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Worldwide Biopharmaceutical Businesses

Mr. Tim Irish
Appeals Committee Vice Chair
National Institute for Health & Care Excellence
10 Spring Gardens
LONDON
SW1A 2BU

30 October 2020

Dear Mr Irish,

APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR TAFAMIDIS FOR TREATING TRANSTHYRETIN AMYLOIDOSIS WITH CARDIOMYOPATHY

EXECUTIVE SUMMARY

Pfizer's appeal is based on the following grounds:

Ground 1

1.1 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;

1,2 The Committee's conclusions regarding the diagnosis of ATTR-CM have misconstrued the European Public Assessment Report for tafamidis;

1.3 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;

1.4 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;

Ground 2

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;

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;

2.3 The Committee's statement indicating that all patients with suspected amyloidosis are referred to the National Amyloidosis Centre for testing is incorrect;

2.4 The Committee's suggestion that biomarkers could have been used as an alternative to NYHA classification to assess disease stage and who would benefit from treatment is unreasonable;

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;

2.6 The Committee's conclusions regarding the time to diagnosis of ATTR-CM is unreasonable;

2.7 The Committee's conclusion that tafamidis has no impact on awareness of ATTR-CM is inconsistent with its view that other products are increasing awareness;

2.8 The Committee's conclusions around the impact of tafamidis in reducing time to diagnosis as demonstrated through EAMS are not reasonable; and

2.9 The assertion that Pfizer failed to make use of longer-term data in its extrapolation of treatment effects is unreasonable.

INTRODUCTION

Pfizer refers to its original submission in this appraisal. While a summary is provided below, this is not intended to replace the details originally supplied to NICE.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare, progressive and ultimately fatal disease, characterised by deposition of transthyretin (TTR) amyloid in the myocardium. This damages the myocardium resulting in cardiomyopathy and progressing to heart failure.

TTR is principally synthesized in the liver. It is made up of four identical subunits or monomers and acts as a carrier for vitamin A and thyroxine. Alterations in the structure of the TTR protein increase its tendency to break down into its constituent monomers, which misfold and aggregate into insoluble amyloid fibrils; these are then deposited in tissues and organs, including the heart.

ATTR-CM has two causes:

- Wild-type ATTR-CM, the more common form (approximately 69% cases in the UK), which is associated with ageing and is not inherited; and

- Hereditary ATTR-CM (approximately 31% of cases in the UK), inherited as an autosomal dominant disease

The average age at diagnosis is 78 years for the wild-type form and 73 years for the hereditary form. Both forms of the disease affect men more commonly than women. The incidence is not known, however increasing use of a non-invasive diagnostic algorithm and greater awareness

among clinicians has increased recognition of ATTR-CM, particularly in patients with wild-type disease.

Median survival among patients with ATTR-CM in the UK ranges from 2.3 to 6.1 years. The disease is also associated with progressive disability, with heart failure causing shortness of breath, fatigue, functional limitation and frequent hospitalisations. Patients often report pain and gastrointestinal symptoms. The disease adversely affects health related quality of life. Studies describe progression of symptoms and functional decline, measured by NYHA class and walking distance respectively.

Management of ATTR-CM in the UK is principally symptomatic, with no disease modifying pharmacological therapies available. Liver transplantation, to remove the source of TTR and heart transplantation have been described but are offered only in exceptional cases in the UK. Affected patients accordingly have a high clinical need for effective treatment.

Tafamidis is a specific stabiliser of transthyretin (TTR) which binds to the native tetramic forms of transthyretin, preventing its dissociation into monomers and reducing amyloid formation.

A 2019 consensus recommendation of the Heart Failure Association of the European Society of Cardiology indicates that tafamidis should be considered in patients with symptomatic heart failure due to confirmed ATTR-CM, to improve exercise capacity and quality of life and to reduce cardiovascular hospitalisations and mortality.

PROCEDURAL HISTORY OF THE APPRAISAL

Date	Event
15 July 2019	Referral to NICE
18 February 2020	Tafamidis approved by the European Commission for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).
15 July 2019	Final scope for appraisal
30 September 2019	Pfizer submission to NICE
7 May 2020	First meeting of the Appraisal Committee
11 June 2020	Appraisal Consultation Document issued "Tafamidis is not recommended, within its marketing authorisation, for treating wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults"
2 July 2020	Pfizer and other consultees and commentators submit responses to consultation on ACD.
1 September 2020	Second meeting of the Appraisal Committee
9 October 2020	Final Appraisal Determination issued Recommendations unchanged from those in ACD

30 October 2020	Deadline for submission of appeal

GROUNDS OF APPEAL

1. **GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS**

   1.1. Appeal Point 1.1a: 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.

At paragraph 3.3 of the FAD, the Appraisal Committee states:

> "*Two of the clinical experts agreed that there were challenges in diagnosing ATTR-CM accurately, but noted the developments in recent years"*.

Then, in paragraph 3.4 of the FAD, the Appraisal Committee states:

> "*Two of the clinical experts explained that transthyretin amyloid deposits are often an incidental finding in people having DPD scans and may not necessarily be associated with a diagnosis of ATTR-CM……In addition because other common comorbidities can lead to increased breathlessness and decreased mobility, reaching a definitive ATTR-CM diagnosis is challenging. At consultation, the company commented that the NAC published a non-invasive diagnostic pathway for ATTR-CM in 2016. It explained that the pathway had been validated and implemented at 17 Early Access to Medicines Scheme (EAMS) sites. It further explained that based on this pathway, only people with symptoms and certain clinical features are eligible for DPD scans. So amyloid deposits identified through the pathway are not incidental…..At the second committee meeting one of the clinical experts confirmed that incidental amyloid deposits would not result in an increase in amyloidosis diagnoses because other clinical features outlined in the ATTR-CM diagnostic pathway would be taken into account… The Committee ….agreed that even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM".*

- The statement at paragraph 3.3 of the FAD represents only part of evidence provided by amyloid disease experts from the NAC at the first meeting of the Appraisal Committee. In particular, it does not reflect the opinion of Professor Hawkins, from the NAC, in his written evidence for this appraisal

  > "…..*cardiac ATTR amyloidosis is now recognised to be a common and easily diagnosed disorder*"

Furthermore, the statement at paragraph 3.3 of the FAD and the conclusion at paragraph 3.4 do not take into account evidence given to the Committee at its second meeting, when, Professor Perry Elliott from University College London was invited to attend as a further clinical expert. Professor Elliott has a 25-year clinical experience in managing cardiomyopathies including ATTR-CM, is past Chairman of the European Society of Cardiology Working Group on Myocardial Diseases, is Principal Investigator in the ATTR-ACT trial of tafamidis and also the Helios-B trial of vutrisiran in ATTR-CM. He also treated patients with tafamidis under

MHRA's Early Access to Medicines Scheme (EAMS). Professor Elliott described an internationally validated algorithm for diagnosis of ATTR-CM, developed by clinicians (including those from the NAC who advised the Appraisal Committee in this appraisal) and published in 2016 (Gillmore et al (2016)[1]), consistent with the recommendation set out by the CHMP in the EPAR.

The algorithm uses non-invasive scintigraphy (DPD scans) and laboratory tests and differentiates ATTR-CM from incidental amyloid deposits, because patients are only eligible for a DPD scan / laboratory tests if they meet the following criteria:

> "*Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/ or cardiac magnetic resonance imaging suggesting/ indicating cardiac amyloid*".

Gillmore et al concludes:

> *"Bone scintigraphy enables the diagnosis of ATTR CM to be made reliably without the need for histology (biopsy) in patients who do not have a monoclonal gammopathy. We propose non-invasive diagnostic criteria for cardiac ATTR amyloidosis that are applicable for the majority of patients with this disease..."*

The algorithm has been supplemented by international expert recommendations, that are endorsed by multiple professional societies across Europe and the United States (see e.g. Dorbala et al 2019[2], Seferovic et al 2019[3], Habib et al 2017[4]).

However, the conclusion at the end of paragraph 3.4 of the FAD indicate that the Committee has failed to take into account the evidence of Professor Elliott. In particular, while the Committee refers to the algorithm, they provide no explanation for rejecting it or for the conclusion, contrary to the evidence of the experts *"even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM"*

The Committee has therefore either failed to take into account or has omitted to explain its reasons in respect of the following matters:

a) The purpose of a diagnostic algorithm such as that proposed by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) is to achieve appropriate diagnosis of ATTR-CM. The algorithm described by Professor Elliott is specifically designed to achieve reliable diagnosis and has been validated and approved internationally. In the UK it has been used at 17 sites across the UK in the context of the EAMS and its success confirmed in the EAMS Cardiac Group's response to

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[1] Gillmore JD et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation.2016;133:2404-2412

[2] Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2—evidence base and standardized methods of imaging. *Journal of Nuclear Cardiology.* 2019;26(6):2065-2123.

[3] Seferovic, Petar M., et al. "Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology." *European journal of heart failure* 21.10 (2019): 1169-1186.

[4] Habib, Gilbert, et al. "Multimodality imaging in restrictive cardiomyopathies: an EACVI expert consensus document In collaboration with the "Working Group on myocardial and pericardial diseases" of the European Society of Cardiology endorsed by the Indian Academy of Echocardiography." *European Heart Journal-Cardiovascular Imaging* 18.10 (2017): 1090-1121.

consultation on the ACD through the NICE website. Clear and cogent reasons must therefore be provided for rejecting use of the algorithm.

b) The algorithm addresses the difficulty in diagnosis of certain patients with NYHA Class 1 as described in the EPAR. A diagnosis of ATTR-CM in accordance with the algorithm requires the presence of specific signs or symptoms of heart failure. These comprise cardiac remodelling on echocardiogram or magnetic resonance imaging, in combination with clinical signs of heart failure that can include swollen legs or fatigue (not necessarily breathlessness required for NYHA 2 classification) or a previous hospitalisation for heart failure.

c) The algorithm also addresses the concern that amyloid deposits identified on DPD scans may be incidental findings. As explained by Professor Elliott, all patients who undergo DPD scans in accordance with the algorithm have a cardiomyopathy phenotype and any identification of amyloid deposits cannot therefore be incidental.

d) Ease of diagnosis was also confirmed by the British Society for Heart Failure. In response to statements in the ACD that ATTR-CM is challenging to diagnose accurately and can take a long time, the they commented "*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….*"

The Committee seems to have adopted certain views of the NAC clinical experts (reported at paragraph 3.3 of the FAD) that there may be challenges in accurate diagnosis of ATTR-CM, but rejected their written opinions, the contrary views of Professor Elliott, the British Society for Heart Failure and the EAMS Cardiology Group. No explanation for this approach is provided.

Furthermore, the Committee has failed to provide any explanation why it has concluded that the internationally validated algorithm, discussed by Professor Elliott at the second meeting of the Appraisal Committee and used successfully by 17 UK centres in the context of the EAMS for tafamidis, does not resolve its diagnostic concerns.

These issues are central to this appraisal. At paragraph 3.26 of the FAD, the Appraisal Committee refers specifically to its view that diagnosis is complicated and can take a long time as well as the need for validated and objective measures for identifying patients who need treatment, as reasons why tafamidis is not recommended:

> "*It noted that awareness of ATTR-CM was improving but getting a definitive diagnosis was complicated and can take a long time (see section 3.3)*".

Adequate reasoning is a fundamental aspect of a fair and transparent procedure, so that a consultee such as Pfizer can engage with the process and understands in sufficient detail why its application has been unsuccessful and what it needs to do in order to achieve a positive result and also as a marker for rigorous decision making. The Committee's position that diagnosis remains "*challenging*", despite the existence of the diagnostic algorithm, specifically developed in order to facilitate consistent diagnosis of ATTR-CM and internationally validated for that purpose, requires proper reasoning and failure to provide this is procedurally unfair.

1.2. <u>Appeal Point 1.2a: The Committee's conclusions regarding the diagnosis of ATTR-CM have misconstrued the European Public Assessment Report for tafamidis</u>

At paragraph 3.4 of the FAD, the Appraisal Committee states:

> *"The Committee was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NYHA 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). The Committee acknowledged this and agreed that even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM".*

The misunderstanding of the European public assessment report (EPAR) for tafamidis may result from the fact that clinical trials for tafamidis were designed some 10 years ago and therefore the EPAR refers to diagnostic procedures used for the purposes of the trials, which would not be used routinely today. In particular, the EPAR makes clear that, while biopsy was conducted historically (including in the ATTR-ACT trial), following ready access to non-invasive tests which provide accurate diagnosis, this is no longer standard practice.

- "*Definitive diagnosis of ATTR-CM had been dependent upon tissue biopsy, in combination with presence of symptomatic heart failure, when the pivotal study B3461028 was initially designed (Rapezzi et al. 2010). More recently, a non-biopsy approach using technetium-labeled bone scintigraphy tracers has emerged. This approach is considered highly sensitive and specific for diagnosing ATTR-CM in both hereditary and wild-type subjects (Gillmore et al. 2016, Castano et al. 2016, Bokhari et al. 2013). It could detect TTR amyloidosis prior to an increase in left ventricular wall thickness or the development of clinical syndrome of heart failure and a rise in cardiac biomarkers, making early identification and treatment more likely (Hag et al. 2017, Glaudemans et al. 2014, Galat et al. 2014)*" (page 11, describing procedures necessary for identification of disease).

- "*Biopsy is currently rarely performed with a suspicion of ATTR-CM in clinical practice because it is an invasive act. However a non-biopsy approach is now recommended*" (page 53, commenting on the clinical trial programme).

The EPAR recommends "*some specific algorithm for diagnosis of ATTR-CM should be used to allow better prognosis with early and adequate treatment of patients*" (page 11).

The Committee has seemingly misconstrued the EPAR and relied upon this to conclude, incorrectly:

- That both biopsy and scintigraphy would be required in order to diagnose ATTR-CM, whereas only one of these two investigations is needed (and invasive investigations, such as biopsy are not recommended now that reliable, non-invasive investigations such as scintigraphy are widely available.);
- That the EPAR supports a view that there is difficulty diagnosing patients with ATTR-CM other than "*patients with NYHA class 1, particularly if they do not have heart failure*", when many patients with NYHA class 1 will have symptoms of heart failure and the EPAR did not suggest that there would be difficulties in diagnosing any other category of patients with ATTR-CM ;

- That scintigraphy is a different investigation from DPD scans, now widely available in the NHS, whereas these are different names for the same procedure.
- That the EPAR supports any difficulty in diagnosis if a specific algorithm is used.

Overall, the Committee seems to misunderstand the EPAR as suggesting that there are difficulties in diagnosis for all patients with ATTR-CM, when it does not make such a statement and this is clearly not the correct interpretation.

1.3. Appeal Point 1.3a: 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

At paragraph 3.7 of the FAD, the Appraisal Committee relies on the fact that the marketing authorisation for tafamidis does not include starting and stopping rules based on NYHA classification, as a reason for not using these in NICE guidance.

However, few marketing authorisations include stopping rules, because such rules are generally developed by payers or HTA bodies based on clinical and cost effectiveness in specific disease scenarios, rather than efficacy data collected during the clinical trial programme. Therefore most stopping rules are applied to technologies in circumstances where the marketing authorisations include no rules on when the product should be discontinued.

As a consequence, the overwhelming majority of stopping rules approved by NICE (if not all of such rules) are based on cost effectiveness rather than any requirement of the marketing authorisation (see the examples at Appeal Point 2.5 below) and the Appraisal Committee's requirement that any stopping rule should be reflected in the SmPC disregards the reason why most stopping rules are developed and is an irrelevant consideration.

1.4. Appeal Point 1.4a/b: 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

At paragraph 3.7 of the FAD, the Appraisal Committee concludes that it is not appropriate to specify starting and stopping rules for tafamidis based on the NYHA classification system, even though it is aware that NYHA classifications have been used in previous NICE recommendations to define populations eligible for treatment with heart failure therapies. No explanation for applying a different approach to the assessment of severity of heart failure in this appraisal, to that followed in other appraisals is provided.

This is not a situation where a difference in the technology under consideration or the available trial data can justify a difference in approach. The NYHA classification is simply a commonly used system to assess heart failure. While the Appraisal Committee states at paragraph 3.6 that it is "*sometimes used to measure the severity of ATTR-CM*", it is the most widely used measure to assess heart failure in ATTR-CM patients and its use is supported by a study conducted at the NAC showing that NYHA class independently predicts prognosis in ATTR-CM (Pinney et

al 2013[5]). In their response to consultation on the ACD, the EAMS Cardiac Group stated their belief that the Committee's view "*that the NYHA class is an unreliable predictor of prognosis is mistaken*", referring to the NAC study and also data from a French Amyloidosis Centre which support those findings. The Committee has not suggested that any other assessment tool is used commonly in clinical practice.

The NYHA classification system was therefore used by NICE in the following technology appraisal guidance:

- Implantable cardioverter defibrillators (TA314, where treatment is recommended for one group, subject to symptoms being NYHA class 1,2 or 3 (but not class4)

- Cardiac resynchronisation therapy (TA120) where treatment is recommended for one group, subject to symptoms of heart failure being NYHA class 2,3 or 4 (but not class 1).

- Sacubitril/valsartan (TA388) for the treatment of chronic heart failure, where treatment is recommended only in patients where symptoms are NYHA classes 2,3 or 4 (but not class 1)

- Ivabradine (TA267) for treating chronic heart failure for people with New York Heart Association (NYHA) class 2 to 4 (but not class 1)

- Dabigatran etexilate (TA249) for the prevention of stroke and systemic embolism…with one or more of the following risk factors…. symptomatic heart failure of New York Heart Association (NYHA) class 2 or above (but not class 1)

In addition, use of the NYHA classification system for assessment and diagnostic purposes has been recommended by NICE in the following NICE Guidelines:

- Chronic heart failure in adults (NG106)
    - it recommended that the specialist heart failure MDT should manage newly diagnosed, recently decompensated or advanced heart failure (NYHA [New York Heart Association] class3 to 4) and,
    - for the use of hydralazine in combination with nitrate - seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class3 to 4]
- Intrapartum care for women with existing medical conditions (NG121)
    - it recommends for women with heart disease, reassess intrapartum risk regularly during pregnancy and the intrapartum period using a number of assessments including New York Heart Association (NYHA) functional class

Pfizer accepts that the Appraisal Committee may reach a different conclusion on the measure of severity of heart failure in this appraisal to that reached in other appraisals. However valid

[5] Pinney, Jennifer H., Carol J. Whelan, Aviva Petrie, Jason Dungu, Sanjay M. Banypersad, Prayman Sattianayagam, Ashutosh Wechalekar et al. "Senile systemic amyloidosis: clinical features at presentation and outcome." *Journal of the American Heart Association* 2, no. 2 (2013): e000098.

reasons justifying an inconsistent approach are required. In this case no such reasons have been provided.

It is Pfizer's case that there are particular reasons why a consistent approach should be applied to different treatments for different causes of heart failure. At paragraph 3.24 of the FAD, the Appraisal Committee acknowledges that "*ATTR-CM disproportionately affected people from certain ethnic groups*" and it is also predominantly a disease affecting older persons. To deprive patients with ATTR-CM access to treatment with tafamidis (the only disease modifying therapy available) on the basis that the Committee concluded that starting and stopping rules should not be based on NYHA classification, whereas patients with other forms of heart failure gain access to effective treatment based on assessment of NYHA status, is potentially discriminating against ATTR-CM patients despite the high proportion of such patients within certain ethnic groups and in older age groups, where race and age are protected characteristic under the Equality Act 2010. In these circumstances, the requirement for the Committee to justify adopting a different approach to the determination of eligibility for heart failure treatment in this appraisal, to that accepted in appraisals of other heart failure treatments is enhanced.

2. GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE

2.1. Appeal Point 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

At paragraph 3.15 of the FAD, the Committee notes evidence from the ERG that "*in the economic model, people in the NYHA class 1-3 health states who stop treatment with tafamidis are assumed to benefit from treatment indefinitely without any treatment costs*".

While Pfizer explained that "*the relative treatment effect for tafamidis was estimated from ATTR-ACT and incorporated the treatment effects for people who remained on treatment and those who stopped. So the effect of stopping treatment is already accounted for in its treatment effectiveness estimates*". This was accepted by the Committee at paragraph 3.16 of the FAD, "*It also acknowledged that reverting to best supportive care outcomes after stopping treatment would be conservative. This was because the estimates of tafamidis' treatment effects already included people who stopped treatment during the trial period (see section 3.15)*".

Nevertheless, the Committee states at the end of paragraph 3.15 "*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)*".

Accordingly, at paragraph 3.16, the Committee accepted alternative analyses conducted by the ERG for the purposes of decision making:

> "*On balance the committee recognised that both of the ERG's alternative analyses had limitations but agreed that they provided realistic alternatives to the company's overly optimistic analyses."*

The conclusions that Pfizer's analyses are "*overly optimistic*" and that the ERG's alternative analyses are "*realistic alternatives*" are unreasonable in the light of the available evidence.

- Deducting treatment benefits from the treatment effectiveness estimates produced by Pfizer, to reflect patients who discontinue treatment in NYHA class 1,2 or 3 would represent a double reduction for those patients, in circumstances where the effects of stopping treatment are already accounted for in the estimates obtained from the ATTR-ACT trial. This was recognised by the Committee in paragraph 3.16. of the FAD, conflicting with the conclusion in paragraph 3.15.

- The Committee refers to the results of a recent in vitro study (Verona et al 2017[6]) and interprets its findings to suggest that transythretin stabilisation does not necessarily inhibit amyloid formation and say that "*the mechanism underlying tafamidis' proposed benefit is unclear*".

    - The reference to "*proposed*" benefit is unexplained, but suggests that benefit is questioned by the Committee, conflicting with the regulatory approval for tafamidis and the data from ATTR-ACT.

    - Furthermore, it is uncertain from the FAD whether the Committee relied on Verona et al to conclude that patients who discontinue tafamidis would experience no further benefit. Such a conclusion, based on in vitro data, would be unreasonable in the context of clinical data from ATTR-ACT which provides empirical treatment effectiveness estimates. We believe the committee's interpretation of the in vitro study is incorrect. The findings of Verona et al do not contradict the mechanism of action of tafamidis but rather demonstrate superior in vitro stabilisation of transthyretin and more potent inhibition of TTR amyloid fibrillogenesis with two experimental compounds (Tolcapone and mds84) under certain conditions. In similar conditions, tafamidis inhibited amyloid formation by 60%, tolcapone by 80% and mds84 by 90%. Rather than contradicting the mechanism of inhibiting amyloid formation, this study is confirmatory of the mechanism. In the ATTR-ACT clinical trial there is robust direct evidence of target engagement providing additional evidence of 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 ($p<0.0001$).

- The ERG's alternative analyses involve either:

  (i) beyond the observed data in the trial, no patients discontinue during NYHA class 1,2 or 3 and therefore full costs of tafamidis treatment are applied throughout, disregarding the evidence from ATTR-ACT where patient did discontinue in NYHA classes 1-3 and the Committee's recognition at paragraph 3.16 of the FAD, that '*some people would likely stop tafamidis for reasons other than disease progression or death, for example adverse events or older age. So, it agreed it was implausible to assume that everyone in the NYHA class 1 to 3 health states would remain on treatment indefinitely after the clinical trial period*.'; or

  (ii) patients continue to discontinue treatment during NYHA class 1,2 or 3 but are assumed to revert immediately to the same level of benefit as the placebo group, despite

[6] Verona et al (2017). Inhibition of the mechano enzymatic Amyloidogenesis of transthyretin: role of ligand affinity, binding cooperativity and occupancy of the inner channel. Sci Rep. 15;7(1):182.

the treatment effect estimates from ATTR-ACT incorporating the effects of patients who did discontinue during the trial.

Both of these analyses are therefore inappropriate because they do not reflect the trial data and no explanation has been provided for rejecting this.

2.2. **Appeal Point 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**

Pfizer's primary case is that in reaching its conclusion at paragraph 3.4 of the FAD that "*even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM*", the Committee failed to take into account all relevant evidence as set out in Appeal Point 1.1 above. However, in the alternative, Pfizer submits that the conclusions of the Committee in this respect do not represent a reasonable interpretation of the available evidence.

Pfizer's submissions under Appeal Point 1.1 are repeated.

2.3. Appeal Point 2.3: The Committee's statement indicating that all patients with suspected amyloidosis are referred to the National Amyloidosis Centre for testing is incorrect

At paragraph 3.4 of the FAD, the Appraisal Committee states that "the clinical experts and the NHS England representative explained that when amyloidosis is suspected people are referred to the NAC for more rigorous testing".

The above statement reflects evidence provided at the first meeting of the Appraisal Committee. The only clinical experts present at that meeting were from the NAC and, without challenging their undoubted expertise in the diagnosis and treatment of amyloid disorders generally, cardiac amyloid is now often managed by expert cardiologists at other centres. In these circumstances, following the first meeting of the Appraisal Committee, Pfizer submitted that it was important for the Committee to have access to evidence from clinicians outside NAC and without a NAC perspective.

At the second meeting of the Appraisal Committee therefore, NICE invited Professor Perry Elliott, as an expert cardiologist, with experience of diagnosis and treatment of ATTR-CM outside the NAC, to attend. He confirmed that while historically, patients with suspected ATTR-CM would be referred to NAC for testing to confirm the diagnosis, the development and ready access to non-invasive tests (such as DPD scans) means that appropriate diagnosis is no longer limited to NAC, but may readily be achieved at other expert centres. Professor Elliott's evidence was confirmed by the evidence of Professor Fontana of the NAC, who stated at the time of her original submission that a "network of 8-10 centres" was being established and experience during the EAMS, where 147 patients were diagnosed with ATTR-CM and received tafamidis treatment across 17 centres. However, the Committee has not revised the earlier incorrect statement regarding referral to NAC for diagnosis, despite the evidence of Professor Elliott at the second Appraisal Committee meeting, the NAC's evidence regarding "a network of centres" and NHS experience during the EAMS.

The issue raised in this point of appeal is central to the issues in this appraisal, because it supports what Pfizer submits is an erroneous conclusion of the Committee that correct diagnosis of ATTR-CM is challenging.

2.4. **Appeal Point 2.4: The Committee's suggestion that biomarkers could have been used as an alternative to NYHA classification to assess disease stage and who would benefit from treatment is unreasonable.**

At paragraph 3.6 of the FAD, the Appraisal Committee stated that cardiac markers (the two mentioned in the FAD were B-type natriuretic peptide and glomerular filtration rate) could have been used to identify disease stage and who would benefit from treatment, rather than the standard approach using NYHA classification, which was rejected as a basis for starting and stopping rules. The basis for the Appraisal Committee's conclusions regarding use of cardiac markers were seemingly:

- A statement by one of the clinical experts that "*a measure based on cardiac markers such as B-type natriuretic peptide and glomerular filtration rate had potential to identify disease stage and who is benefitting from treatment, but evidence of use in ATTR-CM in clinical practice was limited*"; and

- An observation by the ERG (who do not have cardiology expertise and did not (based on the acknowledgements to their report) consult any cardiologists) that there were merits to assessing disease severity using objective measures such as cardiac markers.

In view of the fact that use of cardiac markers to assess severity of disease in ATTR-CM is not standard clinical practice, experience is limited and this concept was not published until after the ATTR-ACT trial was designed and fully enrolled, it is unreasonable for the Committee to state that use of such markers could have been used in preference to the established NYHA classification, to identify disease stage and who would benefit from treatment. It is, furthermore, unreasonable in these circumstances to criticise the design of Pfizer's clinical trials on the basis that they did not incorporate sufficiently frequent measurements of cardiac markers to permit use of such measurements to permit identification of disease stage and who would benefit from treatment.

2.5. Appeal Point 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

At paragraph 3.7 of the FAD, the Committee considers whether a stopping rule for tafamidis would be clinically feasible. It refers to evidence from one clinical cardiology expert (Professor Elliott) with expertise in treating heart failure patients who advised that discontinuation of treatment at NYHA class 4 is common because at this stage patients are very unwell. This view was also supported by the patient organisation in response to the ACD:

- UKATPA 'Both clinicians and patients are perfectly used to starting and stopping medication not only in cardiac disease but in all disease areas.'

- UKATPA 'We feel that it would be reasonable to include a stopping rule for patients with significant disease progression.'

- Cardiomyopathy UK '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.'

However, the two experts from the NAC stated that it would be difficult to withdraw treatment from patients in NYHA class 4 because no other treatment is available. Based on the evidence from the NAC experts, the Appraisal Committee concluded "*on balance it would be difficult for clinicians to implement a stopping rule for tafamidis*". This conclusion by the Committee is unreasonable in light of the evidence submitted for the following reasons:

- The conclusion of the Committee prefers evidence from experts from the NAC, who are not heart failure specialists and presumably have little experience in managing patients with NYHA class 4 symptoms or those with end-stage deterioration transitioning to end of life care (heart failure specialists are responsible for palliative care needs of their patients among whom it is routine to stop medications that are not providing symptomatic benefit), over that from a heart failure specialist and a patient organisation without explanation;

- The Committee seems to place weight on the fact that a patient's disease may fluctuate between NYHA class III and class 4 as arguing against a stopping rule, although previous guidance recommending withdrawal of therapy in this situation has been issued for cardiac resynchronisation therapy (Appeal Point 1.4)

- It disregards the evidence from the heart failure specialists additional to Professor Elliott, who supported his view, during consultation, that treatment is commonly withdrawn from NYHA class 4 patients and (contrary to the suggestion at paragraph 3.14 of the FAD) it already forms part of routine clinical practice; and

- By saying that a stopping rule may not be implemented where no other treatment is available and/or where the rule is not specified in the SmPC for the relevant product, the Committee has disregarded all of the health technologies previously recommended by NICE to which the same matters apply. Most recent 2020 examples include:

    a) **TA655 Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy** - it is stopped at 2 years of uninterrupted treatment, or earlier if their disease progresses (A 2-year stopping rule was not included in the SmPC; A stopping rule was considered acceptable and implementable to both patients and clinicians. (committee papers pg. 13))

    b) **TA597 Dapagliflozin with insulin for treating type 1 diabetes** - Stop dapagliflozin if there has not been a sustained improvement in glycaemic control (that is, a fall in HbA1c level of about 0.3% or 3 mmol/mol); no evidence of this recommendation is present in the SmPC.

2.6. <u>Appeal Point 2.6: The Committee's conclusions regarding the time to diagnosis of ATTR-CM is unreasonable</u>

At paragraph 3.8 of the FAD, the Committee refers to the time to diagnosis of ATTR-CM, stating that average time to diagnosis at the NAC was 3 years or more. The Committee subsequently refers to company observations that 1 in 3 patents were diagnosed in less than 6 months and states that reducing the diagnosis time to an average of less than 6 months would represent a substantial improvement, but "*recognised that these diagnoses were made at a specialist centre and questioned if such reductions could be achieved at other centres in clinical practice*".

However, it is the consistent view of all experts giving evidence in this appraisal that ATTR-CM is now easily diagnosed (see e.g. evidence of Professor Hawkins).

Furthermore, the Committee's view that diagnoses of less than 6 months were "*made at a specialist centre*" and might not be achieved at other centres, conflicts with the experience during the EAMS where diagnosis was made successfully and within a period of months at 17 centres outside NAC. In his evidence to the Appraisal Committee at the second meeting, Professor Elliott stated that average diagnosis times had fallen from "years to months" at the EAMS sites during the scheme.

While Pfizer does not suggest that ATTR-CM would be diagnosed at every hospital in England, it is clear, based on the experience with EAMS, that it may be diagnosed effectively and rapidly at multiple centres. Therefore to the extent that the Committee intended to suggest that there was uncertainty about whether rapid diagnosis (in less than 6 months) would be achieved at more than a single specialist centre (presumably the NAC), this would clearly be unreasonable in light of the available evidence.

2.7. <u>Appeal Point 2.7: The Committee's conclusion that tafamidis has no impact on awareness of ATTR-CM is inconsistent with its view that other products are resulting in increased awareness</u>

At paragraph 3.8 of the FAD, the Committee referred to paragraph 3.3 of the FAD and the conclusion '*that awareness of ATTR-CM had increased'*. The clinical experts from the NAC had stated that new diagnostic tests had improved awareness of ATTR-CM as had NICE's highly specialised technologies guidance for inotersen and patisiran for the treatment of ATTR polyneuropathy. However the Committee proceeds to question whether '*recommending tafamidis would further increase awareness and reduce diagnosis times.'*

There are two inconsistencies with the conclusions of the Committee:

a) at paragraph 3.8 of the FAD, the committee concludes '*when ATTR-CM is suspected the diagnostic pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur*' suggesting new diagnostic tools are not impacting awareness;

b) they appear to conclude that two treatments indirectly related to ATTR-CM (recommended for the treatment of ATTR-polyneuropathy) can increase awareness of the condition but the first disease modifying therapy in ATTR-CM is not expected to increase awareness.

The inconsistencies in the Committee's reasoning are unexplained and are therefore unreasonable.

2.8. <u>Appeal Point 2.8: The Committee's conclusions around the impact of tafamidis in reducing time to diagnosis as demonstrated through EAMS are not reasonable</u>

At paragraph 3.8 of the FAD, the Appraisal Committee states that, "*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 the EAMS data were informative, they can only show that diagnosis delays were reducing when tafamidis was available. They cannot show that the delays were reducing because of tafamidis."*

However, this conclusion is inconsistent with the evidence related to previous delays to diagnosis. In the overall committee's conclusion it has failed to acknowledge that scintigraphy (DPD scanning) was introduced into routine practice at the NAC in 2012 (as stated in Pfizer's response to consultation on the ACD), therefore, the impact of introducing scintigraphy on diagnosis will have been reflected in the previous diagnosis delay data presented from the NAC in 2019 and referenced in the FAD at paragraph 3.3.

Furthermore, in paragraph 3.8 of the FAD "*The ERG highlighted that the trend of earlier diagnosis seen in the EAMS could be explained by improvements in diagnostic tools since the ATTR-ACT trial (see section 3.3)… The committee acknowledged this, and agreed it was not possible to attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis."* However, data on previous UK delays to diagnosis from the NAC have no link to the timing of ATTR-ACT.

In response to consultation on the ACD, the British Nuclear Cardiology Society submitted the results of a survey confirming substantial increase in investigation and testing for ATTR-CM (both in terms of numbers of centres conducting such testing and the number of scans being undertaken), coinciding with publication of the ATTR-ACT trial in 2018.

In summary, the Committee's conclusions in relation to the UK data collected from the NAC from 2000-2017 (which included the impact of introducing DPD scanning in 2012), the data from the tafamidis EAMS programme collected in 2019-2020 and the data from the nuclear scintigraphy society survey are unreasonable. The principal environmental change between these two datasets is the availability of tafamidis. It is furthermore entirely plausible that the availability of the first disease modifying treatment for ATTR-CM would result in increased and quicker diagnosis of the condition in circumstances where there may be less incentive for clinicians to make such a diagnosis if this will not alter management. In these circumstances it is unreasonable to conclude that the introduction of tafamidis during EAMS had no impact on reducing time to diagnosis.

2.9. <u>Appeal Point 2.9: The assertion that Pfizer failed to make use of longer-term data in its extrapolation of treatment effects is unreasonable</u>

At paragraph 3.15 of the FAD, the Appraisal Committee refer to statements by the ERG, including:

> "*It highlighted that the company failed to make use of longer term data in its extrapolation of treatment".*

This statement by the ERG, repeated and presumably relied upon by the Committee, is unreasonable, in circumstances where Pfizer has at all times disclosed the data from the ATTR-ACT trial, including the ATTR-ACT long term extension study (LTE) as these became available.

- The original submission on 30 September 2019 was based on the trial data plus the LTE data available at that time.

- Following the availability of a new data cut from the LTE, updated data for both overall survival and treatment discontinuation were submitted to NICE, together with updated economic modelling, in the technical engagement response (i.e. prior to the first meeting of the Appraisal Committee).

- A further data cut from the LTE is now available; however these data became available too late to be submitted for the second meeting of the Appraisal Committee.

There was accordingly no "failure" by Pfizer in not including such data in its extrapolation of treatment for the purposes of the modelling submitted to NICE.

THE DETERMINATION OF THIS APPEAL

Pfizer requests that this appeal should be determined at an oral hearing.

REQUESTED OUTCOME FOLLOWING APPEAL

Pfizer respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions:

- That it should take into account the evidence of Professor Elliott, the written evidence of Professor Hawkins and other consultees and commentators who have confirmed that ATTR-CM is now an easily and quickly diagnosed disorder and should provide a reasoned explanation for any decision to reject the internationally validated diagnostic algorithm;

- That it should reconsider the EPAR for tafamidis and specifically the statements by CHMP in relation to diagnosis of ATTR-CM;

- That it should reconsider its position in relation to the use of starting and stopping rules for tafamidis treatment, in view of the fact that the absence of such rules in the SmPC is not a relevant consideration, NYHA classification has been used in multiple other appraisals where heart failure is due to other causes to determine eligibility for treatment, that stopping rules are widely and successfully used for other treatments and were supported by patient organisations in response to the ACD.

- That deducting treatment benefits for patients who discontinue treatment in NYHA class 1-3, from the estimates of treatment effect produced by Pfizer, represents a double reduction and is therefore incorrect and the ERG's alternative analyses disregard the evidence from ATTR-ACT.

- To recognise that patients with suspected ATTR-CM may be effectively diagnosed at centres outside the NAC.

- That limited clinical experience with use of cardiac biomarkers means that they do not currently represent a reasonable method for assessing disease stage and who would benefit from treatment.

- That its conclusions regarding the impact of tafamidis on awareness of ATTR-CM and time to diagnosis are not reasonable.

- That the criticism of Pfizer for "failing" to use long term data is incorrect and should be removed.

Yours sincerely,

[redacted], Pfizer UK