Single Technology Appraisal

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (review of TA696) [ID6327]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (review of TA696) [ID6327]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance** from Pfizer

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Cardiomyopathy UK
   b. UK ATTR Amyloidosis Patients' Association (UKATPA)
   c. NHS England

3. **Comments on the Draft Guidance from experts:**
   a. Professor Perry Elliott, Professor of Cardiovascular Medicine – Clinical expert, nominated by Pfizer

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 19 March 2024. Please submit via NICE Docs.

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

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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1	**Revised PAS, an updated treatment discontinuation scenario and Evidence Assessment Group (EAG) preferred base case assumptions incorporated into revised company base-case**
	
	Ahead of the 2nd appraisal committee meeting (ACM2), we have provided a revised PAS, reducing the net price of tafamidis by an additional [redacted] points ([redacted] to [redacted] per pack).
	
	To remove uncertainty for the committee we have accepted all assumptions included in the EAG's preferred base-case, into our new revised company base-case (ACM 1 Issues 1-3 below):
	
	• ACM1 Issue 1: Using a log-normal parametric distribution to model OS for the tafamidis arm.
	  ○ We have incorporated the use of the log-normal model, which was preferred by both the EAG and the NICE appraisal committee.
	• ACM1 Issue 2: Using best supportive care (BSC) utility for patients in the New York Heart Association Functional Classification IV health states (NYHA IV) instead of treatment-dependent utility values.
	  ○ We have updated NYHA IV utilities in line with the expectation of the EAG and the committee by applying treatment-independent utilities to equalise utility in the NYHA IV health state regardless of treatment.
	• ACM1 Issue 3: Applying a cap on health state utility values above the general population age-matched average.
	  ○ We accept that it is clinical opinion that patients cannot have utility greater than the mean of age/sex matched general population regardless of NYHA performance status; despite the increasing number of comorbidities expected in the aging general population.
	
	Our revised base-case also includes assumptions which address the committee's key concern regarding OS outcomes in patients who discontinue tafamidis treatment (see further details in comment boxes 2-4). We believe the updated assumptions address the issues raised in ACM1 and more accurately reflect available long-term clinical evidence.

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2	**Survival after stopping treatment - Committee preference for EAG exploratory scenario analysis 2** We acknowledge the committee considered that none of the scenarios available during ACM1 may have accurately reflected what is likely to happen in clinical practice once patients discontinue tafamidis. Therefore, the committee selected EAG exploratory scenario 2 as the most appropriate for decision making, as this scenario represented a conservative option in the face of uncertainty. However, we believe this scenario substantially underpredicts survival post-discontinuation and is not supported by the long-term evidence from ATTR-ACT LTE. **Issues with this scenario:** **i.** The scenario estimates a very high hazard of death in patients who discontinue tafamidis (off-treatment). Put another way, a patient treated for 3 years with tafamidis who stops treatment has the same likelihood of death when they discontinue as a patient who has received 3 years of no treatment. This contradicts clinical expert opinion expressed in ACM1, which stated "that outcomes would not immediately revert to BSC outcomes when treatment is stopped (Section 3.9, pg.12 of draft guidance)". **ii.** The scenario also fails to adapt the on-treatment hazard of death to compensate for the increased off-treatment hazard. This is problematic as our OS Kaplan-Meier (KM) included those on-treatment and those who have discontinued treatment. In other words, the risk of death for on-treatment patients still includes the observed off-treatment risk of death, thereby double counting risk of death for patients who have discontinued tafamidis. It is due to the above reasons that this scenario underpredicts OS and is not supported by the 7 years of long-term follow up data from ATTR-ACT LTE (Figure 1).

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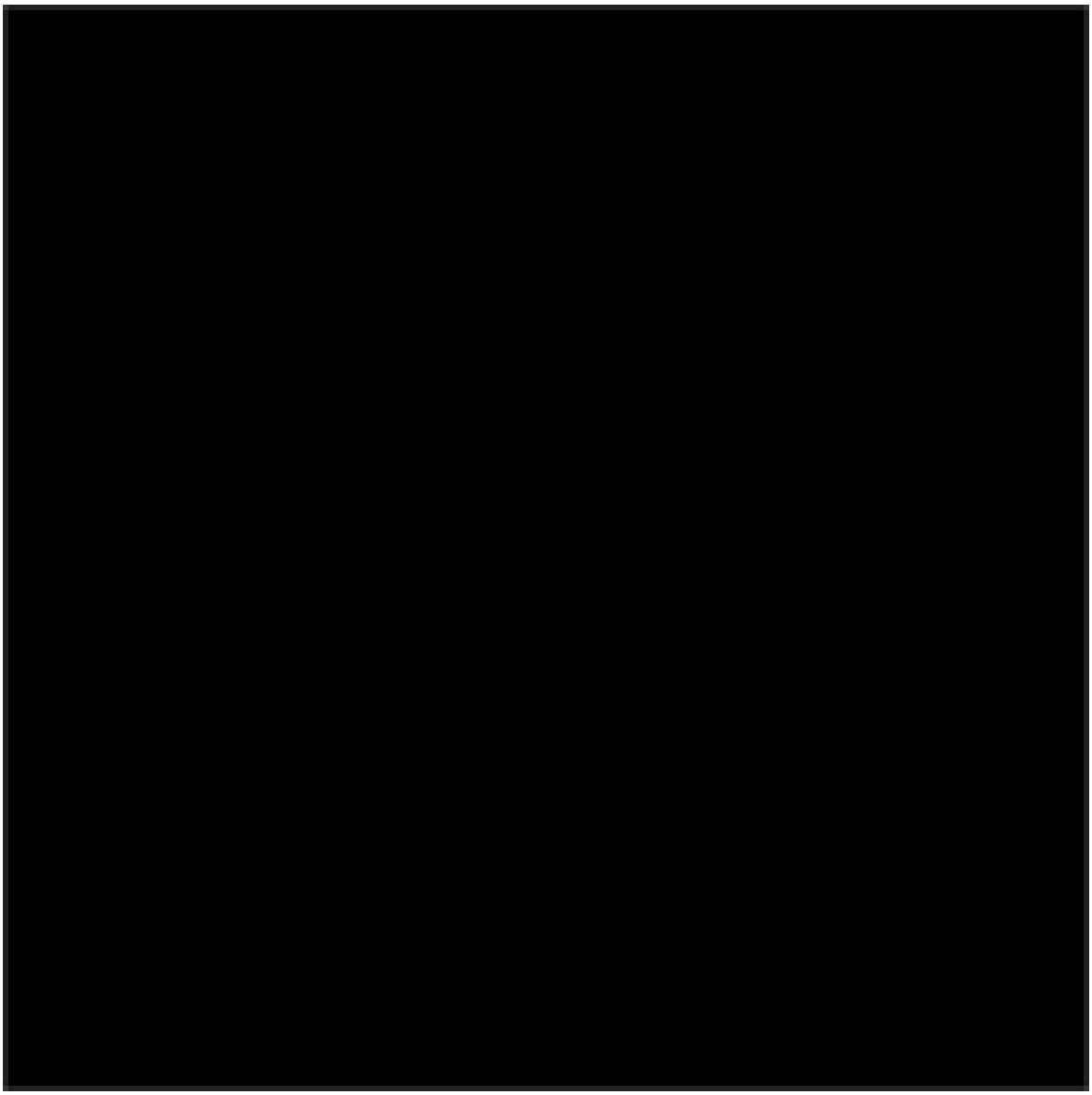
Figure 1. Parametric relative survival models of OS – tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 61mg ATTR-ACT LTE (August 2021 data cut) + EAG log-normal model from TA696



All models fitted in relative survival framework, with baseline hazard informed by nation, age and sex matched contemporary lifetables for the ATTR-ACT analysis subpopulation, extrapolating via the Ederer-I method. 95% confidence interval by non-parametric bootstrap (1000 replications).

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	Proposed amendments: To provide the committee with a scenario which addresses the issues mentioned above and may more accurately reflect what is likely to occur in clinical practice based on ACM1 discussions, we propose: 1. Using the mean survival rate of BSC patients from ATTR-ACT and applying this rate to patients who discontinue treatment**.** We believe this would be more appropriate both clinically and methodologically as it would reflect the build-up of amyloid deposits at the average rate at which it occurs for untreated patients. 2. If patients who discontinue tafamidis are going to be assigned a new survival based on the BSC arm of ATTR-ACT, we will first need to remove these patients from the tafamidis OS extrapolation. We consider both these amendments in our revised company base case in comment boxes 3 and 4 below.

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3	**Adjust overall survival for those who remain on-treatment by censoring off-treatment patients** Currently, our modelled OS data is uncensored for discontinued patients and therefore reflects the survival outcomes for both those on and off-treatment. If we are to capture different survival outcomes for patients who discontinue tafamidis, it is more accurate to censor these patients from the tafamidis OS extrapolation. As seen in **Error! Reference source not found.**, if we censor patients who discontinue treatment (red), as expected this improves the OS KM compared to the version used in the company submission which included patients on treatment and those who have discontinued treatment (blue). This has face validity – if those discontinuing treatment are modelled as being at greater risk of death than the mean over all patients, then those continuing treatment should be exposed to lower risk than the mean. All parametric models displayed similar goodness of fit to the new KM (Figure 4 in Appendix) and therefore we chose to keep the log-normal model as per the EAG and committee's preferred base-case assumptions. **Figure 2. Kaplan-Meier estimators of OS with and without censoring for treatment discontinuation – tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 61mg ATTR-ACT LTE (August 2021 data cut)**  Abbreviations: Cens. disc.: censoring for treatment discontinuation; NAR: number at risk; OS: overall survival censoring for heart transplant and cardiac mechanical assist device implantation.

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4	**Estimating off-treatment overall survival from ATTR-ACT BSC arm** As stated above, in EAG exploratory scenario 2, the modelled hazard of mortality after discontinuation is identical to that of BSC patients at the same time and thus assumes that patients who discontinue experience instantaneous accumulation of amyloid and disease progression to match that of BSC patients at that time point. This results in prediction of survival well below that of the observed data. To adjust the hazard of mortality to better reflect clinical opinion "that outcomes would not immediately revert to BSC outcomes when treatment is stopped (Section 3.9, pg. 12 of draft guidance)", we suggest – whilst still conservative – applying the mean hazard of mortality from the ATTR-ACT BSC arm when discontinuing treatment. In the EAG report and ACM1, it was confirmed that the Weibull model was the preferred model for BSC OS extrapolation, and so Weibull was used to model this (i.e. to determine numbers of expected life years under BSC treatment). The economic model does not track the time from discontinuation, and therefore mortality hazard after treatment discontinuation must be modelled as uniform across the discontinued patients, then the expected number of deaths in a model cycle must be split according to the relative risk of mortality per NYHA class. Thus, a constant hazard (exponential) model predicting the same life expectancy as the BSC arm is used. The exponential rate to achieve a specified life expectancy is simply 1/life expectancy, and this is implemented in the model such that the rate of mortality after discontinuation is dependent upon the currently modelled life expectancy for BSC (i.e. it varies in PSA). **Conclusions** • The committee's preferred base-case (EAG exploratory scenario 2) can be amended to better reflect what is likely to happen when a patient discontinues tafamidis in the clinical setting as well as observed long-term survival data and clinical expert opinion in ACM1. A summary of the amendments is presented in Figure 4 below. ○ These amendments include: (1) adjusting OS for patients who remain on-treatment by censoring for discontinued patients, and (2) estimating OS for patients who have discontinued treatment by applying the mean hazard of mortality from the BSC arm of ATTR-ACT. • The revised company base-case represents a scenario which we believe more closely reflects what is likely to happen when a patient discontinues tafamidis compared to the committee's preferred base-case, and addresses uncertainties raised by the committee in ACM1 whilst still being conservative. • The deterministic and probabilistic base-case ICERs (with revised PAS) for our revised company base-case, the EAG base-base and the committee's preferred base-case are presented in Table 1 and Table 2, respectively. The revised PAS and amendments to the committee's preferred base-case result in a cost-effective revised company base-case ICER.

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Figure 3. Summary of ammendments applied to committee's preffered base-case

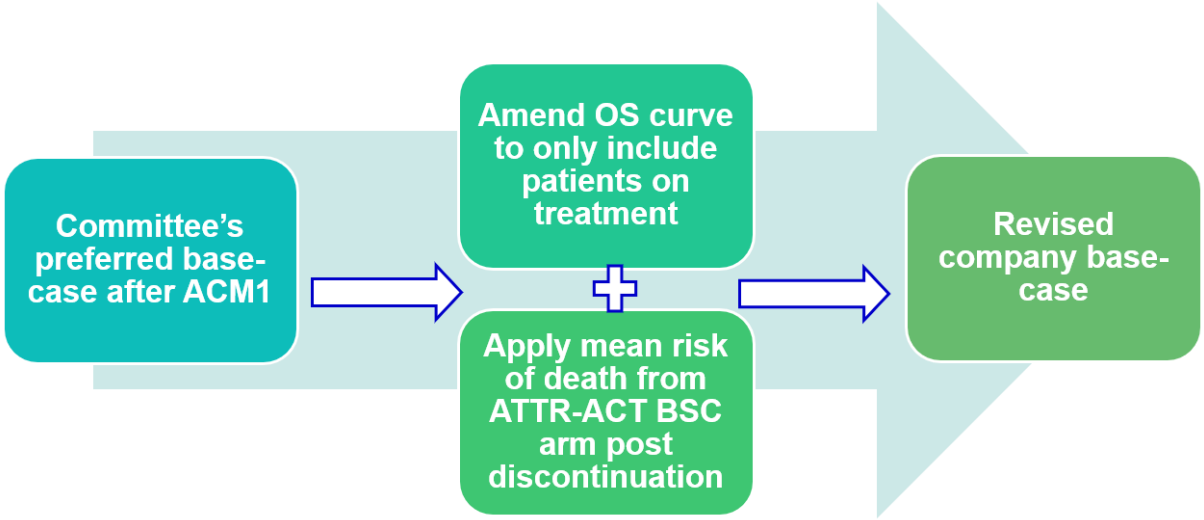

Table 1. Deterministic cost-effectiveness results (with revised PAS)

	Tafamidis	BSC	Incremental
EAG base-case			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)		[redacted]	
Revised company base-case (adjusted on-treatment OS and mean BSC hazard of mortality from ATTR-ACT post discontinuation)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)		[redacted]	
Committee's preferred base case (EAG exploratory scenario 2)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)		[redacted]	

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year.
Instructions to access amended scenarios in the new attached economic model:
EAG base case:

1) Set Cell 'Model Control'!Q16 (named range "setOSModelTrt") to "OS - lognormal/RS - tafamidis 80mg/80mg/free acid ATTR-ACT LTE"

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2) Enable EAG scenario flags "EAG_2", "EAG_3" on sheet "EAG"; all other EAG flags should be set to 0
3) Ensure cell 'Model Control'!D51(named range "discontinued_surv_scenario") is set to "immediate switch"

Committee's preferred base-case:

1) Do the above to reach EAG base-case
2) Enable EAG scenario flag "EAG_5" on sheet "EAG"

Revised company base-case:

1) Do the above to reach committee's preferred base-case
2) Set cell 'Model Control'!D51(named range "discontinued_surv_scenario") to "BSC mean"
3) Set Cell 'Model Control'!Q16 (named range "setOSModelTrt") to "OS cens. disc. - lognormal/RS - tafamidis 80mg/80mg/free acid ATTR-ACT LTE"

Table 2. Probabilistic cost-effectiveness results (with revised PAS)

	Tafamidis	BSC	Incremental
EAG base case			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Revised company base case (adjusted on-treatment OS and mean BSC hazard of mortality from ATTR-ACT post discontinuation)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Committee's preferred base case (EAG exploratory scenario 2)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year.

The probabilistic base-case ICERs when only amending the committee's preferred base-case by adjusting on-treatment OS is [redacted] or when only applying mean hazard of mortality from the ATTR-ACT BSC arm is [redacted] – these have been provided for completeness.

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Appendix

Figure 4. New Parametric relative survival models fitted to OS censoring for TD - ATTR-ACT tafamidis 80 mg (August 2021)

Figures in brackets 95% confidence interval of all-cause mean by non-parametric bootstrap (1000 repetitions). All-cause mean calculated using baseline hazard of country, age and sex matched life tables by the Ederer (I) method.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBL: database lock; Exp: exponential; G. Gamma: generalised gamma; L. Logistic: log-logistic; L. Norm: lognormal; OS: overall survival; TD: treatment discontinuation.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cardiomyopathy UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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1	We recognise that NICE's focus is to assess the benefit of a new technology on the individual receiving it, however our view is that it is also important to consider the benefit that a new technology can bring to a patient wider community. We believe that approval of Tafamidis would have a significant positive impact on the wider ATTR-CM and Amyloidosis community. In particular, approval would lead to an increase in awareness of this condition among healthcare professionals, encourage the greater use of appropriate diagnostic tools, open the door for other technologies and ultimately improve outcomes for all.
2	It should be noted that this is a first in class medication. The community has been waiting for this treatment option, which has been proven to be effective and is available in Europe, since it first went to NICE for appraisal in the 2020. It is now imperative that both NICE and the manufacturer deal with any outstanding issues with real urgency to prevent further delay.
3	The Scottish Medicines Consortium recently approved the use of Tafamidis for patients in Scotland. This fundamentally changes the UK wide landscape, and patient perceptions regarding this treatment. We believe that should NICE not approve this treatment for patients in England, it would further exacerbate regional health inequalities across the UK and create an untenable situation for patients with ATTR-CM. A continued lack of access to the drug in England would likely have a significant negative impact on patients and result in an acute perception of unfairness.
4	We recognise the challenge of reaching an accurate estimate of ATTR-CM prevalence in England but believe that the prevalence figure of around 20,000 that was discussed during the appraisal meeting does not reflect the number of potential recipients of this technology. NICE's draft scope document points to prevalence estimates based on hospital episode statistics. We feel that it is more appropriate for NICE to use these figures in its decision making.
5	It is our belief that since the last appraisal of Tafamidis in 2020, there have been some meaningful improvements to service infrastructure and networks as well as improved access to relevant diagnostic tools. This gives us increased confidence that individuals who would benefit from this technology can be identified should it become available.

Insert extra rows as needed

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Example 1	We are concerned that this recommendation may imply that ……..

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1	• Has all the relevant evidence been taken into account? No. As is acknowledged in the draft guidance the committee would have liked to have seen more evidence. In particular real-world evidence from other countries is lacking. No evidence was presented that would allow the committee to take account of the burden of disease on the patient's family and friends. We know that this impact is very high, it should therefore be considered when assessing the effectiveness of Tafamidis.
2	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The summaries are reasonable interpretations of the evidence that was taken into consideration, however because not all relevant evidence was taken into consideration these summaries are not complete.
3	• Are the recommendations sound and a suitable basis for guidance to the NHS? No. If Tafamidis is not recommended then this will result in different standards of care across the NHS. Tafamidis is already available in Scotland so by not recommending Tafamidis in England NICE is creating a two-tier service for ATTR-CM patients living in the UK. Patients diagnosed with ATTR-CM will be subjected to a 'postcode lottery' that will decide if they can access the only treatment that will slow the progression of their disease or not. It is not unreasonable to think that patients may take the step of moving to an area where Tafamidis is available.
4	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? Tafamidis not being recommended by NICE rases significant equality issues. While the draft guidance acknowledges that there are some equality issues it does not make it clear that there are two protected groups who will be disproportionately disadvantaged by Tafamidis not being recommended. ATTR patients can experience neuropathy, cardiomyopathy (ATTR-CM) or a combination of the two, with different forms of the disease presenting at different points along the spectrum. There are three treatments currently available to patients living with neuropathy yet there remains nothing for those living with cardiomyopathy. The two subgroups most likely to present with cardiomyopathy but no neuropathy (and who, therefor currently do not have access to disease altering treatments) are the wild type (wt) patients and patients with the V122I gene mutation. These two subgroups are therefore disproportionately disadvantaged by the lack of treatment for ATTR-CM, when compared with all ATTR patients. As the draft guidance states, wild type amyloidosis occurs spontaneously in later life, typically presenting after the age of 70. Therefor most wild type patients are 70 or older. The V122I gene mutation is found almost exclusively in individuals of African Caribbean

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	descent. These two protected characteristics groups (age and race) are set to benefit the most if Tafamidis were to be recommended for use by NICE. Conversely these two groups will be harmed the most if Tafamidis is not recommended. This could therefore be considered indirect discrimination against these two groups. Especially given that Tafamidis is known to be safe, effective and is accessible in many other countries, including other parts of the UK. With Tafamidis widely available around the globe, including Scotland, ATTR-CM patients are deeply frustrated by not being able to access this treatment. Living with this degenerative, progressive, and fatal condition is hard enough. Living with it, knowing there is a treatment, yet being unable to access that treatment, is even harder. A V122I describes the impact of the illness and lack of treatment like this: “I am a patient living with the burden of hereditary ATTR Cardiac Amyloidosis, having been diagnosed with the condition two years ago. Living with the disease is an absolute burden on a daily basis, particularly as there is currently no prescribed drug in England for those like me who do not have any nerve damage. After my diagnosis, I subsequently found out that my mother passed away from the condition, I knew she had a heart condition but did not know the type and the hereditary nature of it. Being told at the point of diagnosis, about the hereditary aspects and that there was currently no treatment available was devastating news not just for me, but my wife, my children, siblings, and my thoughts for my three young grandchildren. The sense of guilt that I may have passed on a progressive and potentially fatal condition to my loved ones, with no treatment options available was too much to bear. Breaking the news to my children was one of the worst days of my life. It was no wonder that I sunk into a period of severe anxiety affecting my sleep and work, and bouts of low mood, which exacerbated the fatigue that comes with the condition. Because of the progressive nature of the disease, treatment is required sooner rather than later to prolong and save lives. I also have a personal belief, that there could be a tendency not to diagnose a condition where there is no treatment available. Finally, those that have the disease with nerve damage have access to prescribed drugs, it is therefore unequitable for the current situation to be allowed to continue when we can now have a treatment option.”
5	• could have any adverse impact on people with a particular disability or disabilities. No comment on this.
6	

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	n/a
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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<table>
<tr><td>1</td><td>
We are concerned that this appraisal may not have taken into account the NHS service costs associated with providing this treatment if there was a positive recommendation for tafamidis for treatment of TTR amyloidosis with cardiomyopathy. This includes both workforce and homecare delivery costs.

It is estimated that up to ‘academic / commercial in confidence information removed’ patients currently under the care of the National Amyloids Centre (NAC) will require onboarding to this new treatment, with a view to receiving this medication via homecare. Additional workforce resource will be required for Royal Free (RF) NAC to deliver a roll-out programme to this volume of patients. Taking into consideration the likelihood that a significant proportion of patients eligible for this treatment will have responsibility for prescribing and delivery of medication delegated to regional centres in the planned National Network within the next 24 months, the resource requirement has been split into a fixed-term onboarding need and a long-term substantive expansion for ongoing management of patients expected to stay under the follow-up care of the NAC. See Figure 1 for costed breakdown of resources. Further information on requirement for these costs can be provided on request.

Figure 1 - Total workforce costs for Tafamidis roll out (academic / commercial in confidence information removed)
<table>
<tr><th>Banding</th><th>Fixed-Term</th><th>Substantive</th><th>Cost</th></tr>
<tr><td></td><td></td><td></td><td></td></tr>
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<tr><td>TOTAL</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
Oncosts - The cost of homecare for tafamidis will also need to be covered by NHSE. This is estimated at academic / commercial in confidence information removed per patient per delivery with 8-12 weekly delivery expected.
</td></tr>
<tr><td>2</td><td></td></tr>
<tr><td>3</td><td></td></tr>
<tr><td>4</td><td></td></tr>
<tr><td>5</td><td></td></tr>
</table>

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Name	Perry Elliott
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

All appropriate evidence has been taken into account. There are no additional randomised trial data on tafamidis. There are no real world data for the UK. Real world data from other countries support the beneficial effect of tafamidis on mortality and rate of disease progression

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

The EAG's preferred model seems to be predicated on very conservative assumptions following discontinuation of tafamidis. I agree that it would be unreasonable to expect a persisting effect of tafamidis following discontinuation, but it is also wrong to assume outcomes similar to those of patients who have never been treated with tafamidis. As there are no data to support accelerated disease following discontinuation, the most likely model lies somewhere between these extremes.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The number of diagnosed patients with this fatal disease is growing. Tafamidis is standard of care in other developed economies and is approved in Scotland. The lack of access to this disease modifying therapy for patients living in England creates an unjustifiable disadvantage for a section of the UK population. As such, the recommendation is neither sound nor suitable.

Single Technology Appraisal

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. The document is deficient in that all relevant evidence is not provided, for example;
1. Follow on evidence from the trial and patients experience could be a positive for Tafamidas.
2.Updated current BSC, repurposed medication, does not take into account effects on otherwise healthy organs in patients which could cause increased mortality and health costs, for example, dialysis or organ transplants.

Are the recommendations sound and a suitable basis for guidance to the NHS?

If the end recommendation is not to authorise Tafamidas then it is not sound from a patient perspective.
BSC, palliative care, is the denial of patients expectation of best care under the NHS in this case.

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

I, as a patient, strongly believe that patients are not of the uppermost priority in this system of analysis and recommendation for the NHS.
If I lived in another part of the United Kingdom or another part of Ireland Tafamidas is available to ATTR-CM patients.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	
I don’t feel all the questions have been answered or taken into consideration. The answers from the committee are quite narrow in their	

analysis & have not thought or considered the cost implications for the patients, or for the carers, of which amyloidosis is a new experience/journey. I'm not sure that the benefits of TAFAMIDIS have been totally considered. The time, cost & energy effect it has on the patient's family & carers, I am sure, would out weigh the annual cost of the medication.

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

If ATTR-cm patients are offered no medication, that is actually available to hold the condition, you are in actual fact shortening their life which is not care, as I feel, under the NHS. It's putting narrow cost analysis ahead of quality of life.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I would say definitely not. The committee of NICE are denying these patients and carers a future of positive healthcare. The stress is another issue that has not been addressed & the effect it has on their mental health. Both patients, carers, family & friends are all affected by NICE's decision. The cost implications of the stress alone, I feel in the future, would outweigh the annual
Cost of TAFAMIDIS.

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

I feel that not to provide TAFAMIDIS to amyloidosis -cm patients is a denial of a patient's rights to care under the NHS in the UK. I personally feel that ageism is contributing to the past decisions of the committee & I feel this needs to be addressed. I also feel being isolated in Northern Ireland is part of the problem & this needs to be addressed before a final decision is made.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Good evening, I wanted to express my comment regarding chapter 3.9 relating to the effect of treatment after stopping tafamidis. The company's assumption on the persistence of the effect after discontinuation of the drug is not, to my knowledge, proven in the literature. It is likely that after many years of therapy amyloid deposition starts again with the same rate as people who had not been treated but with a lower level of deposition than a subject in natural history. in the absence of any scientific evidence,	

however, I believe that a rebound effect that rapidly reduces the clinical benefit of the therapy is very unlikely. However, the real question is why the therapy should be interrupted given that in my clinical experience it is absolutely well tolerated and almost free of side effects. It seems reasonable, to optimize its benefit, to consider tafamidis therapy a lifelong chronic therapy, without hypothesizing suspension or interruptions

NICE National Institute for Health and Care Excellence

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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1	**Revised PAS, an updated treatment discontinuation scenario and Evidence Assessment Group (EAG) preferred base case assumptions incorporated into revised company base-case**
	
	Ahead of the 2nd appraisal committee meeting (ACM2), we have provided a revised PAS, reducing the net price of tafamidis by an additional [redacted] points ([redacted] to [redacted] per pack).
	
	To remove uncertainty for the committee we have accepted all assumptions included in the EAG's preferred base-case, into our new revised company base-case (ACM 1 Issues 1-3 below):
	
	• ACM1 Issue 1: Using a log-normal parametric distribution to model OS for the tafamidis arm.
	  ○ We have incorporated the use of the log-normal model, which was preferred by both the EAG and the NICE appraisal committee.
	• ACM1 Issue 2: Using best supportive care (BSC) utility for patients in the New York Heart Association Functional Classification IV health states (NYHA IV) instead of treatment-dependent utility values.
	  ○ We have updated NYHA IV utilities in line with the expectation of the EAG and the committee by applying treatment-independent utilities to equalise utility in the NYHA IV health state regardless of treatment.
	• ACM1 Issue 3: Applying a cap on health state utility values above the general population age-matched average.
	  ○ We accept that it is clinical opinion that patients cannot have utility greater than the mean of age/sex matched general population regardless of NYHA performance status; despite the increasing number of comorbidities expected in the aging general population.
	
	Our revised base-case also includes assumptions which address the committee's key concern regarding OS outcomes in patients who discontinue tafamidis treatment (see further details
		EAG comments:
		The company's base case is now in alignment with the EAG's base case and the committee's preferences for issues 1, 2 and 3. Most uncertainty was however related to what happens after treatment discontinuation, which the EAG modelled in two exploratory scenarios due to uncertainty regarding the most plausible scenario. The company addressed this further in comment boxes 2-4, so please refer our comments there.

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	in comment boxes 2-4). We believe the updated assumptions address the issues raised in ACM1 and more accurately reflect available long-term clinical evidence.	

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2	**Survival after stopping treatment - Committee preference for EAG exploratory scenario analysis 2** We acknowledge the committee considered that none of the scenarios available during ACM1 may have accurately reflected what is likely to happen in clinical practice once patients discontinue tafamidis. Therefore, the committee selected EAG exploratory scenario 2 as the most appropriate for decision making, as this scenario represented a conservative option in the face of uncertainty. However, we believe this scenario substantially underpredicts survival post-discontinuation and is not supported by the long-term evidence from ATTR-ACT LTE**.** **Issues with this scenario:** **i.** The scenario estimates a very high hazard of death in patients who discontinue tafamidis (off-treatment). Put another way, a patient treated for 3 years with tafamidis who stops treatment has the same likelihood of death when they discontinue as a patient who has received 3 years of no treatment. This contradicts clinical expert opinion expressed in ACM1, which stated "that outcomes would not immediately revert to BSC outcomes when treatment is stopped (Section 3.9, pg.12 of draft guidance)". **ii.** The scenario also fails to adapt the on-treatment hazard of death to compensate for the increased off-treatment hazard. This is problematic as our OS Kaplan-Meier (KM) included those on-treatment and those who have discontinued treatment. In other words, the risk of death for on-treatment patients still includes the observed off-treatment risk of death, thereby double counting risk of death for patients who have discontinued tafamidis. It is due to the above reasons that this scenario underpredicts OS and is not supported by the 7 years of long-term follow up data from ATTR-ACT LTE (**Figure 1**).	**EAG comments:** Previously, the OS curve for tafamidis contained both patients on treatment and discontinued patients. This likely resulted in an underestimation of the OS in the on-treatment group and an overestimation of OS in the discontinued group. The EAG recognises the issues mentioned by the company related to their exploratory scenario 2. The company has proposed a new scenario where the tafamidis OS only contains data from patients on treatment by censoring patients at the time of discontinuation. Furthermore, the company proposes to use the mean survival rate of BSC patients for tafamidis patients who discontinued treatment. The EAG generally agrees with the proposed solution to

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	Figure 1. Parametric relative survival models of OS – tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 61mg ATTR-ACT LTE (August 2021 data cut) + EAG log-normal model from TA696	use two separate survival curves for tafamidis on-treatment OS and tafamidis discontinuation OS. Please refer to our comments in the next sections for our considerations regarding this approach.

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[redacted]

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	All models fitted in relative survival framework, with baseline hazard informed by nation, age and sex matched contemporary lifetables for the ATTR-ACT analysis subpopulation, extrapolating via the Ederer-I method. 95% confidence interval by non-parametric bootstrap (1000 replications). **Proposed amendments:** To provide the committee with a scenario which addresses the issues mentioned above and may more accurately reflect what is likely to occur in clinical practice based on ACM1 discussions, we propose: 1. Using the mean survival rate of BSC patients from ATTR-ACT and applying this rate to patients who discontinue treatment**.** We believe this would be more appropriate both clinically and methodologically as it would reflect the build-up of amyloid deposits at the average rate at which it occurs for untreated patients. 2. If patients who discontinue tafamidis are going to be assigned a new survival based on the BSC arm of ATTR-ACT, we will first need to remove these patients from the tafamidis OS extrapolation. We consider both these amendments in our revised company base case in comment boxes 3 and 4 below.	

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3	**Adjust overall survival for those who remain on-treatment by censoring off-treatment patients** Currently, our modelled OS data is uncensored for discontinued patients and therefore reflects the survival outcomes for both those on and off-treatment. If we are to capture different survival outcomes for patients who discontinue tafamidis, it is more accurate to censor these patients from the tafamidis OS extrapolation. As seen in **Error! Reference source not found.**, if we censor patients who discontinue treatment (red), as expected this improves the OS KM compared to the version used in the company submission which included patients on treatment and those who have discontinued treatment (blue). This has face validity – if those discontinuing treatment are modelled as being at greater risk of death than the mean over all patients, then those continuing treatment should be exposed to lower risk than the mean. All parametric models displayed similar goodness of fit to the new KM (Figure 4 in Appendix) and therefore we chose to keep the log-normal model as per the EAG and committee's preferred base-case assumptions.	**EAG comments:** The EAG agrees with using only the data of patients on tafamidis treatment to estimate the tafamidis on-treatment OS. The company selected the log-normal model as per the EAG and committee's preferred base-case assumptions, while the exponential curve has a slightly better statistical fit. As the visual fit of the curves seem similar, this likely has a very small impact on the ICER.

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	Figure 2. Kaplan-Meier estimators of OS with and without censoring for treatment discontinuation – tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 1mg ATTR-ACT LTE (August 2021 data cut) 	

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4	**Estimating off-treatment overall survival from ATTR-ACT BSC arm** As stated above, in EAG exploratory scenario 2, the modelled hazard of mortality after discontinuation is identical to that of BSC patients at the same time and thus assumes that patients who discontinue experience instantaneous accumulation of amyloid and disease progression to match that of BSC patients at that time point. This results in prediction of survival well below that of the observed data. To adjust the hazard of mortality to better reflect clinical opinion "that outcomes would not immediately revert to BSC outcomes when treatment is stopped (Section 3.9, pg. 12 of draft guidance)", we suggest – whilst still conservative – applying the mean hazard of mortality from the ATTR-ACT BSC arm when discontinuing treatment. In the EAG report and ACM1, it was confirmed that the Weibull model was the preferred model for BSC OS extrapolation, and so Weibull was used to model this (i.e. to determine numbers of expected life years under BSC treatment). The economic model does not track the time from discontinuation, and therefore mortality hazard after treatment discontinuation must be modelled as uniform across the discontinued patients, then the expected number of deaths in a model cycle must be split according to the relative risk of mortality per NYHA class. Thus, a constant hazard (exponential) model predicting the same life expectancy as the BSC arm is used. The exponential rate to achieve a specified life expectancy is simply 1/life expectancy, and this is implemented in the model such that the rate of mortality after discontinuation is dependent upon the currently modelled life expectancy for BSC (i.e. it varies in PSA). **Conclusions** • The committee's preferred base-case (EAG exploratory scenario 2) can be amended to better reflect what is likely to happen when a patient discontinues tafamidis in the clinical	**EAG comments:** Accurately modelling OS for patients who discontinued tafamidis is challenging, as patients discontinue at different time points and a tunnel state to track these patients over time is not available in the model. Therefore, the company assumes a constant hazard (exponential) model predicting the same life expectancy as the BSC arm. Using this approach, OS is probably underestimated in the first years and overestimated in later years. As is shown in the figure below, the company's new approach has worse OS than BSC in (approximately) the first 5 years and better OS compared to BSC in (approximately) year 5 to 15. As patients likely discontinue after some time on treatment (median time to tafamidis discontinuation is approximately 5 years), OS for tafamidis discontinuers is likely slightly better than for BSC patients. It is uncertain whether this scenario accurately reflects OS for tafamidis discontinuers. Ideally a tunnel state would be used to track tafamidis discontinuers and an OS curve specific for tafamidis discontinuers would be calculated from the ATTR-ACT LTE study. The Figure below shows the overall survival for BSC patients (in blue) and the company's new approach where

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	setting as well as observed long-term survival data and clinical expert opinion in ACM1. A summary of the amendments is presented in Figure 4 below. ○ These amendments include: (1) adjusting OS for patients who remain on-treatment by censoring for discontinued patients, and (2) estimating OS for patients who have discontinued treatment by applying the mean hazard of mortality from the BSC arm of ATTR-ACT. • The revised company base-case represents a scenario which we believe more closely reflects what is likely to happen when a patient discontinues tafamidis compared to the committee's preferred base-case, and addresses uncertainties raised by the committee in ACM1 whilst still being conservative. • The deterministic and probabilistic base-case ICERs (with revised PAS) for our revised company base-case, the EAG base-base and the committee's preferred base-case are presented in Table 1 and Table 2, respectively. The revised PAS and amendments to the committee's preferred base-case result in a cost-effective revised company base-case ICER. **Figure 3. Summary of ammendments applied to committee's preffered base-case**	a constant hazard (exponential) model predicting the same life expectancy as the BSC arm is use (in orange). 

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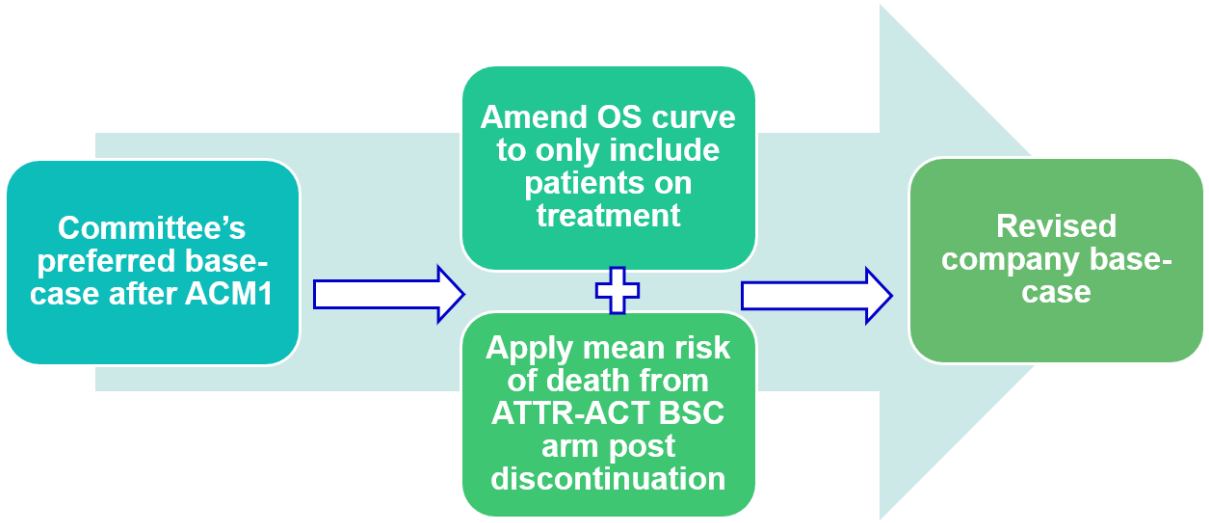

Table 1. Deterministic cost-effectiveness results (with revised PAS)

	Tafamidis	BSC	Incremental
EAG base-case			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Revised company base-case (adjusted on-treatment OS and mean BSC hazard of mortality from ATTR-ACT post discontinuation)			

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Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Committee's preferred base case (EAG exploratory scenario 2)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year.

Instructions to access amended scenarios in the new attached economic model:

EAG base case:

1) Set Cell 'Model Control'!Q16 (named range "setOSModelTrt") to "OS - lognormal/RS - tafamidis 80mg/80mg/free acid ATTR-ACT LTE"
2) Enable EAG scenario flags "EAG_2", "EAG_3" on sheet "EAG"; all other EAG flags should be set to 0
3) Ensure cell 'Model Control'!D51(named range "discontinued_surv_scenario") is set to "immediate switch"

Committee's preferred base-case:

1) Do the above to reach EAG base-case
2) Enable EAG scenario flag "EAG_5" on sheet "EAG"

Revised company base-case:

1) Do the above to reach committee's preferred base-case
2) Set cell 'Model Control'!D51(named range "discontinued_surv_scenario") to "BSC mean"
3) Set Cell 'Model Control'!Q16 (named range "setOSModelTrt") to "OS cens. disc. - lognormal/RS - tafamidis 80mg/80mg/free acid ATTR-ACT LTE"

Table 2. Probabilistic cost-effectiveness results (with revised PAS)

	Tafamidis	BSC	Incremental
EAG base case			
Life years	[redacted]	[redacted]	[redacted]

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QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Revised company base case (adjusted on-treatment OS and mean BSC hazard of mortality from ATTR-ACT post discontinuation)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		
Committee's preferred base case (EAG exploratory scenario 2)			
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]		

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year.
The probabilistic base-case ICERs when only amending the committee's preferred base-case by adjusting on-treatment OS is [redacted] or when only applying mean hazard of mortality from the ATTR-ACT BSC arm is [redacted] – these have been provided for completeness.

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	Appendix **Figure 4. New Parametric relative survival models fitted to OS censoring for TD - ATTR-ACT tafamidis 80 mg (August 2021)**

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	[redacted]	

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	Figures in brackets 95% confidence interval of all-cause mean by non-parametric bootstrap (1000 repetitions). All-cause mean calculated using baseline hazard of country, age and sex matched life tables by the Ederer (I) method. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBL: database lock; Exp: exponential; G. Gamma: generalised gamma; L. Logistic: log-logistic; L. Norm: lognormal; OS: overall survival; TD: treatment discontinuation.

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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