart failure. He stated that only clinicians who did not look after patients with end-stage heart failure had reservations about the application of stopping rules. Jack Brownrigg stated that patients approve the use of stopping rules. He highlighted evidence from the ATTR-ACT clinical trial which showed that patients entering NYHA class IV stopped tafamidis after a median duration of 9 days (despite the absence of a formal stopping rule) as evidence for the feasibility of a stopping rule. In response to questions from the panel, Jack Brownrigg suggested that the implementation of a stopping rule would have improved the cost-effectiveness of tafamidis. Jack Brownrigg suggested that the application of stopping rules for implantable defibrillators supported their efficacy in heart failure.
3. Perry Elliott, for Pfizer, supported the assertion that stopping rules were used routinely in clinical practice for patients in NYHA Class IV. He explained that many medications such as tafamidis were used to prevent deterioration in function rather than to improve symptoms and that when patients entered end-stage heart failure medications that altered prognosis were stopped and the focus was changed to symptom control. The example of implantable cardiac defibrillators was cited. He stated that whilst they were not a drug, they like tafamidis altered prognosis and therefore this comparison was relevant. Perry Elliot suggested that failure to stop tafamidis for over a week when patients entered NYHA class IV in the ATTR-ACR trial was a trivial period of time. Although Perry Elliot could not cite any evidence that stopping rules could be applied successfully in clinical practice his opinion was clear that they were routinely applied in clinical practice.
4. Stephen O’Brien, for NICE, stated that he would have been more comfortable about implementing a stopping rule had one been included in the ATTR-ACT trial. Furthermore, he stated a small but relevant consideration was whether a stopping rule that could be implemented by highly qualified heart-failure specialists could be more generally applied in the NHS. Alex Cale, for NICE, supported this, stating that the committee knew a stopping rule could be applied but were uncertain whether it would be applied. Perry Elliot, for Pfizer, in response, suggested that in the context of large cardiology centres such as the EAMS centres, stopping rules could be applied.
5. During questioning Stephen O’Brien, for NICE, maintained that the committee had heard from a range of specialists, including heart failure specialists and that he felt the committee had given appropriate weight to the expert opinions of heart failure specialists and specialists in amyloidosis. Jasdeep Hayre, for NICE, suggested that the selection of experts for the tafamidis appraisal was entirely consistent with the processes set out in NICE’s methods guide. He suggested that it was unfair to question the competency of clinical experts who were not present to defend themselves.
6. Stephen O’Brien, in response to questioning from the panel stated that the priority was to ensure that the correct decisions were made about model structure and assumptions to reflect clinical practice before considering what impact these decisions had on the ICER. Stephen O’Brien stated that stopping rules had a smaller effect on the possible cost-effectiveness of tafamidis than other considerations, and that several optimistic modelling assumptions were required to be accepted as true for tafamidis to be cost-effective. Paul Tappenden, for NICE, stated that tafamidis only had an ICER of less than £30,000/QALY if every single one of Pfizer’s modelling assumptions were accepted. Considering all the other modelling assumptions that were the subject of this appeal, stopping rules had the most marginal effect.
7. Emma Clifton-Brown, for Pfizer, in response to questioning from the panel about the importance of stopping rules to Pfizer’s submission, stated that all the appeal points discussed should be individually considered on their own merits and rigorously assessed. Sam Large, for Pfizer, supported Emma Clifton Brown’s statement that all the appeal points should be considered individually, however, he agreed that stopping rules had the smallest impact of all the appeal points but were still important to Pfizer’s submission.
8. The appeal panel concluded as follows:
9. The appeal panel accepted the evidence that heart failure medication and therapies that modify prognosis are routinely stopped after clinicians recognise that the patients will no longer benefit and as the patient’s condition deteriorates to the extent that only symptom control is possible. The appeal panel recognise that this does not constitute a stopping rule and that appropriately qualified clinicians gave expert opinion to the appraisal committee explaining why formal stopping rules are difficult to apply in clinical practice and may be particularly difficult to apply in patients with heart failure.
10. If the uncertainty associated with the feasibility of formal stopping rules in clinical practice is set aside the panel felt that consideration must be given to what criteria could be used to define stopping rules.
11. The panel accept the committee’s reservations about the feasibility of applying stopping rules based on NYHA classification as being reasonable. The committee’s reservations about defining a stopping rule based on NYHA classification alone included its subjectivity and fluctuation in NYHA functional status determined by reversible factors such as systemic infection and fluid overload (See Pfizer Appeal, point 1a.4).
12. The panel recognise the committee’s attempts to explore other parameters that may have better defined a stopping rule but accept that the committee were limited by a paucity of evidence (See Pfizer Appeal, point 1a.4).
13. The panel accepted that there was uncertainty about whether a stopping rule could be applied in this patient cohort. The panel also accepted that it was also uncertain whether clinical and biochemical parameters ordinarily used to measure the severity of heart failure, in particular the NYHA classification, could be reliably used to define stopping rules. Given this uncertainty, the panel did not feel that the appraisal committee could be considered to have acted unreasonably.
14. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 2.6 - The Committee’s conclusions regarding the time to diagnosis of ATTR-CM is unreasonable

1. The appeal panel refer to the evidence given in response to the appeal by Pfizer point 1a.1 and point 2.2 which are relevant to this appeal point.
2. Perry Elliot, for Pfizer, described the impact that the widespread access to DPD scintigraphy and MRI scans had on the ease of diagnosis of ATTR-CM and how this had significantly cut the time to diagnosis. He acknowledged it was uncertain to what extent the introduction of tafamidis has had on the time to diagnosis but suggested that the experience from EAMS suggested that the awareness and availability of tafamidis did have an impact on the time to diagnosis. Perry Elliot said that ATTR-CM was analogous to Fabry disease where the availability of treatment significantly improved awareness of the disease to cardiologists.
3. Stephen O’Brien, for NICE, stated that considerations about the time to diagnosis were very important to the appraisal committee in its determination on tafamidis. This had three parts: (1) was there a delay in diagnosis? (2) why did this delay occur? (3) what were the costs associated with this delay? Stephen O’Brien stated that all three assumptions that Pfizer made about the benefits of tafamidis derived from earlier diagnosis were very optimistic and all three had to be true for tafamidis to be arguably cost-effective. Stephen O’Brien said that NICE considered if some or all the assumptions may be true, however there was no evidence to support this. He stated that Pfizer’s modelling assumptions were not simply dismissed; the appraisal committee wanted to understand and (if plausible) accept them. Pfizer were asked for more evidence to support these assumptions, but none was forthcoming.
4. Paul Tappenden, for NICE, stated that evidence was presented as part of the technical engagement process to support a reduction in time to diagnosis by 2.5 years. This was based on comparison of a historical NAC cohort with data from the EAMS centres. It was assumed that all the effect was because of tafamidis. He stated that it was unclear what effect other factors such as awareness of ATTR-CM and access to diagnostic tests had on this reduction in time to diagnosis relative to tafamidis. He stated that the appraisal committee were concerned that all patients were assumed to have anxiety or depression prior to diagnosis which completely resolved afterwards in Pfizer’s model. Finally, he said that the appraisal committee where uncertain how the figure of £20,000 savings in healthcare expenditure associated with early diagnosis was calculated. Paul Tappenden stated that whilst they asked the company to justify these modelling assumptions no further evidence was provided. Finally, he stated that these modelling assumptions were not present in Pfizer’s initial modelling but were introduced in the technical engagement phase. Paul Tappenden was asked by the panel if he were certain that these benefits could be excluded. He stated that there was uncertainty about whether other factors could explain the reduction in time to diagnosis but no evidence to support the valuation of the benefits associated with the reduction in time to diagnosis.
5. In response, Paul Brownrigg, for Pfizer, stated there was good evidence to support the effect that tafamidis had on the reduction in time to diagnosis as tafamidis was the key change in the landscape and most likely cause of the difference between the historic NAC and contemporary EAMS cohort. He stated that as this was a UK based MHRA regulated scheme it shows that this could be translated to NHS practice. This data also supported the modelling assumption that ATTR-CM was being diagnosed at an earlier stage. Paul Brownrigg cited the fact that patients attended hospital 17 times before a diagnosis of ATTR-CM as justification for the cost savings and the recognised diagnostic odyssey that patients underwent as justification for the modelled improvement in anxiety and depression associated health-related quality of life.
6. In response to questioning from the panel Stephen O’Brien, for NICE stated that it was plausible that tafamidis could explain the improvement in the time to diagnosis, however alternative explanations were also reasonable. Furthermore, the appraisal committee were asked to believe modelling assumption about the benefits of earlier diagnosis without any evidence.
7. Helen Knight, for NICE, suggested that the benefits associated with earlier diagnosis that could be attributed to tafamidis have already been realised as it was currently available to patients and therefore could not be included in an economic model. Emma Clifton-Brown, for Pfizer, challenged Helen Knight asking if Pfizer were being penalised for participating in the EAMS. Helen Knight said she was only suggesting that there was significant uncertainty and NICE had to consider how to maximise benefit for the whole system.
8. Carol Whelan, for BSH, stated that there had been a reduction in diagnosis because of DPD scintigraphy and MRI and this was further improved by tafamidis. She suggested, however, that removal of the only available treatment would result in these benefits to patient care being lost as interest waned.
9. In conclusion, Jack Brownrigg, for Pfizer, stated that despite there being plausible benefits from earlier diagnosis associated with tafamidis it was not reflected in the ICER. Consequently, the appraisal committee’s position was unreasonable.
10. The appeal panel concluded as follows:
11. The appeal panel heard evidence that there had been a reduction in the time to diagnosis in EAMS centres compared to the historical data from the NAC.
12. The panel acknowledge that there is uncertainty about whether this is explained by better access to diagnostic tests, increased awareness of ATTR-CM in general and specifically the diagnostic algorithm, access to tafamidis, or other factors, or a combination of some or all of these. The panel therefore acknowledge that there is uncertainty about whether this improvement in diagnostic time can be realised more generally following introduction of tafamidis.
13. The panel shared the concerns that the appraisal committee had about the way that the benefits of early diagnosis were modelled. There was significant uncertainty whether the modelled benefits in health-related quality of life associated with depression and anxiety, and the cost-savings associated with early diagnosis would be realised, given the absence of evidence and scant justification.
14. Whilst this cannot be described in detail in the FAD for reasons of confidentiality, there is evidence from written submissions to the panel from NICE that the appraisal committee considered the impact on the cost-effectiveness of tafamidis of accepting some, all, or none of Pfizer’s modelling assumptions. It is clear however that tafamidis was only arguably cost-effective if every modelling assumption in Pfizer’s base case was accepted. In effect then for the recommendation to be unreasonable it would have to have been unreasonable not to accept each of Pfizer’s assumptions. But the panel considered there were reasonable alternatives to those assumptions and no evidence that would compel acceptance of Pfizer’s preferred values.
15. The panel concluded that the appraisal committee could not have been said to have acted unreasonably given the uncertainty associated with the causes of improved time to diagnosis; the uncertainty about whether this can be applied more generally in NHS practice; the uncertainty about the modelling strategy employed by Pfizer, and finally, the appraisal committee’s rigor in exploring the implications of these assumptions in the form of scenario analysis.
16. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 2.8 - The Committee’s conclusions around the impact of tafamidis in reducing time to diagnosis as demonstrated through EAMS are not reasonable.

1. The panel considered that the arguments raised under this appeal point together with points raised during the appeal by Pfizer grounds 1.1a, 2.2 and 2.6.
2. The appeal panel therefore dismissed the appeal on this ground for the reasons given under the appeal by Pfizer grounds 1.1a, 2.2 and 2.6.

## Appeal by the British Society of Heart Failure (BSH)

### Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

### Appeal point Ground 2.1 - The conclusion ‘But clinical benefit varies across different types and stages of ATTR-CM’ is unreasonable

1. Lisa Anderson, for BSH, stated that the FAD concludes that clinical benefit varies across different types and stages of ATTR-CM. This is an unreasonable thing to say given the results of ATTR-ACT as it is well recognised that sub-group analysis is problematic. She stated that it is well recognised that outcomes are worse in NYHA III-IV, and this is the case in every heart failure trial. Furthermore, she stated that the sub-group analysis of ATTR-ACT was underpowered to look at differences between wild-type and hereditary ATTR-CM. Lisa Anderson therefore concluded that it would be unreasonable to deny tafamidis to any sub-group of patients with ATTR-CM if it were approved. Consequently, she thought that the inclusion of this statement in the FAD was unreasonable. Lisa Anderson also stated that had heart failure specialists been consulted appropriately the committee would not have made errors of this kind.
2. In response to this appeal point and questions from the panel Stephen O’Brien, for NICE, stated that it is a statement of fact that patients in different NYHA classes had different outcomes associated with tafamidis. This is based on statistically significant sub-group analysis. He stated, however, that subgroup analysis did not play any role in the decision to recommend or reject the technology. He stated that at no point during the appraisal process was there any plan to exclude any sub-group from the guidance.
3. The appeal panel concluded as follows:
4. The panel are satisfied that this is a factual statement in the FAD based on data from the ATTR-CM clinical trial. The panel is also satisfied that the appraisal committee did not plan or do any modelling based on an under-powered sub-group analysis to define which groups would benefit from tafamidis. The appraisal committee can therefore not be judged to have behaved unreasonably.
5. The appeal panel therefore dismissed the appeal on this point.

### Appeal point Ground 2.2 - The conclusion “The measure used to assess how severe ATTR-CM is, has limitations. This makes it difficult to clearly identify who benefits from tafamidis and whether they should continue treatment.’” is unreasonable.

1. The appeal panel refer to the evidence given in response to the appeal by Pfizer point 1a.4 and point 2.5 which are relevant to this appeal point.
2. Carol Whelan, for BSH, stated that a fundamental problem with the ATTR-ACT trial was that it was being treated as a rare disease trial rather than a heart failure trial and that clinicians make decisions about stopping treatment every single day. In response to questions from the panel about how we know that clinicians apply stopping rules and what evidence is available, Carol Whelan stated that, she is on-call now, and this is what she does every day.
3. Lisa Anderson, for BSH, supported the statement of Carol Whelan that stopping medications that no longer help the patient is part of routine clinical practice. She suggested that in the case of tafamidis this was entirely feasible as the drug did not make patients feel any different. She stated that the ATTR-ACT trial showed that patients stop tafamidis within a short period of time following deterioration into NYHA class IV. This was congruent with her own experience as she has stopped medication for an ATTR-ACT participant in end-stage heart failure. Lisa Anderson did not feel that fluctuation between NYHA class III and IV was a problem as patients were optimised before assessment.
4. The appeal panel concluded as follows:
5. The appeal panel are satisfied that the committee understood that the NYHA system is extensively used in clinical practice, the academic literature, NICE guidelines, and technology appraisals.
6. The committee recognised the difficulty in defining a stopping rule based on the NYHA classification alone. This was supported by the oral and written evidence of experts during the appraisal process. Evidence heard by the panel during the hearing from BSH and Pfizer clinical experts, who asserted that NYHA was not used in isolation when making this decision but in conjunction with other clinical and diagnostic tests appear to support the committee’s reservations about using NHYA alone to define stopping rules. Consequently, the panel cannot be said to have acted unreasonably.
7. The appeal panel therefore dismissed the appeal on this point.

## Appeal by Cardiomyopathy UK

### Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

1. There was no appeal under this ground.

## Conclusion and effect of the appeal panel’s decision

1. The appeal panel therefore dismissed the appeal on all grounds.
2. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE’s decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.
3. The final evidence the appeal panel heard was that of Vince Nicholas. He talked eloquently about his experience of living with ATTR-CM. The panel were moved by his account of the impact of having a diagnosis of ATTR-CM with no available treatment, and the effect that this also had on family and carers. He urged NICE and Pfizer to find a way to make tafamidis available to patients.
4. The appeal panel share the regret expressed by the chair of the appraisal committee, patients, and others that tafamidis could not be approved within the NICE TA framework. ATTR-CM is a rare disease with a very poor prognosis. Tafamidis is the only treatment available for most patients. The technology is innovative and the clinical trial data is compelling.
5. An appeal is a limited and defined process and the appeal panel’s role is circumscribed. Without in any way casting doubt on the outcome of this appeal or criticising the appraisal committee which the appeal panel has found has performed its role correctly, the appeal panel hope that there might be a way for NICE’s Guidance Executive to facilitate discussion between Pfizer Ltd and NHS England for those two bodies to explore ways to make tafamidis available to ATTR-CM patients in the NHS. The appeal panel is not concluding that the publication of the guidance has to be postponed while this is done, but would encourage the progression of resolution prior to publication.