NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

# Committee Papers

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## SINGLE TECHNOLOGY APPRAISAL

## Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Pfizer:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Society for Heart Failure
   b. Cardiomyopathy UK
   c. UK ATTR Amyloidosis Patients' Association, *endorsed by patient expert Paul Pozzo*
   d. British Cardiovascular Society, *endorsed by Royal College of Physicians*
   e. Royal College of Pathologists

4. **Expert personal perspectives** from:
   a. Professor Perry Elliott, Professor of Cardiovascular Medicine and Director UCL Institute of Cardiovascular Science – clinical expert, nominated by Pfizer
   b. Professor Philip Hawkins, founder of National Amyloidosis Centre – clinical expert, nominated by National Amyloidosis Centre
   c. Ben Laryea – patient expert, nominated by UK ATTR Amyloidosis Patients Association
   d. Fiona Marley – NHS Commissioning Expert, nominated by NHS England

5. **External Assessment Group Report** prepared by Kleijnen Systematic Reviews
   a. External Assessment Group report
   b. Initial appendix to EAG report
   c. Further appendix to EAG report

6. **External Assessment Group response to factual accuracy check of EAR**

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

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Tafamidis for transthyretin amyloid cardiomyopathy (review of TA696) [ID6237]

## Company evidence submission

**September 2023**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID6327_Tafamidis_Evidence Submission_29SEP23[CON]** | **v1.0** | **Yes** | **29th September 2023** |

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# 1. Purpose

Untreated transthyretin amyloidosis with cardiomyopathy (ATTR-CM) incurs burden on both patients and their caregivers, and burden increases as the condition worsens.[1] Tafamidis (Vyndaqel®) is a breakthrough treatment for ATTR-CM, and remains the only approved therapy which stabilises transthyretin (TTR) directly, preventing amyloid aggregation in the myocardium. Tafamidis has already been shown to reduce all-cause mortality and cardiovascular-related (CV) hospitalisations as well as reduced the decline in functional capacity and quality of life as compared with placebo.[2] More recent data also shows tafamidis sustained a reduction in all-cause mortality in continuous tafamidis treatment compared with delayed tafamidis treatment (placebo then tafamidis) in patients with late-stage disease at baseline over a median follow-up of ~5 years.[3]

In 2021, NICE published a negative recommendation for tafamidis in ATTR-CM [TA696].[4] Since then, no additional therapies have been authorised for use in ATTR-CM in the UK, therefore, tafamidis still represents a paradigm shift in the management of a rare, progressive and fatal disease with a significant unmet need. Recognising this unmet need, as well as the availability of new long-term clinical data and a revised Patient Access Scheme (PAS), we are re-submitting an evidence package for tafamidis in ATTR-CM to be assessed in this current single technology appraisal (STA).

As agreed during the decision problem meeting, this abbreviated document summarises:

- Preferred assumptions from the committee in TA696[4] and where these have been applied in the new economic base case
- New evidence which has become available since the original STA for tafamidis in ATTR-CM [TA696[4]] and where these data have been applied in the new economic base case
- Cost-effectiveness analysis results (with new PAS)
- Overview of the budget impact of tafamidis (with new PAS)

The economic model previously developed by the EAG during TA696[4] has been updated with new data and enhanced user functionality elements, and has been used to estimate ICERs in the updated economic analysis in the current submission. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) functionality has also been added to the


 

model. To aid review, a change log has been included with in the model. Furthermore, a non-modified version of the EAG model from TA696[4] with data has also been included to validate that there has been no changes applied to the model engine.

The TA696[4] submission package, which includes document A and B as well as associated appendices and materials has also been provided for reference. Updated versions of these documents with new confidentiality marking will be provided at a later date as agreed in the decision problem meeting.


 

# 2. Executive summary

- Tafamidis overall survival (OS) and time to treatment discontinuation (TTD) data included in the economic analysis in the original STA [TA696[4]] was limited to 30 months (observation period of ATTR-ACT clinical trial).

- New long-term OS and TTD data from the ATTR-ACT long term extension study (ATTR-ACT LTE) is now available and has been incorporated into the updated economic analysis– data extends up to 84 months (4.5 years of additional data)

- New OS and TTD data substantially reduce the uncertainty associated with long-term extrapolations in TA696[4]; which were key uncertainties raised by committee in TA696[4]

- All other committee preferred assumptions from TA696[4] have been included in the updated base case resulting in low levels of uncertainty. These include: the continuation of treatment in NYHA IV, the use of treatment-independent utilities in NYHA IV, the use of age adjusted utility decrements after month 30, the inclusion of drug wastage costs, the removal of early diagnosis assumptions, and the use of the committee's preferred parametric distributions functions for the extrapolation of best supportive care (BSC) OS beyond observed data.

- Pfizer have increased the PAS from [redacted] ([redacted] per pack) to [redacted] ([redacted] per pack)

- When applying the most appropriate updated extrapolation for OS and TTD and the new PAS, the new base case ICER is [redacted]

- Many scenarios explored had substantial reduction on the ICER including: incorporating cost savings associated with earlier diagnosis, reflecting potential real-world usage of tafamidis in NYHA IV, excluding cardiovascular (CV) related hospitalisation costs, and reducing the age of diagnosis due to improved service pathway redesign. Given the additional follow-up data from ATTR-ACT LTE, the selection of the most appropriate OS and TTD extrapolation distributions now has a relatively minor impact on the ICER.


 

# 3. Decision problem and description of the technology

## *3.1. Decision problem*

The submission covers the technology's full marketing authorisation for this indication, as shown alongside further details of the decision problem in Table 1.

**Table 1. The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Intervention** | Tafamidis | As per final scope | Not applicable |
| **Population** | People with transthyretin amyloid cardiomyopathy (ATTR-CM) | As per final scope | Not applicable |
| **Comparator(s)** | People with ATTR-CM:<br>• Established clinical management without tafamidis (including diflunisal)<br>People with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy [TTR-FAP] and hereditary ATTR-CM)<br>• Patisiran<br>• Inotersen<br>• Vutrisiran | Best supportive care (established clinical management without tafamidis) | **We do not consider inotersen, patisiran, vutrisiran or diflunisal to be appropriate comparators as none of these medicines are licensed for the treatment of ATTR-CM.**[5-8]<br>**It is also important to note these medicines have higher list price to tafamidis and are either administered via disposable pre-filled injections/ infusions[9] (list price of diflunisal not available via BNF):**<br>**Inotersen:**<br>• **List price per pack: £23,700**<br>• **Annual cost: £308,100**<br>**Patisiran:**<br>• **List price per dose: £7,676**<br>• **Annual cost: £399,176**<br>**Vutrisiran:** |

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| | | | • **List price per dose: £95,862**<br>• **Annual cost £383,449**<br><br>**Inotersen, patisiran, and vutrisiran** licensed for hereditary transthyretin amyloidosis in adult patients with Stage 1 or 2 polyneuropathy[5-7], have been included as comparators in the final scope, for the treatment of people with ATTR and a mixed phenotype, expressing symptoms of both cardiomyopathy and polyneuropathy.[10]<br><br>We agree there is a small UK population of hereditary ATTR patients with a mixed phenotype; estimated 16.6% presenting with polyneuropathy also suffer from ATTR-CM.[11] However, Patisiran, inotersen and vutrisiran have not been satisfactorily evaluated in patients with heart failure:<br><br>(1) the safety and efficacy of these drugs has not been established in symptomatic ATTR-CM. Evidence from NEURO-TTR and APOLLO and HELIOS-A only support use of patisiran, inotersen and vutrisiran in patients with ATTR polyneuropathy. This is consistent with their marketing authorisations.[5-7] In contrast, the ATTR-ACT study was powered to compare all-cause mortality rates and rates of cardiovascular-related hospitalisations in patients receiving tafamidis versus placebo for ATTR-CM.[2]<br><br>(2) APOLLO and NEURO-TTR studies defined 'cardiac' subgroups on the basis of a measurement of the thickness of the heart wall. The echocardiogram criteria (LV wall thickness ≥13mm) used to define a cardiac (mixed phenotype) subpopulation in APOLLO and NEURO-TTR does not meet the consensus diagnostic criteria for ATTR-CM.[12] It is a structural finding and may be sub-clinical. A thickened heart wall does not imply cardiac deposition of TTR amyloid nor the presence of clinical heart failure.<br><br>(3) From a demographic perspective, the Val122Ile mutation found in Afro-Caribbean patients is causative in 63% of cases of hereditary ATTR-CM in the UK.[13] This manifests with a predominant cardiac phenotype. Only 3 patients (1.7%) with Val122Ile mutation were enrolled in NEURO-TTR and |

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| | | | a further 2 patients (0.9%) in APOLLO. Of the patients with hereditary ATTR-CM in ATTR-ACT, 61 (57.5%) had a causative Val122Ile mutation.<br><br>(4) The endpoints assessed in APOLLO, NEURO-TTR and HELIO-A were reflective of the disease burden of patients with ATTR-PN and did not include any clinical cardiac endpoints included in the scope for tafamidis. Thus, these studies do not provide sufficient evidence of safety or efficacy of treatment in a population with ATTR-CM.[14-16] These studies do not provide a valid indirect treatment comparison based on the lack of shared endpoints and distinct populations.<br><br>**Patisiran**<br>The Food and Drug Administration (FDA) are assessing an application to approve patisiran for the treatment of ATTR-CM. This is based on data derived from an exploratory analysis of the APOLLO phase 3 trial.[17]<br><br>**Diflunisal**<br>Diflunisal is not licensed for the treatment of ATTR-CM.[8] To our knowledge, there are currently no randomised clinical trials (RCTs) investigating diflunisal in ATTR-CM. As per the comment from NHSE on the NICE Final Scope; "The National amyloidosis centre at the Royal Free NHS FT also use an unlicensed treatment, diflunisal for patients in the latter stages of the disease." Whereas tafamidis is started in patients at NYHA class I to III. Therefore, diflunisal is not considered a relevant comparator. |

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| **Outcomes** | The outcome measures to be considered are:<br>• Overall survival<br>• Cardiovascular-related mortality<br>• Cardiac function (such as longitudinal strain or brain natriuretic peptide [BNP] level)<br>• Cardiovascular-related hospitalisation<br>• Functional exercise capacity<br>• Signs and symptoms of heart failure (such as breathlessness)<br>• Adverse effects of treatment<br>• Health-related quality of life | As NICE scope. | Not applicable |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or | As NICE scope. | Not applicable. |

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| | outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. | | |
| **Other considerations** | If the evidence allows, the following subgroups will be considered:<br>• severity of heart failure (such as by New York Heart Classification class)<br><br>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. | As NICE scope. | In the FAD associated with TA696[4], there was uncertainty around the benefit of treatment in patients in NYHA III. The latest interim analysis from ATTR-ACT LTE showed continuous treatment benefit across NYHA I/II and NYHA III (Table 5, see Section 6.3).[3] |

### 3.1.2. Equality considerations

Tafamidis is will predominately be used in older populations (65+years). Despite age being protected by the Equality Act (2010)[18], diseases which typically impacting older populations – such as ATTR-CM – are unable to qualify for NICE's severity modifier, and so it is important to consider the wider impact of the disease within the assessment even burden is not captured directly in the ICER.

Val122Ile is the most common mutation of hereditary ATTR-CM in the UK (63% of cases)[19], and manifests in a predominant cardiac phenotype.[13,19] The Val122Ile mutation is found almost exclusively in people of Afro-Caribbean origin [20,21], among whom it is the 4th most common cause of heart failure.[13,19] These patients have the poorest survival of all forms of ATTR-CM, including those with wild-type and non-Val122Ile hereditary ATTR-CM (2.6, 5.7 and 4.7 years, respectively, $p<0.0001$).[19]


 

## *3.2. Description of technology being appraised*

Details of the technology being appraised in this submission are summarised in Table 2.

**Table 2. Technology being appraised**

| | |
|---|---|
| **UK approved name and brand name** | Tafamidis (Vyndaqel®) |
| **Mechanism of action** | Tafamidis is a specific stabiliser of TTR.[22] Alterations in the structure of the TTR protein, caused by ageing or by genetic mutations, increase its tendency to dissociate into its constituent monomers, which misfold and aggregate into insoluble amyloid fibrils which accumulate in tissues and organs.[2,23,24] The dissociation of TTR tetramers to monomers is the rate limiting step in the pathogenesis of ATTR-CM.[25]<br>Tafamidis binds to the native tetrameric form of transthyretin, preventing its dissociation into monomers and reducing amyloid formation. |
| **Marketing authorisation/CE mark status** | Tafamidis is licensed by the European Medicines Agency (EMA) for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).[26]<br>Based on the innovative nature of tafamidis, it was granted a Promising Innovative Medicine (PIM) designation by the MHRA in December 2018. In 2019, tafamidis subsequently received an Early Access to Medicines Scheme (EAMS) positive scientific opinion from the MHRA.[27] Tafamidis EAMS enrolled patients at 17 sites across the UK. |
| **Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)** | Tafamidis is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).[22] |
| **Method of administration and dosage** | *Method of administration:*<br>Tafamidis is a soft capsule for oral administration.[22]<br><br>*Dosage:*<br>The recommended dose is one tafamidis 61 mg capsule taken once a day.[22] Vyndaqel 61 mg (tafamidis) corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.[22] |
| **Additional tests or investigations** | Use of tafamidis does not require any additional tests or investigations beyond those already used to identify the condition in clinical practice.[12] |
| **List price and average cost of a course of treatment** | **List price:** £10,685 per pack of 30 capsules<br>**Annual cost:** £130,089.88 per patient at list price<br>**Average cost of a course of treatment**: Based on the mean treatment duration of [redacted] derived from the cost-effectiveness model, the average cost of treatment is approximately [redacted] at list price. |


 

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| **Patient access scheme (if applicable)** | [redacted] |

Abbreviations: ATTR-CM: transthyretin amyloidosis with cardiomyopathy; EAMS: Early Access to Medicines Scheme; EMA: European Medicines Agency; PASLU: Patient Access Scheme Liaison Unit; PIM: Promising Innovative Medicine; TTR: transthyretin.

# 4. Committee preferred assumptions from TA696

Committee preferred assumptions detailed in the TA696[4] final advice document (FAD) and preferred assumption included in the new economic base case (Section 8) are presented in Table 3.

**Table 3. Summary of EAG preferred assumptions in new economic base case**

| Assumptions | Committee preferred base-case [TA696] (Yes/No) | Company preferred base-case [TA696] (Yes/No) | Company new base case [ID6327] (Yes/No) | Company comments |
|---|---|---|---|---|
| Log-normal OS for tafamidis | Yes | Yes | No | Generalised Gamma distribution used to extrapolate tafamidis OS due to best fit for new data from ATTR-ACT LTE data. Refer to Section 7.2.<br>Scenario analysis exploring alternative distributions for tafamidis OS extrapolation presented in Section 8.1.3. |
| Exponential TTD extrapolation | Yes | Yes | Yes | Exponential distribution used to extrapolate tafamidis TTD due to best fit for new data from ATTR-ACT LTE data. Refer to Section 7.5.<br>Scenario analysis exploring alternative distributions for tafamidis TTD extrapolation presented in Section 8.1.3. |
| Weibull OS for BSC | Yes | Yes | Yes | Weibull is used to extrapolate BSC OS in the new economic base case. |
| Discontinuation plateau at month 42 | Yes | No | No | Discontinuation plateau removed due to newly available long-term data from ATTR-ACT LTE which accounts for treatment discontinuation and extends to 84 months. Refer to Section 7.5. |
| Continuation of treatment in NYHA IV | Yes | No | Yes | Insights from EAMS show that clinicians would not explicitly always stop treatment due to progression to NYHA IV but on balance we expect patients to discontinue treatment shortly after reaching NYHA IV due to poor prognosis associated with severe heart failure. Therefore, the new base case where treatment is continued in NYHA IV may represent a slight overestimation of the ICER, and as such, a scenario where no treatment is used beyond progression is |

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| | | | | utilised to demonstrate the potential (downward) impact of this assumption on the ICER – refer to Section 8.1.3. |
| Treatment independent utilities (BSC) for NHYA IV | Yes | Yes | Yes | BSC utility value applied in NYHA IV in the new economic base case.<br>Scenario analysis exploring the use of treat-dependent utilities in NHYA IV is present in Section 8.1.3 to demonstrate potential impact of this assumption. |
| Age adjusted utility decrements after month 30 | Yes | Yes | Yes | Age adjusted utility decrements after month 30 have been used in the new economic base case. |
| BSC costs after treatment discontinuation | Yes | Yes | Yes | BSC costs are assumed for patients who discontinue tafamidis in the new economic base case. |
| Drug wastage costs included | Yes | No | Yes | Drug wastage costs are included in the new economic base case.<br>Scenario analysis exploring the exclusion of drug wastage costs is presented in Section 8.1.3 to demonstrate potential impact of this assumption. |
| Includes early diagnosis assumptions | No | Yes | No | Costs savings associated with early diagnosis have been excluded from the new economic base case. Scenario analysis exploring the inclusion of early diagnosis cost savings is presented in Section 8.1.3 to demonstrate potential impact of this assumption. |

Abbreviations: ATTR-ACT LTE: ATTR-ACT long-term extension study; BSC; best supportive care; EAG: external assessment group; NYHA: New York Heart Association Functional Classification; OS: overall survival; TTD: time to treatment discontinuation.

# 5. Recap of ATTR-ACT and ATTR-ACT long-term extension (ATT-ACT LTE)

The tafamidis clinical trial program included two phase 3 multicentre clinical trials: (i) ATTR-ACT[2] (ii) ATTR-ACT long-term extension (ATTR-ACT LTE)[3,28]. A summary of the methodology as well as outcomes used for the economic model from ATTR-ACT and the ATTR-ACT LTE is presented in Table 4.

**Table 4. Summary of the trial methodology for ATTR-ACT and the ATTR-ACT LTE**

| Trial acronym (trial number): | ATTR-ACT (NCT01994889)[2] | ATTR-ACT LTE (NCT02791230)[3,28] |
|---|---|---|
| **Trial design** | Phase III, multicentre, international, double-blind, randomised placebo-controlled trial. | Phase III, multicentre, long-term extension study of ATTR-ACT with a 60 month treatment phase. |
| **Eligibility criteria for participants** | Patients between 18 and 90 years of age with ATTR-CM (wild-type or hereditary). | Cohort A: Patients who successfully completed 30 months of ATTR-ACT.<br>Cohort B: Patients diagnosed with ATTR-CM who had not participated in ATTR-ACT. |
| **Settings and locations where the data were collected** | Conducted at 48 sites worldwide (including 2 UK sites). The trial sites were secondary or tertiary care settings. | ATTR-ACT sites and additional sites worldwide. |
| **Trial drugs** | 2:1:2 ratio of 80 mg* of tafamidis meglumine (n=176), 20 mg of tafamidis meglumine (n=88) or placebo (n=177); oral QD for 30 months. | Cohort A: tafamidis meglumine (20 mg or 80 mg* QD). After Protocol Amendment 3 (20 July 2018) patients were assigned to open-label treatment of tafamidis free acid 61 mg (or if not available, tafamidis meglumine 80 mg*).<br>Cohort B: tafamidis free acid 61 mg QD (or if not available, tafamidis meglumine 80 mg*). |
| **Permitted and disallowed** | Patients could use non-prohibited supplements and medications during the study. Medications taken after the first dose of trial medication were documented as concomitant medications. This | Patients could use non-prohibited supplements and medications during the study with the exception of those listed below:<br>• Any investigational therapy |

| Trial acronym (trial number): | ATTR-ACT (NCT01994889)[2] | ATTR-ACT LTE (NCT02791230)[3,28] |
|---|---|---|
| **concomitant medication** | included prescription and over-the-counter medicines, vitamins, and herbal remedies.<br><br>Medications considered to be BSC were permitted and were to be stabilised for at least 4 weeks of therapy (other than diuretics) prior to baseline. Changes in diuretic dose were permitted within 4 weeks of the baseline visit.<br>The following medication was prohibited:<br>• Any investigational therapy<br>• Tauroursodeoxycholate and doxycycline<br>• Digitalis and calcium channel blockers. If used prior to randomisation, these medications were to be stopped at least 30 days before Baseline (Day 1)<br>• Patients discontinued use of diflunisal at least 30 days prior to the Baseline visit (Day 1). All NSAIDs apart from the following permitted NSAIDs: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam and sulindac. | • Diflunisal<br>• Tauroursodeoxycholate and doxycycline<br>• Digitalis and calcium channel blockers (e.g. verapamil, diltiazem) |
| **Randomisation and blinding** | An interactive web-based response system was used for randomisation. Blinding was achieved by means of a matching placebo. Patients and investigators were blinded to treatment allocation. | • Cohort A: As described in the pivotal study, then open-label after Protocol Amendment. Patients initially randomised to placebo in ATTR-ACT were re-randomised 2:1 to 80 mg* and 20 mg, until the Protocol Amendment when all patients were switched to the higher dose.<br>• Cohort B: All patients were assigned tafamidis free acid 61 mg (or if not available, tafamidis meglumine 80 mg*) treatment. |
| **Primary outcomes** | All-cause mortality and frequency of CV-related hospitalisation at Month 30 using the Finkelstein-Schoenfeld method<br>Details of outcome measures and timings of assessment for all relevant outcomes (primary and other) are provided in **Error! Reference source not found.**. | • All-cause mortality<br>• Incidence of treatment-emergent adverse events |

| Trial acronym (trial number): | ATTR-ACT (NCT01994889)[2] | ATTR-ACT LTE (NCT02791230)[3,28] |
|---|---|---|
| **Other outcomes used in the economic model/specified in the scope** | • **All-cause mortality**<br>• **CV-related hospitalisation**<br>• CV-related mortality<br>• Cardiac function (6MWT, NT-proBNP, echocardiographic parameters)<br>• **NYHA functional classification**<br>• Transthyretin stabilisation<br>• **Adverse effects of treatment**<br>• **Health-related quality of life (**KCCQ-OS, **EQ-5D-3L**, EQ-5D-VAS**)**<br>All outcomes were pre-specified. An independent, endpoint adjudication committee, who were unaware of trial group assignments, determined whether investigator-reported events met the definition of disease-related efficacy end points, with the use of predefined endpoint criteria.<br>**Outcomes used in the economic modelling are shown in bold** | • **All-cause mortality**<br>**Outcomes used in the economic modelling are shown in bold** |
| **Pre-planned subgroups** | Stratification factors<br>• *TTR* genotype (wild-type versus hereditary)<br>• NYHA class at baseline (class I/II versus class III)<br>Dose analysis<br>• Dose (20 mg vs. placebo, 80 mg vs. placebo) | • *TTR* genotype (wild-type versus hereditary) |

*Tafamidis (Vyndaqel) 61mg corresponds to 80mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.
Abbreviations: 6MWT: 6-minute walk test; ATTR-ACT: Tafamidis in transthyretin cardiomyopathy clinical trial; BSC: Best Supportive Care; CMAD, transplantation/cardiac mechanical assist device; CV: cardiovascular; EQ-5D: EuroQoL-5 Dimensions; KCCQ-QS: Kansas City Cardiomyopathy Questionnaire; LTE: long-term extension; NSAID: Nonsteroidal anti-inflammatory drugs; NYHA: New York Heart Association Functional Association; PGA: patient global assessment; QD: once daily.

# 6. Key new clinical effectiveness evidence

## 6.1. *ATTR-ACT LTE: Tafamidis overall survival*

In TA696[4], overall survival (OS) data was derived from the ATTR-ACT trial (NCT01994889)[2] which was limited to 30 months post treatment initiation. ATTR-ACT was a Phase III, multicentre, international, three-arm, parallel design, placebo-controlled, randomised study with a 30-month double-blind treatment phase, to determine the efficacy of tafamidis meglumine administered orally as soft gel capsules compared to placebo, based on clinical outcomes in patients with wild-type or hereditary ATTR-CM.[2] Patients treated with tafamidis showed statistically significant and clinically meaningful treatment benefits compared with the placebo group.[2]

Moreover, in TA696[4], long-term data from the ATTR-ACT LTE (August 2019 cut-off date)[29] was used to validate goodness-of-fit statistics and assessment of visible fit for parametric distribution functions used to extrapolate overall survival beyond the observed period of ATTR-ACT.

As of September 2021, more recent tafamidis OS data from the ATTR-ACT LTE has become available[28] and been incorporated into the updated economic analysis (refer to Section 7.2 for further details). Data now extends to 84 months[28] of tafamidis treatment and substantially reduces uncertainty associated with OS extrapolations.

The Kaplan-Meier estimator for patients who entered the ATTR-ACT LTE continuing from the tafamidis meglumine 80mg arm of ATTR-ACT showed a trend towards decreasing hazards in the most recent data cut (August 2021) (Figure 1).[28] Tafamidis (Vyndaqel) 61mg – technology being appraised in this submission – corresponds to 80mg of tafamidis meglumine.[22]

**Figure 1. Kaplan-Meier plot of overall-survival – 80mg tafamidis meglumine in ATTR-ACT to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)**

Abbreviations: CMAD: cardiac mechanical assist device; HT: heart transplant; NAR: numbers at risk; OS: overall survival
Source: Pfizer data on file.[28]

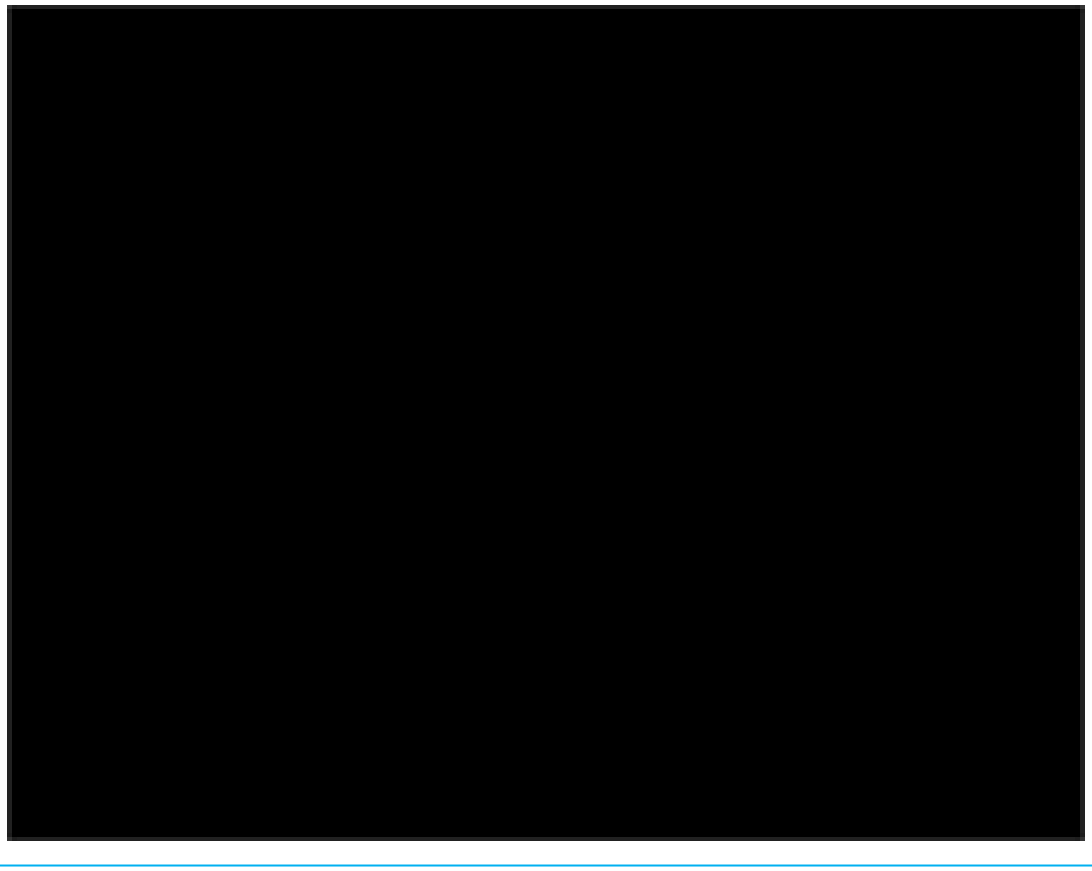
## 6.2. *ATTR-ACT LTE: time to treatment discontinuation*

Time to treatment discontinuation (TTD) data included in economic analysis in TA696[4] was also derived from the ATTR-ACT clinical trial and limited to 30 months post treatment initiation.[2] Similar to OS, data from the ATTR-ACT LTE (August 2019 cut-off date)[29] was also used to validate goodness-of-fit statistics and assessment of visible fit for parametric distribution functions used to extrapolate overall survival beyond the observed period of ATTR-ACT.

As of September 2021, more recent TTD data from the ATTR-ACT LTE has become available[28] and been incorporated into the updated economic evaluation (refer to Section 7.2 for further details). Data now extends to 84 months (Figure 2).[28]

**Figure 2. Proportion of patients not discontinued – 80mg tafamidis meglumine in ATTR-ACT to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)**



Abbreviations: CMAD: cardiac mechanical assist device; HT: heart transplant; NAR: numbers at risk.
Source: Pfizer data on file.[28]

## *6.3. ATTR-ACT LTE: treatment benefit in NHYA class I to III*

In TA696[4], there was uncertainty regarding tafamidis treatment reducing cardiovascular-related mortality in people with ATTR-CM classified as NHYA III (refer to Section 3.11 in FAD for TA696[4]). A more recent data analysis of all-cause mortality from the ongoing ATTR-ACT LTE (August 2021 data cut), is also shown below (Table 5).[3]

The analysis integrates data on all-cause mortality from two groups were compared: (i) Continuous tafamidis group: patients who initially received tafamidis meglumine 80 mg in ATTR-ACT and ATTR-ACT LTE, followed by tafamidis free acid 61 mg after the protocol amendment.[3] (ii) Placebo to tafamidis group: patients who received placebo in ATTR-ACT and then tafamidis meglumine 80 or 20 mg in ATTR-ACT LTE, followed by tafamidis free acid 61 mg after the protocol amendment. Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT are not included in this analysis.[3]

Over ~5 years, tafamidis treatment continued to improve survival.[3] The latest interim analysis showed across NYHA classes I–III and patients who received continuous tafamidis continued to have better survival than those who received placebo in ATTR-ACT followed by tafamidis in the ATTR-ACT LTE:

- NYHA I/II: HR, 0.50 (95% CI, 0.346–0.727); exploratory P=0.0003.[3]
- NYHA III: HR, 0.64 (95% CI, 0.408–0.992); exploratory P=0.0460.[3]

Despite all patients receiving tafamidis in ATTR-ACT LTE, the persistent difference in survival between these groups confirms that treatment should be initiated as early as possible. Even though patients' disease may have progressed, there was an improvement in survival with tafamidis treatment in ATTR-ACT LTE for patients who had previously received placebo in ATTR-ACT.

**Table 5. All-cause mortality over ~5 years' treatment with tafamidis by NYHA class at baseline (ATTR-ACT LTE August 2021 data cut)**

| | **NYHA class I or II at baseline** | | **NYHA class III at baseline** | |
|---|---|---|---|---|
| **At end of ATTR-ACT** | **Tafamidis meglumine 80mg** | **Placebo** | **Tafamidis meglumine 80mg** | **Placebo** |
| Median months' follow-up | 30 | 30 | 30 | 30 |
| All-cause mortality, n/n (%) | 25/121 (20.7) | 37/114 (32.5) | 29/55 (52.7) | 39/63 (61.9) |
| HR | 0.635 (0.382-1.055) | | 0.769 (0.473-1.250) | |
| **ATTR-ACT LTE data cut (1 August 2021)** | **All patients receiving tafamidis receive tafamidis free acid 61mg†** | | | |
| | **Continuing from tafamidis meglumine 80mg** | **Placebo to tafamidis** | **Continuing from tafamidis meglumine 80mg** | **Placebo to tafamidis** |
| Median months' follow-up | 61 | 60 | 60 | 56 |
| All-cause mortality, n/n (%) | 49/121 (40.5) | 70/114 (61.4) | 35/55 (63.6) | 51/63 (81.0) |
| HR | 0.502 (0.346-0.727)* | | 0.636 (0.408-0.992)* | |

*P<0.05. †Patients completing ATTR-ACT could enrol in ATTR-ACT LTE to receive up to 60 additional months of tafamidis treatment (NCT02791230). Patients receiving tafamidis meglumine (80 or 20 mg) in ATTR-ACT initially continued this dose in ATTR-ACT LTE. Those who had received placebo in ATTR-ACT were randomised 2:1 to tafamidis meglumine 80 or 20 mg, stratified by genotype. Following a protocol amendment in July 2018, all patients transitioned to the approved tafamidis dosage of once-daily tafamidis free acid 61 mg.
HR presented with 95% CI. Abbreviations: CI: confidence intervals, HR: hazard ratio.
Source: Elliott et al. 2023[3]

## 6.4. *ATTR-ACT LTE: adverse events*

As of 1 August 2021, no new safety concerns have emerged from the tafamidis meglumine 80 mg and free acid 61 mg arm in the ATTR-ACT LTE compared with observations with tafamidis treatment in ATTR-ACT.[3] The most common classes of adverse events experienced by patients in the continuous tafamidis group are shown below in Table 6[3], and are consistent with that previously reported in ATTR-ACT and at earlier time points in the LTE.

**Table 6. Most common adverse events – 80mg tafamidis meglumine to 61mg tafamidis in ATTR-ACT LTE (August 2021 data cut)**

| n (%) | Continuous tafamidis n= 110 |
|---|---|
| Any adverse event in the ATTR-ACT LTE | 108 (98.2) |
| System organ classes where ≥30% of patients had an adverse event: | |
| Cardiac disorders | 79 (71.8) |
| Infections and Infestations | 64 (58.2) |
| Injury, poisoning, and procedural complications | 57 (51.8) |
| Respiratory, thoracic, and mediastinal disorders | 55 (50.0) |
| General disorders and administration site conditions | 54 (49.1) |
| Nervous system disorders | 51 (46.4) |
| Gastrointestinal disorders | 50 (45.5) |
| Musculoskeletal and connective tissue disorders | 49 (44.5) |
| Metabolism and nutrition disorders | 43 (39.1) |
| Skin and subcutaneous tissue disorders | 42 (38.2) |
| Renal and urinary disorders | 35 (31.8) |

Events coded per Medical Dictionary for Regulatory activities v 24.0.
Source: Elliott et al. 2023[3]

## 6.5. Additional caregiver burden in ATTR-CM

Recent findings have been published from a multicentre, international, real-world study which evaluated the burden of ATTR-CM on patients who were naïve to disease-modifying treatment and their unpaid primary caregivers using study-specific and established surveys (patients: Kansas City Cardiomyopathy Questionnaire Overall Summary [KCCQ-OS], 12-Item Short Form Health Survey [SF-12], Hospital Anxiety and Depression Scale [HADS], Patient-Reported Outcomes Measurement Information System [PROMIS] Fatigue and Dyspnea; caregivers: SF-12, HADS, PROMIS Fatigue, Zarit Burden Interview [ZBI]).[1] The company became aware of this new data as the study was sponsored by Pfizer, we did not conduct any additional literature searches for data. This study was also mentioned during the decision point meeting as newly available evidence.

Finding from Ponti et al. suggested that untreated ATTR-CM was a substantial burden on caregivers, despite patients being relatively newly diagnosed and with a short caregiving duration.[1] Data from Ponti et al. was not utilised in the economic model, but has been presented to highlight the humanistic burden of untreated caregivers of patients with untreated ATTR-CM.

The study included 208 pairs of patients with treatment naïve ATTR-CM and their unpaid caregivers from 7 countries (n=95 Italy, n=34 France, n=31 Spain, n=17 Australia, n=10 Canada, n=15 Australia, n=6 Russia).[1] Around 10% of unpaid caregivers reported that their caregiving responsibilities meant that they could not complete their typical daily chores at least once in the prior 3 months (median number of days = 7; Table 7).[1] This proportion was 14% among caregivers to patients who were NYHA class III and 9% among caregivers to patients who were NYHA class I/II. Similar but slightly higher proportions of caregivers reported that they had to ask another family member to help with their daily chores because of their caregiving responsibilities.[1]

**Table 7. Caregiver demographics and characteristics by the patient's NYHA class**

| | All patients n = 208 | Caregivers to patients who were NYHA class I/II n = 156 | Caregivers to patients who were NYHA class III n = 43 |
|---|---|---|---|
| Caregiver and patient live in the same house, n (%) | 138 (66.3) | 102 (65.4) | 34 (79.1) |
| Hours spent providing care per week, median (IQR) | 4.5 (0.0, 27.0) [n = 176] | 2.0 (0.0, 21.0) [n = 130] | 17.5 (4.0, 75.0) [n = 38] |
| Years caregiving to date, median (IQR) | 1.5 (0.0, 3.0) [n = 166] | 1.0 (0.0, 3.0) [n = 123] | 2.0 (1.3, 3.5) [n = 37] |
| Caregivers reporting that there were days in the last 3 months when they were unable to complete typical household chores due to caregiving responsibilities, n (%) | 21 (10.3) [n = 204] | 14 (9.2) [n = 153] | 6 (14.0) [n = 43] |
| Median days (IQR) | 7.0 (2.0, 21.0) [n = 15] | 6.0 (2.0, 20.0) [n = 10] | 7.0 (4.0, 30.0) [n = 5] |
| Caregivers reporting that there were days in the last 3 months when a family member had to do their household chores due to caregiving responsibilities, n (%) | 23 (11.4) [n = 202] | 15 (9.9) [n = 152] | 7 (16.7) [n = 42] |
| Median days (IQR) | 11.0 (3.5, 17.5) [n = 20] | 11.0 (3.0, 15.0) [n = 14] | 11.0 (4.0, 20.0) [n = 6] |

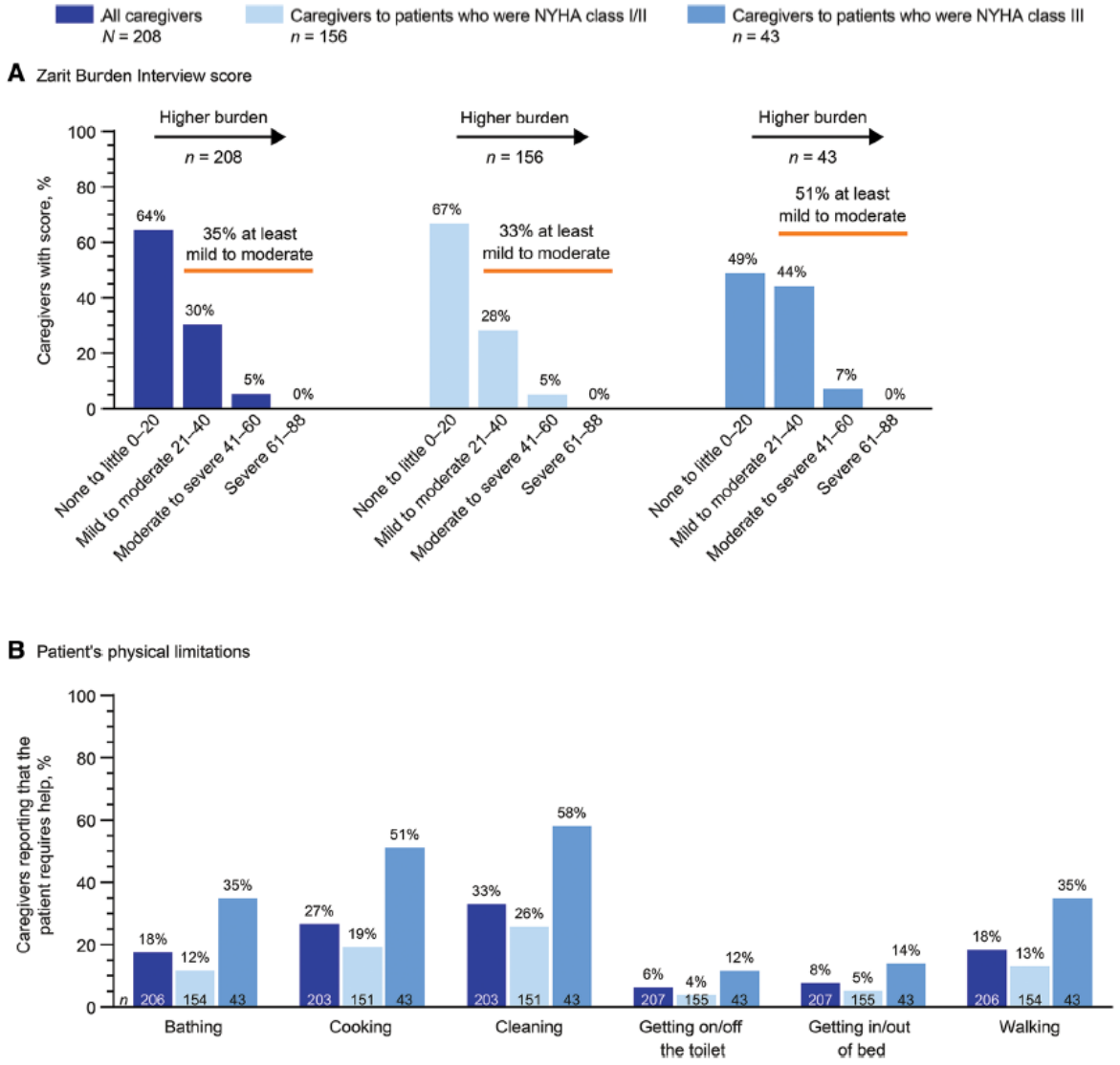
Abbreviations: IQR: interquartile range; NYHA: New York Heart Association Functional Classification; SD: standard deviation.
Source: Ponti et al. 2023[1]

In the ZBI, over one third (35%) of all caregivers reported at least mild-to-moderate burden of care (score ≥21; Figure 3A).[1] Over half (51%) of caregivers to patients who were NYHA class III reported at least a mild-to-moderate burden of care, compared with 33% of caregivers to patients who were NYHA class I/II.

Caregivers reported that patients required help with many everyday physical tasks (Figure 3B).[1] The proportion of patients requiring help with each task was numerically higher among those who were NYHA class III vs. those who were NYHA class I/II, including cleaning (58.1% vs. 25.8%), cooking (51.2% vs. 19.2%), walking (34.9% vs. 13.0%), bathing (34.9% vs. 11.7%), getting in or out of bed (14.0% vs. 5.2%), and getting on or off the toilet (11.6% vs. 3.9%). Caregivers (n = 202) reported that 11.4% of patients had some form of incontinence. This proportion was 27.9% in patients who were NYHA class III and 6.6% in patients who were NYHA class I/II.[1]

**Figure 3. Caregiver-reported ATTR-CM burden by NYHA class**




199/208 patients had NYHA classification data. Abbreviations: NYHA: New York Heart Association Functional Classification.
Source: Ponti et al. 2023[1]

# 7. Key new economic evidence

## *7.1. Parametric extrapolation of overall survival: methodology*

In TA696[4], OS in the model was estimated based on fully parametric survival curves fitted to ATTR-ACT disease related survival with excess non-disease related survival hazard from the ONS (2019 England lifetables) applied. This was based on guidance from the NICE Decision Support Unit (DSU)[30] and Bagust and Beale (2014)[31] (see Section B.3.3.4.4 in Document B from TA696[4]). A similar approach was followed in this submission; fully parametric survival curves fitted to the ATTR-ACT LTE trial disease related survival with excess non-disease related survival hazard from the ONS (2018-2020) applied.

Six parametric distributions were considered following guidance from the NICE DSU[30]: Exponential, Weibull, Log-logistic, Log-normal, Gompertz and Generalised-Gamma. Independently for tafamidis and BSC, the distributions for the base-case and scenario analyses reference arm were selected following the guidance inform the NICE DSU.[30] The model selection process included the following considerations:

- Ranking distributions based on statistical goodness-of-fit to the observed data according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)

- A visual inspection consisting of an analysis of the “Observed vs Predicted” plot. The Kaplan Meier (KM) and parametric survival curves were plotted to assess the fit during the trial period

- Assessment of the hazard profiles in the parametric models versus the observed data

## *7.2. Tafamidis OS extrapolation*

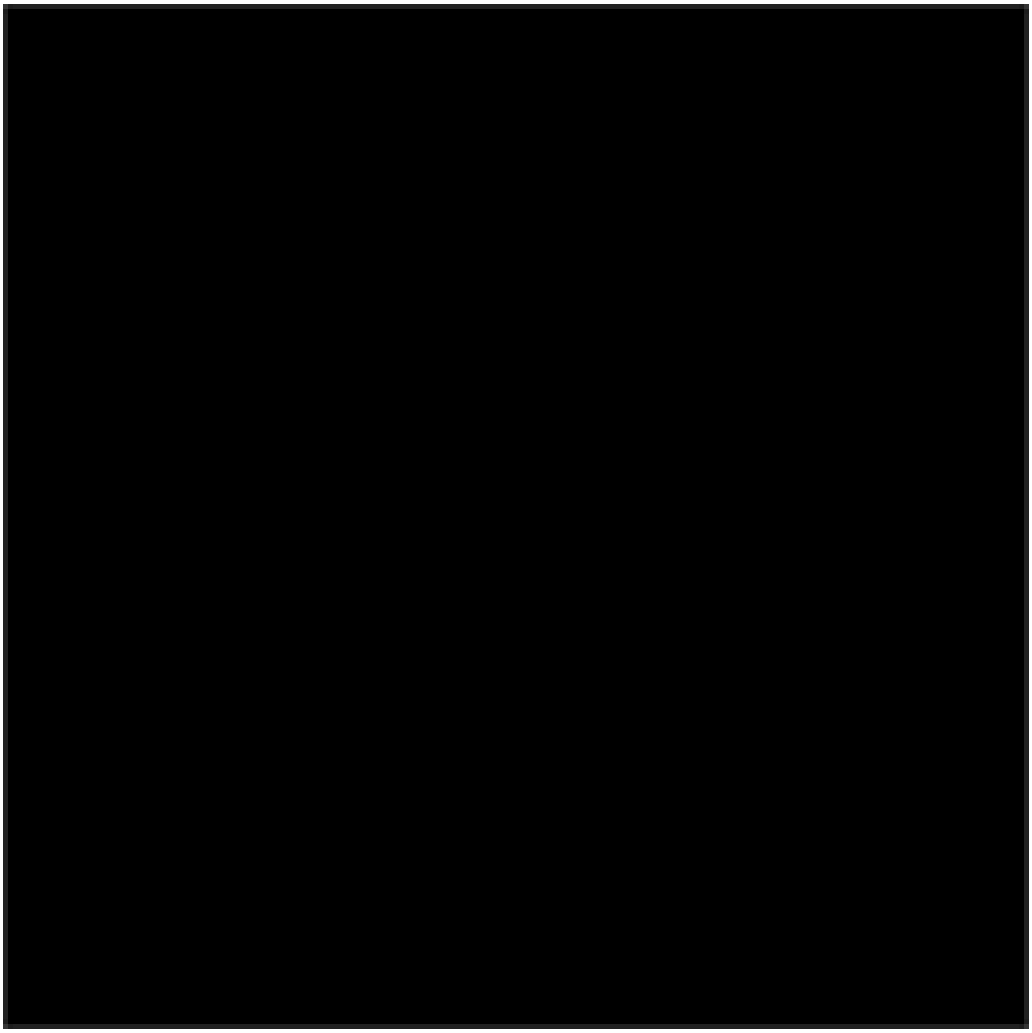
In TA696[4], the AIC/BIC (Figure 4 – corresponds to Figure 35 in Document B of TA696[4]) indicated the exponential and log-normal provided the best fits to the observed data with all other model providing very similar statistical fits. All distributions provided similar visual fits to the observed KM data (Figure 4) with slight overestimations of the observed data for approximately the first 20 months.

Thus, given the similarities in the goodness-of-fit statistics and assessment of visible fit and the available long-term data, the log-normal extrapolation was considered the most

appropriate model with the exponential and log-logistic applied in scenario analyses, as more optimistic and conservative scenarios, respectively; this was also agreed upon by the EAG during TA696[4] and log-normal used to extrapolate tafamidis OS in their preferred base case scenario. Please refer to Section B.3.3.4.5 in Document B of TA696[4] for further information.

**Figure 4. Overall survival parameterisations – Overall population – tafamidis (TA696)**

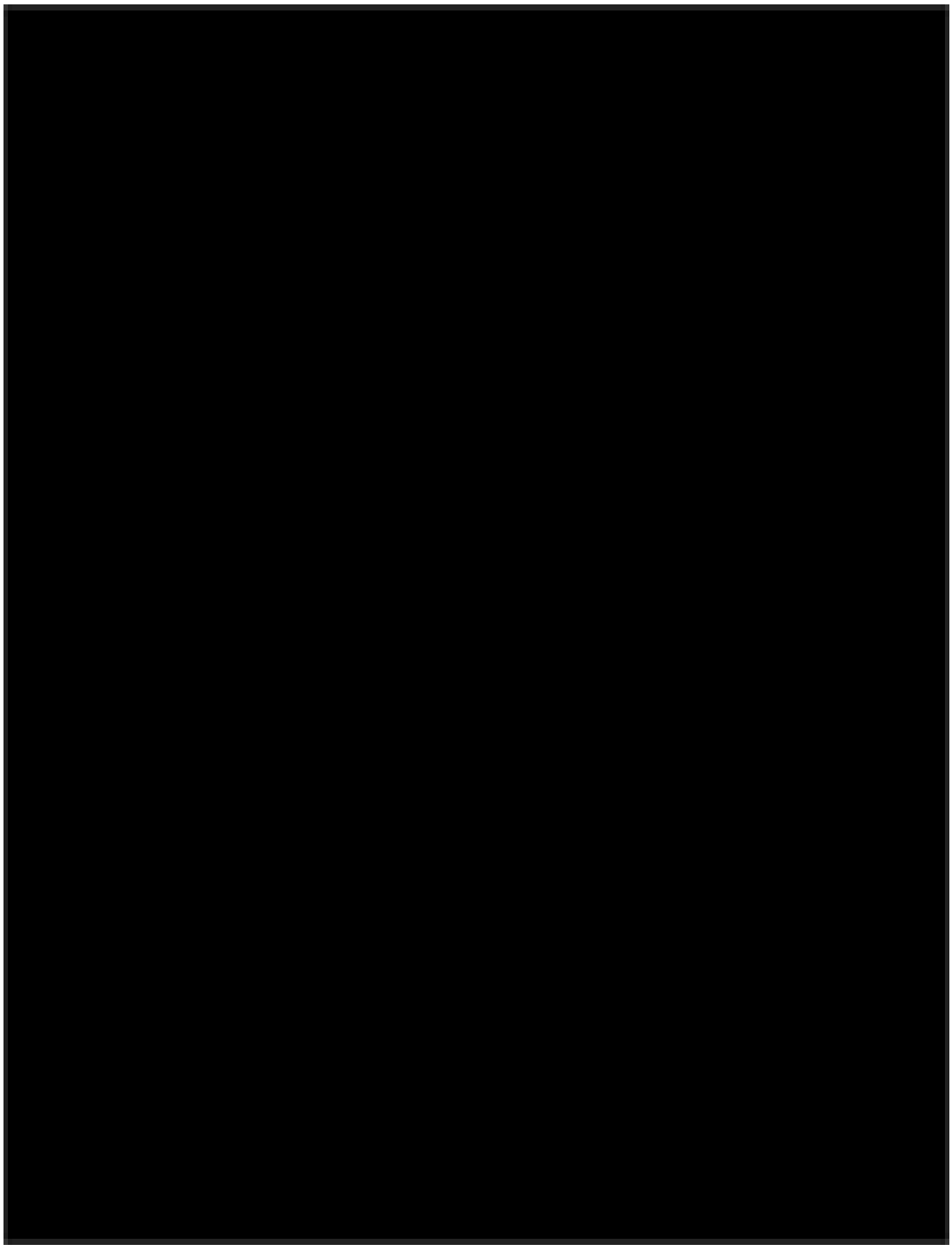


Abbreviations; AIC: Akaike information criterion; BIC: Bayesian information criterion; CMAD: cardiac mechanical assist device; HT: heart transplant; LTM: life table mortality; OS: overall survival.
LTM applied patient age/country specific life tables hazards.
Note, For NYHA class I/II, a number of gompertz and generalised gamma failed to converge.

When analysing new long-term tafamidis OS data from the ATTR-ACT LTE, parametric survival models of excess mortality gave similar statistical fits in the population, regardless of distribution family (Figure 5).[28]

**Figure 5. Parametric relative survival models of OS, tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)**



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).



The generalised Gamma model showed the most rapid reduction in excess hazard, matching well the gradient of the observed hazard during the third year whilst peak hazard was higher than other models (

Figure ***6***).[28]The generalised Gamma had the lowest AIC of candidate models; in the context of the 2 unit penalty term versus the log-normal model due to the additional fitted parameter in the generalised Gamma model, the low AIC indicates highest log-likelihood by greater than 2 units.[28] This higher likelihood is visible in the overlay of the model predictions upon the KM estimator (Figure 5) where over much of current follow-up the generalised Gamma model predicts closest to the contemporary value of the KM estimate.

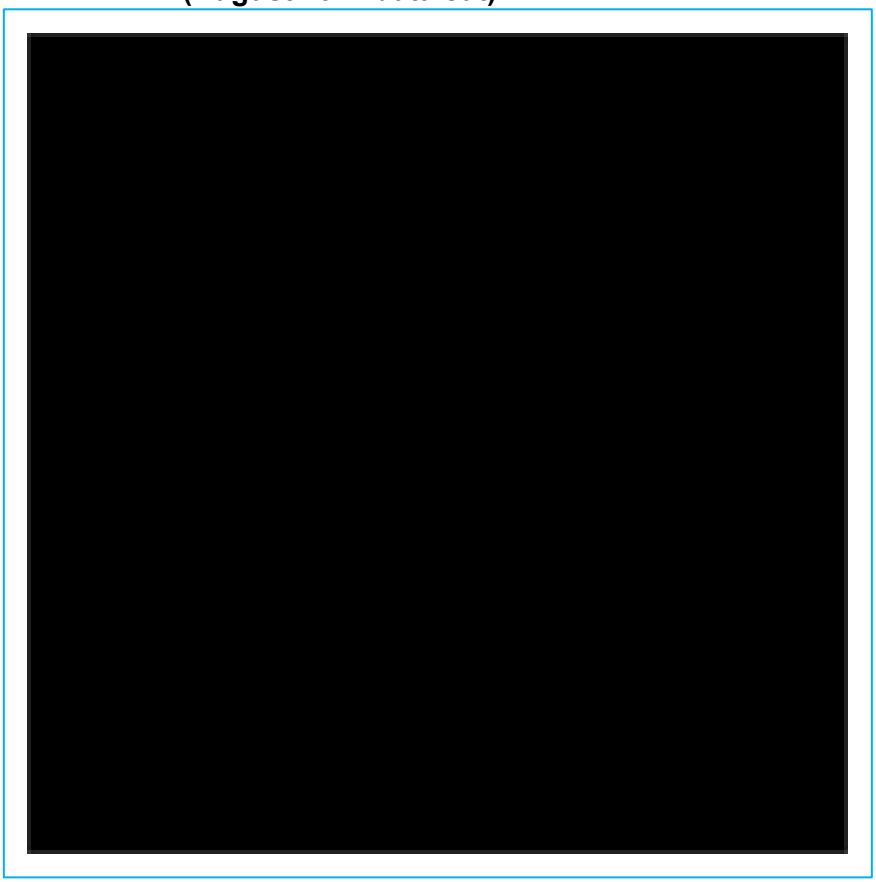
Hazard associated with all models was substantially greater than lifetable at 84 months (

Figure ***6***).[28] The log-normal model does not display the peak in total hazard and consequent medium-term reduction expected from the non-parametric estimators, but was the second closest in profile after the generalised Gamma.[28]

**Figure 6. Parametric relative survival models, all-cause hazard predictions, OS (HT/CMAD as censor), Tafamidis 80mg in ATTR-ACT crossover to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)**



Note: the marginal lifetable hazards and parametric models have been estimated with differing discretisation grids, resulting in the positions of hazard "spikes" as patients roll over piecewise constant hazard changes (and end of life tables) differing between the lifetable and other hazard estimates. BSpline: Non-parametric B-spline estimator of hazard from September 2021 database lock; L. Logistic: Log-logistic; L. Norm.: Log-normal; G. Gamma: Generalised Gamma; LTR: Long-term response; LT: Life-table hazards.

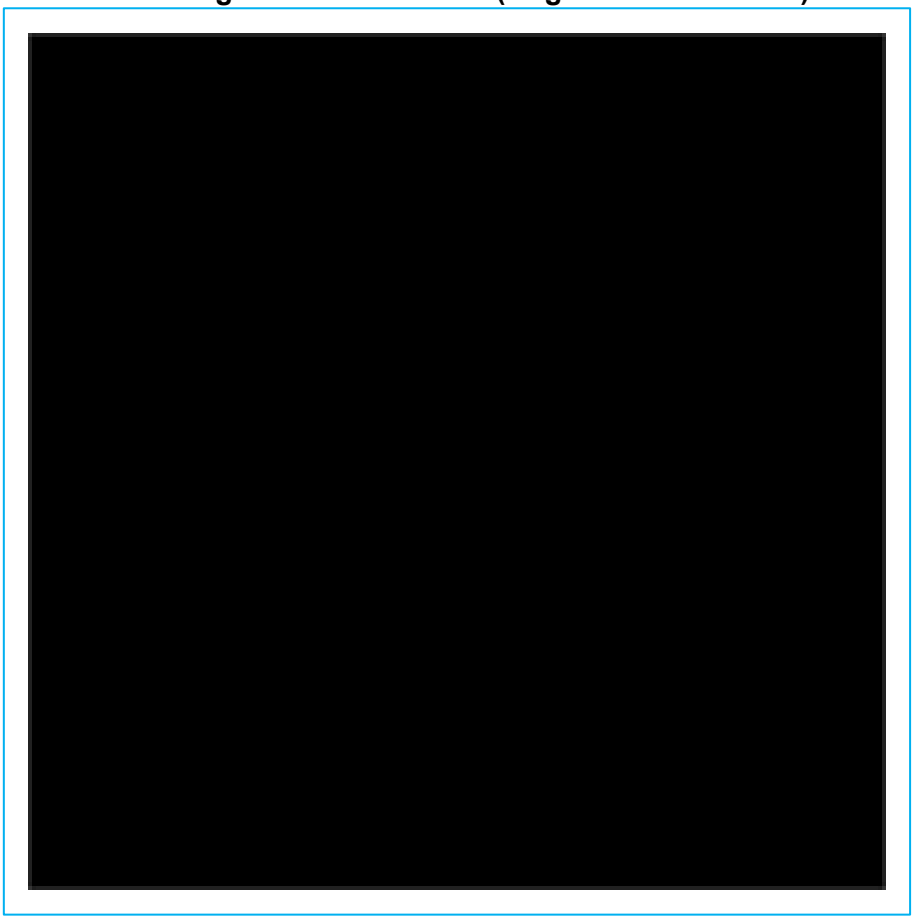
Non-parametric hazard profiles show a clear peak at around 2 years, followed by absolute decline towards a rising general population hazard (Figure 7).[28] This suggested that the extrapolative relative survival model should show a clear peak followed by a decline in hazard. The intercept of the Kernel-smoothed estimator with the lifetable rates of mortality is not plausible and is likely due to edge effects on the kernel filter; plausible relative survival models would be expected to follow a profile more similar to the b-spline model and preserve a measurable excess hazard to 84 months. It is noted that with current follow-up, the presence of a local maximum hazard of mortality followed by a medium-term absolute decline as predicted by the non-parametric hazard estimators precludes the use of monotonically increasing or constant excess hazard models – i.e. the exponential, Weibull, Gamma and Gompertz models. Only the log-logistic, lognormal and generalised Gamma relative survival models have the capability of predicting such a local peak hazard, with the generalised

Gamma sufficiently flexible to give nominally better goodness of fit, visibly better prediction against the KM estimator, and closest agreement with the non-parametric hazard estimators.

On the basis of similarity of goodness of fit (numerical advantage on AIC) as well as agreement with the non-parametric hazard profile estimated to 84 months follow-up, the generalised Gamma model was selected as the new base case model (Section 8) with log-logistic and log-normal explored in scenario analysis (Section 8.1.3).

**Figure 7. Hazards, OS (HT/CMAD as censor), Tafamidis 80mg in ATTR-ACT crossover to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)**



Bspline: Non-parametric B-spline hazard estimator; Kernel smoothed: Non-parametric convolutional hazard estimator with Epanechnikov kernel; KM: Kaplan-Meier survival estimator. Top panel shows numerical integration of B-spline estimator overlying Kaplan-Meier survival estimator. Bottom panel shows hazard estimators, with population matched lifetable hazards via the Ederer-I method (grey line) and 95% confidence intervals around the B-spline hazard estimator

## 7.3. BSC OS extrapolation

Details of BSC OS extrapolation are described in Section B.3.3.4.6 in Document B for TA696[4]. In the FAD for TA696[4], the committee preferred Weibull distribution be used to extrapolate BSC OS beyond observed ATTR-ACT trial period. Considering no new data is available for the placebo arm as all placebo patients transitioned to tafamidis free acid 61mg at the start of ATTR-ACT LTE, Weibull distribution has been used BSC OS extrapolation in the new company base case.

## 7.4. Relative risk of death per NYHA class

Updated disaggregated cox proportional hazard models of death by any cause for tafamidis arm from ATTR-ACT LTE are presented in Table 8. Hazards associated with BSC did not differ from TA696[4] due to lack of new data.

**Table 8. Cox proportional hazard model on OS by last observed NYHA class (LOCF)**

| NYHA class | Coefficient | Hazard ratio | SE of coefficient | Z score of coefficient | Pr(>\|z\|) |
|---|---|---|---|---|---|
| **Tafamidis** | | | | | |
| NYHA I | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NYHA II | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NYHA IV | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | | | | | |
| NYHA I | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NYHA II | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NYHA IV | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Note: Hazards are relative to NYHA class III.
Abbreviations; LOCF: last observation carried forward; SE: standard error; Pr(>|z|): probability of observation of data if coefficient is truly 0.

Cox proportional hazard models of death by any cause were formed conditional upon the NYHA class of the patient at the last (six-monthly) assessment point. These relative hazards were assumed to be constant over the time horizon of the economic model. A further assumption was made of the equivalence of relative hazard and the relative risk of mortality when evaluated over a single cycle of the economic model.

Within the economic model, the probability of death within the current model cycle, conditional upon being alive at the start of the model cycle, is computed and is converted to a total number of deaths expected. The contribution of each NYHA class to this total number of deaths is then proportional to the number of patients in the NYHA class at the start of the cycle and the relative hazard of mortality in that class.

## *7.5. Tafamidis TTD extrapolation*

The fitting and selection process employed for the time-to-event discontinuation curves was consistent with that employed for the excess hazard parametric models of OS (Section 7.2). Fully parametric time-to-event models were fit to discontinuation event data, censoring for heart transplant, CMAD implantation and loss of follow-up. Analyses were conducted with death as a competing risk. This was considered appropriate to avoid double counting of death events as discontinuation events when implemented in the economic model.

Several causes for discontinuation were analysed as censored for the purpose of estimating the spontaneous discontinuation rate. Firstly, the overall cohort size within the economic model decreases with model time due to patient death, therefore discontinuations proximate to patient death are not considered as events, and are censored at the time of discontinuation. In common with the analysis of overall survival, time to treatment discontinuation is assumed confounded by heart transplant or implantation of CMAD, and patients undergoing these procedures are censored.

Secondly, some patients in the ATTR-ACT LTE discontinued from study therapy as they gained access to commercial tafamidis. As these patients would not discontinue treatment under modelled practice, but the true time for discontinuation is censored, these patients are censored at their time of discontinuation from study-dispensed therapy.

Thirdly, model scenarios where treatment with tafamidis ceases when the patient is assessed as NYHA class IV were explored (Section 8.1.3) to reflect potential real-world treatment usage (clinicians would not explicitly always stop treatment due to progression to NYHA IV but on balance we expect patient to naturally discontinue treatment shortly after reaching NYHA IV given the overall condition of the patients). For these scenarios, patients were censored at the time of their first assessment as NYHA IV.

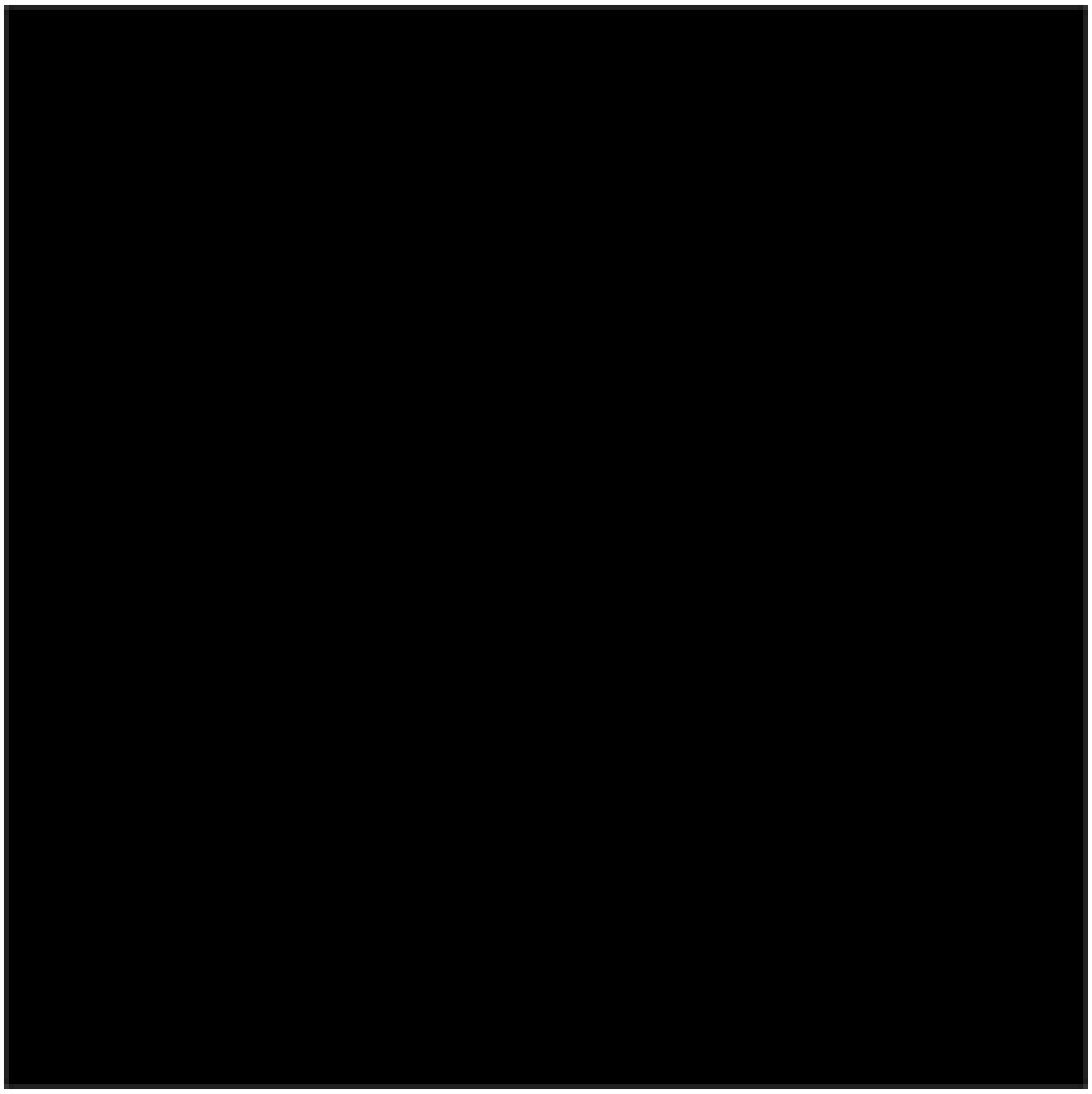
Parametric models fitted to these data did not show discrimination per AIC or BIC (Figure 8).[28] The exponential model showed numerically lowest values for both information criteria, indicating best parsimonious fit. The maximum likelihood shape parameter for the Weibull model was 1, indicating that the maximum likelihood Weibull model was very close to exponential; the exponential rate parameter was also close to 0, which in this parameterisation also indicates degeneration of the model to constant-hazard form.[28]

Given the low AIC, BIC and degeneration of multi-parameter models to the exponential form, for reasons of parsimony there is no compelling reason to use an alternative assumption to

the exponential distribution in order to model time to treatment discontinuation; therefore, exponential distribution has been used in the updated base case as per the EAG's preferred assumption in TA696[4].

**Figure 8. Proportion of patients not discontinued, tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)**

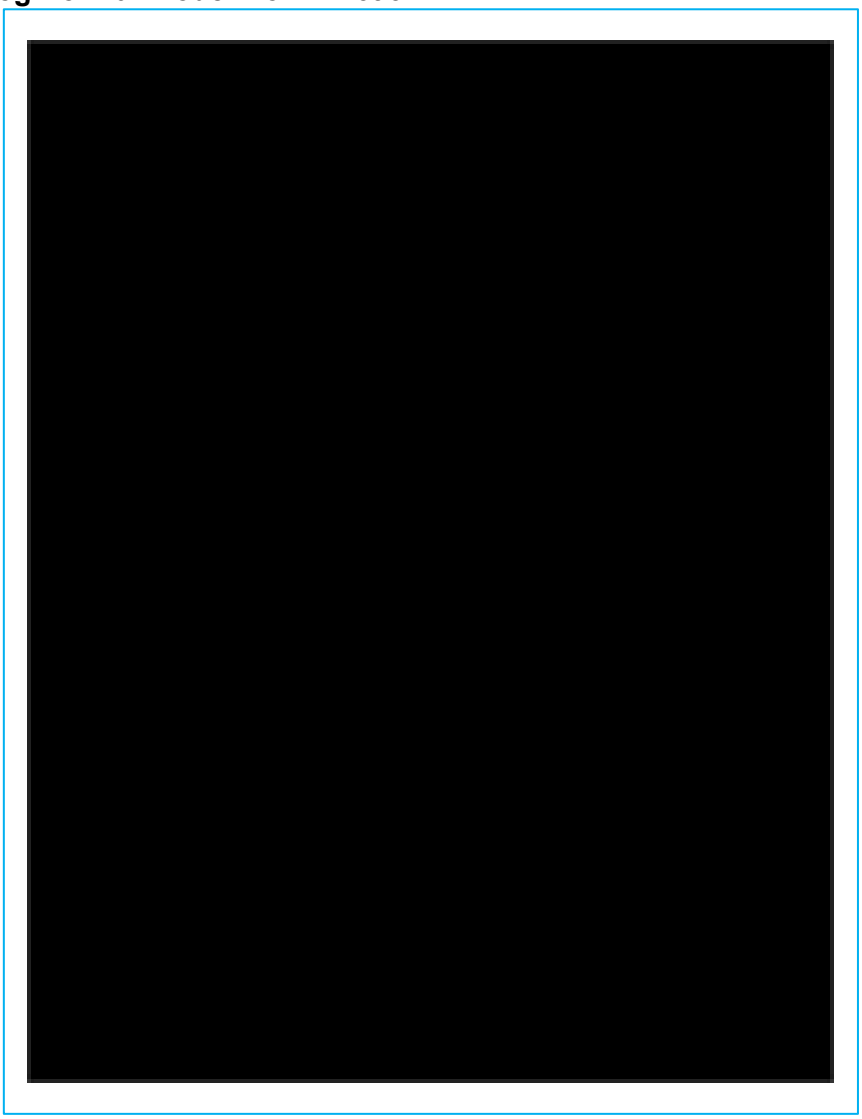


All models fitted in all-cause parametric survival framework. 95% confidence interval by non-parametric bootstrap (1000 replications) AIC: Akaike information criterion; BIC: Bayesian information criterion; L. Logistic: Log-logistic; L. Norm.: Log-normal; G. Gamma: Generalised Gamma.

## *7.6. EAG's alternative analyses in TA696*

In the FAD of TA696[4] the committee acknowledged that reverting to best supportive care outcomes after stopping treatment would be conservative (3.16 in FAD). It also agreed it was implausible to assume that everyone in the NYHA class I to III health states would remain on treatment indefinitely after the clinical trial period. On balance, the committee recognised that both of the EAG's alternative analyses had limitations, but agreed they provided realistic alternatives. However, given the new long-term data from ATTR-ACT LTE, it can be observed that the EAG scenarios for OS and TTD extrapolations substantially under predict the observed OS (Figure 9) and treatment discontinuation (Figure 10) and therefore cannot be considered appropriate scenarios for decision making.

**Figure 9. 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).
Source: Pfizer data on file.[28]

**Figure 10. Proportion of patients not discontinued, tafamidis meglumine 80mg in ATTR-ACT crossover to tafamidis free acid 61mg (August 2021 data cut) + EAG discontinuation plateau from TA696**

All models fitted in all-cause parametric survival framework. 95% confidence interval by non-parametric bootstrap (1000 replications) AIC: Akaike information criterion; BIC: Bayesian information criterion; L. Logistic: Log-logistic; L. Norm.: Log-normal; G. Gamma: Generalised Gamma.
Source: Pfizer data on file.[28]

## *7.7. Updated costs in the economic model*

Costs in the economic model were updated using 2022 eMIT database costs[32], 2021/22 NHS reference costs[33] and 2021/22 PSSRU unit costs (Table 9). End-of-life care costs originally from Hollingworth et al.[34] were inflated using PSSRU Health Services (NHSCII Pay + Prices) inflation index[35].

**Table 9. Updated costs added to the economic model**

| Cost description | Original cost [TA696] | Updated cost [ID6327] | Data source |
|---|---|---|---|
| **Concomitant medications costs** | | | |
| Concomitant medications (Tafamidis arm) | [redacted] | [redacted] | Dosing and acquisition costs obtained from 2022 eMIT database[32]<br><br>Usage levels obtained from ATTR-ACT[2] |
| Concomitant medications (BSC arm) | [redacted] | [redacted] | |
| **Resource component – unit costs** | | | |
| Electrocardiogram (ECG) | [redacted] | [redacted] | NHS reference costs 2021/22[33] |
| Consultant cardiologist visit - Initial | [redacted] | [redacted] | |
| Consultant cardiologist visit - Follow-up | [redacted] | [redacted] | |
| Community nurse visit | [redacted] | [redacted] | PSSRU 2021/22 unit costs. [35] |
| **Event costs** | | | |
| CV-related hospitalisation | [redacted] | [redacted] | NHS reference costs 2021/22 [33] |
| Treatment-related adverse events (TRAE) – Diarrhoea | [redacted] | [redacted] | |
| TRAE – Nausea | [redacted] | [redacted] | |
| TRAE – UTI | [redacted] | [redacted] | |
| **End-of-life care costs** | | | |
| End-of-life care | [redacted] | [redacted] | Hollingworth et al.[34] cost inflated to 2021/22 values using the PSSRU Health Services (using NHSCII Pay + Prices) inflation index[35] |

Abbreviations: BSC: best supportive care; ECG: electrocardiogram; TRAE: treatment-related adverse events.

## *7.8. Summary of new base case analysis inputs and assumptions*

Table 10 summarises assumptions used in the economic model as well as justifications for these assumptions.

**Table 10. List of assumptions used in the model, with justifications**

| Assumption/decision | Submission Section | Rationale/justification and source |
|---|---|---|
| ***Model structure/techniques*** | | |
| Removal of NYHA IV stopping rule from economic base case | Section 4 | A NYHA IV stopping rule has not been included in new economic base case.<br>Insights from EAMS show that clinicians would not explicitly always stop treatment due to progression to NYHA IV but on balance we expect patients to discontinue treatment shortly after reaching NYHA IV due to poor prognosis associated with severe heart failure. Therefore, the economic new base case where treatment is continued in NYHA IV may represent a slight overestimation, thus a scenario where no treatment is used beyond progression is utilised to demonstrate the potential impact of this assumption – refer to Section 8.1.3.<br>Refer to Appendix E for extrapolation parameters used. |
| BSC OS extrapolation using Weibull parametric distribution function | Section 7.3 | In TA696[4], the committee preferred Weibull distribution be used to extrapolate BSC OS beyond observed ATTR-ACT trial period. Considering no new data on BSC OS from ATTR-ACT LTE, Weibull was used to extrapolate BSC OS in the new economic base case. |
| Tafamidis OS extrapolation using generalised Gamma parametric distribution function | Section 7.2 | Generalised gamma distribution displayed best fit for new tafamidis OS data from ATTR-ACT LTE (Figure 5).<br>Scenario analysis exploring alternative distributions for tafamidis OS extrapolation presented in Section 8.1.3. |
| TTD discontinuation extrapolation using exponential parametric distribution function | Section 7.5 | Given the low AIC, BIC and degeneration of multi-parameter models to the exponential form, for reasons of parsimony there is no compelling reason to use an alternative assumption to the exponential distribution in order to model time to treatment discontinuation; therefore, exponential distribution has been used in the new base case.<br>Scenario analysis exploring alternative distributions for TTD extrapolation presented in Section 8.1.3 |
| ***Costs and resource use*** | | |
| No cost-savings incurred from early diagnosis | Section 4 | Costs savings associated with early diagnosis have been excluded from the new economic base case as per the committee's preference during TA696[4].<br>Scenario analysis exploring the inclusion of early diagnosis cost savings is presented in Section 8.1.3 to demonstrate potential impact of this assumption. |

Abbreviations: BSC: Best Supportive Care; HRQoL: health related quality of life; NYHA: New York Heart Association Functional Classification; OS: overall survival; TRAE: treatment-related adverse events; TTD: time to treatment discontinuation.

# 8. Base-case results

Results of the base-case incremental cost-effectiveness analyses with tafamidis with new net price (with PAS) are presented in Table 11. Disaggregated results are presented in Appendix D.

**Table 11. Base case results (with new PAS)**

| | Tafamidis | BSC | Incremental |
|---|---|---|---|
| Life years | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] |
| Total costs (£) | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | [redacted] | | |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

The modelled outcomes were aligned with the head-to-head evidence from ATTR-ACT which showed tafamidis has a longer survival than BSC. Tafamidis was associated with higher total LYs ([redacted]) versus BSC ([redacted]) and QALYs ([redacted] versus [redacted]). In line with clinical expectation, most of the clinical benefit was derived in earlier NYHA stages with incremental LYs of [redacted], [redacted], [redacted] and [redacted] in NYHA I to IV, respectively.

Total discounted costs associated with tafamidis treatment, accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with BSC were notably lower ([redacted]), with most costs attributable to hospitalisations and end of life care. Incremental discounted costs were estimated to be [redacted] over BSC, under base case assumptions. The resultant ICER for tafamidis was [redacted].

## *8.1. Sensitivity analyses*

### 8.1.1. Probabilistic sensitivity analysis

The joint influence of all model parameters was evaluated via the conduct of probabilistic sensitivity analysis (PSA). In a PSA, all parameters are varied simultaneously to assess the impact of uncertainty in chosen model input values with respect to the model results. The model is evaluated over many iterations (2,000), using a new set of sampled model input values each time; results are then averaged across all iterations.

Results of the probabilistic sensitivity analyses are summarised in Table 12.

**Table 12. Probabilistic base-case results (with new PAS)**

| | Tafamidis | BSC | Incremental |
|---|---|---|---|
| Life years | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] |
| Total costs (£) | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | [redacted] | | |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Results of the probabilistic analysis were very similar to those from the deterministic analysis. Tafamidis resulted in higher LYs and QALYs compared to BSC with 100% of simulations falling in the North East quadrant indicating incrementally higher patient outcomes and costs (Figure 11). The cost-effectiveness acceptability curve (Figure 12) indicated that there is an approximately [redacted]% chance of tafamidis being cost-effective compared to BSC at the £30,000 per QALY threshold when applying the new PAS.

**Figure 11. Cost-effectiveness scatter plot (with new PAS)**

Abbreviations: WTP: willingness-to-pay

**Figure 12. Cost-effectiveness acceptability curve (with new PAS)**

Abbreviations: WTP: willingness-to-pay.

### 8.1.2. Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted for all key variables in the model.

A tornado plot showing the impact on the ICER of the various deterministic sensitivity analyses is presented in Figure 13.

Table 13 details numeric output for the most influential parameters.

Most scenarios revealed relatively small differences in cost-effectiveness outcomes. The most influential parameters were model time horizon, discounting of benefits, discounting of costs, tafamidis health state utilities, placebo health state utilities, and age.

Plausible alternative scenarios have been further investigated in Section 8.1.3, to assess the impact of the uncertainty in the analysis, with relatively little impact on cost-effectiveness outcomes.

**Figure 13. Deterministic sensitivity analysis: impact on ICER (with new PAS)**

Abbreviations: BSC: best supportive care; CV: cardiovascular; ICER: incremental cost-effectiveness ratio; NHYA: New York Heart Association Functional Classification; QALY: quality adjusted life year; OS: overall survival; PAS: patient access scheme; TTD: time to treatment discontinuation; TTE: time to event.

**Table 13. Deterministic sensitivity analysis: Summary output for the most influential parameters (with new PAS)**

| Parameter | Parameter variation | Incremental | | | ICER |
|---|---|---|---|---|---|
| | | Life years | QALYs | Costs | |
| QALYs discounting | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost discounting | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| NHYA class health state utilities - Tafamidis | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| NYHA class health state utilities - BSC | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| CV-related hospitalisation event rates – Tafamidis | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| CV-related hospitalisation event rates – BSC | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| CV-related hospitalisation costs | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| Age (years) | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| NYHA class health costs | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |
| Female (%) | Lower | [redacted] | [redacted] | [redacted] | [redacted] |
| | Upper | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BSC: Best supportive care; CV: Cardiovascular; ICER, incremental cost-effectiveness ratio; NYHA: New York Health Association Functional Classification; QALY, quality-adjusted life year; PAS: Patient access scheme.

### 8.1.3. Scenario analyses

Scenario analyses were conducted to assess the sensitivity of the model to various assumptions. Details of each scenario are provided in Table 14.

**Table 14. Scenario analysis results: additional scenarios**

| No. | Scenario | Base-case | Scenario description | Reference section in submission |
|---|---|---|---|---|
| 1 | Tafamidis OS extrapolation | Generalised Gamma | Log-logistic | Section 7.3 |
| 2 | | | Log-normal | |
| 3 | TTD extrapolation | Exponential | Generalised Gamma | Section 7.5 |
| 4 | | | Log-logistic | |
| 5 | | | Log-normal | |
| 6 | | | Gompertz | |
| 7 | | | Weibull | |
| 8 | No treatment usage in NHYA IV | Excluded | Included: Insights from EAMS show that clinicians would not explicitly always stop treatment due to progression to NYHA IV but on balance we expect patients to discontinue treatment shortly after reaching NYHA IV due to poor prognosis associated with severe heart failure. Refer to Appendix E for parameters used. | Section 4, 7.8 |
| 9 | Treatment specific utilities in NYHA IV | Treatment-independent utilities (BSC) used in NHYAIV | Treatment specific utility from ATTR-ACT used in NYHA IV: [redacted] | Section 4 |
| 10 | Service redesign: Early diagnosis impact on outcomes | Not included | Patients are diagnosed 28.7 months earlier[1], start age 71.95. Does not capture impact of diagnosing with lower disease severity and patient who would have been mis/undiagnosed. | Section 4 |
| 11 | Service redesign: Early diagnosis impact on costs | Not included | Average diagnosis is expected to reduce to ≤6 months, resulting in the majority of the estimate >£20,000 cost prior to diagnosis being avoided. Given the true cost is estimated to be more than £20,000 per patient this can be considered a conservative estimate. | Section 4 |
| 12 | CV-related hospitalisation costs | Included | Excluded | Section B.5.4 in document B from TA696[4] |
| 13 | AE costs | Included | Excluded | Section B.5.5 in document B from TA696[4] |
| 14 | End-of-life costs | Included | Excluded | Section B.5.6 in document B from TA696[4] |
| 15 | Drug wastage costs | Included | Excluded | Section 4 |

[1]Weighted average time to diagnosis 34.7 months (wild-type 39 months, hereditary 25 months). Abbreviations: AE: adverse events; BSC: best supportive care; CV: cardiovascular; NYHA: New York Heart Association Functional Classification; OS: overall survival.

Table 15 details numeric output for the scenarios. Many scenarios explored had substantial reduction on the ICER including: incorporating cost savings associated with earlier diagnosis, reflecting potential real-world usage of tafamidis in NYHAIV, excluding cardiovascular (CV) related hospitalisation costs, and reducing the age of diagnosis due to improved service pathway redesign. Given the additional follow-up data from ATTR-ACT LTE, the selection of the most appropriate OS and TTD extrapolation distributions now has a relatively minor increase to the ICER.

**Table 15. Scenario analysis results: additional scenarios (with new PAS)**

| Scenario | Incremental | | ICER | % change |
|---|---|---|---|---|
| | Costs | QALY | | |
| **Base case** | [redacted] | [redacted] | [redacted] | [redacted] |
| 1 | [redacted] | [redacted] | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] |
| 7 | [redacted] | [redacted] | [redacted] | [redacted] |
| 8 | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] |
| 10 | [redacted] | [redacted] | [redacted] | [redacted] |
| 11 | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] |
| 13 | [redacted] | [redacted] | [redacted] | [redacted] |
| 14 | [redacted] | [redacted] | [redacted] | [redacted] |
| 15 | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

### 8.1.4. Summary of sensitivity analyses results

Many scenarios explored had substantial reduction on the ICER including: incorporating cost savings associated with earlier diagnosis, reflecting potential real-world usage of tafamidis in NYHA IV, excluding cardiovascular (CV) related hospitalisation costs, and reducing the age of diagnosis due to improved service pathway redesign. Given the additional follow-up data from ATTR-ACT LTE, the selection of the most appropriate OS and TTD extrapolation distributions now has a relatively minor impact on the ICER.

# 9. Validation

## *9.1. Comparison of clinical trial inputs and modelled outputs*

A comparison of clinical trial inputs versus modelled outputs is provided in Appendix D. Outcomes describing OS and time on treatment were assessed to ensure face validity. As can be seen, model outputs closely represent outcomes observed during ATTR-ACT LTE.

# 10. Budget impact

A summary of the budget impact over the first 5-years at new net price, is presented in Table 16.

**Table 16. Budget impact (with new PAS)**

| | **Company estimate** |
|---|---|
| **Number of people in England who would have treatment** | [redacted] patients in 2024, rising to [redacted] in 2028 |
| **Average treatment cost per person** | Tafamidis:<br>- Annual cost: [redacted]<br>BSC:<br>- Annual cost: [redacted] |
| **Estimated annual budget impact on the NHS in England** | Versus standard of care:<br>• Year 1: [redacted]<br>• Year 2: [redacted]<br>• Year 3: [redacted]<br>• Year 4: [redacted]<br>• Year 5: [redacted] |

Abbreviations: BSC: best supportive care; NHS: National Health Service.

# 11. Interpretation and conclusion of economic evidence

## *11.1. Summary of the results*

In the new base case analysis (with PAS) over a life time horizon, it was estimated that tafamidis use would result in gains of [redacted] QALYs and [redacted] LYs compared to current BSC. Discounted incremental costs were expected to be [redacted] over BSC under base case assumptions and the resultant ICER was [redacted].

## *11.2. Generalisability*

The ATTR-ACT (and by extension ATTR-ACT LTE) population is generalisable to the patient population with ATTR-CM in the UK.

## *11.3. Strengths and limitations of the economic evaluation*

### 11.3.1. Strengths of the economic evaluation

The economic analysis has several key strengths:

- The economic model used for this submission was originally developed by the EAG in TA696[4]. Key preferred assumptions raised by the committee in TA696[4] were also incorporated to the new economic base case, including:
    - Extrapolation of BSC OS using Weibull distribution
    - Continuing treatment with tafamidis in NYHA IV
    - The use of treatment-independent utilities for NYHA IV
    - The use of age adjusted utility decrements after month 30
    - Inclusion of drug wastage costs
    - Removal of cost-savings associated with early diagnosis assumptions
- Newly available tafamidis OS and TTD data from ATTR-ACT now extends up to 84 months and substantially reduced uncertainty associated with long term extrapolations in TA696[4]; data was previously limited to the 30-month ATTR-ACT observational period.
- The structure was relatively simple whilst utilising the available data from the pivotal trial and capturing the key outcomes of interest in ATTR-CM and ATTR-ACT LTE.
- EQ-5D-3L was collected in ATTR-ACT. This allowed the NYHA utilities to be aligned with the NICE reference case (EQ-5D; measured directly from patients; valued using UK general population tariff). In addition, autocorrelation was accounted for with in the generation of the mean values, which avoided patients with longer term follow-up biasing the estimated values.
- Despite a lack of published resource usage for NYHA disease management, a chart review was commissioned to identify appropriate resource usage in the UK and other resource usage associated with hospitalisation was derived directly from ATTR-ACT, providing an element of certainty in these values.

- DSA and scenario analysis demonstrated that the results are relatively insensitive to many of parameters and assumptions.

- It is estimated that 16.6% of patients who present with polyneuropathy also suffer from ATTR-CM.[11] The economic analysis does not consider costs associated with polyneuropathy drugs such as those mentioned in the final scope in the BSC arm; reflecting a conservative approach.

### 11.3.2. Limitations of the economic evaluation

A limitation of the analysis was that both OS and treatment duration data had to be extrapolated as neither were complete (i.e. not all patients had experienced the corresponding event) in ATTR-ACT or ATTR-ACT LTE. Despite this, by extrapolating based on the observed data in ATTR-ACT and ATTR-ACT LTE (which had complete follow-up up to 84 months), the best available long-term evidence has been considered. Also, scenario analyses investigating different extrapolations demonstrated limited uncertainty.

In addition, all-cause mortality from ATTR-ACT and ATTR-ACT LTE was deemed not to be appropriate for application in the model. However, with a novel adjustment method, the survival applied within the model more accurately captured the increasing hazard of death due to other causes and was more generalisable to the UK population.

The systematic literature review reviews conducted to identify economic evidence to support this submission were last updated in January 2020. However, since 2020, no new therapy for ATTR-CM has been granted a positive reimbursement decision, therefore, we do not expect there to be substantial economic evidence which as not already been captured.

## *11.4. Conclusions from the economic evidence*

This analysis of cost-effectiveness of tafamidis versus BSC in the treatment of ATTR-CM was conducted from the perspective of the NHS and PSS. The comparison was performed using head-to-head data from the randomised phase III study, ATTR-ACT. Statistically and clinically meaningful benefits favouring tafamidis over BSC were observed in all outcomes relevant to patients, including overall survival ([redacted]), CV-related hospitalisations, physical functioning (6MWT) and quality of life (KCCQ-OS, EQ-5D). Evidence from ATTR-ACT LTE demonstrated a continued survival benefit for tafamidis, and benefit in NYHA II patients beyond the 30-month ATTR-ACT study period. When applied in the model, these substantial benefits translated into a transformative QALY gain of [redacted] in the base-case analysis.

The availability of a disease-modifying treatment, in conjunction with widespread adoption of a diagnostic pathway,[12] could potentially lead to earlier diagnosis of ATTR-CM before irreversible cardiac damage has occurred. This enables patients to derive optimal benefit from tafamidis (longer survival, fewer hospitalisations, and improved quality of life).

ATTR-CM is a rare disease with debilitating morbidity and premature mortality. Since 2021 (year of ID1351), no therapies for ATTR-CM have been granted a positive reimbursement decision in the UK. Tafamidis addresses an urgent and significant unmet patient need. Tafamidis offers meaningful improvements in outcomes that are important to patients including survival, functional capacity and quality of life, while reducing CV-related hospitalisations. The introduction of tafamidis would transform a previously fatal diagnosis into a treatable chronic condition.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Tafamidis for transthyretin amyloid cardiomyopathy (review of TA696) [ID6237]

## Summary of Information for Patients (SIP)

**September 2023**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6327_Tafamidis in ATTR-CM_Summary of Information for patients_29SEP23[CON] | 1.0 | No | 29th September 2023 |

# Summary of Information for Patients (SIP):

## The pharmaceutical company perspective

### What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

### SECTION 1: Submission summary

**1a) Name of the medicine** (generic and brand name):

| |
|---|
| Response: Tafamidis (Vyndaqel®) |

**1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

| |
|---|
| Response:<br><br>Adult patients with wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM). |

**1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

| |
|---|
| Response:<br><br>Tafamidis is licensed for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).[1, 2]<br><br>Based on the innovative nature of tafamidis, it was granted a Promising Innovative Medicine (PIM) designation by the MHRA in December 2018. In 2019, tafamidis subsequently received an Early Access to Medicines Scheme (EAMS) positive scientific opinion from the MHRA.[3] Tafamidis EAMS enrolled patients at 17 sites across the UK. |

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

**Cardiomyopathy UK**

A grant has been made to Cardiomyopathy UK in relation to the following:
Regional Advocacy Project – Year Three (2nd January 2023 to 18th December 2023)

## SECTION 2: Current landscape

### 2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

**What is Transthyretin Amyloid Cardiomyopathy (ATTR-CM)?**

Normally the heart relaxes to fill with blood, and then squeezes to pump blood out, which then travels around the body. Transthyretin is a protein that exists as a tetramer ('tetra' means four), which means that it is made up of four structural units called monomers ('mono' means one). In ATTR-CM, the transthyretin protein dissociates (separates) into its four subunits, which then misfold and 'clump together' (aggregate) into insoluble amyloid fibrils. These fibrils are deposited in the heart muscle, which causes it to stiffen. This affects the relaxation/filling and pumping function of the heart, and leads to symptoms of heart failure.[4] As the heart muscle is affected in ATTR-CM, this condition is considered to be a cardiomyopathy: 'cardio' means heart, 'myo' means muscle, and 'pathy' means disease.[5]

**Types of ATTR-CM**

There are two forms of the disease: (i) wild-type ATTR-CM, the more common form, which is age related and mainly affects the heart; and (ii) hereditary ATTR-CM, which is caused by a fault in the transthyretin (*TTR*) gene and is inherited.[4] Hereditary ATTR-CM can therefore affect multiple generations of a family.

**Disease prognosis**

The disease outlook for people with ATTR-CM is poor: average survival of patients receiving best supportive care (BSC) in the UK varies between 2.6 and 5.8 years from diagnosis, depending on wild-type or hereditary disease.[6-9] The disease progresses and causes functional disability that can impact their quality of life.

**Incidence**

Incidence estimates (new cases per year) for ATTR-CM have been derived from UK incidence and survival data from the National Amyloidosis Centre (NAC), specific to each form of the disease. There are an estimated 200-400 new cases of ATTR-CM per year in the UK.[10]

**New York Heart Association Functional Classification**

The most commonly used disease classification system for heart failure, the New York Heart Association (NYHA) functional classification, places patients in one of four categories based on limitations of physical activity.[5]

The table below describes the different classes in the NYHA Functional Classification.[5]

| Class | Patient Symptoms |
|---|---|
| **I** | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath. |
| **II** | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain. |
| **III** | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain. |
| **IV** | Symptoms of heart failure at rest. Any physical activity causes further discomfort. |

**2b) Diagnosis of the condition (in relation to the medicine being evaluated)**

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

Cardiac amyloidosis can be diagnosed using a variety of tests.[11] Invasive tests need to be used to diagnose all forms of cardiac amyloidosis, whereas ATTR-CM specifically requires both invasive and non-invasive tests to be accurately diagnosed.[11] Invasive tests include blood tests, heart tissue biopsy, and bone marrow biopsy.[11, 12] Non-invasive tests include urine tests, imaging studies such as heart ultrasound, cardiac magnetic resonance imaging (MRI), echocardiogram (EKG), computed tomography, and different types of scintigraphy.[11, 12] Depending on the type of amyloidosis suspected, diagnostic testing requirements will vary.

Once an adult patient is confirmed to have ATTR-CM, no further tests are required for them to be eligible to receive tafamidis. However, it is recommended that patients with diagnosed ATTR-CM undergo further genetic testing to find out if they have wild-type or hereditary ATTR-CM.[11]

**2c) Current treatment options:**

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

There are currently no approved disease-modifying drugs for the treatment of ATTR-CM. Patients undergo management of heart failure symptoms using a variety of medicines as per the NICE heart failure guidelines. This can involve the use of diuretics to manage fluid retention and medicines to reduce the risk of heart rhythm problems or blood clots.[13]

**2d) Patient-based evidence (PBE) about living with the condition**

**Context:**

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Patients with ATTR-CM have reported that they experience progressive deterioration in physical function and quality of life.[6] Moreover, significant burden on caregivers has also been reported, with negative impact on their physical and emotional well-being.[15] Living with ATTR-CM can permanently change family dynamics, as patients become more dependent on family members for their care. In a study looking at patient experience with ATTR-CM, one patient noted that "*my family help me in every way, they do all the heavy work, they clean and tidy the house. I can still manage to cook but I stick to the very simple things*".[16]

Recently, findings from the first real-world international study investigating the humanistic burden of untreated ATTR-CM on patients and their unpaid caregivers were published.[17] The study used questionnaires to allow 208 pairs of patients and their caregivers across 6 different countries to provide responses. People with untreated ATTR-CM who took part in the study were mostly men over 80 years with newly diagnosed wild-type ATTR-CM. Unpaid caregivers who took part in the study were most often female partners or adult daughters of the person with untreated ATTR-CM. They usually lived with the person they cared for.[17]

Findings showed that patients with untreated ATTR-CM commonly suffered from shortness of breath, heart problems, mental and physical tiredness, leg and ankle swelling, weakness (especially in the legs), and stomach trouble.[17] People with untreated ATTR-CM often reported that they had problems walking normally due to their symptoms. Many were also unable to take part in social, leisure, or household activities. These reports were more common in people with worsened condition (patients who were NYHA III).[17]

Caregivers to people with ATTR-CM had been providing care for an average duration of 1.5 years and spent an average of 4.5 hours per week providing care.[17] The average number of hours caregiver spent providing care per week was 8-fold higher (17.5 hours) among those who cared for patients with worsened condition (NYHA III). Caregivers reported that the person they cared for needed help with common daily activities such as cleaning, cooking, bathing, walking, getting in or out of bed, and getting on or off the toilet; again, this was more commonly reported in caregivers caring for patients with worsened disease (NYHA III).[17]

Overall, untreated ATTR-CM was found to be a burden on both patients and their caregivers.[17] In worsened disease which displayed symptoms of heart failure (NYHA III) the burden was higher on both patients and caregivers. [17]

## SECTION 3: The treatment

### 3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Transthyretin is a protein that exists as a tetramer ('tetra' means four), which means that it is made up of four structural units called monomers ('mono' means one). In ATTR-CM, the transthyretin protein dissociates (separates) into its four subunits, which then misfold and 'clump together' (aggregate) into insoluble amyloid fibrils. These fibrils accumulate in tissues and organs (including the heart) causing damage.

The separation of the transthyretin protein is the rate-limiting step (also known as the rate-determining or slowest step) in amyloid formation. Tafamidis works by sticking to (binding) the transthyretin protein, slowing down its separation into subunits, thereby reducing amyloid fibril production and build-up in tissues.[2]

### 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

Response:

Tafamidis is not required to be used in combination with other medicines.

### 3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Tafamidis is a soft capsule which should be taken orally. The soft capsule should be swallowed whole, not crushed or cut. The capsule may be taken with or without food.[2]

If vomiting occurs after dosing, and the intact Vyndaqel capsule is identified, then an additional dose of Vyndaqel should be administered if possible. If no capsule is identified, then no additional dose is necessary, with resumption of dosing the next day as usual.[2]

### 3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Tafamidis's clinical trial program included the two phase 3 multicentre clinical trials: (i) ATTR-ACT (ii) ATTR-ACT long-term extension study (ATTR-ACT LTE).

| **Trial acronym (trial number):** | **ATTR-ACT (NCT01994889)[18]** | **ATTR-ACT LTE (NCT02791230)[19, 20]** |
|---|---|---|
| **Study design** | Phase III, multicentre, international, double-blind, randomised placebo-controlled trial | Phase III, multicentre, long-term open label extension study with a 60-month treatment phase |
| **Trial period** | 30 months | 60 months |
| **Eligibility criteria for participants** | Patients between 18 and 90 years of age with ATTR-CM (wild-type or hereditary). | Cohort A: Patients who successfully completed 30 months of ATTR-ACT. Cohort B: Patients diagnosed with ATTR-CM who had not participated in ATTR-ACT. |
| **Settings and locations where the data were collected** | Conducted at 48 sites worldwide (including 2 UK sites). The trial sites were secondary or tertiary care settings. | ATTR-ACT sites and additional sites worldwide. |
| **Recruitment status** | Completed | Active, not recruiting |

Abbreviations: ATTR-ACT: Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy clinical trial; ATTR-ACT LTE: Long-term Safety of Tafamidis in Subjects with Transthyretin Cardiomyopathy clinical trial.

### 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

**ATTR-ACT**

In ATTR-ACT, tafamidis demonstrated a significant reduction in the combined risk of death and hospitalisations for cardiac causes, when compared to placebo.[18]. Tafamidis also showed a reduction in the decline of both how far patients could walk in 6 minutes, and health-related quality of life, which was measured with questionnaires compared to placebo.[18]

**ATTR-ACT LTE**

In ATTR-ACT LTE patients first treated with tafamidis in ATTR-ACT had better survival than those first treated with placebo.[19, 20]

### 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Tafamidis has a beneficial effect on the quality of life of patients with ATTR-CM.[18] In ATTR-ACT, tafamidis was shown to significantly reduce the rate of decline in health-related quality of life (which were measured with questionnaires) when compared to placebo. Patients were asked questions that covered a number of domains, such as symptom burden and frequency, physical and social limitation, pain levels and ability to self-care. Furthermore, tafamidis slowed the rate of decline of how far patients could walk (measured by the 6-minute walk test).[18]

### 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Like all medicines, tafamidis can cause side effects, although not everybody gets them. Common (may affect up to 1 in 10 people) side effects whilst taking tafamidis include diarrhoea, rash, and itching.[21]

### 3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Response:

Unlike current heart failure care, tafamidis stabilises the TTR protein and so limits further build-up of amyloid fibrils in the heart. In clinical trials tafamidis has been shown to reduce the chance of death and hospitalisations for patients with ATTR-CM.[18, 19] Tafamidis has also been shown in clinical trials to be well tolerated with regards to the safety profile.[18, 19]

Tafamidis is an oral daily capsule that can be taken at home.[2]

### 3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

As with all medicines there are side effects, however, in clinical trials side effects in patients taking tafamidis were well tolerated.[2] Therefore, the company does not consider that tafamidis has disadvantages compared to BSC currently received by patients with ATTR-CM.

### 3i) Value and economic considerations

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

**How the model reflects ATTR-CM**

ATTR-CM is a chronic condition which worsens over time, as abnormal clumps of protein build up in the heart. This build-up prevents the heart from working properly, causing heart failure symptoms. Heart failure causes shortness of breath, fatigue and physical functional limitations (e.g. difficulty climbing stairs).[22, 23] The NYHA Functional Classification system is a four-stage classification and provides a simple way of classifying the severity of the physical functional limitations in a person with heart failure.[5]

The economic model is based on the NYHA Functional Classification, as it reflects the natural progression of ATTR-CM by modelling a group of patients as they progress through NYHA functional classes or die. Typically, patients progress from lower to higher NYHA classes. However, as physical function is affected by more than just the abnormal build-up of proteins in the heart (for example due to changes in general fitness and injury), it is also possible patients to be move down to a lower NYHA class from a higher NYHA class (if their heart failure symptoms improve).

**Modelling how much tafamidis extends life**

The movement of patients between NYHA classes and the risk of dying in the economic model is informed by the outcomes of patients in the ATTR-ACT[18] and ATTR-ACT LTE[19, 20] clinical trials. NYHA class transitions and rates of death were extrapolated from these data to the maximum lifetime of patients in the modelled patient population.

**Modelling how much tafamidis improves quality of life**

Quality of life for patients with ATTR-CM is related to their ability to function normally, so it varies with NYHA class. The values for quality of life were derived from patient responses to a widely-used questionnaire in ATTR-ACT[18]. This questionnaire asked patients how they feel about their health according to five different topics: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Replies from patients were used to model quality of life in the economic model.

Treatment with tafamidis was shown to slow the decline of a patient's quality of life over the 30-month clinical trial period of ATTR-ACT[18]. Patients receiving placebo saw a larger decline in their quality of life compared to tafamidis patients over the same period. In the model, patients who stopped treatment were assumed to have the same quality of life as patients who received placebo and were at the same NYHA class.

**Modelling costs**

Tafamidis treatment costs more than the usual heart failure medicines currently used as best supportive care, but it has the potential to extend a patient's healthy life. The economic model predicts that more people receiving tafamidis may require hospitalisation (incurring hospitalisation costs) due to cardiovascular issues compared to best supportive care, but this is only because their risk of death due to ATTR-CM and so their extended lives expose them to more accumulated risk of hospitalisation.

**Model assumptions**

- In ATTR-ACT[18] patients' NYHA class was only measured every six months. Therefore, in the model, the risk of death associated with NYHA class can only be measured at these six-month intervals. As such, NYHA class is assumed to change every six months.
- Rates of transition between NYHA classes beyond the 30-month period of ATTR-ACT[18] are assumed to be consistent with rates observed during the ATTR-ACT[18]
- Survival benefit trend of tafamidis was assumed to extend beyond observational data from clinical trials so as to be modelled across a patient's entire expected lifetime

**Benefits and disadvantages not captured in the modelling**

There are two key benefits of tafamidis not captured in the economic model. Firstly, the availability of tafamidis is expected have a positive impact on caregivers and a patient's family. ATTR-CM is a progressive and debilitating disease, which currently lacks UK-approved disease-modifying treatments. As such, a diagnosis of ATTR-CM can be devastating. The availability of a treatment that may slow disease progression and slow the decline in quality of life, can give people with the disease the reassurance that there is a treatment available – both for themselves and for family members who may be affected in the future.

Secondly, caregivers of patients with ATTR-CM report a substantial impact on their physical and emotional well-being due to the enduring progressive functional disability from ATTR-CM.[15, 17] By reducing the decline in functional capacity and quality of life, tafamidis has the potential to help relieve the caregiver burden associated with this progressive disease.

The Company does not believe that there are any disadvantages of tafamidis not captured in the modelling.

## 3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Tafamidis is an innovative treatment for patients with ATTR-CM. Tafamidis is a once daily oral medication, that is a disease modifying treatment for patients with ATTR-CM that moves beyond symptomatic heart failure management.

Given the clinical benefits versus placebo observed in the clinical trials related to mortality, CV hospitalisation and quality of life, tafamidis is expected to generate greater quality life years compared to UK-approved drugs for symptomatic heart failure treatments alone.[24, 25] As such, it represents a paradigm shift in the management of a rare, progressive and fatal disease with a significant unmet need.

In conjunction with widespread adoption of the ATTR-CM diagnostic pathway, access to tafamidis could have a positive impact on the timely diagnosis of ATTR-CM. This could lead to cost savings resulting from reduced hospital admissions/ attendances, minimising unnecessary investigations and addressing mis/undiagnosed patients. Improved outcomes could be achieved by treating patients before they progress to advanced heart failure.

Tafamidis received a PIM designation by the MHRA and subsequently received an EAMS positive scientific opinion from the MHRA.[3] To date, 147 patients have been enrolled across 17 EAMS sites across the UK.

### 3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

Tafamidis is not likely to raise any equality or equity issues in adult patients with wild-type and hereditary ATTR-CM who are eligible to receive treatment.

Of note, some TTR variants are common in selected populations within the UK. The most common TTR variants associated with hereditary ATTR-CM are Val122Ile, which is prevalent in the Afro-Caribbean population[9], and T60A, prevalent in the white Caucasian population and endemic to parts of Ireland and Northern Ireland.[23] Numerous other rare TTR variants are also associated with ATTR-CM and afflict specific minority groups.[26]

## **SECTION 4:** Further information, glossary and references

### 4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

- NICE, Tafamidis for treating transthyretin amyloidosis with cardiomyopathy. Technology appraisal guidance [TA696] (2021): https://www.nice.org.uk/guidance/ta696
- American Heart Association, information on ATTR-CM: https://www.heart.org/-/media/files/health-topics/answers-by-heart/what-is-attrcm.pdf
- NHS, general information on amyloidosis: https://www.nhs.uk/conditions/amyloidosis/
- Cardiomyopathy UK, information on cardiomyopathy:
- Clinical trial information for ATTR-ACT: https://classic.clinicaltrials.gov/ct2/show/NCT01994889
- Clinical trial information for ATTR-ACT LTE: https://classic.clinicaltrials.gov/ct2/show/NCT02791230

- Tafamidis (Vyndaqel®) Patient Information Leaflet: https://www.medicines.org.uk/emc/files/pil.11141.pdf
- Tafamidis (Vyndaqel®) Summary of Product Characteristics: https://www.medicines.org.uk/emc/product/11141/smpc#gref

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

**4b) Glossary of terms**

Response:

| Abbreviation | Definition |
|---|---|
| **ATTR-ACT** | Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy clinical trial |
| **ATTR-CM** | Transthyretin amyloidosis with cardiomyopathy |
| **ATTR-ACT LTE** | Long-term Safety of Tafamidis in Subjects with Transthyretin Cardiomyopathy clinical trial |
| **BSC** | Best supportive care |
| **CV** | Cardiovascular |
| **EAMS** | Early Access to Medicines Scheme |
| **EFPIA** | European Federation of Pharmaceutical Industries and Associations |
| **EUPATI** | European Patients' Academy on Therapeutic Innovation |
| **HFpEF** | Heart failure with preserved ejection fraction |
| **HFrEF** | Heart failure with reduced ejection fraction |
| **MHRA** | The Medicines and Healthcare products Regulatory Agency |
| **MRI** | Magnetic resonance imaging |
| **NAC** | National Amyloidosis Centre |
| **NYHA** | New York Heart Association |
| **NICE** | The National Institute for Health and Care Excellence |
| **NHS** | National Health Service |
| **NSAID** | Nonsteroidal anti-inflammatory drugs |

| | |
|---|---|
| **PIM** | Promising Innovative Medicine |
| **SIP** | Summary of Information for Patients |
| **SmPC** | Summary of Product Characteristics |
| ***TTR*** | Transthyretin gene |
| **UC** | Ulcerative colitis |
| **UK** | United Kingdom |

**4c) References**

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:


1. European Medicines Agency. EMA/447104/2016 - EPAR summary for the public - Vyndaqel (tafamidis) 2016 [Available from: https://www.ema.europa.eu/en/documents/overview/vyndaqel-epar-summary-public_en.pdf.
2. Pfizer Ltd. Vyndaqel 61 mg soft capsules: Summary of Product Characteristics. 2023 [Available from: https://www.medicines.org.uk/emc/product/11141/smpc#about-medicine.
3. Medicines and Healthcare products Regulatory Agency. Expired early access to medicines scheme scientific opinions: Tafamidis (for amyloid cardiomyopathy) 2020 [Available from: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-expired-scientific-opinions/expired-early-access-to-medicines-scheme-scientific-opinions#tafamidis-for-amyloid-cardiomyopathy.
4. American Heart Association. What is Transthyretin Amyloid Cardiomyopathy (ATTR-CM)? 2023 [Available from: https://www.heart.org/-/media/files/health-topics/answers-by-heart/what-is-attrcm.pdf.
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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Tafamidis for transthyretin amyloid cardiomyopathy (review of TA696) [ID6237]

## Clarification questions response

**November 2023**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6327_Tafamidis_Calrification Response_02NOV23_Redacted | 1.0 | Yes | 02 November 2023 |

Dear Linda,

Pfizer would like to thank KSR and the NICE technical team for the clarification questions and opportunity to provide further detail to aid the evaluation of our evidence submission. Please find Pfizer's response to the questions in the subsequent sections.

Tafamidis is a paradigm shift in the management of a rare, progressive and fatal orphan cardiovascular disease with a significant unmet need that generates greater than [redacted] incremental QALYs (undiscounted). Tafamidis is also currently the only licensed treatment for ATTR-CM[1] and since our previous NICE STA appraisal (TA696[2]), no new pharmacological therapies for ATTR-CM have been licensed or reimbursed in the UK; further emphasising the unmet medical need for an effective and well-tolerated treatment that can slow the progression of ATTR-CM.

Pfizer's commitment to meet this treatment gap is reflected in [redacted] as well as the incorporation of almost all committee preferred assumptions from TA696[2] in the updated base case, resulting in low levels of uncertainty.

[redacted]

Sincerely,

[redacted]

# Section A: Clarification on clinical effectiveness data

## *Decision problem*

**A 1. Priority Question: The EAG notes that the company have excluded the only comparators in the scope for mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy [TTR-FAP] and hereditary ATTR-CM), patisiran, inotersen and vutisiran. The EAG notes that the FAD for TA696 stated that BSC is the relevant comparator, ruling out inotersen and patisiran given the presumption of insufficient evidence in the population of those with both cardiomyopathy and polyneuropathy. However, over two years has passed since the issuance of the FAD on 12 May 2021. Therefore, without a systematic review, it cannot be confirmed that there is still insufficient evidence: in fact, the EAG has located conference abstracts for what appear to be two relevant trials.[3-6] Therefore, please conduct a systematic review and:**

**a) Provide comparative analyses (clinical effectiveness and cost effectiveness) versus all three of these comparators for this population.**

**b) Consider comparative analyses for all three comparators for the whole transthyretin amyloid cardiomyopathy population if there are clinical effectiveness data for patients without polyneuropathy.**

Following the previous NICE STA appraisal for tafamidis in ATTR-CM (TA696[2]), no new major data relating to the use of patisiran, inotersen or vutrisiran for the treatment of ATTR-CM have emerged and these drugs are still not licenced for the treatment of ATTR-CM nor have they received positive recommendations by NICE for the treatment of this indication.[7-9]

Patisiran, inotersen and vutrisiran have marketing authorisations and positive NICE recommendations only for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.[7-9] Patients receiving these drugs for polyneuropathy may also manifest with other amyloidosis symptoms such as cardiomyopathy (i.e. patients with a mixed phenotype, a very small population estimated to be between 6.5-11.9% of ATTR-CM patients[10]). However,

anecdotal evidence derived from conversations with UK clinicians indicates that in clinical practice these patients would receive treatment appropriate to address their predominant symptoms i.e. if polyneuropathy symptoms are predominant they may be considered for treatment with ATTR-PN drugs (patisiran, inotersen, or vutrisiran), whereas, if cardiomyopathy is predominant they may be considered for treatment with tafamidis.

Of note, in October 2023, the U.S. FDA rejected patisiran for the treatment of ATTR-CM.[11] The FDA indicated that the lack of clinical meaningfulness of patisiran's treatment effects for ATTR-CM had not been established from APOLLO-B (**Error! Reference source not found.**; one of the trials referenced in question A1 by the EAG), and therefore, the supplemental New Drug Application for patisiran could not be approved in its present form.[11] The manufacturer has since announced they will no longer pursue an expanded indication for patisiran in the U.S.[11] In APOLLO-B patisiran did meet the primary endpoint as well as the first secondary endpoint at Month 12, demonstrating a significant difference compared to placebo in functional capacity, as measured by the 6-Minute Walk Test (6-MWT), and health status and quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score, respectively.[12]

However, patisiran did not meet significance on its other secondary endpoints.[12] For the composite end point of death from any cause, cardiovascular events, and change from baseline in the distance covered on the 6-minute walk test, the win ratio over the 12-month double-blind period was 1.27 (95% CI, 0.99 to 1.61) and was not significant. For the composite end point of death from any cause, hospitalisations for any cause, and urgent visits for heart failure, the estimated hazard ratios were 0.88 (95% CI, 0.58 to 1.34) in the overall trial population and 0.10 (95% CI, 0.62 to 1.60) in the patients who were not receiving tafamidis at baseline. The confidence interval for these results was also not significant.[12]

Of note, these composite secondary endpoints in APOLLO-B that were not significant comprise of measures such as mortality, and CV hospitalisation visits which may be viewed as having strong clinical meaningfulness for ATTR-CM. This is demonstrated by their inclusion as primary endpoints in the ATTR-ACT trial.

Although as mentioned above, we do not consider patisiran, inotersen and vutrisiran, as relevant competitors, for completeness we have provided a summary of primary and secondary endpoints in both the trials the EAG identified, as well as the phase 3 inotersen trial, ATTR-ACT and ATTR-ACT LTE (**Error! Reference source not found.**). In summary, carrying out a comparative analysis of completed phase 3 clinical trial data for patisiran, inotersen, vutrisiran and tafamidis would not be appropriate, as the primary endpoints differ markedly (**Error! Reference source not found.**) and secondary endpoints relating to ATTR-CM were not met in APOLLO-B. Furthermore, there is also the concern of introducing selection bias when comparing outcomes for patisiran, inotersen and vutrisiran against tafamidis as patient eligibility for these trials is based primarily on ATTR-PN disease criteria and not ATTR-CM criteria.

**Table 1. Comparison of primary and secondary endpoints – Tafamidis versus ATTR-PN drugs**

| Drug | Indicated to treat ATTR-CM (Yes/No) | Trial | Primary outcome measure | Key secondary outcome measure |
|---|---|---|---|---|
| **Tafamidis** | Yes | ATTR-ACT[13] (NCT01994889) | All-cause mortality followed by frequency of CV hospitalisation | Change from baseline to month 30 for the 6-minute walk test (6MWT) and the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) |
| **Tafamidis** | Yes | ATTR-ACT LTE[14-16] (NCT02791230) | All-cause mortality | All-cause mortality by NYHA class I/II and III |
| **Patisiran** | No | APOLLO-B[12] (NCT03997383) | Change from baseline 6MWT | Health status and quality of life (KCCQ-OS score), composite score of all-cause mortality, CV events, and change from baseline in 6MWT at 12 months, composite score of all-cause mortality, hospitalization, and urgent visits for heart failure over 12 months |
| **Inotersen** | No | 24 months open label trial[6] (NCT03702829) | Longitudinal LV strain compared to baseline | LV mass measurement by cardiac MRI, ECV-extracellular volume by cardiac MRI |
| **Vutrisiran** | No | HELIOS-A[17] (NCT03759379) | Change from baseline in modified Neuropathy Impairment Score | Exploratory cardiac endpoints included change from baseline in NT-proBNP levels, echocardiography parameters, and 99mTc scintigraphy parameters at 18 months |

Abbreviations: CV, cardiovascular; ECV, extracellular volume; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary, LV, left ventricular; MRI, magnetic resonance imaging; NYHA, New York Hearth Association functional Classification; NT-proBNP; N-terminal prohormone of brain natriuretic peptide; 6MWT, 6 -minute walk test; 99mTc, technetium-99m.

**A 2. Priority Question: Please provide evidence as to what is standard of care in UK clinical practice for both the whole transthyretin amyloid cardiomyopathy population and for the transthyretin familial amyloid polyneuropathy [TTR-FAP] and hereditary ATTR-CM) subgroup, specifying the percentages of patients currently receive each of BSC, patisiran, inotersen, vutisiran, and any other treatments.**

There are currently no UK treatment guidelines or approved disease-modifying pharmacological treatments for wild type or hereditary ATTR-CM. Tafamidis is currently the only licensed treatment for ATTR-CM.[1] Symptomatic management of heart failure is the mainstay of BSC in the UK.[18]

In the UK, a single centre – the National Amyloidosis Centre (NAC) – currently provides diagnostic and management advice services for the national case load of ATTR-CM patients (including patients with TTR-FAP and hereditary ATTR-CM). In 2019, a tafamidis EAMS service consisting of 17 centres was created, however, enrolment of new patients has since closed.[19]

In the existing paradigm, the main aims of BSC are to relieve symptoms of congestive heart failure and prevent arrhythmic/thromboembolic events (Table 2).[20, 21] Diuretics, including aldosterone antagonists, bioavailable loop diuretics, and more recently sodium–glucose co-transporter 2 inhibitors are the main strategy to manage heart failure symptoms in ATTR-CM patients.[21, 22] The use of some conventional heart failure and anti-arrhythmic medications in ATTR-CM may actually cause harm[20, 21] adding to the difficulty in managing the disease.

Organ transplantation has been reported for hereditary ATTR-CM but is rarely used in the UK, due to the advanced age of the patient population and the scarcity of donor organs.[23] In addition, implantable cardiac devices are not generally suitable for ATTR-CM patients.[21]

Three agents are licensed and reimbursed in the UK for adult patients with stage 1 and 2 transthyretin familial amyloid polyneuropathy (TTR-FAP): patisiran, inotersen and vutrisiran.[7-9] As mentioned in the response to question A1, patients receiving these drugs for polyneuropathy may manifest with other amyloidosis symptoms such as cardiomyopathy (i.e. mixed phenotype patients). Anecdotal evidence derived from

conversations with UK clinicians indicates that in clinical practice these patients would receive treatment appropriate to address their predominant symptoms i.e. if polyneuropathy symptoms are predominant they would be treated with ATTR-PN drugs (patisiran, inotersen, and vutrisiran), whereas, if cardiomyopathy is predominant they would be treated with tafamidis.

Tafamidis 20mg has a marketing authorisation for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.[24], however tafamidis 20mg is not reimbursed in the UK and so there is minimal use of this medicine in the UK. Data on usage of patisiran, inotersen and vutrisiran in ATTR-CM in the UK was not available.

In summary, the only relevant therapy for ATTR-CM in UK clinical practice is BSC, comprising of symptomatic management of heart failure. Thus, there is a significant unmet medical need for an effective and well-tolerated treatment that can slow the progression of ATTR-CM.

**Table 2. Non-disease modifying therapy for ATTR-CM – BSC in the UK**

| Therapy | Considerations in ATTR-CM patients |
|---|---|
| **Loop diuretics** | Recommended, especially bioavailable loop diuretics (e.g., furosemide) to avoid diuretic resistance in advanced cardiomyopathy |
| **Aldosterone antagonists** | Consider addition of low dose spironolactone 12.5 mg every other day |
| **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers** | Usually poorly tolerated due to risk of symptomatic hypotension as disease progresses |
| **Beta-blockers** | Risk of symptomatic hypotension, given fixed stroke volume and reliance of higher heart rate to maintain cardiac output |
| **Calcium channel blockers** | Contraindicated<br>May lead to high-degree heart block and profound negative inotropic effect with resulting cardiogenic shock |
| **Digoxin** | Relatively contraindicated<br>Hypersensitivity may lead to abrupt cardiac rhythm disturbances and sudden death |

Source: Adapted from Castano et al. 2015[21]

**A 3. Priority Question: Please elaborate on the relevance of partisiran, inotersen and vutrisiran as comparators for tafamidis in the ATTR-CM population and any subgroups.**

Please refer to response to question A1.

## *Systematic review*

**A 4. Priority Question: Please conduct a full systematic review to provide supporting evidence for this submission, including studies of partisiran, inotersen and vutrisiran and any other treatments used in UK clinical practice for the whole ATTR-CM population as well as any subgroups. This should include:**

a) **The eligibility criteria and search strategy, methods, and results for this full systematic review.**
b) **The methods of study selection, data extraction and quality assessment for the systematic review.**
c) **The results in terms of a full description of included studies.**
d) **The results of the quality assessment for studies included in the systematic review.**
e) **The list of excluded studies with reasons for exclusion.**

Please refer to response to question A1.

## *Clinical effectiveness evidence*

**A 5. Priority Question: Page 20 of the company submission (CS) states that the data cut for the ATTR-ACT long-term extension (LTE) trial was August 2021. Please provide further longer-term data from this ATTR-ACT LTE trial for all outcomes reported.**

No further data reporting on outcomes of interest from the ATTR-ACT LTE is available.

**A 6. Priority Question: Of the list of outcomes in the scope, only overall survival is presented. Please provide the results from the ATTR-ACT LTE for all outcomes in the scope.**

Treatment-emergent adverse events from ATTR-ACT LTE are presented in the response to question A14. The following outcomes were not collected within the ATTR-ACT LTE:

- cardiovascular-related mortality
- cardiac function (such as global longitudinal strain or brain natriuretic [BNP] level)
- cardiovascular-related hospitalisation
- functional exercise capacity
- signs and symptoms of heart failure (such as breathlessness)
- health-related quality of life (of patients and carers)

However, data on these outcomes was captured in ATTR-ACT and were presented in the original submission and inform the cost-effectiveness analysis in the previous and current CS.

**A 7. Priority Question: The CS only presents data from the ATTR-ACT LTE, which excludes any comparative evidence of tafamidis vs. placebo, which might be used to inform an indirect treatment comparison (ITC) with patisiran, inotersen, vutisiran, or any other treatments relevant to UK clinical practice. Therefore, please present all ATTR-ACT trial data relating to tafamidis vs. placebo, which might be used to inform any ITC.**

Please refer to Sections B.2.6.2 and B.2.10.1 in TA696[2] Document B for comparative evidence of tafamidis vs placebo associated with clinical effectiveness and safety, respectively. At the start of the ATTR-ACT LTE trial all patients previous receiving placebo in ATTR-ACT crossed over to tafamidis treatment.

An ITC with patisiran, inotersen, and vutrisiran is not deemed appropriate – please refer to response to question A1.

A 8. Please provide the baseline characteristics of the ATTR-ACT LTE trial.

Please find the baseline patient characteristics of the ATTR-ACT LTE trial in Table ***3***.

**Table 3. Patient characteristics at baseline by NYHA class – ATTR-ACT LTE**

| | NYHA class I/II | | NYHA class III | |
|---|---|---|---|---|
| | **Continuous tafamidis (n=121)** | **Placebo to tafamidis (n=114)** | **Continuous tafamidis (n=55)** | **Placebo to tafamidis (n=63)** |
| Age, years | | | | |
| Mean (SD) | 75(7.1) | 73 (6.5 ) | 76 (7.6) | 76 (6.8) |
| Medican (range) | 75 (56-88) | 74 (53-86) | 76 (46-87) | 76 (51-89) |
| Male sex, n (%) | 113 (93.4) | 105 (92.1) | 45 (81.8) | 52 (82.5) |
| Race, n (%) | | | | |
| White | 102 (84.3) | 94 (82.5) | 34 (61.8) | 52 (82.5) |
| Black | 9 (7.4) | 16 (14.0) | 17 (30.9) | 10 (15.9) |
| Asian | 8 (6.6) | 4 (3.5) | 3 (5.5) | 1 (1.6) |
| Other | 2 (1.7) | 0 | 1 (1.8) | 0 |
| Transthyretin genotype, n (%) | | | | |
| Wildtype | 99 (81.8) | 90 (78.9) | 35 (63.6) | 44 (69.8) |
| Variant | 22 (18.2) | 24 (21.1) | 20 (36.4) | 19 (30.2) |
| NT-proBNP, pg/ml, median (UQ-LQ) | 2672 (1722.0-4235.6) | 2816 (1766.0-4360.0) | 4410 (2625.0-7166.0) | 4079 (2321.0-5269.0) |
| Troponin I[a], ng/ml, median (UG-LQ) | 0.13 (0.08-0.18) | 0.13 (0.08-0.18) | 0.18 (0.13-0.30) | 0.14 (0.08- 0.22) |
| 6MWT distance, m, median (UQ-LQ) | 383 (310-451) | 409 (327-475) | 256 (195-340) | 250 (80-333) |

Abbreivations: 6MWT, 6-min walk test; LQ, lower quartile; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association Functional Classification; SD, standard deviation; UQ, upper quartile.
Patients continouslt treated with tafamidis meglumine 80 mg/free acid 61 mg, or placebo then tadamidis. n denotes number of patients.
[a]Troponin I level missing for one placeo-treated patient with NYHA I/II symptoms (n=113).
Source: Elliott et al. 2023[14]

A 9. Please provide a discussion of the generalisability of the ATTRACT-ACT-LTE trial, including a comparison between the baseline characteristics of the ATTR-ACT LTE trial and those of the ATT-CM population in UK clinical practice.

In ATTR-ACT, four patients were enrolled from the UK; most patients were enrolled from the USA (n=279).[13] However, ATTR-ACT patients, and by extension ATTR-ACT LTE, can be considered highly representative of the UK patient population in terms of baseline characteristics, as shown by comparison with a retrospective UK cohort published by Gillmore et al. of untreated ATTR-CM patients who attended the National Amyloidosis Centre (NAC) (n=869), a national diagnostic and advisory service for

amyloidosis (Table 4).[25] In Section 3.9 of the FAD in TA696[2], the committee concluded that the ATTR-ACT and ATTR-ACT LTE studies were appropriate for decision making.

**Table 4. Comparison of baseline characteristics in ATTR-ACT LTE and a UK cohort**

| | ATTR-ACT LTE[14] | | | | Untreated patients |
|---|---|---|---|---|---|
| | NYHA class I/II | | NYHA class III | | |
| | Continuous tafamidis | Placebo to tafamidis | Continuous tafamidis | Placebo to tafamidis | Gillmore et al. 2018[25] |
| Number of patients | 121 | 114 | 55 | 63 | 869 |
| Median age (range) | 75 (56-88) | 74 (53-86) | 76 (46-87) | 76 (51-89) | NR |
| Median age at diagnosis (range) | NR | NR | NR | NR | 77 (41-95) |
| Male sex, n (%) | 113 (93.4) | 105 (92.1) | 45 (81.8) | 113 (93.4) | 737 (85) |
| **NYHA classification, n (%)[a]** | | | | | |
| Class I/II | 235 (67) | | | | 656 (75) |
| Class III | 118 (33) | | | | 205 (24) |
| Class IV | 0 | | | | 8 (1) |
| **TTR genotype, n (%)** | | | | | |
| Wild-type TTR | 99 (81.8) | 90 (78.9) | 35 (63.6) | 44 (69.8) | 553 (63.6) |
| Hereditary TTR | 22 (18.2) | 24 (21.1) | 20 (36.4) | 19 (30.2) | 316 (36.3) |

[a] NYHA class: I = without resulting limitations, II = slight limitation, III = marked limitation, IV = inability to carry on any physical activity without discomfort.
Abbreviations: NR: not reported; NYHA: New York Heart Association; TTR: transthyretin.

A 10. Please provide the methods for estimating the hazard ratios of all-cause mortality for the ATTR-ACT LTE trial.

The hazard ratios observed in the ATTR-ACT LTE trial, inclusive of outcomes in patients who received placebo in ATTR-ACT and then tafamidis in ATTR-ACT LTE study (and therefore cannot be considered informative and were not used), were provided on page 23 (Section 6.3) of the current CS and referenced the reporting article, Elliott et al. (2023).[14] Per this publication: 'all-cause mortality was assessed using a Cox proportional hazards model with treatment and genotype included in the model. Heart transplantation or implantation of a mechanical ventricular assist device were considered equivalent to death'.[14]

A 11. Please provide the methods and results on the assessment of the proportional hazards assumption for all-cause mortality for the ATTR-ACT LTE trial.

There was no placebo arm in the ATTR-ACT LTE trial, therefore, assessment of the proportional hazards assumption for all-cause mortality was not feasible. In TA696[2] a Cox proportional hazards model was used to analyse time to all-cause mortality. Please refer to Section B.2.6.2.1 and B.2.6.2.2 in TA696[2] Document B for more details.

A 12. Please provide the results of subgroup analysis based on ATTR genotype (wild-type versus hereditary) of the ATTR-ACT LTE trial.

ATTR-ACT was powered based on the primary analysis which used the Finkelstein-Schoenfeld approach to look at the hierarchical combination of mortality and CV-related hospitalisations. Analyses by the stratification factors of NYHA class and genotype group were included as exploratory analyses only to confirm the consistency of results with that for the overall group; therefore, the lack of statistical significance is not unexpected. Similarly, the ATTR-ACT LTE is also powered on primary outcome measure and lacks statistical power for genotype sub-group analysis. In Section 3.11 of the FAD in TA696[2] the committee accepted the company's point about a lack of statistical power in the subgroup analyses, recognising that ATTR-ACT was powered on the primary outcome measure.

Since TA696[2], a genotype subgroup analysis of all-cause mortality in ATTR-ACT and an earlier ATTR-ACT LTE data cut (March 2020) was published by Elliot et al.[15] Mortality reductions were generally consistent across the subgroups in line with data previously provided in TA696[2] (Section 3.11 of the FAD). In patients with continuous tafamidis treatment, there was a 39% reduction in the risk of all-cause mortality in patients with wild type ATTR-CM (hazard ratio, 0.61 [95% CI, 0.43–0.87]; P=0.006), and a 43% reduction in patients with hereditary ATTR-CM (0.57 [0.33–0.99]; P=0.05), compared with the placebo to tafamidis group.[15] This long-term follow up data from Elliot et al.[15] validates previous observations in hazard ratios between genotype subgroups presented in TA696[2] (Section 3.11 of the FAD).

## *Indirect treatment comparison (ITC)*

**A 13. Priority question. Please conduct ITCs to compare tafamidis with all three comparators listed in the scope, patisiran, inotersen and vutisiran or any other treatment relevant to UK clinical practice. These analyses should be in the TTR-FAP and hereditary ATTR-CM subgroup, and, if data are available,**

**also in the whole ATTR-CM population. Please perform all analyses for the following outcomes:**

a) **All-cause mortality and cardiovascular-related hospitalisations**
b) **Overall survival**
c) **Cardiovascular-related hospitalisations**
d) **Cardiovascular- related mortality**
e) **Mobility decline (6-minute walk test)**

Please refer to response to question A1.

## *Adverse events*

A 14. Please provide data on treatment-related adverse events from the ATTR-ACT LTE trial.

Safety outcomes in ATTR-ACT have been published previously with the safety profiles of tafamidis 80 mg, tafamidis 20 mg, and placebo shown to be similar.[13, 26] In the ATTR-ACT LTE, there were 164 patients treated with tafamidis 80 mg in ATTR-ACT transitioning to tafamidis 61 mg free acid. Incidence and types of adverse events (Table 5) were similar, or lower, than that with pooled tafamidis (80 and 20 mg) or placebo in ATTR-ACT.[13, 14] No new safety concerns emerged in patients treated with tafamidis 80 mg or tafamidis 61 mg free acid in the ATTR-ACT LTE.[14]

**Table 5. Adverse events - ATTR-ACT LTE August 2021 (Tafamidis 80 mg / tafamidis 61 mg free acid)**

| **Patients, *n* (%)** | **Continuous tafamidis** |
|---|---|
| **Any adverse effect in the LTE** | **108 (98.2)** |
| **Cardiac disorders** | **79 (71.8)** |
| Cardiac failure | 28 (25.5) |
| Atrial fibrillation | 21 (19.1) |
| Ventricular tachycardia | 13 (11.8) |
| Cardiac failure (acute) | 11 (10.0) |
| Cardiac failure (congestive) | 9 (8.2) |
| Pericardial effusion | 7 (6.4) |
| **Infections and infestations** | **64 (58.2)** |
| Cellulitis | 17 (15.5) |

| | |
|---|---|
| Urinary tract infection | 14 (12.7) |
| Pneumonia | 13 (11.8) |
| Upper respiratory tract infection | 8 (7.3) |
| Bronchitis | 7 (6.4) |
| Nasopharyngitis | 7 (6.4) |
| **Injury, poisoning, and procedural complications** | **57 (51.8)** |
| Fall | 31 (28.2) |
| Skin abrasion | 9 (8.2) |
| Contusion | 7 (6.4) |
| Skin laceration | 7 (6.4) |
| **Respiratory, thoracic, and mediastinal disorders** | **55 (50.0)** |
| Dyspnoea | 20 (18.2) |
| Cough | 18 (16.4) |
| Pleural effusion | 18 (16.4) |
| Epistaxis | 9 (8.2) |
| **General disorders and administration site conditions** | **54 (49.1)** |
| Oedema (peripheral) | 16 (14.5) |
| Fatigue | 12 (10.9) |
| Asthenia | 9 (8.2) |
| Chest pain | 8 (7.3) |
| **Gastrointestinal disorders** | **50 (45.5)** |
| Constipation | 11 (10.0) |
| Nausea | 11 (10.0) |
| Ascites | 9 (8.2) |
| Diarrhoea | 8 (7.3) |
| Dysphagia | 7 (6.4) |
| **Nervous system disorders** | **51 (46.4)** |
| Dizziness | 15 (13.6) |

| | |
|---|---|
| Balance disorder | 9 (8.2) |
| **Musculoskeletal and connective tissue disorders** | **49 (44.5)** |
| Arthralgia | 21 (19.1) |
| Pain in extremity | 12 (10.9) |
| Back pain | 9 (8.2) |
| Osteoarthritis | 8 (7.3) |
| Muscle spasms | 7 (6.4) |
| Muscular weakness | 7 (6.4) |
| **Metabolism and nutrition disorders** | **43 (39.1)** |
| Hypokalaemia | 12 (10.9) |
| Gout | 10 (9.1) |
| Hyponatraemia | 8 (7.3) |
| Decreased appetite | 7 (6.4) |
| **Skin and subcutaneous tissue disorders** | **42 (38.2)** |
| Pruritus | 11 (10.0) |
| Skin ulcer | 8 (7.3) |
| **Renal and urinary disorders** | **35 (31.8)** |
| Acute kidney injury | 18 (16.4) |
| Renal failure | 8 (7.3) |

Patients continuously treated with tafamidis meglumine 80 mg or free acid 61 mg. Includes system organ classes where ≥30% of patients in the study had an adverse event, and within these, MedDRA Preferred Terms in ≥6% of patients. Adverse events reported up to 28 days after the patient's last dose of tafamidis. Data from the interim ATTR-ACT LTE (August 2021 data cut). Events coded per MedDRA v24.0.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities.
Source: Elliott et al. 2023[14]

A 15. Table 6 of the CS shows the most common adverse events in the ATTR-ACT LTE, in which high numbers of adverse events were reported.

a) Please elaborate on these findings and compare them to expected adverse events in best supportive care. Are these adverse events expected to be related to treatment with tafamidis?

b) Please elaborate on the 51.8% of patients that had “injury, poisoning and procedural complications”. Are these adverse events expected to be related to treatment with tafamidis?

a) As there was no placebo (BSC) arm in the ATTR-ACT LTE, findings from ATTR-ACT can be used to compare adverse events profiles of tafamidis and BSC. In the ATTR-ACT trial the frequency of adverse events in patients treated with 80mg tafamidis meglumine was generally similar and comparable to placebo.[27] Please refer to Section B.2.10.1 in TA696[2] Document B for further information.

As mentioned in the response to question A14, safety outcomes in ATTR-ACT have been published previously with the safety profiles of tafamidis 80 mg, tafamidis 20 mg, and placebo shown to be similar.[13, 26] In the ATTR-ACT LTE, there were 164 patients treated with tafamidis 80 mg in ATTR-ACT transitioning to tafamidis free acid 61 mg. Incidence and types of adverse events (Table 5) were similar, or lower, than that with pooled tafamidis (80 and 20 mg) or placebo in ATTR-ACT.[13, 14] No new safety concerns emerged in patients treated with tafamidis 80 mg or tafamidis 61 mg free acid in the ATTR-ACT LTE.[14] The overall safety profile of tafamidis in the ATTR-ACT LTE August 2021 data cut was consistent with that previously reported in ATTR-ACT and at earlier time points in the ATTR-ACT LTE.[14]

b) In the ATTR-ACT LTE population, overall incidence and types of adverse events were similar, or lower, than that with pooled tafamidis (80 and 20 mg) or placebo in ATTR-ACT.[13, 26] As mentioned before, safety outcomes in ATTR-ACT have been published previously with the safety profiles of tafamidis 80 mg, tafamidis 20 mg, and placebo shown to be similar.[13, 14] Therefore, although the ATTR-ACT LTE trial did not include a placebo arm, its similarities

to the ATTR-ACT treatment arm lead us to believe that these adverse events are not treatment specific.

Please also note that a large portion of the "injury, poisoning and procedural complications" category is comprised of the "fall" adverse event (28.2%, Table 5).[14] Falls account for one of the most common and serious issues contributing to a disability, especially among elderly individuals.[28] The ATTR-ACT and ATTR-ACT LTE study populations have a large proportion of elderly individuals, who have continued to age over time as they graduated into the ATTR-ACT LTE trial population.[13, 14] A similar number of events were observed in the placebo arm of ATTR-ACT for the "injury, poisoning and procedural complications" and "fall" adverse event categories.[19]

## Section B: Clarification on cost-effectiveness data

**B1. Priority question. The company's health economic model was updated with new long-term follow-up data from the ATTR-ACT long-term extension study.**

a) **Please describe all adjustments, and the impact of each individual adjustment on the cost-effectiveness results, that were made in the updated economic model as compared to the original submission model.**

b) **Please provide updated tables of all input parameters used in the model, including uncertainty measures and distributions used, sources and an indication whether the parameter was updated since the last submission.**

c) **Please provide a list of model assumptions underlying the current version of the model and the company base case.**

d) **Please confirm that all input parameters were updated with the latest evidence from the ATTR-ACT LTE, whenever applicable.**

We wish to reiterate that the reference model updated for the current CS is the model created by the EAG during TA696[2] [ID1531] and implements the committee preferred assumptions. The model has been extended to allow for more extensive scenario and sensitivity analysis and parameterised with more contemporary data.

a) In order to describe the impact of model updates upon the cost-effectiveness results, the EAG model was first set to the new company base case assumptions outlined in Table 3 of the current CS Evidence Submission Document; incorporating all previous committee preferred assumptions with the exception of TTD and OS where new data was available. Incremental updates were then applied as follows:

1) Application of current PAS discount ([redacted]), updating from previous PAS discount of [redacted]. This forms the reference case to which all further incremental updates were added.

2) Update of the tafamidis OS model to generalised Gamma using parameters from the August 2021 data cut from ATTR-ACT LTE, tafamidis 80mg/ tafamidis free acid 61mg population.

3) Update of the tafamidis TTD model exponential rate parameter to that derived using the August 2021 data cut from ATTR-ACT LTE, tafamidis 80 mg/ tafamidis free acid 61mg population.

4) Update of the tafamidis OS hazard ratios per NYHA class.

5) Update the concomitant medication costs for tafamidis and BSC using eMIT 21/22.[29]

6) Update the resource unit costs for health state costing using NHS reference costs 21/22[30] and PSSRU unit costs 21/22[31].

7) Update the resource costs for adverse events (including CV-related hospitalisation cost) using NHS reference costs 21/22.[30]

8) Update the resource costs for end of life care using Hollingworth et al.[18], inflated using PSSRU Health Services (NHSCII Pay + Prices) inflation index[30].

9) Update life tables to England 2018-20[32]

10) Correction of the discontinued_utils_flag scenario. The note for this flag was transposed with the CV_events_IV_flag in the EAG model of TA696[2], but reads "Turn on flag to use BSC utilities for NYHA IV once patients discontinue (uses an IF statement in parameters sheet to use BSC utility)". This was coded under the assumption of a NYHA IV stopping rule and applied BSC utilities to all patients in the tafamidis trace in NYHA IV. Logic was added to ensure that this only applied to patients in a discontinued NYHA IV health state.

11) Extension of traces and sums. In order to allow for sampling of ages in PSA and for scenario analysis, the traces and sums were extended. The trace

always functionally ends as the mean age of patients exceeds 100, due to the end of lifetables.

The impact of each of these changes is presented in Table 6.

**Table 6. Impact of updates to TA696 [ID1531] EAG model**

| Change | Incremental – single change | | ICER – single change | ICER – cumulative changes | % change – single change | % change – cumulative changes |
|---|---|---|---|---|---|---|
| | Costs | QALY | | | | |
| **Previous base case (using TA696 [post technical engagement] PAS discount)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous base case (using current PAS discount)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of tafamidis OS model | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of tafamidis discontinuation model | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of tafamidis OS hazard ratios per NYHA class | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of concomitant medication costs for tafamidis and BSC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of resource unit cost for health state costing | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of adverse event costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of end of life costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Update of life tables | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Correction of discontinued_utils_flag scenario | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Extension of traces and sums | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **New base case (includes all above)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BSC, best supportive care; ICER: incremental cost-effectiveness ratio; NHYA: New York Heart Association functional classification; OS: overall survival; PAS: patient access scheme; QALY: quality adjusted life years.

b) Parameters for the company base case are provided in the following tables (Table 7-Table ***39***). The 'Updated' column describes where parameters have been updated since the previous EAG base case in TA696[2] – updated parameters are marked noted with 'Y' and those not updated are noted with 'N'.

**Table 7. Demographic parameters used in company base case**

| Parameter | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Age (years) | [redacted] | [redacted] | Mean age of ATTR-ACT ITT population | N |
| Proportion female | [redacted] | [redacted] | Proportion female of ATTR-ACT ITT population | N |

Abbreviations: ITT, intention to treat, SE, standard error.

**Table 8. Demographic parameters used in company in scenario analysis (scenario 10 in CS - service redesign: early diagnosis impact on outcomes)**

| Parameter | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Age (years) | [redacted] | [redacted] | Mean age of ATTR-ACT ITT population | N |
| Proportion female | [redacted] | [redacted] | Proportion female of ATTR-ACT ITT population | N |

Abbreviations: ITT, intention to treat, SE, standard error.

**Table 9. Baseline NYHA distribution used in company base case**

| Parameter | Count | Source | Updated |
|---|---|---|---|
| Count in NYHA I | [redacted] | Baseline NYHA distribution of ATTR-ACT ITT population | N |
| Count in NYHA II | [redacted] | | N |
| Count in NYHA III | [redacted] | | N |
| Count in NYHA IV | [redacted] | | N |

Abbreviations: ITT, intention to treat; NHYA: New York Heart Association functional classification.

**Table 10. BSC NYHA transitions used in company base case**

| NYHA transitions - counts | | | | | Source | Updated |
|---|---|---|---|---|---|---|
| Months 0–6 | | | | | Observed transitions, ATTR-ACT ITT population, placebo arm | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 6–12 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 12–18 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 18–24 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 24–30 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 30+ | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |

Abbreviations: ITT, intention to treat; NHYA: New York Heart Association functional classification.

**Table 11. Tafamidis NYHA transitions used in company base case**

| NYHA transitions - counts | | | | | Source | Updated |
|---|---|---|---|---|---|---|
| Months 0–6 | | | | | Observed transitions, ATTR-ACT ITT population, tafamidis arms | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 6–12 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 12–18 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 18–24 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 24–30 | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |
| Months 30+ | | | | | | |
| From\To | NYHA I | NYHA II | NYHA III | NYHA IV | | |
| NYHA I | [redacted] | | | | | N |
| NYHA II | [redacted] | | | | | N |
| NYHA III | [redacted] | | | | | N |
| NYHA IV | [redacted] | | | | | N |

Abbreviations: ITT, intention to treat; NHYA: New York Heart Association functional classification.

**Table 12. BSC OS Weibull relative survival model parameters used in company base case**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| Shape | [redacted] | Model fitted to placebo OS censoring for HT, CMAD – ATTR-ACT randomised period | N |
| Scale | [redacted] | | N |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 13. Tafamidis OS generalised Gamma relative survival model parameters used in company base case**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| μ | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| σ | [redacted] | | Y |
| Q | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 14. Tafamidis OS log-logistic relative survival model parameters used in scenario analysis (scenario 1 in CS – tafamidis OS extrapolation)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| α | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| β | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 15. Tafamidis OS log-normal relative survival model parameters used in scenario analysis (scenario 1in CS – tafamidis OS extrapolation)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| μ | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| σ | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 16. Tafamidis discontinuation exponential model parameter used in company base case**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| Rate | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg time to treatment discontinuation censoring for death, CMAD, HT and access to commercial tafamidis – ATTR-ACT LTE, August 2021 data cut | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant.

**Table 17. Tafamidis discontinuation generalised Gamma relative survival model parameters used in company base case**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| μ | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| σ | [redacted] | | Y |
| Q | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 18. Tafamidis discontinuation log-logistic relative survival model parameters used in scenario analysis (scenario 1 in CS – tafamidis OS extrapolation)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| α | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| β | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 19. Tafamidis discontinuation log-normal relative survival model parameters used in scenario analysis (scenario 1 in CS – tafamidis OS extrapolation)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| μ | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| σ | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 20. Tafamidis discontinuation Weibull relative survival model parameters used in scenario analysis (scenario 1 in CS – tafamidis OS extrapolation)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| A | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| B | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 21. Tafamidis Gompertz relative survival model parameters used in scenario analysis (scenario 1 in CS – tafamidis OS extrapolation)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| μ | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg OS censoring for HT, CMAD – ATTR-ACT LTE, August 2021 data cut | Y |
| σ | [redacted] | | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

**Table 22. Tafamidis discontinuation exponential model parameter used in scenario analysis (scenario 8 in CS – no treatment in NYHAIV)**

| Parameter | Value | Source | Updated |
|---|---|---|---|
| Rate | [redacted] | Model fitted to tafamidis 80 mg / tafamidis free acid 61 mg time to treatment discontinuation censoring for death, CMAD, HT, NYHA IV, and access to commercial tafamidis – ATTR-ACT LTE, August 2021 data cut | Y |

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant, NYHA, New York Heart Association Functional Classification.

**Table 23. BSC mortality log hazard ratios used in company base case**

| Parameter | Mean | SE | Source | Updated |
|---|---|---|---|---|
| NYHA I ln(HR) | [redacted] | [redacted] | Cox model conditional upon time-varying NYHA status, ATTR-ACT placebo arm | N |
| NYHA II ln(HR) | [redacted] | [redacted] | | N |
| NYHA III ln(HR) | [redacted] | [redacted] | | N |
| NYHA IV ln(HR) | [redacted] | [redacted] | | N |

Abbreviations: NHYA: New York Heart Association functional classification. SE, standard error.

**Table 24. Tafamidis mortality log hazard ratios used in company base case**

| Parameter | Mean | SE | Source | Updated |
|---|---|---|---|---|
| NYHA I ln(HR) | [redacted] | [redacted] | Cox model conditional upon time-varying NYHA status, ATTR-ACT LTE tafamidis 80 mg / tafamidis free acid 61 mg arm | Y |
| NYHA II ln(HR) | [redacted] | [redacted] | | Y |
| NYHA III ln(HR) | [redacted] | [redacted] | | Y |
| NYHA IV ln(HR) | [redacted] | [redacted] | | Y |

Abbreviations: NHYA: New York Heart Association functional classification, SE, standard error.

**Table 25. BSC rates of CV-related hospitalisation used in company base case**

| Parameter | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Log rate (1/6 months) – NYHA I | [redacted] | [redacted] | Poisson model of CV-related hospitalisation events, ATTR-ACT placebo arm | N |
| Log rate (1/6 months) – NYHA II | [redacted] | [redacted] | | N |
| Log rate (1/6 months) – NYHA III | [redacted] | [redacted] | | N |
| Log rate (1/6 months) – NYHA IV | [redacted] | [redacted] | | N |

Abbreviations: CV, cardiovascular, SE, standard error.

**Table 26.Tafamidis rates of CV-related hospitalisation used in company base case**

| Parameter | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Log rate (1/6 months) – NYHA I | [redacted] | [redacted] | Poisson model of CV-related hospitalisation events, ATTR-ACT tafamidis arms | N |
| Log rate (1/6 months) – NYHA II | [redacted] | [redacted] | | N |
| Log rate (1/6 months) – NYHA III | [redacted] | [redacted] | | N |
| Log rate (1/6 months) – NYHA IV | [redacted] | [redacted] | | N |

Abbreviations: CV, cardiovascular, SE, standard error.

**Table 27. BSC adverse event rates used in company base case**

| Adverse event | Incidence | SE | Source | Updated |
|---|---|---|---|---|
| Diarrhoea | [redacted] | [redacted] | Incidence of treatment related adverse events, ATTR-ACT placebo arm | N |
| Nausea | [redacted] | [redacted] | | N |
| UTI | [redacted] | [redacted] | | N |

Abbreviations: UTI, urinary tract infection, SE, standard error.

**Table 28. Tafamidis adverse event rates used company in base case**

| Adverse event | Incidence | SE | Source | Updated |
|---|---|---|---|---|
| Diarrhoea | [redacted] | [redacted] | Incidence of treatment related adverse events, ATTR-ACT tafamidis arms | N |
| Nausea | [redacted] | [redacted] | | N |
| UTI | [redacted] | [redacted] | | N |

Abbreviations: UTI, urinary tract infection, SE, standard error.

**Table 29. BSC direct treatment costs used in company base case**

| Cost component | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Concomitant medications | [redacted] | [redacted] | eMIT 21/22[29] | Y |

Abbreviations: eMIT, Drugs and pharmaceutical electronic market information tool; SE, standard error.

**Table 30. Tafamidis direct treatment costs used in company base case**

| Cost component | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Drug acquisition (PAS inclusive) | [redacted] | [redacted] | Pfizer | Y |
| Administration | [redacted] | [redacted] | | N |
| Concomitant medications | [redacted] | [redacted] | eMIT 21/22[29] | Y |
| Concomitant medications | [redacted] | [redacted] | eMIT 21/22[29] | Y |

Abbreviations: eMIT, Drugs and pharmaceutical electronic market information tool; SE, standard error.

**Table 31. Tafamidis adherence rate used in company base case**

| Adherence | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Percentage of patients | [redacted] | [redacted] | | N |
| Percentage doses missed | [redacted] | [redacted] | Relative dose intensity, ATTR-ACT tafamidis arms | N |

Abbreviations: SE, standard error.

**Table 32. Health state monthly resource use (NYHA I) used in company base case**

| Resource | Mean | SE | Source | Updated |
|---|---|---|---|---|
| ECG | [redacted] | [redacted] | Guy's and St Thomas' NHS Foundation trust chart review | N |
| Cardiologist visit - Initial | [redacted] | [redacted] | | N |
| Cardiologist visit - Follow-up | [redacted] | [redacted] | | N |
| Community nurse | [redacted] | [redacted] | | N |

Abbreviations: ECG, SE, standard error.

**Table 33. Health state monthly resource use (NYHA II-IV) used in company base case**

| Resource | Mean | SE | Source | Updated |
|---|---|---|---|---|
| ECG | [redacted] | [redacted] | Guy's and St Thomas' NHS Foundation trust chart review | N |
| Cardiologist visit - Initial | [redacted] | [redacted] | | N |
| Cardiologist visit - Follow-up | [redacted] | [redacted] | | N |
| Community nurse | [redacted] | [redacted] | | N |

Abbreviations: ECG, electrocardiogram; SE, standard error.

**Table 34. Health state resource unit costs used in company base case**

| Resource | Mean | SE | Source | Updated |
|---|---|---|---|---|
| ECG | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |
| Cardiologist visit - Initial | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |
| Cardiologist visit - Follow-up | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |
| Community nurse | [redacted] | [redacted] | PSSRU 21/22[31] | Y |

Abbreviations: ECG, electrocardiogram; SE, standard error.

**Table 35. Adverse event costs used in company base case**

| Adverse event | Mean | SE | Source | Updated |
|---|---|---|---|---|
| Diarrhoea | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |
| Nausea | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |
| UTI | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |
| **CV hospitalisations** | | | | |
| CV-related hospitalisation | [redacted] | [redacted] | NHS ref costs 21/22[30] | Y |

Abbreviations: ECG, electrocardiogram; SE, standard error

**Table 36. Costs incurred at end of life used in company base case**

| Cost component | Mean | SE | Source | Updated |
|---|---|---|---|---|
| End of life care | [redacted] | [redacted] | Hollingworth et al., 2016[18] inflated using PSSRU inflation index[31] | Y |

Abbreviations: SE, standard error

**Table 37. BSC health state utilities used in company base case**

| Health state | Mean | SE | Source | Updated |
|---|---|---|---|---|
| NYHA I | [redacted] | [redacted] | EQ-5D-3L with Dolan TTO valuation, SE corrected for autocorrelation using Prais-Winsten estimator – ATTR-ACT placebo arm | N |
| NYHA II | [redacted] | [redacted] | | N |
| NYHA III | [redacted] | [redacted] | | N |
| NYHA IV | [redacted] | [redacted] | | N |

Abbreviations: SE, standard error; TTO, time trade-off.

**Table 38. Tafamidis health state utilities used in company base case**

| Health state | Mean | SE | Source | Updated |
|---|---|---|---|---|
| NYHA I | [redacted] | [redacted] | EQ-5D-3L with Dolan TTO valuation, SE corrected for autocorrelation using Prais-Winsten estimator – ATTR-ACT tafamidis arm | N |
| NYHA II | [redacted] | [redacted] | | N |
| NYHA III | [redacted] | [redacted] | | N |
| NYHA IV (on treatment) | [redacted] | [redacted] | | N |

Abbreviations: SE, standard error; TTO, time trade-off.

**Table 39. General population life tables used in company base case**

| Age | Male | Female | Source | Updated |
|---|---|---|---|---|
| 0 | 0.004244 | 0.003519 | Office for National Statistics. National life tables: England (2018-20)[32] | Y |
| 1 | 0.000231 | 0.000211 | | |
| 2 | 0.000128 | 0.000113 | | |
| 3 | 0.000099 | 0.000093 | | |
| 4 | 0.000090 | 0.000061 | | |
| 5 | 0.000077 | 0.000079 | | |
| 6 | 0.000081 | 0.000069 | | |
| 7 | 0.000068 | 0.000051 | | |
| 8 | 0.000065 | 0.000053 | | |
| 9 | 0.000062 | 0.000056 | | |
| 10 | 0.000073 | 0.000065 | | |
| 11 | 0.000074 | 0.000056 | | |
| 12 | 0.000102 | 0.000054 | | |
| 13 | 0.000116 | 0.000088 | | |
| 14 | 0.000124 | 0.000094 | | |
| 15 | 0.000169 | 0.000102 | | |
| 16 | 0.000190 | 0.000129 | | |
| 17 | 0.000284 | 0.000157 | | |
| 18 | 0.000373 | 0.000205 | | |
| 19 | 0.000415 | 0.000202 | | |
| 20 | 0.000524 | 0.000177 | | |
| 21 | 0.000473 | 0.000195 | | |
| 22 | 0.000463 | 0.000232 | | |
| 23 | 0.000478 | 0.000200 | | |
| 24 | 0.000514 | 0.000215 | | |
| 25 | 0.000540 | 0.000251 | | |
| 26 | 0.000567 | 0.000253 | | |
| 27 | 0.000585 | 0.000290 | | |
| 28 | 0.000629 | 0.000299 | | |
| 29 | 0.000657 | 0.000318 | | |
| 30 | 0.000730 | 0.000374 | | |
| 31 | 0.000778 | 0.000366 | | |
| 32 | 0.000775 | 0.000437 | | |
| 33 | 0.000888 | 0.000472 | | |
| 34 | 0.000917 | 0.000549 | | |
| 35 | 0.000990 | 0.000560 | | |
| 36 | 0.001043 | 0.000625 | | |
| 37 | 0.001257 | 0.000724 | | |
| 38 | 0.001230 | 0.000757 | | |
| 39 | 0.001359 | 0.000791 | | |
| 40 | 0.001486 | 0.000849 | | |
| 41 | 0.001576 | 0.000943 | | |
| 42 | 0.001718 | 0.001058 | | |

| Age | Male | Female | Source | Updated |
|---|---|---|---|---|
| 43 | 0.001878 | 0.001149 | | |
| 44 | 0.002074 | 0.001300 | | |
| 45 | 0.002307 | 0.001417 | | |
| 46 | 0.002440 | 0.001532 | | |
| 47 | 0.002638 | 0.001667 | | |
| 48 | 0.002836 | 0.001894 | | |
| 49 | 0.003145 | 0.001988 | | |
| 50 | 0.003424 | 0.002155 | | |
| 51 | 0.003691 | 0.002379 | | |
| 52 | 0.003920 | 0.002506 | | |
| 53 | 0.004277 | 0.002682 | | |
| 54 | 0.004579 | 0.002836 | | |
| 55 | 0.004888 | 0.003158 | | |
| 56 | 0.005426 | 0.003517 | | |
| 57 | 0.005882 | 0.003783 | | |
| 58 | 0.006523 | 0.004210 | | |
| 59 | 0.007035 | 0.004482 | | |
| 60 | 0.007698 | 0.005043 | | |
| 61 | 0.008354 | 0.005424 | | |
| 62 | 0.009328 | 0.006235 | | |
| 63 | 0.010187 | 0.006627 | | |
| 64 | 0.010952 | 0.007091 | | |
| 65 | 0.012212 | 0.007802 | | |
| 66 | 0.013476 | 0.008460 | | |
| 67 | 0.014450 | 0.009197 | | |
| 68 | 0.016038 | 0.010337 | | |
| 69 | 0.017609 | 0.010981 | | |
| 70 | 0.018771 | 0.012445 | | |
| 71 | 0.020325 | 0.013209 | | |
| 72 | 0.022155 | 0.014992 | | |
| 73 | 0.025341 | 0.016776 | | |
| 74 | 0.027949 | 0.019080 | | |
| 75 | 0.031470 | 0.020998 | | |
| 76 | 0.035003 | 0.023674 | | |
| 77 | 0.039289 | 0.027191 | | |
| 78 | 0.044240 | 0.030486 | | |
| 79 | 0.049105 | 0.034883 | | |
| 80 | 0.055031 | 0.038718 | | |
| 81 | 0.061031 | 0.043823 | | |
| 82 | 0.067994 | 0.049164 | | |
| 83 | 0.075946 | 0.056024 | | |
| 84 | 0.085848 | 0.063838 | | |
| 85 | 0.096293 | 0.072610 | | |
| 86 | 0.109147 | 0.083158 | | |
| 87 | 0.121649 | 0.094540 | | |

| Age | Male | Female | Source | Updated |
|---|---|---|---|---|
| 88 | 0.136498 | 0.106614 | | |
| 89 | 0.153243 | 0.120013 | | |
| 90 | 0.162051 | 0.134717 | | |
| 91 | 0.181591 | 0.151716 | | |
| 92 | 0.198647 | 0.169583 | | |
| 93 | 0.222409 | 0.188218 | | |
| 94 | 0.244193 | 0.205915 | | |
| 95 | 0.269641 | 0.228175 | | |
| 96 | 0.292512 | 0.251732 | | |
| 97 | 0.314221 | 0.277129 | | |
| 98 | 0.335243 | 0.298496 | | |
| 99 | 0.375447 | 0.319343 | | |
| 100 | 0.397366 | 0.348823 | | |
| 101 | 1.000000 | 1.000000 | | |

c)

d) Table ***40*** provides a list of all model assumptions underlying the current version of the economic model and the company base case. The model assumptions used in the company base case incorporate the committees' preferred assumptions from TA696[2], with exceptions due to the removal of the assumption that patients discontinue therapy in NYHA IV and the use of ATTR-ACT LTE data (August 2021) for tafamidis OS and TTD extrapolation.

**Table 40. List of assumptions used in the economic model with justifications**

| Assumption/ decision | Submission Section | Rationale/justification and source | Alignment with previous committee preferred assumptions (Yes/ New data) |
|---|---|---|---|
| ***Model structure/techniques*** | | | |
| *NHYA IV treatment:* Removal of NYHA IV stopping rule from economic base case | Section 4 in ID6327 Evidence Submission Document | A NYHA IV stopping rule has not been included in new economic base case.<br>Insights from EAMS show that clinicians would not explicitly always stop treatment due to progression to NYHA IV but on balance we expect patients to discontinue treatment shortly after reaching NYHA IV due to poor prognosis associated with severe heart failure. Therefore, the economic new base case where treatment is continued in NYHA IV may represent a slight overestimation, thus a scenario where no treatment is used beyond progression is utilised to demonstrate the potential impact of this assumption – refer to Section 8.1.3 in the current CS.<br>Refer to Appendix E in the current CS for extrapolation parameters used. | Yes |
| *BSC extrapolation*: BSC OS extrapolation using Weibull parametric distribution function | Section 7.3 in ID6327 Evidence Submission Document | In TA696[2], the committee preferred Weibull distribution be used to extrapolate BSC OS beyond observed ATTR-ACT trial period. Considering no new data on BSC OS from ATTR-ACT LTE, Weibull was used to extrapolate BSC OS in the new economic base case. | Yes |

| | | | |
|---|---|---|---|
| *Tafamidis extrapolation*: Tafamidis OS extrapolation using generalised Gamma parametric distribution function | Section 7.2 in ID6327 Evidence Submission Document | Generalised gamma distribution displayed best fit for new tafamidis OS data from ATTR-ACT LTE (Figure 5 in the current CS).<br>Scenario analysis exploring alternative distributions for tafamidis OS extrapolation presented in Section 8.1.3 in the current CS. | New data |
| *TTD extrapolation*: Tafamidis TTD discontinuation extrapolation using exponential parametric distribution function | Section 7.5 in ID6327 Evidence Submission Document | Given the low AIC, BIC and degeneration of multi-parameter models to the exponential form, for reasons of parsimony there is no compelling reason to use an alternative assumption to the exponential distribution in order to model time to treatment discontinuation; therefore, exponential distribution has been used in the new base case.<br>Scenario analysis exploring alternative distributions for TTD extrapolation presented in Section 8.1.3 in the current CS. | New data |
| *NYHA transition probabilities*: A singular transition matrix is employed for the entirety of the extrapolation phase. | Section B.3.3.3 in TA696[2] Document B | Data from ATTR-ACT provides observations on patients' NYHA class status at 6-month intervals, allowing for the derivation of within-trial period specific NYHA transition matrices. In the absence of data to inform transitions during the extrapolation phase, a singular transition matrix is assumed, with rates informed by all transitions observed within each arm during the within-trial phase. | Yes |
| ***Utility*** | | | |

| | | | |
|---|---|---|---|
| *Health state utilities*: Applied health state utility profiles are assumed to be treatment-specific, except in NYHA IV | Section B.3.4.5 in TA696[2] Document B | Treatment-specific utility data from ATTR-ACT were applied as the values may reflect some of the differences in HRQoL between placebo and tafamidis associated with hospitalisation and adverse events. However, given that EQ-5D was only measured at 6 monthly intervals, the HRQoL benefits of tafamidis through reduced hospitalisations and improved safety profile are not fully captured. | Yes |
| *Adverse event utility decrements*: Adverse event utility decrements not explicitly modelled. | Section B.3.4.4 in TA696[2] Document B | The EQ-5D data used to inform the NYHA-specific utility values may implicitly capture patients who were suffering an AE, so that additional application of AE-related disutility could result in double counting. | Yes |
| ***Costs and resource use*** | | | |
| *Early diagnosis cost-savings*: No cost-savings incurred from early diagnosis | Section 4 in ID6327 Evidence Submission Document | Costs savings associated with early diagnosis have been excluded from the new economic base case as per the committee's preference during TA696[2]. Scenario analysis exploring the inclusion of early diagnosis cost savings is presented in Section 8.1.3 in the current CS to demonstrate potential impact of this assumption. | Yes |
| *Treatment-related costs on discontinuation*: On discontinuation of tafamidis, patients are assumed to incur no further treatment-related costs. | Section B.3.5.2 in TA696[2] Document B | Data on treatments received post-discontinuation of tafamidis are not available from ATTR-ACT and ATTR-ACT LTE and, hence, it is assumed that patients who discontinue tafamidis incur no further treatment-related costs. This is in line with clinical expert opinion, which suggested that patients discontinuing tafamidis would not be fit enough to receive additional therapies for symptom management, which may be over-represented in the basket of therapies comprising BSC. | Yes |

| | | | |
|---|---|---|---|
| *Treatment discontinuation*: Patients treated with BSC (placebo arm) are assumed to remain on-treatment until death or the model horizon has elapsed. | Section B.3.5.5 in I TA696[2] Document B | BSC, comprised of symptomatic heart failure treatment, represents the only relevant treatment option for ATTR-CM patients (i.e., excluding tafamidis, no alternative pharmacological therapies exist) and is assumed to encompass all therapies patients may receive until death. | Yes |
| *Cost of adverse events*: The cost of adverse events are applied as a one-off cost at the start of treatment | Section B.3.5.5 in TA696[2] Document B | Cost of adverse events: The cost of adverse events are applied as a one-off cost at the start of treatment. | Yes |

Abbreviations: BSC: Best Supportive Care; CS, current submission; HRQoL: health related quality of life; NYHA: New York Heart Association Functional Classification; OS: overall survival; TRAE: treatment-related adverse events; TTD: time to treatment discontinuation.

d) We confirm all input parameters were updated with the latest evidence from the ATTR-ACT LTE, whenever applicable. Tafamidis OS and TTD model parameters have been updated using data from the ATTR-ACT LTE (August 2021). Further follow-up of patients in ATTR-ACT LTE is highly confounded by access to commercial tafamidis, and so this is the final data cut where reliable outcomes were captured. Updates to the NYHA transition matrices are not available from this data cut as this data was not collect during the ATTR-ACT LTE.

### *Population*

B2. In relation to question A12 regarding a subgroup analysis for hereditary versus wildtype ATTR-CM: If applicable, provide an updated economic model including additional scenario analyses in these subgroups.

The ATTR-ACT LTE was not powered to inform a genotype subgroup analysis. In Section 3.11 of the FAD in TA696[2] the committee accepted the company's point about a lack of statistical power in the subgroup analyses, recognising that ATTR-ACT was powered on the primary outcome measure. Long-term follow up data which has been published since TA696[2] validates previous observations in hazard ratios between genotype subgroups presented in TA696[2].[15] Please refer to the response to question A12 for further information.

## *Intervention and comparators*

**B3. Priority question. Relating to question A1 regarding the request for an updated SLR.**

a) **Please provide an updated economic model and analyses including patisiran, inotersen, and vutrisiran as comparators for tafamidis in the mixed phenotype transthyretin amyloidosis population.**

b) **If deemed relevant, please provide an updated economic model and analyses including patisiran, inotersen, and vutrisiran as comparators for tafamidis for the whole transthyretin amyloidosis population.**

As mentioned in the response to A1, we do not consider patisiran, inotersen, and vutrisiran appropriate comparators to tafamidis in the ATTR-CM population.

B4. The NICE scope lists diflunisal as one of the concomitant treatments in established clinical management.

a) Please elaborate on why diflunisal was not considered as part of best supportive care.

b) Please provide an updated economic model and analysis including diflunisal as part of best supportive care.

a) Diflunisal is not licensed for the treatment of ATTR-CM.[33] To our knowledge, there are currently no randomised clinical trials (RCTs) investigating diflunisal in ATTR-CM. As per the comment on the NICE Final Scope; "The National amyloidosis centre at the Royal Free NHS FT also use an unlicensed treatment, diflunisal for patients in the latter stages of the disease." Whereas tafamidis is initiated in patients at NYHA class I to III.

From anecdotal evidence, the company understand that diflunisal may have been prescribed in the past for ATTR-CM patients given the lack of any other treatments available for ATTR-CM. However, patients diagnosed more recently with ATTR-CM are no longer initiated on diflunisal given that the drug is poorly tolerated, due to the negative side effect profile (typically associated with nonsteroidal anti-inflammatory drugs).[22]

For the above reasons, diflunisal was not considered a relevant comparator.

b) Given the above response, it was not considered appropriate to include diflunisal into BSC. However, we would have also been unable to apply this change due to a UK price being unavailable for diflunisal across eMIT, BNF, and NHS databases. ***Note***: NHS website specifically stated “no price priced when manufactured” for diflunisal 250mg tablets.[34]

## *Treatment effectiveness and extrapolation*

**B5. Priority question. The estimation of parametric survival models seems inconsistent with reported guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses. Please provide, for overall survival (OS) and time to treatment discontinuation (TTD) separately for tafamidis and BSC:**

a) **Tables with the numbers of patients at risk, per 3 months.**

b) **To examine the proportional hazard assumption:**

    i. **Plot the scaled Schoenfeld residuals versus time (all survival curves)**

    ii. **Plot the log cumulative hazard versus log time**

c) **To examine the heuristics of the hazard function over time:**

    i. **Plot the smoothed hazards over time**

d) **To examine diagnostics of parametric survival models (using the observed data):**

    i. **Plot the cumulative hazard versus time**

    ii. **Plot the log smoothed hazard versus time**

    iii. **Plot the standard normal quartiles versus log time**

    iv. **Plot the log survival odds versus log time**

e) **Please justify the selection of the approaches to estimate and extrapolate OS and TTD, taking into account the responses to the**

**preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.**

f) **As recommended in NICE DSU TSD 14, please provide "substantial justification" in case different types of parametric models are used for different treatment arms.**

g) **In page 29 of the CS, it is stated that "a similar approach" to the one from Document B from TA696 was used in this submission for the parametric extrapolation of overall survival. Please clarify the differences between the approach from TA696 and this submission.**

a) The number of patients at risk for OS and time to treatment discontinuation, with censoring for death, heart transplant, implantation of CMAD and access to commercial tafamidis, is provided in Table 41.

**Table 41. The numbers of patients at risk, per 3 months, OS and TTD – ATTR-ACT LTE (August 2021)**

| | | Number at risk at month: | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Month: | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 | 63 | 66 | 69 | 72 | 75 | 78 | 81 | 84 |
| **OS*** | Tafamidis 80 mg/Tafamidis 80 mg/Tafamidis acid free | 176 | 172 | 170 | 164 | 155 | 148 | 144 | 139 | 132 | 128 | 117 | 107 | 104 | 99 | 95 | 91 | 85 | 79 | 72 | 59 | 52 | 41 | 33 | 29 | 27 | 18 | 13 | 6 | 1 |
| | Placebo/tafamidis | 177 | 173 | 171 | 163 | 161 | 150 | 141 | 131 | 118 | 113 | 92 | 76 | 69 | 61 | 57 | 54 | 51 | 45 | 36 | 32 | 27 | 22 | 15 | 8 | 8 | 4 | 1 | 0 | 0 |
| **TTD**** | Tafamidis 80 mg/Tafamidis 80 mg/Tafamidis acid free | 176 | 170 | 165 | 159 | 145 | 139 | 133 | 123 | 120 | 118 | 113 | 107 | 104 | 98 | 95 | 91 | 84 | 78 | 71 | 59 | 51 | 41 | 32 | 27 | 27 | 18 | 13 | 6 | 1 |
| | Placebo/tafamidis | Undefined | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

* Censoring for heart transplant, implantation of cardiac mechanical assist device.

** Time to treatment discontinuation censoring for death, heart transplant, implantation of cardiac mechanical assist device, access to commercial tafamidis.

b) A scaled Schoenfeld residual plot for the treatment covariate in a univariate Cox model of OS based upon the ATTR-ACT LTE data (August 2021) is provided in Figure 1. It demonstrates an increasing treatment effect for tafamidis (decreasing hazard ratio) despite cross-over of placebo patients onto active treatment. A Grambsch-Therneau test upon the residuals gives a p-value of 0.031 that the treatment effect is constant, rejecting the null hypothesis of constant hazard ratio at an α of 0.05.

**Figure 1. Scaled Schoenfeld residuals for univariate Cox model upon OS censoring for HT, CMAD - tafamidis 80 mg / tafamidis free-acid 61 mg vs placebo/tafamidis – ATTR-ACT LTE (August 2021)**

Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; OS, overall survival.

Schoenfeld residuals are not available for time to treatment discontinuation as this outcome is undefined for the placebo/tafamidis arm.

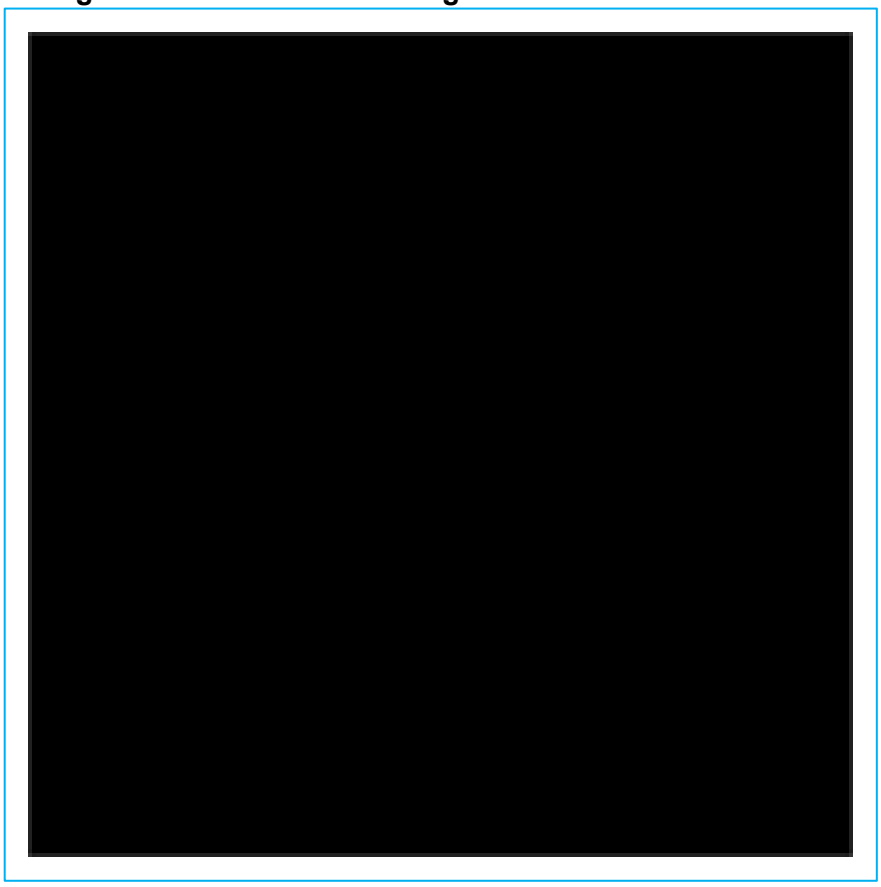
Log cumulative hazard plots in Figure 2 in Appendix L of TA696[2] Document B, demonstrated clear violation of the proportional hazards assumption and therefore, individual parametric models were fitted for each treatment.

Figure 7 within the current CS shows two non-parametric estimators for hazard of mortality (censoring for heart transplant and CMAD) within the

tafamidis 80 mg in ATTR-ACT crossover to tafamidis free acid 61mg in ATTR-ACT LTE population. As discussed there, the overall hazard plateau rises to a maximum over the first two years, and from that point, it is likely that hazards begin to decline. Relative to general population mortality rates, which increase rapidly due to the age of the population, the excess hazard is observed to decline even faster.

Figure **2** shows smoothed hazards for discontinuation (censoring for death, HT, CMAD and access to commercial tafamidis). The hazards due to lifetable mortality for this outcome acts only as a scale reference, as it does not act as a plausible floor for the hazard and models for this outcome are not relative to general population mortality. There is no consistent trend between the hazard smoothers, and an assumption of constant hazard is plausible.

**Figure 2. Hazards of discontinuation censoring for death, HT, CMAD and access to commercial tafamidis - ATTR-ACT LTE (August 2021) – Tafamidis 80 mg /tafamidis free acid 61 mg**



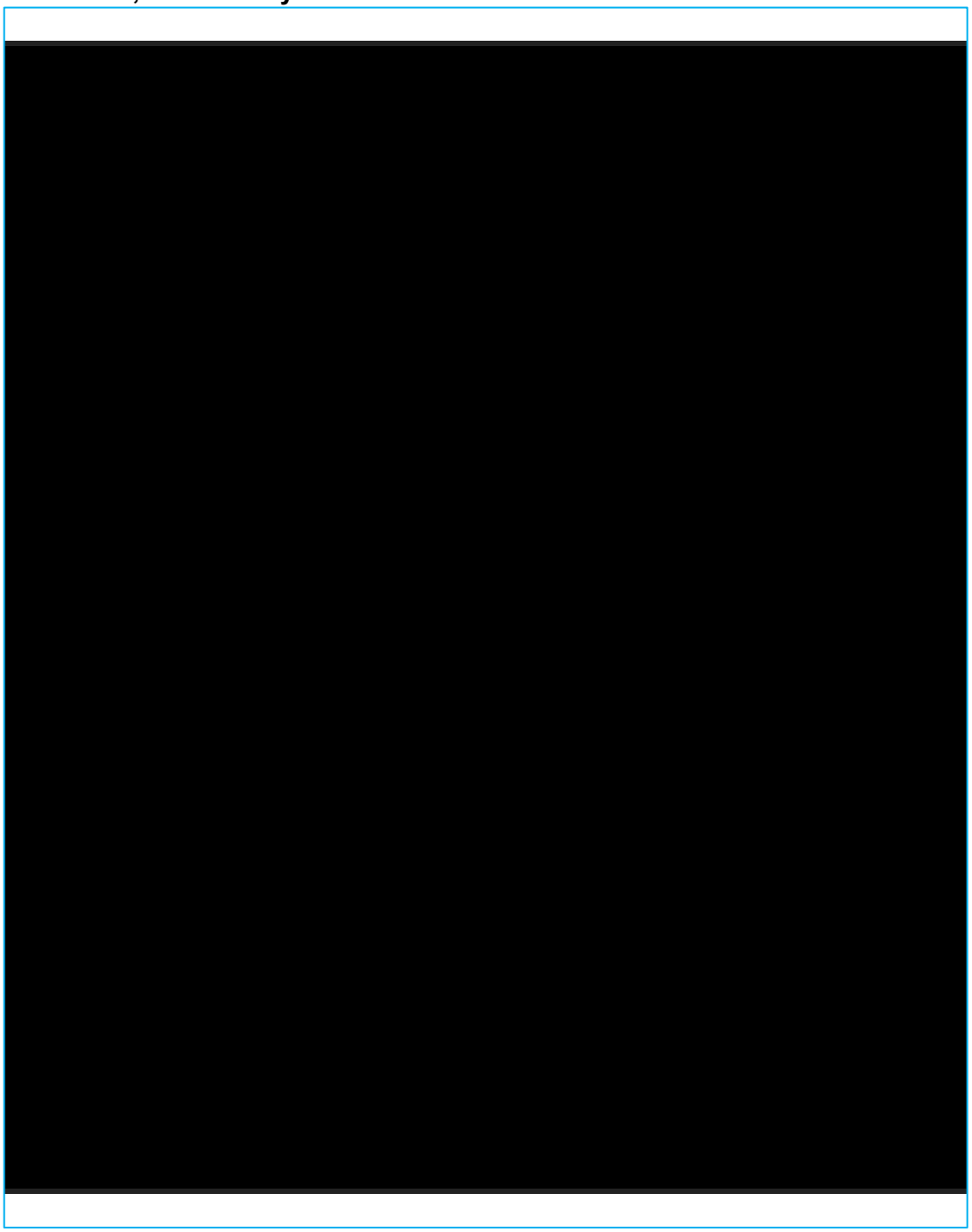
Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant; KM, Kaplan-Meier; OS, overall survival.

d) Figure 3 shows the requested transformations of the survival estimates for OS. The hazards shown are piecewise constant based upon the Kaplan-Meier estimator as an alternative method of smoothing complementary to the ones presented in the response to part c). The interpretation of these plots for tafamidis is academic as the baseline hazard informs a substantial fraction of the total hazard, and these transformations are inappropriate for assessing the forms of relative survival models.

For placebo, as the disease-specific hazard dominates, one may tentatively interpret the data as being consistent with a Weibull model, due to multiple cross-over. The log-logistic model appears to show high divergence at the tail, which is distorted by the log transformation to have low visual importance, but back-transformed to survival space would show a substantial difference. The same applies to log-normal, but the direction of divergence is transposed due to the axis set-up on this plot. The Gompertz transform is on an identity time transform and clearly shows a reduction in the rate of increase of hazard after 30 months, and following a Gompertz gradient based upon the first 30 months only would overestimate hazard beyond 60 months, but it should be considered that this data is confounded by cross-over.

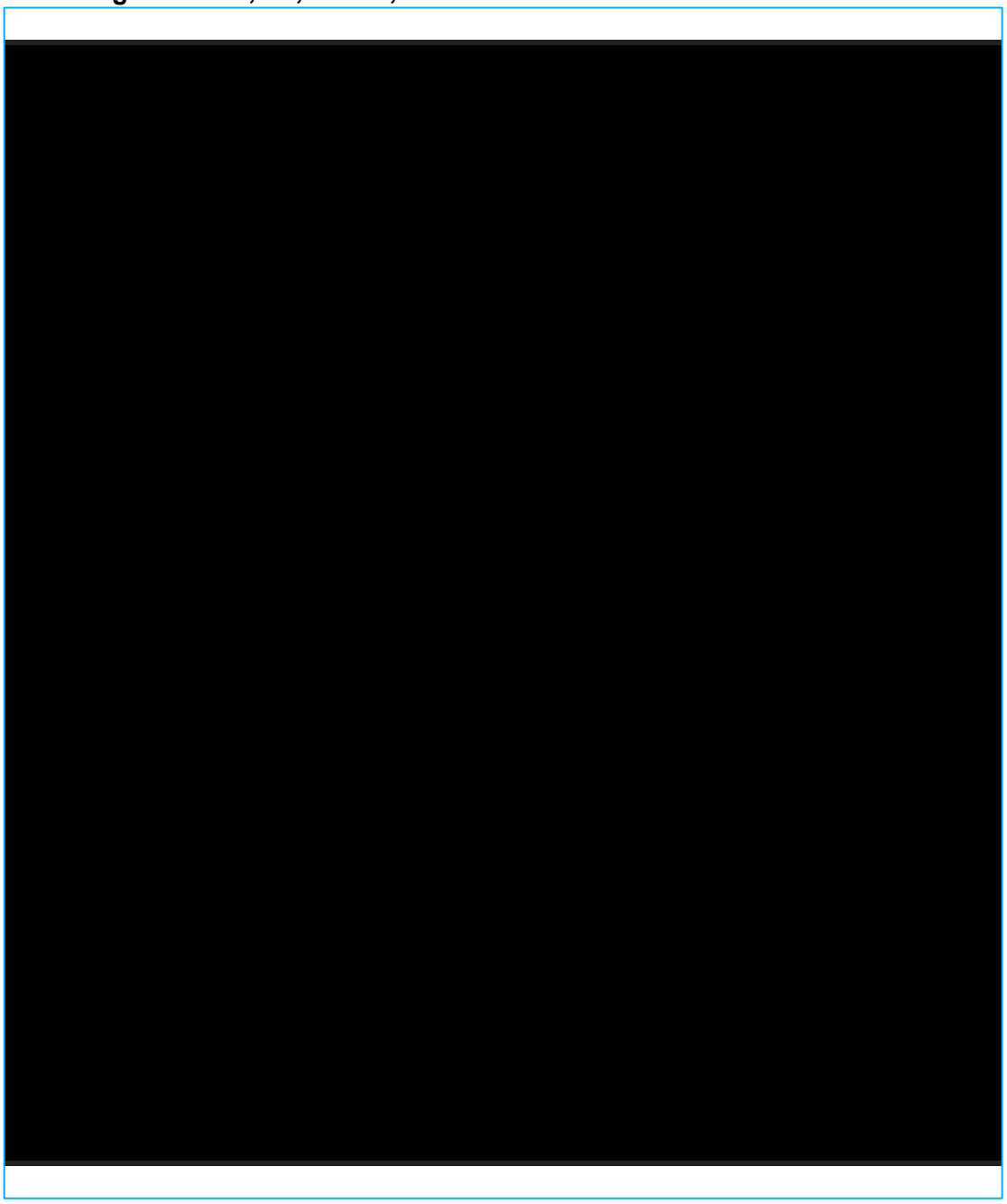
Figure 4 shows the same transformations for discontinuation (censoring for death, heart transplant, CMAD, access to commercial tafamidis). Multiple crossings are seen in panel (b), transforming for the exponential model, supporting the use of a constant hazard model to represent these data. The least-squares line for panel (d) is strongly influenced by the final window for hazard, and consideration of the full profile is not inconsistent with constant hazards. The log-normal transform shows a classically “bowed” shape over the least squares regression line, suggesting an over-under-over estimation pattern using a lognormal model. The log-logistic model does show multiple crossings, and from this plot it would be considered further as a candidate model.

**Figure 3. Transformations of survival curves, overall survival censoring for HT and CMAD, stratified by ATTR-ACT randomisation arm**



Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant.

**Figure 4. Transformations of survival curves, time to treatment discontinuation censoring for death, HT, CMAD, access to commercial tafamidis**



Abbreviations: CMAD, cardiac mechanical assist device; HT, heart transplant.

e) In addition to the guidance provided in TSD 14, the NICE DSU also provided guidance for survival modelling in TSD 21. This guidance was produced during the assessment period of TA696[2] , and provided an independent suggestion to incorporate external data into survival modelling. One of the methods suggested in TSD 21 was the use of the "Excess mortality / cause-specific mortality (relative survival)" model, which was the method adopted in TA696[2] and in the current submission ID6327. "General recommendation" III of TSD 21

is the incorporation of background mortality, with the suggestion that "Background mortality rates should either be incorporated when making the extrapolation, or used as a sense-check when plotting the marginal survival". The former suggestion was used for modelling of OS in TA696[2] and in the current submission ID6327, due to the relatively high rate of background mortality in the elderly population of the ATTR-ACT trial and the impact this was expected to have on the long-term hazard projection, which may not have been detectable within the relatively short timeframe of the ATTR-ACT trial. It was undesirable to use a parametric all-cause mortality model that would have to be post-hoc modified due to intercept of hazards with those of the matched general population. This would imply the breakdown of model assumptions at some intervening point and may have removed some parametric representations of the hazard profile from consideration due to "implausibility", simply because the models did not have information about the Gompertz-law increase in hazard expected in extrapolation from within the trial period.

By using a relative hazard profile, models that incorporated a medium-term constancy or decrease in total hazard consistent with the observed trial data would not be rejected due to "implausibility" of hazards being predicted lower than the general population due to being structurally constrained to this minimum hazard value.

As a result of the above considerations, the "Survival Model Selection Process Algorithm" from TSD 14 was slightly modified for model selection for this submission, as described below:

- Compare log-cumulative hazard plots, quantile-quantile plots or suitable residual plots to allow initial selection of appropriate models
    - This suggestion is only strictly valid for models following the simple parametric forms. In a relative survival context, the baseline hazard would be expected to distort each plot; for instance, if it is assumed that excess hazard is in proportional hazards, the ability of the Schoenfeld residuals to detect failure of the proportional hazards assumption is compromised as the baseline hazard

component of each are is assumed to be the same, and so the observed hazard as the sum of these two components would no longer be proportional. This component of the algorithm is discussed in responses to parts b) and d).

- "Plots are not straight lines" / "Plots are not parallel" / "Plots are parallel"
    - As described above, these assessments only strictly apply in an all-cause survival modelling framework, as the assessments are distorted by the presence of a baseline hazard. However, the decision was made to fit individual models per arm for OS, supported by the observation of overlying/diverging survival rates which precluded the use of simple scaling rules (proportional hazards; accelerated failure time) and clear differences in the smoothed hazard profile (see response to part c)
- Compare model fits to select the most appropriate model taking into account the completeness of the survival data:
    - Visual inspection
    - External data
    - Clinical validity
    - AIC
    - BIC
    - Log-cumulative hazard plots
    - Other suitable tests of internal and external validity
    - Consider duration of treatment effect

Considerations for BSC OS remain as discussed in Document B of TA696[2]:

- Similar visual fits except exponential.

- Only external data from Lane et al.,[35] but comparison inappropriate due to potential for significant lead time bias due to time from diagnosis to study entry on ATTR-ACT.
- Discussions with clinicians agreed with the selection of Weibull or Gompertz as most appropriate distributions.
- Only small difference in AIC and BIC between models, with Weibull lowest on both measures.
- Log cumulative hazard plots not relevant for assessment of independent models.
- Plausibility of model enforced by relative modelling framework.
- Not a relative model, no treatment effect to consider.

Considerations for tafamidis OS:

- Visual fit is described in the Section 7.2 of the current CS. “over much of current follow-up the generalised Gamma model predicts closest to the contemporary value of the KM estimate.”
- External data – no longer-term external data for equivalent patients with ATTR-CM treated with tafamidis are available. Data from the long-term extension of the Phase II study are of lower follow-up than in the ATTR-ACT LTE and differ in population characteristics, particularly in proportion NYHA I/II and genotype.
- AIC and BIC of the fitted parametric relative survival models spanned a small range (less than 3 units AIC, less than 6 units BIC) as shown in Figure 5 of the CS. The generalised Gamma showed lowest AIC whilst the exponential showed lowest BIC due to the heavier penalisation of number of degrees of freedom in the BIC.
- Log cumulative hazard plots are not relevant to this model type. A plot of the predicted hazards versus time for each model was

provided as Figure 6 of the CS. This demonstrated that only the generalised Gamma and lognormal models followed the peaking-falling hazard profile observed over ATTR-ACT/LTE, with the generalised Gamma being closest in profile.

- The plausibility of long-term extrapolations of these models are enforced by the relative survival framework.

Considerations for time to treatment discontinuation:

- Visual fit is shown in the current CS Document B ID6327, Figure 8. There is very little visible difference between the models over the available follow-up.
- No external data are available to validate the rate of discontinuation censoring for death, HT, CMAD or access to commercial tafamidis.
- AIC and BIC of the candidate models span a small range. The exponential model shows lowest AIC and BIC.
- Log cumulative hazard plots are not relevant to this model type.
- The degeneration of the Weibull (shape ~1) and Gompertz (rate ~ 0) to exponential form is consistent with the constant hazard assumption.
- No treatment effect is considered for this outcome.

- Choose the most suitable model based upon above analysis. Complete sensitivity analysis using alternative plausible survival models, and taking into account uncertainty in model parameter estimates.
  - As described in the CS, the Weibull model was chosen for BSC OS, consistent with the ERG's preferred base case in TA696[2]. The generalised Gamma model was chosen for tafamidis OS due to its agreement with the non-parametric hazard estimators. The exponential model was chosen for TTD by the principal of

parsimony and due to the degeneration of more complex model types to exponential form. Sensitivity analyses were undertaken using alternative survival models and parameter uncertainty was used to inform the distribution of survival model parameter samples in probabilistic sensitivity analysis.

This concludes the implementation of the NICE TSD14 model section algorithm.

f) The choice of different types of parametric models for different treatment arms is consistent with the EAG preferred base case for TA696[2]. The empirical hazard profiles for tafamidis OS and placebo OS are visibly different, with tafamidis showing a peaking-falling profile made more likely in a relative survival context, whilst placebo shows monotonically increasing hazards over the ATTR-ACT period.

g) The difference from TA696[2] Document B is primarily that follow-up from the August 2021 data cut of ATTR-ACT LTE was used to inform the model parameters, and so could not be used to verify extrapolations. Use of this extended data resulted in a switch from the two-parameter lognormal model to the three-parameter generalised Gamma model, in part due to the greater quantity of data supporting a more flexible model. Otherwise, the approach is equivalent.

**B6. Priority question. As per NICE DSU TSD 14, exponential, Weibull, Gompertz, log-logistic, log normal and Generalised Gamma parametric models should all be considered when performing survival analysis modelling. Please assess the suitability of said distributions by providing the following information for both tafamidis and BSC:**

**a) To examine the validity of the extrapolation of OS and TTD beyond the observed trial data, please provide supporting evidence that the extrapolations are consistent with relevant external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted. Please complete the following tables with the gathered information:**

a) The requested tables are completed below (Table 42 and Table 43). Considering the low discrepancy between results from the parametric distribution models and the trial data, an expert opinion was not deemed viable to validate the suitability of the distributions.

**Table 42. Modelled and observed rates of OS and TTD – Tafamidis 80 mg / Tafamidis free acid 61 mg, ATTR-ACT LTE August 2021**

| Tafamidis | Weibull | Log-normal | Log-logistic | Exponential | Gamma | Generalised gamma | Gompertz | Trial data |
|---|---|---|---|---|---|---|---|---|
| OS median (months) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS(%) 2 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS (%) 5 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS (%) 10 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD median (months)‡ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD (%) 2 years‡ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD (%) 5 years‡ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD (%) 10 years‡ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

†OS relative survival models fitted to ATTR-ACT LTE applied above a baseline of the ATTR-ACT population marginal hazard by matched lifetables, extrapolated using Ederer-I method.
‡Time to treatment discontinuation; censoring for death, HT, CMAD.
Gamma model not fitted to discontinuation censoring for death, heart transplant or CMAD.
Trial data from ATTR-ACT LTE August 2021 – follow-up to 10 years not available.

**Table 43. Modelled and observed rates of OS – Placebo / Tafamidis free acid 61 mg, ATTR-ACT LTE August 2021**

| BSC | Weibull | Log-normal | Log-logistic | Exponential | Gamma | Generalised gamma | Gompertz | Trial data |
|---|---|---|---|---|---|---|---|---|
| OS median (months) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS(%) 2 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS(%) 5 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS (%) 10 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

†OS relative survival models fitted to ATTR-ACT applied above a baseline of the ATTR-ACT population marginal hazard by matched lifetables, extrapolated using Ederer-I method.
‡Result after cross-over to tafamidis treatment

**b) Please justify the choice of the selected distributions based on relevant external data and/or expert opinion, as described above.**

b) ***Tafamidis OS extrapolation***:

As expected from data presented in the CS, when the Tafamidis OS models were fitted directly to the ATTR-ACT LTE data, prediction to the selected landmarks within follow-up is very good for most models, excepting the exponential. (Table 42). However, the excess hazard profile for this outcome, shown in Figure 6 in the CS, requires a peak of excess hazard in the near term and a reduction in the medium term, precluding models predicting constant or monotonically increasing hazards. In Section 7.2 in the CS, the generalised Gamma model showed the most rapid reduction in excess hazard, matching well the gradient of the observed hazard during the third year whilst peak hazard was higher than other models (Figure 6 in Section 7.2).[16]

The generalised Gamma model estimated the most similar proportion of surviving patients at both 2 and 5 years compared to trial data. The generalised Gamma also had the lowest AIC of candidate models; in the context of the 2 unit penalty term versus the log-normal model due to the additional fitted

parameter in the generalised Gamma model, the low AIC indicates highest log-likelihood by greater than 2 units.[16] This higher likelihood is visible in the overlay of the model predictions upon the KM estimator (Figure 5 in Section 7.2) where over much of current follow-up the generalised Gamma model predicts closest to the contemporary value of the KM estimate.

Considering the data in Table 42 as well as the data presented in Section 7.2 in the CS, we believe the generalised Gamma model is appropriate for OS modelling within the observed period and extrapolation beyond the observed period.

***Tafamidis TTD extrapolation***:

TTD models also validated well to observed follow-up, inclusive of the constant hazard model used in base case. Due to cross-over in the placebo arm, the observed data can only act as an upper bound of plausibility under the assumption of no effect due to tafamidis; the exponential model exceeds this boundary, but the log-logistic and lognormal model are also close at 5 years and are not supported by the observed hazard profile during the ATTR-ACT randomised period.

As mentioned in Section 7.5 in the CS, given the low AIC, BIC and degeneration of multi-parameter models to the exponential form, for reasons of parsimony there is no compelling reason to use an alternative assumption to the exponential distribution in order to model time to treatment discontinuation; therefore, exponential distribution has been used in the updated base case as per the EAG's preferred assumption in TA696[2].

The choice of parametric model for tafamidis TTD extrapolation was shown to have minor impact on the base case ICER ([redacted]% change) – refer to Table 15 in Section 8.1.3 in the CS.

***BSC OS extrapolation***

In the FAD for TA696[2], the committee preferred Weibull distribution be used to extrapolate BSC OS beyond observed ATTR-ACT trial period. Weibull was

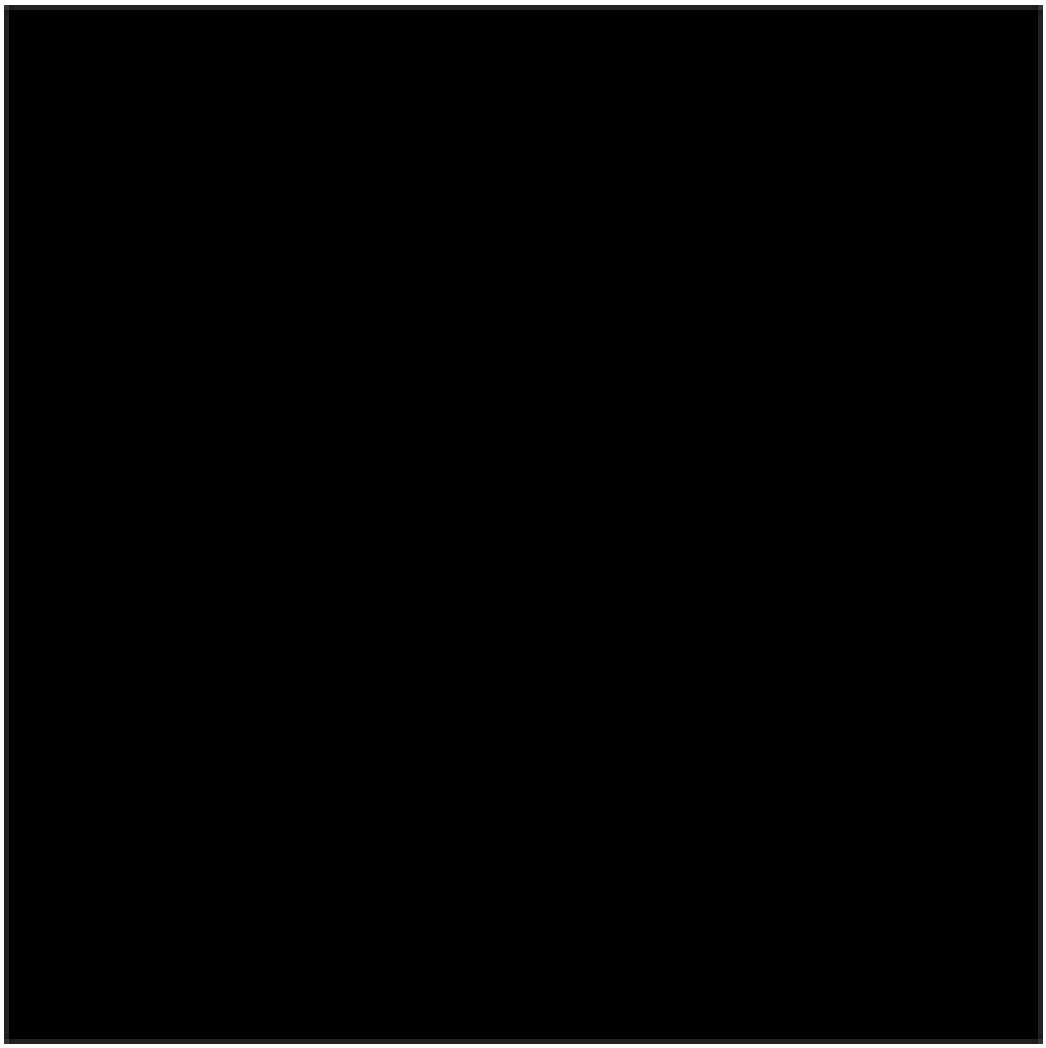
applied in the base-case analysis as it had one of the best statistical fits; it had a good visual fit to the observed data and the underlying hazard was aligned with KOL opinion gathered in ID1531 Document B (Figure 5).

In clarification questions for TA696[2] the EAG asked the company to justify selection of using Weibull for BSC OS extrapolation. The empirical hazard functions for OS were estimated using a kernel-smoothing function ("muhaz") in R with the default bandwidth setting algorithm (local optimisation around each grid point minimising local mean squared error) and default kernel shape (epanechnikov). Also plotted are the hazards from a spline smoother (single internal knot fitted to the log hazards with likelihood-optimised knot placement), and the marginal hazard of mortality from the matched lifetable population (Figure 6). The BSC arm showed the clinically expected monotonically increasing absolute and relative hazards of death that could be considered almost linear over the ATTR-ACT time horizon; and therefore, a Weibull excess hazard model was appropriate.

Considering no new data was available for the placebo arm as all placebo patients transitioned to tafamidis free acid 61mg at the start of ATTR-ACT LTE, Weibull distribution has been used BSC OS extrapolation in the new company base case.

From the response to question B6a) (Table 43) the Weibull OS median ([redacted] months) most closely matched that of the trial data ([redacted] months). At 2 years, the Weibull model most closely estimated the portion of surviving patients compared to trial data ([redacted]% vs [redacted]% respectively). At 10 years, Weibull OS% was almost [redacted]%. For these reasons, we believe the Weibull model is appropriate for BSC OS extrapolation beyond the observed period of ATTR-ACT.

**Figure 5. Overall survival parameterisations – Overall population – placebo**



Abbreviations; AIC: Akaike information criterion; BIC: Bayesian information criterion; CMAD: cardiac mechanical assist device; HT: heart transplant; LTM: life table mortality; OS: overall survival.
LTM applied patient age/country specific life tables hazards.

**Figure 6. Smoothed hazard estimates for overall survival censoring for heart transplant and CMAD implantation for the BSC arm in ATTR-ACT.**

The dotted period exceeds maximum survival follow-up in study.

**B7. Priority question. In the updated base case provided by the company, treatment is continued in the NYHA IV state, as preferred by the committee in TA696. However, the EAG could not find the full description of how this was modelled. The only reference mentioned is Appendix E, which only includes a figure of the proportion of patients that did not discontinue tafamidis. Please, provide a detailed step-by-step explanation (including the model cells involved) on how continued treatment in the NYHA IV state was implemented in the updated model.**

In the updated company base case, in which treatment is continued in the NYHA IV state, as preferred by the committee in TA696[2], patients in ATTR-ACT and the ATTR-ACT LTE were not censored when they reached NYHA IV in the observed period of the TTD model and treatment was also not stopped.

Figure 8 in the current CS presents the parameters associated with not censoring NYHA IV patients throughout the observed trial period for each parametric extrapolation model. In the economic model, these parameters can be found in the

'Survival' tab when referring to the following tables in the treatment discontinuation section:

- *Exponential*: discontinuation **without** NYHA IV stop - exp - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Weibull*: discontinuation **without** NYHA IV stop - Weibull - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Gompertz*: discontinuation **without** NYHA IV stop - Gompertz - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Log*-logistic: discontinuation **without** NYHA IV stop - log-logistic - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Log-normal*: discontinuation **without** NYHA IV stop - lognormal - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Generalised Gamma*: discontinuation **without** NYHA IV stop -gen. Gamma - tafamidis 80mg/80mg/acid free ATTR-ACT LTE

In Table 15 in the current CS, we also presented results from a scenario analysis in which patients discontinued treatment when they reached NHYA IV (Scenario 8). In this scenario patients in the observed period of ATTR-ACT and ATTR-ACT LTE were censored when they reached NHYA IV in the TTD model. The parameters associated with each parametric extrapolation model when censoring for NHYA IV were presented in Appendix E. Similar to the above stated parameters, these parameters can also be located in the 'Survival' tab of the economic model. Please refer to the following tables in the treatment discontinuation section:

- *Exponential*: discontinuation **with** NYHA IV stop - exp - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Weibull*: discontinuation **with** NYHA IV stop - Weibull - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Gompertz*: discontinuation **with** NYHA IV stop - Gompertz - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Log*-logistic: discontinuation **with** NYHA IV stop - log-logistic - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Log-normal*: discontinuation **with** NYHA IV stop - lognormal - tafamidis 80mg/80mg/acid free ATTR-ACT LTE
- *Generalised Gamma*: discontinuation **with** NYHA IV stop -gen. Gamma - tafamidis 80mg/80mg/acid free ATTR-ACT LTE

To allow the economic model to select between different parametric extrapolation models for tafamidis TTD, the following can be changed in the 'General Model Settings' section of the 'Model Control tab':

- To select TTD model which do not censor NHYA IV patients (i.e. no NYHA IV treatment stop), select the 'No' option in the drop down menu next to the 'Stop at NYHA IV' cell. Once this is selected, proceed to select a specific parametric model from the drop down menu in the cell below.

- To select TTD model which censor NHYA IV patients (i.e. NYHA IV treatment stop), select the 'Yes' option in the drop down menu next to the 'Stop at NYHA IV' cell. Once this is selected, proceed to select a specific parametric model from the drop down menu in the cell below.

In the company base case, the 'No' option in the drop down menu next to the 'Stop at NYHA IV' cell was selected, as well as the associated exponential parametric model option 'discontinuation **without** NYHA IV stop - exp - tafamidis 80mg/80mg/acid free ATTR-ACT LTE'. For the NYHA IV stop scenario (Scenario 8 in Table 15), the 'Yes' option in the drop down menu next to the 'Stop at NYHA IV' cell, as well as the associated exponential parametric model option 'discontinuation **with** NYHA IV stop - exp - tafamidis 80mg/80mg/acid free ATTR-ACT LTE'.

B8. As per the CS, all placebo patients transitioned to tafamidis free acid 61mg at the start of ATTR-ACT LTE. Therefore, the same parametric distribution from the original CS (i.e., Weibull) was used to model the OS of BSC. Likewise, the same mortality risk associated with BSC from TA696 were used in this submission.

a) Please elaborate on how survival time estimates for BSC were adjusted after treatment switching. Please describe the methods for cross-over correction and if they were consistent to NICE DSU 16.
b) Considering the response to question B6, please discuss the applicability of other distributions to model BSC in the long-term.
c) In Table 48 from Document B (Section 3.3.4.8) of TA696, the coefficient for NYHA IV in the tafamidis group ([redacted]) is higher than for the placebo group ([redacted]). In table 8 of the current CS, this coefficient for the placebo group remained the same, but decreased significantly for the tafamidis group ([redacted]). Please elaborate on the validity of assuming the same hazards associated with BSC for the extended period of time.

a) As mentioned in Section 7.3 of the CS, no new data was available for the placebo arm as all placebo patients transitioned to tafamidis free acid 61mg at

the start of ATTR-ACT LTE. Survival time estimates for BSC were not adjusted after treatment switching in ATTR-ACT LTE; placebo arm data from the observed period of ATTR-ACT was used to model BSC OS in the economic model (as in TA696[2]) as this is the most robust data available.

b) Please refer to response to question B6b).

c) It is appropriate to assume that the coefficient for NYHA IV in the tafamidis group would be lower than that of BSC, considering new data from ATTR-ACT LTE which now extends to 84 months of follow up; 84 months on continuous treatment with tafamidis. NYHA IV patients in the tafamidis group have likely experienced benefit from tafamidis treatment for an extended period of time (likely started treatment at NYHA I or II). Assuming the same hazards associated with BSC for the extended time period is a conservative assumption as it is likely that patients in this group would have deteriorated more readily compared to the tafamidis group over time. However, due to lack of data as a result of the cross-over in ATTR-ACT LTE the company used the most robust available data for BSC hazards from ATTR-ACT.

B9. After an extended period of time, waning of the tafamidis treatment effect may occur. However, from the CS it seems treatment effect waning is not applied.

a) Please justify why waning of the tafamidis treatment effect was not incorporated in the economic model. If available, please provide information on the presence of treatment effect waning in the trials.

b) Please provide hazard ratio plots for OS with numbers of patients at risk over time.

c) Please provide an updated economic model and scenario analyses exploring treatment waning at different time points.

a) The best estimate of the treatment effect relevant to cost-effectiveness, i.e. the difference in population marginal mean survival, is obtained using the current method – independent extrapolation of the observed hazard profiles. Absent any temporal discontinuity in patient management, there is no reason to believe

that the hazard profile described by either the placebo or tafamidis model would change arbitrarily. Should there be a waning of tafamidis treatment effect, as there is no time at which such waning should be delayed until, outliers in the population experiencing early waning may have already affected the observed data and so impacted the hazard profile of the fitted model, and so this waning is already incorporated in the extrapolation.

If waning is so delayed that it has had no impact on the ATRR-ACT LTE data, then this is an acknowledged risk of the use of parametric extrapolation of survival data common to almost all technology assessments of life-extending treatments – i.e. the risk that the extrapolation model breaks down. Similar risks exist for the placebo arm. Best practice guidance has been followed in extrapolating survival outcomes for both arms, therefore, barring any known external influence, the extrapolative models chosen stand as the best estimators of lifetime population average treatment effect.

b) A plot of the ratio of B-spline estimated hazard of mortality (censoring for HT and CMAD) for tafamidis 80 mg / tafamidis free acid 61mg versus placebo / tafamidis as of the ATTR-ACT LTE August 2021 data cut is shown in Figure 7.

Despite cross-over of the placebo arm to active treatment, the hazard ratio decreases monotonically through follow-up and is similar to the plot of Schoenfeld residuals given as response to question B5 part b). From this plot, it is clear that hazard ratio is not a useful expression of treatment effect in this instance, as it is highly time-dependent. It should also be noted that a hazard ratio is only meaningful whilst a baseline hazard is defined, and it is plausible based upon selected extrapolations that a substantial fraction of the tafamidis population would remain alive after the population modelled as receiving only BSC had been exhausted.

**Figure 7. Estimated hazard ratio of tafamidis versus placebo/tafamidis – ATTR-ACT LTE (August 2021)**

Abbreviations: NAR, numbers at risk.

c) As described in point a) and further highlighted in point b), there is no simple parametric "treatment effect" that can be sensibly varied. Reduction of the difference in mortality hazards ignores the clearly diverging hazards of the observed data, and is implausible as a result of the loss of randomisation between arms over time as a result of NYHA and genotype-specific mortality as modified by tafamidis treatment; the population distribution of each arm is highly unlikely to be equivalent at any time other than initiation, and so it is highly implausible that hazards would regress to the same value even in the complete absence of further treatment.

The survival curves can be post-hoc modified, for instance by inflation of the baseline mortality rate, but there is no evidence for the time at which this should occur or the magnitude of the inflation. It should be noted that this inflation should be considered at the model fitting stage to allow for a larger proportion of the total hazard to be accounted for by this baseline. This baseline already accounts for a large proportion of the total hazard for the tafamidis arm, as shown in Figure 6 in the CS, so the inflation factor could not be great and would be likely to result in models with lower peak excess hazards). As such, any

modification would be entirely arbitrary. The best estimate of future outcomes is obtained by extrapolation of the observed hazards using standard parametric techniques, augmented by external data to ensure base plausibility, as in the company base case.

B10. Tafamidis time to treatment discontinuation (TTD) was extrapolated beyond the observed trial data. The company censored patients that discontinued treatment due to undergoing heart disease or receiving a CMAD implant.

a) Please provide the number of patients undergoing heart transplant or implantation of CMAD at each timepoint in the trial.

b) Please provide the number of patients that discontinued from the ATTR-ACT LTE trial at each time point and the reason for discontinuation (e.g. because they gained access to commercial tafamidis).

c) The need for heart transplant or implantation of CMAD could be associated with lack of treatment efficacy in both arms. Therefore, censoring those patients may not be appropriate, Please repeat the TTD extrapolation without censoring for transplants or implants and include: assessment of how well each parametric survival model visually fits the clinical trial data from the Kaplan Meier curve, ranking based on the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), and assessment of clinical plausibility filling out the same table from B6a.

a) Of the 176 patients assigned to Tafamidis 80 mg in ATTR-ACT and those subsequently followed-up in the LTE until August 2021, seven patients received heart transplant (six within the ATTR-ACT period, one in the LTE period) and two underwent implantation of CMAD, both in the ATTR-ACT period.

b) Given the timings of the NICE clarification question response process, data on the number of patients that discontinued the ATTR-ACT LTE trial at each time point and the reason for discontinuation could not be generated. However, please find below the number of continuous tafamidis patients (received 80mg / 61mg free acid) who discontinued from ATTR-ACT to ATTR-ACT LTE (August 2021) and reasons for discontinuation (Table 44).

**Table 44. Categorised discontinuation events – Continuous tafamidis ATTR-ACT LTE (August 2021 data cut)**

| | Tafamidis 80mg / 61mg free acid | |
|---|---|---|
| | Censored (N=136) | Discontinued (N=40) |
| **Categorised discontinuation event** | | |
| Access to commercial tafamidis | 6 (4.4%) | 0 (0%) |
| Cardiac Mechanical Assist Device | 2 (1.5%) | 0 (0%) |
| Deaths | 57 (41.9%) | 18 (45.0%) |
| End of follow-up | 65 (47.8%) | 0 (0%) |
| Heart or Heart-Combo Transplantation | 6 (4.4%) | 1 (2.5%) |
| Loss of function or clinical decision | 0 (0%) | 15 (37.5%) |
| Protocol Violation | 0 (0%) | 1 (2.5%) |
| Voluntary withdrawal | 0 (0%) | 5 (12.5%) |

c) Inclusion of events which are not viable treatment choices in England will not produce an unbiased estimate of discontinuation rates. As can be seen in the response to a), the majority of discontinuations due to HT or CMAD intervention occurred in the first 30 months. Increasing the rate of discontinuation through this period is highly likely to improve the cost-effectiveness ratio of tafamidis by lowering treatment cost, and the company submission is thus conservative in this regard. However, inclusion of these non-permissible events is likely to distort the hazard profile and increase the likelihood that a model with long – term declining hazard of discontinuation is preferred, purely due to distortion of the early evidence, without any modification of the later follow-up for which the constant hazard assumption continues to be reasonable. As we do not believe these events to be representative of the treatment decisions made in the modelled population, we consider the current model to present a more accurate estimation of rate of discontinuation from tafamidis. We have also censored OS so not to include the positive benefit associated with HT.

**B11. Priority question. In the original CS, tafamidis discontinuation was assumed to have no effect on mortality risks, transition probabilities,**

**cardiovascular related hospitalisation rates or HRQoL, i.e. the same outcomes are applied to all tafamidis treated patients, irrespective of whether they are still receiving treatment. This assumption was criticized by the ERG in their report section 5.3.3(2b).**

a) **Please describe how the consequences of treatment discontinuation were modelled for all health states in the current model.**

b) **Please elaborate on how the ERGs comments regarding discontinuation were addressed in the current model, especially the assumptions regarding no effect mortality risks, transition probabilities, cardiovascular related hospitalisation rates or HRQoL that led to an indefinite treatment effect for patients who stopped treatment with tafamidis.**

c) **Assuming BSC transition probabilities, utilities and cost was found not appropriate according to the company, as treatment effect of tafamidis may continue after treatment has stopped. Please provide additional evidence supporting this argument.**

d) **If applicable, please provide a scenario analysis based on the additional evidence provided in B11c.**

e) **If additional evidence is not available, the current assumptions regarding effects after treatment discontinuation are not supported, please update the base case scenario assuming BSC transition probabilities, utilities and cost after treatment discontinuation.**

a) Within the company base case, the following applies to patients once discontinued from tafamidis treatment.

- Rates of transition between NYHA classes remain identical to those remaining on treatment, as informed by the within-ATTR-ACT observed transition rates and the smoothed extrapolative matrix. This is justified by the high level of follow-up after treatment discontinuation achieved in ATTR-ACT.

- Rates of mortality within each NYHA class remain identical to those remaining on treatment. The overall rate of mortality of the cohort is derived from a parametric survival model based upon data observed in the tafamidis 80 mg / tafamidis free acid 61 mg ATTR-LTE arm to the August 2021 data cut, which demonstrate a very low rate of loss of follow-up after treatment cessation; i.e. mortality after treatment discontinuation is captured in the tafamidis hazard. Relative rates of mortality are assumed to be highly dependent upon NYHA class, and interaction of this dependence with treatment is assumed to be relatively weak and is challenging to determine given the relatively low total number of observations post treatment discontinuation.

- AEs due to treatment with BSC are not assumed to be incurred on treatment discontinuation.

- Health-state utilities after discontinuation are assumed to be equivalent to those associated with the same NYHA class and tafamidis treatment, with the exception of those in the NYHA IV state, for whom BSC utilities are assumed.

- Treatment costs due to BSC are assumed for all discontinued patients.

b) Within the ERG report to ID1531 the following response was quoted: "…given the complete follow-up in ATTR-ACT the current model design reflects an ITT data approach with complete follow-up for the first 30 months (no censoring of patients). Therefore, the efficacy data for the tafamidis group includes those patients that discontinued therapy, thereby underestimating the treatment effect for patients that remain on therapy. Consequently, the treatment efficacy inputs, reflect the impact of discontinuations observed in the trial which translates into the extrapolated phase. Therefore, artificially adjusting the outcomes of discontinued people is not appropriate given the design of the trial". In critique of this, the ERG stated: "The ERG believes that the company's statement is accurate, but only with respect to the observed period of the trial; during the extrapolation phase, the company's model

maintains the level of treatment effect observed within the trial whilst also reducing the cycle costs of treatment as more patients discontinue".

The ERG's critique is addressed by the use of data with increased follow-up, which has not only continued to support the overall survival benefit predicted by the company at that time (see response to B1, noting positive impact in incremental QALYs of additional survival data), but provides updated parameters to further decrease the uncertainty in outcomes extrapolation for the tafamidis arm. For the outcome of OS censoring for heart transplant and implantation of CMAD, [redacted] of [redacted] ([redacted]%) patients assigned to tafamidis 80 mg / tafamidis free acid 61 mg had censored observations at the August 2021 DBL. However, of these, [redacted] ([redacted]%) were administratively censored at "date of last assessment" and had not discontinued study, [redacted] ([redacted]%) were censored due to "date of study completion", [redacted] ([redacted]%) were censored due at either "date of CMAD or "date of heart transplant" and only [redacted] patients ([redacted]%) were censored due to "date of discontinuation", and of these only [redacted] ([redacted]%) at less than [redacted] months and an additional [redacted] ([redacted]%) at less than 60 months. Thus the rate of loss of follow-up in the ATTR-ACT LTE was very low, both for those on and off of treatment. The rate of loss of follow-up for NYHA status was higher, and for this reason the NYHA transition matrices used in the company submission are limited to the ATTR-ACT period.

c) The company has adopted a data-driven approach to outcomes modelling. Due to the heterogenous nature of the patients enrolled in the ATTR-ACT trial and the impact of tafamidis upon disease progression, randomisation is rapidly lost after treatment initiation and thus patients discontinuing from tafamidis cannot be assumed to have equivalent outcomes to those experienced on the placebo arm. This may manifest as an apparent treatment effect, of unknown magnitude and direction, causally linked to tafamidis at the population level and not necessarily at the individual level. Thus, due to the high level of follow-up after treatment discontinuation in the ATTR-ACT trial, it was considered more appropriate to model the data as observed, rather than modify the data in ignorance of this loss of randomisation by assigning outcomes due to the placebo arm.

In Section 7.6 of the current CS, we show how the previous EAG scenarios of OS and TTD extrapolations substantially under predict the observed OS and treatment discontinuation in long-term follow up data ATTR-ACT LTE (August 2021) and therefore cannot be considered appropriate for decision making.

d) No scenario is applicable.

e) As justified in point b and c), this assumption is not appropriate particular in light of the increased follow-up.

### *Health-related quality of life*

**B12. Priority question. Modelled health state utility values in health states NYHA I (BSC: [redacted], Tafamidis:[redacted]) and II (Tafamidis: [redacted]) were higher or just below than the general population utility value for the same age group of 65-74 (0.779).[36] The EAG acknowledges that the modelled utility values came from the baseline utilities from the ATTR-ACT ITT population; however, this seems to overestimate the effect of both intervention and comparator and lacks face validity. Please provide an updated economic model and scenario analyses adjusting the utility values in line with general population utility values (e.g. by applying a cap to the utility values higher than the general population utility values).**

According to the NYHA Functional Classification[37] (Table 45) patients in NHYA I are typically asymptomatic and have no limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath. Furthermore, patients in NYHA II only suffer from slight limitations of physical activity and are comfortable at rest.[37] Considering individuals aged between 65-74 years in the general population may suffer from other illnesses and/ or have worst physical limitations it can be argued that NHYA I and II patients could have higher health state utilities, especially when they receive tafamidis treatment; which has been shown to improve patient outcomes.[13]

**Table 45. New York Heart Association Functional Classification [37]**

| Class | Patient Symptoms |
|---|---|
| I | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath. |
| II | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain. |
| III | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain. |
| IV | Symptoms of heart failure at rest. Any physical activity causes further discomfort. |

**B13. Priority question. As per CS, treatment-independent utility values were applied in the NYHA IV health state in the base case. However, in the economic model provided, the BSC utility value for NYHA IV appears to be [redacted], while the tafamidis utility value is [redacted] for NYHA IV.**

**a) Please elaborate on the current approach to utility values in NYHA state IV for both treatment arms.**

**b) Within ATTR-ACT, EQ-5D-3L data collection was restricted to the on-treatment period. However, patients progressing to NYHA IV would discontinue from the trial. Is it appropriate to use ATTR-ACT utility data in this state given the limited number of respondents in the tafamidis arm? Also discuss how "informative censoring" is addressed, as discussed by the ERG in the original ERG report.**

**c) Please provide an analysis in which the same utility values are used in NYHA state IV for all treatment arms.**

a) In the company base case, all patients in NYHA IV on the BSC arm received the BSC utility value whilst in state ([redacted]). On the Tafamidis arm, those currently receiving treatment received the tafamidis utility ([redacted]) whilst those who had discontinued received the BSC value.

In the TA696[2] technical report, the technical team gave the following judgement: 'The utility values used in the economic model should be adjusted to account for age and should be treatment independent (equal for both tafamidis and BSC) in the NYHA IV health state.'

This judgement was given in the context of an economic model assuming that patients entering NYHA IV would discontinue from tafamidis, and where the only scenarios that had been presented enforcing treatment independent utilities did so under this assumption.

It is plausible that the average patient-day in NYHA IV on tafamidis treatment would on average have higher utility than those on best supportive care, as their lack of discontinuation indicates clinician and patient willingness to continue, and so these patients continuing treatment are likely to be healthier than those who have discontinued. Thus, the use of treatment independent utilities in NYHA IV for patients who have discontinued but not with patients on treatment is consistent with the scenario discussed by the committee for in TA696[2], and the scenario implemented as worded by the EAG in their interpretation of the cost-effectiveness model was implemented in the base case by setting "discontinued_utils_flag" to 1.

***Note***: text in cell 'Model Control'!E18 is from the ERG scenario and describes the intent of this setting. Due to the removal of the stopping rule, consistency with this intention required a slight re-write of the model logic to ensure that only patients discontinued received NYHA IV utilities.

b) It is not true that all patients proceeding to NYHA IV would discontinue from the trial or treatment; treatment in ATTR-ACT could continue under existing consent at the discretion of the investigator. However, once reaching NYHA IV, the majority of patients would experience a short time to death. As discussed in the response to part a), the continuation of treatment implies that the patient was healthier than those who did not continue treatment, and it can be seen in the response to B10 that among patients who discontinued, many did so due to lack of ability to travel to continue in the trial. It is therefore expected that on-treatment utility in the NYHA IV state should be higher than that for patients not receiving treatment.

"Informative censoring" is addressed by assigning the discontinued patients to a utility value representative of patients not receiving tafamidis in NYHA IV, i.e. that of the BSC state. Due to the very low value of this state, but due to it

being plausibly higher than 0, scenarios reducing this value to account for any missingness not at random among the placebo respondents are unlikely to have a great impact on the cost-effectiveness result.

c) The cost effectiveness model was modified to set the on-treatment NYHA IV utilities for the tafamidis arm equal to BSC. The off-treatment values may be set to either tafamidis or BSC, but as these are equal under this setting, there is no difference in off-treatment utility value. The deterministic results of this scenario are given in Table 46.

**Table 46. Scenario analysis - treatment status independent NYHA IV utilities (with PAS)**

| Scenario | Incremental | | ICER | % change |
|---|---|---|---|---|
| | Costs | QALY | | |
| **Base case** | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment status independent NYHA IV utilities | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ICER: incremental cost-effectiveness ratio; NYHA, New York Heart Association Functional Classification, QALY, quality adjusted life year.

B14. The health state utility values used in the economic model were derived from the observed EQ-5D-3L data collected within ATTR-ACT. As per table 4 of the new CS, EQ-5D-3L data from ATTR-ACT LTE was not used in the economic model.

a) Please provide an overview of the utility values used in each health state and treatment arm and clarify whether the utility values used in the original CS have been re-estimated including longer-term HRQoL data from ATTR-ACT LTE.

b) Please provide the pattern of missingness of EQ-5D data per arm and per time point.

c) Please provide an analysis in which EQ-5D-3L utilities are estimated through a statistical model fitted to the ATTR-ACT data, including both NYHA stage and treatment group, using a mixture model as described by the ERG in the original ERG report.

d) If applicable, also provide information on the covariates and coefficients used in the mixture model.

a) No EQ-5D-3L data were available for the ATTR-ACT LTE to inform updates to these values. The utility values used in the NYHA health states are informed by the mean of observations of EQ-5D-3L health states valued by the Dolan et al. (1997)[38] time-trade-off value set within collected data from ATTR-ACT. EQ-5D-3L values are associated with NYHA class by the most recent NYHA assessment for that patient, and independent means were taken for the tafamidis and placebo arms. Data were collected and analysed per randomised arm and not categorised by treatment status, therefore it is assumed in the base case that for NYHA classes I-III tafamidis patients continue to experience the same mean utility whether on treatment or off treatment. For NYHA IV, the assumption is made that patients who discontinue treatment experience the mean utility assumed for NYHA IV modelled for BSC.

b) ATTR-ACT LTE was not designed to detect the pattern of missingness of EQ-5D data per arm or per time point.

c) Multi-level mixture models are tools useful for describing the patient-level impact of an intervention, but are inappropriate for estimating the population and time-average treatment effect. The coefficients estimated by such models do not capture the impact of conditional dwell time in health states upon the mean utility considered across dimensions of both time and population; i.e., patients are more likely to remain in a health state if they have a higher utility due to being healthier, then that should be reflected in the mean utility of that health state, as random samples of utility within a model state should reflect the propensity for a patient to be sampled within that state. Under the assumption of missingness completely at random, the simple mean of EQ-5D valuations within each NYHA state thus represents a good estimate of the mean utility of the state, and would be expected to approach the true value with increasing number of samples and follow-up.

   By contrast, the coefficients obtained using a multilevel model represent the average effect of NYHA on utility at a patient level, and to obtain an accurate estimate of the QALYs accrued over both patients and time it would be necessary to model patients as being at greater or lower risk of state transition dependent upon their individual utility value in order to account for any utility-

dependent differences in state dwell time. The simple means approach, where samples informing the mean are regularly and randomly acquired, is thus more appropriate when considering a population modelled over an extended time.

d) Not applicable.

B15. Utility values estimated from the ATTR-ACT data were extrapolated over time and differ per treatment arm.

a) Please elaborate on potential causes of the difference in utility values for patients in the same health state between treatment arms.

b) Please elaborate on how likely it is that this difference in utility values will last over time, i.e. in the unobserved period.

c) Please provide a scenario analysis using treatment independent utility values for all health states (i.e., NYHA I,II,III, and IV) after the observed period.

a) As mentioned in Section B.3.4.1 in Document B of TA696[2], EQ-5D-3L data (both index and visual analogue scale [VAS] scores) were collected at baseline and at 6-monthly review up to final review at Month 30 in ATTR-ACT. Responses to each of the EQ-5D-3L dimension questionnaires for tafamidis and placebo patients at the Month 0 and Month 30 timepoints are summarised in Appendix M.2 of TA696[2]. Level 1 responses are those where a patient indicates they have 'no problems', level 2 indicates 'some problems', and level 3 indicates the greatest level of impairment. In Section 3.20 in the FAD for TA696[2], the committee stated NYHA health state utility values were appropriate for decision making.

   Differences in utility values for patients in the same health state between treatment arms were due to:

   - Across most dimensions, the placebo arm was associated with a greater reduction in level 1 responses over the 30-month period (i.e. a greater reduction in observations with no noted disutility for that dimension). The greatest reduction in level 1 responses in the placebo arm was seen in

the “self-care” dimension, and the greatest proportional loss in the “usual activities” dimension.

- Both treatment arms experienced a general decline in mobility from a baseline which itself was highly compromised, with more than half of patients reporting ‘some problems’ at baseline. For all other dimensions, the proportion of patients in the tafamidis arm reporting ‘some problems’ remained very consistent over time. This implies that patients treated with tafamidis experienced a slow reduction in utility over time, driven primarily by continued gradual loss of mobility-related function in the mean.

- On BSC, a much more rapid reduction in utility is implied, driven by all dimensions, but particularly by deterioration in “self-care” and “usual activities”.

- Despite its limitations, a similar pattern was observed in the VAS scores where they were similar between arms at baseline and Month 6, but scores in the BSC arm became notably lower in the mean and quartiles at subsequent timepoints (Appendix M.3 of TA696[2]).

b) We would expect the difference in utility values to last over time (i.e. in the unobserved period) as long-term data from ATTR-ACT LTE shows that over ~5 years tafamidis treatment continued to improve survival across NYHA I-III, and patients who received continuous tafamidis continued to have better survival than those who received placebo in ATTR-ACT followed by tafamidis in the ATTR-ACT LTE; demonstrating durability of treatment effect (Section 6.2 in CS). Moreover, there was an improvement in survival with tafamidis treatment in ATTR-ACT LTE for patients who had previously received placebo in ATTR-ACT; further confirming tafamidis treatment may incur utility benefit compared to BSC over time. And as requested in Section 3.21 in the FAD in TA696[2] age adjusted utilities were added into the current economic model .

c) For the reasons mentioned in the response of question B15b), we do not advise this analysis; the difference in tafamidis and BSC health state utilities is expected to continue over time.

### *Disease severity*

B16. In the CS, it is stated that "Tafamidis is will predominately be used in older populations (65+years). Despite age being protected by the Equality Act (2010), diseases which typically impacting older populations – such as ATTR-CM – are unable to qualify for NICE's severity modifier". However, no formal disease severity assessment was provided. Please provide a severity assessment in line with the current NICE guidance, including absolute and proportional QALY shortfall calculations.

NICE considers the severity of the disease via absolute QALY shortfall (AS) and proportional QALY shortfall (PS). When carrying out a disease severity assessment in line with the current NICE guidance, it is evident that tafamidis in ATTR-CM does not qualify for disease severity modifiers; AS and PS do not meet criteria for willingness to pay (WTP) threshold uplift.

Age-adjusted utilities for the general population from Aza and Brazier, 2011[39] were used to calculate QALYs in the sex and age matched general population.

The calculation used to determine AS was as follows:

$$Absolute\ QALY\ shortfall = QALYs\ in\ BSC - QALYs\ in\ age\ and\ sex\ matched\ general\ population$$

The calculation used to determine PS was as follows:

$$Proportional\ QALY\ shotfall = \frac{Absolute\ QALY\ shortfall}{QALYs\ in\ age\ and\ sex\ matched\ general\ population}$$

Table 47 shows starting age and sex distribution for the analysis.

**Table 47. Summary features of QALY shortfall analysis**

| Factor | Value | Reference to table and section in submission |
|---|---|---|
| Sex distribution | 90% male, 10% female | Table 40 in TA696[2] Document B |
| Starting age | 74.34 | |

Results of the calculation are shown in Table 48. In the base case analysis, with a mean age at baseline of 74.34 and a proportion of males at 90%, the AS estimate is

[redacted] and the PS is [redacted]. This gives a severity modifier of [redacted]. Note that the values are calculated based on discounted QALYs.

**Table 48. QALY shortfall calculation results**

| Outcomes | Totally QALYs | Shortfall | |
|---|---|---|---|
| | | Absolute | Proportional |
| General population | [redacted] | | |
| Disease specific | [redacted] | [redacted] | [redacted] |
| QALY multiple | | [redacted] | [redacted] |
| WTP threshold | | [redacted] | |

Abbreviations: QALY, quality adjusted life year; WTP, willingness to pay.

## *Results*

B17. Patient baseline characteristics (i.e. age and proportion female) were included in the probabilistic sensitivity analyses (PSA).

a) Please justify the inclusion of patient characteristics in the PSA.

b) Please provide an updated economic model excluding patient characteristics from the PSA.

a) As with all other cost-effectiveness analysis we aware are of, patient characterises are included within the PSA. Patient characteristics within the cost-effectiveness analysis were informed by aggregate statistics from the ATTR-ACT trial. Under the assumption that the population of the ATTR-ACT trial represents a random sample of the population to be modelled, the sample mean age and proportion female are used as unbiased estimators. However, these estimators are associated with some uncertainty. To reflect the uncertainty of the estimators it is conventional to allow these parameters to vary in PSA, informed by the standard error of the mean, as calculated using the sample standard deviation and sample size.

b) We disagree with this analysis, as the population mean age and sex distribution are not known exactly, and the uncertainty of these parameters should be included in the PSA.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | British Society for Heart Failure |
| **3. Job title or position** | |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes<br>A specialist in the treatment of people with this condition? Yes<br>A specialist in the clinical evidence base for this condition or technology? Yes<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | British Society for Heart Failure |
| **5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | £10,000 for sponsorship/exhibition space at the BSH Annual Meeting 2022 – one off payment - Pfizer<br>£7,500 for Partners of BSH 2023-2024 one off payment – Pfizer<br>£60,000 for exhibition space and symposium at the BSH Annual Meeting 2023 – one off payment – Pfizer |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## The aim of treatment for this condition

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| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | The main aim is to reduce all cause mortality and heart failure hospitalisations plus reduce the rate of decline in quality of life and functional capacity. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | 20% reduction in all-cause mortality compared to standard of care.<br>A >20% reduction in cardiovascular admissions compared to standard of care.<br>Better KCCQ-measured quality of life compared to standard care. >10 points difference = moderate effect, >5 points = small effect)<br>Better 6-minute walk distance (>55 metres difference) compared to standard of care. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | Yes, there is no approved disease modifying treatment for the vast majority of patients with ATTR cardiac amyloid (a small subgroup around 11%, have access to Patisiran, Inotersen and Vutrisiran if they have an ATTR variant associated with amyloid polyneuropathy). ATTR-CM is associated with a very poor quality of life, even for heart failure, with recurrent heart failure admissions and relentless progression to death. |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Supportive management with diuretics is all that is available for most ATTR-CM patients (89% without polyneuropathy) plus palliative care in the later stages of the disease. |
| **9a. Are any clinical guidelines used in the** | Standard heart failure medications (eg the NICE Heart Chronic Failure Guidelines) are not effective for this cardiomyopathy and are frequently poorly tolerated due to hypotension or bradycardia. |

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| **treatment of the condition, and if so, which?** | |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | The only care available to most ATTR-CM patients (89% without polyneuropathy) is supportive therapy with diuretics.<br>As there are no approved therapies available, awareness of the condition is variable, and this is reflected in very variable detection rates around the country. |
| **9c. What impact would the technology have on the current pathway of care?** | An approved technology would significantly approve clinician awareness and there would be an emphasis on early detection when the patients are most likely to benefit from therapy. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | Tafamidis was made available via the Early Access to Medicines Scheme in 2019 to a subset of ATTR-CM patients. Tafamidis patients are managed alongside patients who are not taking tafamidis in the outpatient clinic setting (this is a once daily oral medication), but have an improved clinical trajectory with less hospital admissions. |
| **10a. How does healthcare resource use differ between the technology and current care?** | Patients taking tafamidis are living longer with less hospital admissions and better quality of life compared to peers. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Specialist clinic in secondary care around the country, using a hub and spoke model, with access to the National Amyloidosis Centre for advice on complex patients. |
| **10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)** | No new facilities are needed. |

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| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | Yes, Tafamidis extends life and reduces hospital admissions in patients with ATTR-CM. |
| **11a. Do you expect the technology to increase length of life more than current care?** | Yes – the ATTRACT trial showed reduced all-cause mortality after 18months of treatment. |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | Yes – ATTR-CM is associated with a relentlessly progressive fall in quality of life – with a higher rate of reduction than other forms of heart failure. Tafamidis resulted in a significantly slower decline in quality of life for treated patients in the ATTRACT trial. |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | |

## The use of the technology

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| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors** | Tafamidis is a once daily, well tolerated oral tablet. No specific additional monitoring is required.<br><br>Reduced hospital admissions will result in improved workload for heart failure clinical teams. |

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| **affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | No specific rules are required. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | No |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Yes, there are no currently available treatments for ATTR-CM, so Tafamidis would represent a breakthrough for patients and clinicians. Tafamidis has been shown to reduce all-cause mortality and cardiovascular admissions in ATTR-CM.<br><br>Reduced admissions lead to reduced work load for heart failure teams. |
| **16a. Is the technology a 'step-change' in the management of the condition?** | Yes, there are no currently available treatments for the majority (89%) of patients with ATTR-CM. ATTR-CM steadily progresses to death in 31 months in variant ATTR-CM and 57 months in wild type ATTR-CM. |

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| **16b. Does the use of the technology address any particular unmet need of the patient population?** | Mortality, cardiovascular admissions, quality of life and functional capacity are all addressed. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Tafamidis is a well-tolerated once daily oral medication with no specific additional monitoring required. |

## Sources of evidence

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| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Yes |
| **18a. If not, how could the results be extrapolated to the UK setting?** | |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | Quality of life, all-cause mortality and cardiovascular admissions are the most important outcomes and were al measured in the ATTRACT trial. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | N/A |
| **18d. Are there any adverse effects that were not apparent in clinical** | No |

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| **trials but have come to light subsequently?** | |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal and highly specialised technology guidance HST9, HST10 or TA868?** | Vutrisiran, inotersen and patisiran are only recommended for ATTR patients with polyneuropathy. ATTR patients with polyneuropathy represent only 11% of all ATTR-CM patients (Lane et al Circulation 2019). |
| **21. How do data on real-world experience compare with the trial data?** | Real world data with propensity score matching has shown that Tafamidis is associated with a significant reduction in HF admissions and all-cause mortality. (Ghoneem et al Current Problems in Cardiology 2023). |

## Equality

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| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | ATTR-CM disproportionately affects people of African and Caribbean family origin where the V122I variant is carried by 4%, predisposing to the development of ATTR-CM in later life. V122I ATTR-CM is not associated with polyneuropathy so patients do not have access to disease modifying therapy.<br><br>Although detection rates have improved enormously in wild type ATTR due to ready access to cardiac MRI and DPD scanning, this benefit has not been seen in V122I ATTR where detection rates have been unaffected and remain unacceptably low (Lane et al, Circulation 2019; 140:16-26). Availability of an effective treatment has the potential to improve this situation as there will be an onus on clinicians not to miss a condition where an approved treatment is available. This could in turn enable equitable access for patients of African and Caribbean ethnicity to appropriate investigations that they are not able to access at present. |
| **22b. Consider whether these issues are different from issues with current care and why.** | See above |

## Key messages

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| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • There is no disease modifying therapy available to most ATTR-CM patients (around 89% do not have a polyneuropathy so are not eligible for Vutrisiran, Patisiran or Inotersen).<br>• Untreated ATTR-CM is a relentlessly progressive condition with very poor quality of life.<br>• Tafamidis results is a marked slowing of the deterioration in quality of life for patients.<br>• Tafamidis reduces cardiovascular admissions in ATTR-CM.<br>• Tafamidis reduces all-cause mortality in ATTR-CM. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

# Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

## About you

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| **1.Your name** | xxxx xxxx xxx xxxxxxxxx xxxxxxxx |
| **2. Name of organisation** | Cardiomyopathy UK |
| **3. Job title or position** | xxxx xxxx x xxxxx xxxxxxxxx<br>xxxxxxxxxx xxxxxxxxx xxxx xx xxxxxxxxxxxxxxxxxxxxxxx |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | Cardiomyopathy UK is the national charity for people affected by cardiomyopathy. The charity provides a range of support and information services, provides clinical education opportunities, raises awareness of the condition among the general public, facilitates research and advocates for improved access to quality treatment.<br><br>The charity's database contains 18,000 individuals and there are around 150 active volunteers who facilitate support groups, provide peers support, advocate for improvements in health services, undertake fundraising activities and take on a range of other roles.<br><br>The charity's trustees, the majority of whom have personal experience of the condition, are ultimately responsible for the charity and are supported by a professional staff team.<br><br>The charity is funded by community fundraising (39%), donations and legacies (19%) charitable trusts and companies (29%) and the pharmaceutical industry (13%). Total income from the year January 2022-December 2022 was £1,031,133. |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the** | The charity received funding of £21,100 from Pfizer in 2022 which represents 2% of the charity's total income in that year. The total income received from the pharmaceutical industry in 2022 was £131,340 (13% of all income). This was made up by: |

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| **comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of the company, amount, and purpose of funding.** | £21,100 received from Pfizer for our local volunteer advocacy project<br>£10,000 received from Alnylam for online healthcare professional education<br>£62,300 received from Bristol Mayers Squibb for awareness raising and research activity<br>£36,000 received from Tenaya (unrestricted donation)<br>£1,940 received from Bristol Mayers Squibb for consultancy advice (unrestricted) |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | None |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | The information from this response has been drawn from the charity's 2022 national survey for people with all forms of cardiomyopathy **(n.507)** and the partners, carers and loved ones of people with cardiomyopathy **(n.62)** The charity has also worked alongside The UK ATTR Amyloidosis Patients' Association (UKATPA) to ensure that comments made by the wider cardiomyopathy community are an accurate reflection of the experience of diagnosis, treatment and living with ATTR-CM. |

## Living with the condition

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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | Survey respondents indicated that the most impactful physical symptoms of the condition were breathlessness, exhaustion and the inability to carry out day to day tasks. Respondent told us;<br><br>***"I would say that the grinding daily fatigue is the hardest of all the symptoms to cope with as it takes away much of the enjoyment of life"***<br><br>***"I'm existing, not living, I've lost much of my mobility and have to rely on a walking stick, can't walk more than about 3 feet without having to stop due to the pain and breathlessness and sheer exhaustion, have had to have a wet room fitted as can't use a bath, can't lay down at all so have to sleep on my recliner sofa sitting bolt upright… I barely leave the house anymore except for appointments mainly. I want a life back"***<br><br>Our national survey also looked at the impact of cardiomyopathy on emotional wellbeing of someone with the condion. Over 50% of respondents felt that they struggled to cope emotionally over the last 6 months due to their cardiomyopathy. Comments included:<br><br>***"I find it hard sometimes to not do what I used to do and my close family find it hard too. I try to be philosophical and appreciate what I can do though. It's difficult when out and about and I can't walk as far as others or go upstairs easily - some disabilities are hidden"***<br><br>***"I live alone and I get very scared about my condition and how to cope with it. Also I feel anxious a lot of the time as I never know what will happen next in my body"***<br><br>When we asked the loved ones of people with cardiomyopathy about their experience, they told us that they were also struggling emotionally with the impact of cardiomyopathy. 60% of respondents said that they found it hard to cope and 28% believed that counselling could help their emotional wellbeing. |

## Current treatment of the condition in the NHS

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | The only medicines that are available to patients with cardiac amyloidosis are those which aim to manage symptoms and support heart function, such as diuretics, blood thinners or medicines to control the heart rhythm. |
| **8. Is there an unmet need for patients with this condition?** | There are currently no specific treatments available for amyloidosis with cardiomyopathy. |

## Advantages of the technology

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| **9. What do patients or carers think are the advantages of the technology?** | Our understanding is that Tafamidis has shown an ability to slow down or stop the build-up of amyloid deposits in the heart, meaning patients can remain active and healthy for a longer time than if they did not have a treatment.<br>Broadly, our community is highly in favour of new treatments options, especially where there are no options at present. |

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | Our understanding is that this treatment has been used outside of the UK for a number of years and is well tolerated. We see no significant disadvantages in this technology |

## Patient population

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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | No |

## Equality

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| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | There is some evidence that ATTR-CM disproportionately impacts certain populations including individuals of African and Hispanic descent. |

## Other issues

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| **13. Are there any other issues that you would like the committee to consider?** | If recommended, this will be the first treatment designed specifically for people with amyloidosis with cardiomyopathy. As such it is important that NICE considers the impact of the treatment not just in terms of an individual's quality of life but also the impact a new treatment would have on the wider cardiomyopathy and amyloidosis community.<br><br>We believe that a recommendation is likely to increase the recognition of the condition among the clinical community and improve health care professionals' understanding of the importance of providing a detailed diagnosis rather than just treating the symptoms as heart failure without considering aetiology. Recommendation would also lead to increased diagnosis, encourage the development of further treatments and best practice and ultimately provide much needed hope to the community. |

## Key messages

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| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • There is no specific treatment for this condition currently available in the UK<br>• This is a serious, progressive, disabling and fatal condition.<br>• The burden of the disease is significant on relatives and carers<br>• Tafamidis can stop or slow disease progression<br>• Since NICE's last review of the medication there have been significant improvements in the infrastructure, processes, training and understanding needed in the healthcare system to identify this condition. |

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NICE National Institute for Health and Care Excellence

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# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

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- Your response should not be longer than 10 pages.

## About you

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| **1.Your name** | [redacted] |
| **2. Name of organisation** | UK ATTR Amyloidosis Patients Association (UKATPA) |
| **3. Job title or position** | [redacted] |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | The UKATPA is a charitable organisation with the following purposes:<br>1. To inform, support and advocate for people living with ATTR amyloidosis: patients, relatives, and caregivers.<br>2. To work closely with all stakeholders to facilitate the availability of effective treatments for ATTR amyloidosis.<br>3. To raise awareness of ATTR amyloidosis to promote and facilitate early diagnosis.<br>4. To support research programs that will be of benefit to those living with ATTR amyloidosis.<br>The UKATPA has a mailing list of approximately 70 patients, family members, and caregivers, along with a mailing list of XXX healthcare providers with an interest in ATTR amyloidosis. UKATPA is governed by six Trustees who are all patients with ATTR amyloidosis, supported by a range of volunteers, most of whom have prior professional knowledge & experience working with amyloidosis. We interact with the UK ATTR amyloidosis community by means of email updates, virtual information sessions, social media, our website, and outreach activities such as attending the National Amyloidosis Center on ATTR clinic days and attendance at relevant national and international conferences.<br><br>As a relatively new organisation, the UKATPA does not have a regular and formalized funding stream at present. We have received grants and sponsorships from the pharmaceutical industry and regularly receive donations raised by patients, their families, and friends. |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in** | No |

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| **the appraisal stakeholder list.]**<br>**If so, please state the name of the company, amount, and purpose of funding.** | |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | We gathered information about the experiences of patients and caregivers in the following ways:<br>1. By speaking to our members about their experience of cardiac ATTR amyloidosis<br>2. By engaging with healthcare professionals and professional patient advocates who have a wealth of experience in caring for patients with ATTR amyloidosis and conducting research into the disease, including the burden of the disease for patients and caregivers. Some of the quotes presented below are from a study conducted at the UK National Amyloidosis Centre.<br>3. By reading websites, articles, and publications on the disease.<br>4. Over the last few years the Trustees have attended and participated in several conferences and seminars that have been aimed at both patients and healthcare professionals.<br>5. Through lived experience as ATTR amyloidosis patients. |

**Living with the condition**

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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | Cardiac ATTR amyloidosis (ATTR-CM) is a life limiting, progressive & debilitating disease. It causes loss of mobility and independence, leading to a poor quality of life for both sufferers and their carers. Patients with ATTR-CM can experience a wide range of multisystemic symptoms and severely delayed or misdiagnoses are common, meaning patients often live with these symptoms for years without appropriate treatment and management and without understanding what is going on.<br><br>Below is a description of some of the impacts of living with ATTR-CM **as expressed by patients:**<br><br><u>Severely reduced exercise/exertion tolerance</u><br><br>Many patients struggle to walk up the stairs in their homes. One patient said he needs to rest after climbing every 2 to 3 steps, so it can take a long time, sometimes resorting to using his hands and knees to 'crawl' up the stairs. Many patients have to simply avoid walking up even small inclines. This can affect every aspect of life from work, shopping, visiting family and friends, to holidays. Another patient described the feeling of not being able to join in with the dancing at a family party, saying how this made him feel frustrated and upset.<br><br>*[Patients with ATTR-CM] reported low energy, malaise, and "heaviness" in their limbs, 'twitching, clumsiness, buckling knees, and trouble maintaining their balance*.[1]<br><br>1. Rintell, D., Heath, D., Braga Mendendez, F., Cross, E., Cross, T., Knobel, V., Gagnon, B., Turtle, C., Cohen, A., Kalmykov, E. and Fox, J. (2021). Patient and family experience with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) amyloidosis: results of two focus groups. *Orphanet Journal of Rare Diseases*, 16(1). doi:https://doi.org/10.1186/s13023-021-01706-7.<br><br><u>Fatigue</u><br><br>Fatigue is very common among ATTR-CM patients. One patient described how he struggles to walk 300 to 400 yards from his car to his desk at work and is fatigued by the time he gets to his desk. Fatigue has a substantial impact on every aspect of life, including work, social and family life. It frequently interferes with the patient's ability to take part in everyday tasks or activities that previously brought enjoyment. Many ATTR-CM patients are forced to retire early due to fatigue.<br><br><u>Breathlessness</u><br><br>Breathlessness is another symptom common symptom that contributes to reduced mobility and can be very distressing. Almost all patients with cardiac ATTR amyloidosis, even those at earlier stages of the disease, find that the breathlessness is extremely limiting in their usual daily activities, and for some can be the cause of anxiety or panic. |

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| | *'I used to walk the dog all the time, every day, morning and at night. Now, when I physically start to walk, I get really tired, my legs ache, get out of breath, that is the thing that really bugs me, is getting out of breath.'* – Patient<br><br>Dizziness, falling and fainting.<br><br>Many patients have unstable blood pressure so if they stand up too quickly it can cause them to feel very dizzy such that they have to sit down again, or they fall over or faint. This can happen anywhere, is dangerous, and can result in serious injury and hospitalisation. The fear of fainting or falling is very common among patients with some restricting their activities for fear of fainting when out in public or alone.<br><br>'I*f I get up too quick, I might faint or when I am walking and out of breath or if I bend over try to do my shoelaces or whatever and I find I get a little bit lightheaded'.* - Patient<br><br>Abnormal heart rhythms<br><br>One of the effects of ATTR-CM is that the heart develops abnormal rhythms- beating too slow, too fast or skipping beats. These can be distressing when they happen and can also be dangerous, causing people to faint or the heart can even stop beating which can result in death. To manage these arrhythmias patients often need to have pacemakers and/or other medical devices fitted. Sometimes, even that does not work, patients, therefore, must live with the constant spectre of a potential heart attack.<br><br>Pain<br><br>People with cardiac amyloidosis can experience severe chest pain, as well as pain in the limbs. Water retention in the legs can make them swell and become uncomfortable or painful further restricting mobility. ATTR-CM can cause gastric symptoms, so stomach pain and cramps are also common among patients.<br><br>Loss of independence<br><br>Being less mobile and breathless after even minor tasks means that patients must depend on their caregivers more and more as the disease advances. Male and female patients alike find this difficult as they are less and less able to care for themselves independently or to carry out household tasks. Frequently patients' partners and sometimes their children become carers. Patients often struggle with the loss of independence coupled with feeling like a burden on their loved ones.<br><br>Financial burden<br><br>Having to retire earlier than expected can place a financial strain on patients and their families. **Caregivers** often also retire or reduce working hours due to the burden of care. Traveling (sometimes very long distances) to hospital appointments can cost significant amounts of time and money. Purchasing mobility aids (e.g., wheelchair, mobility |

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| | scooter) and modifying the home to aid mobility can lead to further expense. With NHS social care services under strain, many families must foot the bill for care themselves. This coupled with family members' reduced ability to work further compounds the financial burden carried by ATTR-CM patients and their loved ones.<br><br>Psychological burden<br><br>One form of ATTR-CM is hereditary meaning that multiple members of the same family may be affected. This brings a huge psychological burden to the patient and their family members. Many have watched their grandparents, parents or even siblings succumb painfully to the disease; they therefore worry for themselves and for their children and grandchildren who may inherit the disease. Many patients suffer from low mood or even depression.<br><br>Caregivers<br><br>The burden on caregivers is significant. Most caregivers are partners or spouses, sometimes children. Watching the health of someone you love deteriorate is inherently stressful. In addition to the financial burden mentioned above caregivers often experience chronic fatigue; apart from caring for their spouse they also gradually assume more and more of the household duties as their spouse/parent becomes less and less able to help. Caregivers also experience isolation as they are either afraid or unable to leave their spouses alone or simply spend so much of their time caring that they have limited opportunity to get out of the house and socialise. Caregivers often suffer from low mood, depression, or anxiety because of the impact of the disease on them and their families.<br><br>There is a vast range of symptoms associated with ATTR-CM all of which have an impact on patients' quality of life. A recent research paper identified the following list of symptoms as experienced by ATTR-CM patients:<br>Atrial fibrillation; Enlarged heart; Fluid retention/swelling; “hearing” own heartbeat; Increased fatigue with altitude; Intolerance to activity; Passing out/Fainting; Shortness of breath; Abdominal pain; Changes in or loss of taste in food; Constipation; Feeling full quickly; Loss of appetite; Upset stomach; Weight loss; Night sweats; Rash; Difficulty with balance when walking: Bi lateral carpal tunnel; Clumsiness/dropping things; Contraction of fingers; Inability to exercise; Loss of muscle tone; Muscle twitching, cramps & spasms; Weakness; Knees buckling; Dizziness; Erectile dysfunction; Fatigue; General malaise; Heat intolerance; Lower back pain; Reduced sexual drive; Sensitive to touch/unusual burning; Vision impairment; Depression; Mood changes; Sleep disorders/Insomnia[1]. |
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## Current treatment of the condition in the NHS

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | There are no treatments currently available on the NHS. Only supportive medications used for managing symptoms are available, but these do not impact the progression of the disease. |
| **8. Is there an unmet need for patients with this condition?** | Yes. There are currently no disease-modifying medicines available to ATTR-CM patients. The continuous build-up of amyloid deposits in the heart leads to progressive disability and a drastic shortening of life for those who have the disease. |

## Advantages of the technology

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| **9. What do patients or carers think are the advantages of the technology?** | 1. The treatment may slow down or stop the build-up of amyloid deposits in the heart, meaning patients live longer and can remain active and healthy for a longer time than if they would without treatment.<br><br>2. Some patients may have early symptoms and by having the drug it may let them be able to continue working longer and continue to contribute to the family and society for longer.<br><br>3. Many patients end up with pacemakers because of abnormal heart rhythms or their heart stopping. The medication may remove this requirement for some.<br><br>4. Having treatment available will bring hope to the ATTR-CM community. We anticipate this will have a positive impact on the emotional and psychological well-being of both patients and their loved ones.<br><br>5. It is an advantage that the medicine is in tablet form making it easy to distribute and administer. |

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | We do not see any disadvantages to this technology. |

## Patient population

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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | The group of patients whose amyloidosis manifests primarily as cardiac issues will benefit the most as they currently have no other treatments available to them. These patients include the wild-type population and certain hereditary forms including patients with the V122i gene. At present these patients do not have any disease-modifying treatments available to them. The slowing of the disease progression would be the direct benefit, which brings with it all the benefits that being healthier for longer. Having a treatment available, where currently there is none, would bring hope to the whole ATTR-CM community.<br>Additionally, in part due to the lack of available treatments, ATTR-CM patients often go undiagnosed. We believe that making this treatment available, coupled with growing awareness of ATTR-CM within the medical community will lead to more patients receiving a timely diagnosis and therefore being able to access appropriate care. |

## Equality

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|---|---|
| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | Because of its genetic nature, it is thought that ATTR-CM disproportionately impact certain populations including individuals of African and Hispanic descent.<br>*It has been reported that subjects of African descent present with heart failure at a younger age and because of different causes than whites… In Afro-Caribbean patients, ATTR V122I is an underappreciated cause of heart failure, and cardiomyopathy is often misattributed to hypertension.*[2]<br>2) Dungu, J.N., Papadopoulou, S.A., Wykes, K., Mahmood, I., Marshall, J., Valencia, O., Fontana, M., Whelan, C.J., Gillmore, J.D., Hawkins, P.N. and Anderson, L.J. (2016). Afro-Caribbean Heart Failure in the United Kingdom. *Circulation: Heart Failure*, 9(9). doi:https://doi.org/10.1161/circheartfailure.116.003352. |

## Other issues

| | |
|---|---|
| **13. Are there any other issues that you would like the committee to consider?** | We hope that patients all over the country will be able to have equal access to this medicine. With other medicines people in Scotland and Northern Ireland have had problems getting treatments. In addition, we are aware other similar drugs are currently under development, we hope that making this medicine available will not prevent patients from accessing new treatments as they emerge in the future. This medication is widely available in other countries and has been seen to be safe with very few side effects. |

## Key messages

| | |
|---|---|
| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • ATTR-CM is a progressive, debilitating, and Fatal condition that significantly shortens the life of patients with no treatment currently available in the UK.<br>• The burden of the disease on patients is very significant, impacting; physical, financial, social, emotional, and psychological wellbeing.<br>• The burden of the disease on the carers, friends, and family of patients is also very significant impacting all aspects of life.<br>• Due to its genetic nature, ATTR-CM is thought to disproportionately affect certain populations including those of African and/or Hispanic descent.<br>• If approved this medicine would be the first treatment available to ATTR-CM patients in the UK, this would bring hope to the ATTR-CM patient community and a greater willingness to diagnose ATTR-CM among the medical community. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

## Your privacy

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | British Cardiovascular Society |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes<br>A specialist in the treatment of people with this condition? Yes<br>A specialist in the clinical evidence base for this condition or technology? Yes<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | United Kingdom-wide health organisation which aims to represent all healthcare professionals working in the field of cardiology, set standards for prevention, diagnosis, and clinical care, and communicate those standards to the community and the patients through training, education and public outreach. |
| **5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | No |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## The aim of treatment for this condition

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| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | To ameliorate the progression of transthyretin amyloid cardiomyopathy (ATTR-CM) and reduce mortality and hospitalisations for heart failure. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | Maintenance of NYHA Class, stabilisation of functional capacity and quality of life scores |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | Yes, there has been a near exponential increase in the number of patients diagnosed with wild-type ATTR cardiac amyloidosis (wtATTR-CA) and there is still no available disease modifying therapy available on the NHS. The increased clinician awareness around this condition means that patients are being diagnosed at an earlier stage of the disease (Ionnoau et al Circulation 2022; 146:1657-70) and these patients are likely to benefit most from access to this TTR stabiliser therapy (Elliot et al Circ Heart Fail 2022; 15: e008193). |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Treatment of wtATTR-CM is currently limited to prevention of complications and supportive care with diuretic therapy, anticoagulation and pacemakers. |
| **9a. Are any clinical guidelines used in the** | The BSE guidelines have just been released to guide echocardiography community and help standardise reporting in patients suspected with this condition (Moody et al 2023, Echo Res Pract). A UK specific DPD practice guideline commissioned by the BNMS has been accepted for publication but is not yet in print |

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| **treatment of the condition, and if so, which?** | (Wechelakar et al. Nuc Med Comm 2023, in print). A position statement of the ESC Working Group on Myocardial and Pericardial Diseases was also published in 2021 (Garcia-Pavia et al Eur Heart J 2021; 42: 1554-68). |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | There is a well-validated diagnostic algorithm (Gillmore et al 2016 Circulation), which if followed closely, permits accurate diagnosis. At present all specialised amyloidosis healthcare is delivered in England at the National Amyloidosis Centre, Royal Free London. There is an increasing unmet need to offer what is largely an elderly frail population, access to TTR disease modifying therapies beyond London. There were initial plans to draw up an amyloidosis network led by Prof Helen Lachmann in 2019 but as COVID-19 enveloped the UK, NHSE funding was withdrawn and further discussions have not been forthcoming. |
| **9c. What impact would the technology have on the current pathway of care?** | The likely impact of introducing this treatment will be an increase in the number of patients diagnosed and a need to develop a formal UK amyloidosis network. This is vital to help ensure equity of patient access to treatment for the increasing number of elderly patients being diagnosed with this condition. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | N/A |
| **10a. How does healthcare resource use differ between the technology and current care?** | |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Specialist clinics. Without standardisation of diagnoses and care via a network, there is a risk that patients with other types of cardiac amyloidosis will be inappropriately put on treatment with tafamidis. |
| **10c. What investment is needed to introduce the technology? (For example,** | There has been significant increase in the level of knowledge and education around amyloidosis in the last 3-4 years, in particular among the cardiology community. A common way to co-ordinate and integrate care for patients and populations with specific conditions has been to establish care pathways and networks. The existing individuals, facilities, equipment to run an amyloidosis service will I expect be already largely available for most university teaching hospitals within the largest UK cities. The development of integrated clinical networks do not |

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| **for facilities, equipment, or training.)** | necessarily require the creation of new organisational entities or physical facilities but there will be a need to broker care across providers for patients with amyloidosis in a form of virtual integration.<br><br>The prescribing of tafamidis might initially be best restricted to a number of specialist regional centres with the requisite expertise in this area. These centres will require access not only to multimodality imaging (DPD/CMR) and interventional cardiologists with experience in endomyocardial biopsy, but the ability to forward histology to a centre with experienced histopathologists for the 10-20% of ATTR patients with a concomitant paraproteinaemia, in whom tissue amyloid typing with immunohistochemistry is required to exclude AL-cardiac amyloidosis. |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | Yes, based on the UK EAMS real-world experience and the long-term data from the ATTR-ACT trial, I anticipate that patients offered tafamidis at an early stage of their disease will gain significant functional and mortality benefit beyond that compared with current care. |
| **11a. Do you expect the technology to increase length of life more than current care?** | Yes (Elliot et al Circ Heart Fail 2022; 15: e008193). |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | Yes (Elliot et al Circ Heart Fail 2022; 15: e008193). |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | Patients in NYHA Class IV should not be started on this treatment. |

## The use of the technology

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| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | The data on safety are very good and the drug is easily administered orally with no major side effects offering excellent patient acceptability. No extra monitoring / testing is required beyond standard of care. |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | It may be reasonable to consider withdrawal of the drug once patients reach end-stage heart failure (NYHA Class IV) but I do not think there needs to be formal arrangements for this and this decision could be made after discussion with the patient and at the discretion of the individual clinician. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | It will further improve clinician awareness of amyloidosis in general. This will likely result in the earlier detection of other forms of cardiac amyloidosis (e.g. light chain amyloid cardiomyopathy) which in turn, could lead to improvements in outcomes in these disease cohorts. Similarly, it is likely to result in improved detection of hereditary forms of ATTR since TTR genotyping is an established part of the treatment/management algorithm (Gillmore et al Circulation 2016.). This has the potential to transform care and outcomes in families and not just individual patients. |

| | |
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| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Yes, it is innovative. If approved, it would be the first disease modifying treatment we could offer patients with wtATTR-CA that targets the underlying cause of their condition rather than merely treating its complications. |
| **16a. Is the technology a 'step-change' in the management of the condition?** | Yes, it will address a large unmet treatment need for this population. |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | Having access to this drug will accelerate the development of integrated clinical networks which will help address the health inequalities that currently exist for the more elderly, frail patients with wtATTR-CA that cannot currently easily travel to access expert care in London. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | No concerning side effects reported. Excellent patient tolerability. |

**Sources of evidence**

| | |
|---|---|
| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Based on the results of the ATTRibute-CM trial (phase III RCT of AG10, acoramidis) which was only recently presented at an ESC 2023 Hotline session, I suspect that the efficacy of TTR stabilisers as a class of drugs to treat amyloidosis may have been underestimated. The ATTR-ACT trial is now more than 5 years old. The patients enrolled into the ATTR-ACT trial were much sicker than in ATTRibute-CM – note that the mortality in the treatment arm of ATTR-ACT was higher than the mortality in the placebo arm of ATTRibute-CM. Although mortality was reduced by tafamidis, QoL and functional status (6MWT) still declined in the trial but at a slower rate than in the placebo arm. It is possible that if patients had not had such advanced disease by the time they received tafamidis |

| | |
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| | in the trial, I suspect that we may have seen improvements in 6MWT and functional status in ATTR-ACT (akin to the results of ATTRibute-CM). This is relevant because we are detecting patients in the UK at an earlier stage in their disease process compared with 5 years ago (Ioannou et al 2022 Circulation). |
| **18a. If not, how could the results be extrapolated to the UK setting?** | Results are applicable. |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | QoL, functional status, CV mortality. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | N/A. |
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | No. |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No. |
| **20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal and highly specialised technology** | No. |

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| **guidance HST9, HST10 or TA868?** | |
| **21. How do data on real-world experience compare with the trial data?** | I am not aware of any EAMS real-world UK data being published but anecdotal reports of our experience and others involved in EAMS have been consistent with the trial data. |

**Equality**

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| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | If prescribing is going to be limited to specialist centres there will need to be a level of investment and resource from NHSE to facilitate the development of an integrated clinical care network that provides acceptable local / regional access to patients. While treatment of rare disease needs to be of high quality and standardised within certain expert centres, this concept needs to be balanced with the Long Term NHS Plan's vision that patients should have an ability to choose where they are offered treatment. This is particularly important for the majority of patients diagnosed with wtATTR who are very often over the age of 80 years. |
| **22b. Consider whether these issues are different from issues with current care and why.** | |

**Key messages**

| | |
|---|---|
| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • Tafamidis will help reduce a large unmet need for the increasing number of patients with ATTR cardiac amyloidosis by not only reducing mortality but importantly, improving quality of life and functional status.<br>• The prescribing of tafamidis might initially be best restricted to a number of specialist regional centres with the requisite expertise in this area. These centres will require access to multimodality imaging (DPD/CMR) and to experienced histopathologists for the 10-20% of ATTR patients with a concomitant paraproteinaemia in whom tissue typing is still required to exclude AL-cardiac amyloidosis.<br>• A key requirement will be to develop in parallel an integrated clinical care network between a number of regional centres but rather than decentralising care have on-going central support available from the National Amyloidosis Centre, Royal Free Hospital, London.<br>• There should be an emphasis on suspecting and making the diagnosis early as well as offering timely treatment to patients. |

Thank you for your time.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

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## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | Royal College of Pathologists |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes<br>A specialist in the treatment of people with this condition? Yes<br>A specialist in the clinical evidence base for this condition or technology? Yes<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | Royal College of Pathologists is the professional body that oversees training and governance for all consultant haematologists (amyloidosis is part of this from a haematology perspective) |
| **5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | No |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | no |

## The aim of treatment for this condition

| | |
|---|---|
| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | The goal is to delay progression and improve survival |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | Yes – there is clinically meaningful improvement in quality of life and survival with this drug |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | Yes – ATTR cardiac amyloidosis is increasingly diagnosed. There is no treatment for this condition on the NHS and the median survival without treatment is 2-5 yrs depending on degree of cardiac damage at presentation. It is huge and growing unmet need. |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Only supportive treatment for heart failure and there is not disease modifying treatment |

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| **9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?** | No UK clinical guidelines for treatment of ATTR amyloidosis. Trhere are international guidelines<br>Ando et al Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosisAmyloid . 2022 Sep;29(3):143-155. doi: 10.1080/13506129.2022.2052838. Epub 2022 Jun 2. |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | The diagnostic pathway is well defined. In the UK, we have central national centre for diagnosis and management advice at the Royal Free London NHS trust |
| **9c. What impact would the technology have on the current pathway of care?** | More treatment will be available locally |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | This will be new treatment and define new pathways for management of amyloidosis |
| **10a. How does healthcare resource use differ between the technology and current care?** | There is currently no treatment! |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | This should be used by secondary care and diagnosis rigorously confirmed by appropriately trained cardiologists |
| **10c. What investment is needed to introduce the technology? (For example,** | No additional investment needed. NHSE has agreed to fund a UK amyloidosis networ and this will be perfectly suitable for such a network |

| | |
|---|---|
| **for facilities, equipment, or training.)** | |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | Yes |
| **11a. Do you expect the technology to increase length of life more than current care?** | Yes – definitely |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | Yes – definitely |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | This will have special utility in the black afro-caribbean population where there is higher incidence of ATTR amyloidosis (due to V122I mutation) and is often advanced due to delayed diagnosis. |

## The use of the technology

| | |
|---|---|
| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant** | No |

| | |
|---|---|
| **treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | The defined pathway for accurate confirmation of diagnosis of cardiac ATTR amyloidosis is absolutely critical. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | No |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Yes – it is first in class drug that has transformed approach to ATTR amyloidosis s |
| **16a. Is the technology a 'step-change' in the** | Yes |

| | |
|---|---|
| **management of the condition?** | |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | This will have special utility in the black afro-caribbean population where there is higher incidence of ATTR amyloidosis (due to V122I mutation) and is often advanced due to delayed diagnosis. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | No |

**Sources of evidence**

| | |
|---|---|
| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Yes – the populations are same in UK but we don't have any treatments. |
| **18a. If not, how could the results be extrapolated to the UK setting?** | |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | Cardiac hospitalization and death |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | Yes |

| | |
|---|---|
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | No serious adverse effects that need special monitoring |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal and highly specialised technology guidance HST9, HST10 or TA868?** | No |
| **21. How do data on real-world experience compare with the trial data?** | They are very comparable and support trial evidence |

## Equality

| | |
|---|---|
| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | This will have special utility in the black afro-caribbean population where there is higher incidence of ATTR amyloidosis (due to V122I mutation) and is often advanced due to delayed diagnosis. |
| **22b. Consider whether these issues are different from issues with current care and why.** | |

## Key messages

| | |
|---|---|
| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • Large and growing unmet need<br>• Novel oral easy to use well tolerated treatment<br>• Improves symptoms of heart failure<br>• Improves QOL<br>• Improves survival |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

## Your privacy

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**Single Technology Appraisal**

**Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]**

**Clinical expert statement**

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **26 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received, 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 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.**

Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

NICE National Institute for Health and Care Excellence

# Part 1: Treating transthyretin amyloidosis with cardiomyopathy and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Perry Elliott |
| **2. Name of organisation** | University College London (Role in STA: company nominated expert) |
| **3. Job title or position** | Director UCL Institute of Cardiovascular Science |
| **4. Are you (please tick all that apply)** | ☐ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with transthyretin amyloidosis?<br>☒ A specialist in the clinical evidence base for transthyretin amyloidosis or tafamidis?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |

Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

| | |
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| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |
| **8. What is the main aim of treatment transthyretin amyloidosis with cardiomyopathy?**<br>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | Amyloidosis encompasses a family of diseases characterised by the abnormal deposition of misfolded proteins within various tissues. The clinical course and management of the different subtypes of amyloidosis are dependent on the type of precursor protein. Transthyretin amyloid (ATTR) can be classified into wild type (ATTRwt) caused by deposition of native TTR and mutant or familial type (ATTRv) caused by a mutation in the TTR gene encoding transthyretin. Patients with ATTRv can suffer both neurological and cardiac symptoms whereas ATTRwt primarily affects the heart.<br><br>ATTR related cardiomyopathy (ATTR-CM) is a late-onset disease with symptom onset in patients aged 60 years or older. Typical symptoms include dyspnoea, fatigue, postural hypotension and syncope. In patients with untreated ATTRwt cardiomyopathy, median survival ranges from 26 to 67 months from diagnosis and 72 months from symptom onset. Patients with the commonest genetic mutation–Val122Ile–have a median survival time from diagnosis ranging from 36 months to 43 months. Death in most patients with cardiac amyloidosis is sudden or caused by progressive heart failure.<br><br>The aim of existing therapies is to ameliorate symptoms of heart failure and to protect against the effects of cardiac rhythm disturbance (principally atrial fibrillation and heart block). No drugs in current use (in the UK) slow progression of ATTR-CM or improve prognosis. The development of disease modifying therapies such as tafamidis offer the prospect of improving survival.<br><br>The therapeutic goals, based on the putative mechanisms of tafamidis, are to stop or slow disease progression and to preserve mobility, independence and |

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| | quality of life and to reduce disease related mortality. At the present time, there is no evidence that TTR stabilisers cure the disease. |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | The ATTR-ACT trial demonstrated both a reduction in mortality and a significant reduction in the decline of quality of life and six minute walk test.<br>In an individual patient, it is difficult to determine whether there has been prolongation of life, but survival beyond the median of untreated patients would be supportive evidence. The ATTR-ACT long-term extension trial has shown persistence of this effect beyond 30 months.<br><br>Of more immediate relevance is slowing of disease progression. In ATTR-ACT, the impact of tafamidis on exercise tolerance became apparent from the onset of therapy and so stability (within 10% of baseline values) in six minute walk and symptom score at 6 and 12 months represents a reasonable therapeutic goal. |
| **10. In your view, is there an unmet need for patients and healthcare professionals in transthyretin amyloidosis with cardiomyopathy?** | Improvements in cardiac imaging and raised awareness amongst cardiologists has resulted in an increase in the frequency of ATTR-CM diagnosis in clinical practice. Until very recently, this improvement has not been matched by disease modifying treatments that prevent disease progression or improve prognosis. Consequently, ATTR-CM is analogous with other fatal and incurable disorders including some cancers and neurogenerative diseases.<br>The promise of therapy with clinically proven drugs represents a step change in care and has been adopted by the US, Japan, other European Nations as well as NHS Scotland. The greatest unmet need for HCP, patients and families is the lack of tafamidis in the UK. |
| **11. How is transthyretin amyloidosis with cardiomyopathy currently treated in the NHS?** | US and European Cardiac Societies have provided guidance on the management of ATTR-CM that includes use of tafamidis: |

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| • Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | *Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2021;42:1554–1568.* https://doi.org/10.1093/eurheartj/ehab072<br><br>*Elena Arbelo, et al. ESC Scientific Document Group , 2023 ESC Guidelines for the management of cardiomyopathies: Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC), European Heart Journal, Volume 44, Issue 37, 1 October 2023, Pages 3503–3626,* https://doi.org/10.1093/eurheartj/ehad194<br><br>*Kittleson, M, Ruberg, F. et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023 Mar, 81 (11) 1076–1126.* **https://doi.org/10.1016/j.jacc.2022.11.022**<br><br>In the absence of tafamidis in the UK, treatment of ATTR-CM is palliative, using standard heart failure medication. However, beta blockers may reduce compensatory tachycardia and induce greater negative inotropic effects in amyloid infiltrated hearts. Digoxin is contraindicated as it can bind to amyloid fibrils and lead to a toxic effect. ARBs and ACE inhibitors are often not tolerated because of hypotension. Consequently, therapeutic options to relieve symptoms are often limited to diuretics alone.<br><br>Patients with ATTR-CM are prone to arrhythmia, in particular heart block and atrial fibrillation. The first is potentially fatal but can be treated with a cardiac |

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| | pacemaker. The second may increase symptoms and be associated with thromboembolic stroke and so usually requires prophylactic anticoagulation.<br><br>In other advanced healthcare systems, ATTR-CM is diagnosed and managed by cardiologists. This is understandable (and appropriate) given the predominance of cardiac signs and symptoms, the need for advanced cardiac imaging, and the experience required in the differential diagnosis and management of more common diseases that resemble or mimic ATTR-CM. Some concerns have been voiced about this model in the UK because of a perceived lack of knowledge and experience on the part of 'non-specialists'. However, experience in other countries shows that clear guidance and education results in timely and accurate diagnosis of ATTR-CM. The experience from the 16 centres designated in the EAMS scheme for tafamidis confirmed that this is also true of the UK.<br><br>The administration and monitoring of tafamidis is feasible within existing cardiac services and care pathways. |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | Tafamidis represents a new therapeutic option for patients with ATTR-CM in the UK but not elsewhere in North America, Europe or Japan. Experience in these settings show that diagnosis and treatment with tafamidis is feasible using existing cardiac services.<br><br>Main-streaming of clinical testing for ATTR-CM is necessary due to the size and distribution of the populations that can reasonably be considered for screening (for example, patients with heart failure and preserved ejection fraction). Moreover, the demographic of the at risk population–namely, elderly individuals with varying degrees of limitation–means that diagnosis and care should be delivered as close to patients as possible. |

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| | Some degree of specialisation in the diagnosis of heart muscle disease is desirable for HCPs involved in the diagnosis and management of ATTR-CM, to ensure appropriate usage of tafamidis. Fortunately, the UK already has a network of centres that specialise in the assessment of heart muscle disorders ( https://www.theaicc.org).<br>All such services have access to advanced cardiac imaging and genetic testing via the UK genetic testing service and the requirement for new investment to support amyloid treatment and diagnosis will be small. A new service specification for cardiomyopathy services (within the rubric of inherited cardiac conditions) is expected from NHSE in 2024. |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | Data from ATTR-ACT and ATTR-ACT LTE demonstrates a significant survival benefit over standard of care.<br><br>Tafamidis slows physical decline and thus maintains independence and quality of life for individuals with ATTR-CM. |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | Benefit has not been demonstrated in patients with NYHA class IV symptoms, severe aortic stenosis, or impaired renal function (glomerular filtration rate <25 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ body surface area). |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?** | As tafamidis is a once daily oral preparation with a good safety profile, its use in addition to conventional heart failure therapy is not problematic in clinical practice as there are no investigations beyond standard of care required for disease monitoring. |

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| (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | Disease progression without therapy in ATTR-CM is inevitable, but is slowed with tafamidis if started as early as possible following the diagnosis.<br><br>The indications for therapy are informed by the inclusion criteria for the pivotal ATTR-ACT trial and are clearly stated in current practice guidelines.<br><br>They include the presence of a cardiac phenotype consistent with ATTR-CM and confirmatory diagnostic tests for ATTR-CM such as bone scintigraphy have been shown to have very high sensitivity and specificity for the diagnosis of ATTR-CM; Evidence supports treatment in people with NYHA class 1-3 symptoms.<br><br>Some patients may develop progressive heart failure in spite of therapy, in common with all forms of heart failure even with the use of best evidence based care.<br><br>Most patients with heart failure progress through a number of phases: a relatively stable primary phase needing routine chronic disease management; one or more secondary phases of decline requiring increased utilization of hospital care and a supportive and palliative care strategies; and a third terminal phase of inexorable decline lasting for days or weeks. There are many prognostic markers in advanced heart failure, including clinical indicators such as NYHA, biochemical markers and more complex cardiac investigations. In ATTR-CM, several measures of response and disease progression have been proposed including hospitalizations, functional capacity (NYHA class, 6-minute walk test, gait speed, cardiopulmonary exercise stress testing), quality of life, and cardiac biomarkers and imaging (echocardiography, magnetic resonance |

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| | imaging, or positron emission tomography) but there are no validated scoring methods for patients receiving disease modifying therapy such as tafamidis.<br><br>In my opinion, management of advanced ATTR-CM is no different from that of advanced heart failure of any cause. In everyday practice, complex scoring systems are unnecessary in the vast majority of elderly patients with advanced HF, as features such as progressive renal dysfunction, weight loss and escalating diuretic dose requirements provide evidence for preterminal disease.<br>Imposition of stopping rules for tafamidis is unnecessary as therapeutic decisions on supportive therapies should be made in consultation with patients and carers.<br>There is no evidence for or reason to suspect that withdrawal of therapy in a patient with refractory NYHA IV symptoms will suffer an acute exacerbation of their clinical condition. |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | ATTR-CM imposes a major burden on carers. Maintenance of quality of life and independence will impact favourably on this burden. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | At present, there are no licensed disease modifying therapies for ATTR-CM available in the UK. Data from RCT and real world observational cohorts consistently demonstrate improved survival, reduced hospitalisations and a slowing of disease progression in patients treated with tafamidis. In this respect, tafamidis represents a significant step-change for patients with ATTR-CM, |

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| • Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Tafamidis has been shown to have an excellent side-effect profile and has not been a concern in real world experience of the drug in other countries. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | The ATTR-ACT trial inclusion criteria mirror those used routinely to diagnosis ATTR-CM in the UK. The study population characteristics are identical to those of untreated patients with ATTR-CM in the UK. I see no reason why the results cannot be extrapolated to the UK setting.<br><br>The reduction in mortality in elderly patients with advanced disease is remarkable, but the slowing of disease progression is even more impressive and likely to be of most relevance to patients and families.<br><br>Functional parameters such as 6 minute walk test and KCCQ are validated instruments used in multiple trials to assess response to therapy. |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | **Sub-studies from ATTR-ACT and ATTR-ACT LTE:**<br><br>Rapezzi C, Elliott P, Damy T, et al. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. *JACC Heart Fail* 2021;9:115–23. [PubMed] [Google Scholar]<br><br>Miller AB, Januzzi JL, O'Neill BJ, et al. Causes of cardiovascular hospitalization and death in patients with transthyretin amyloid cardiomyopathy (from the |

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| | tafamidis in Transthyretin Cardiomyopathy Clinical Trial [ATTR-ACT]). *Am J Cardiol*2021;148:146–50. [PubMed] [Google Scholar]<br><br>Elliott P, Drachman BM, Gottlieb SS, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail* 2022;15:e008193. [PMC free article] [PubMed] [Google Scholar]<br><br>Shah SJ, Fine N, Garcia-Pavia P, Klein AL, Fernandes F, Weissman NJ, Maurer MS, Boman K, Gundapaneni B, Sultan MB, Elliott P. Effect of Tafamidis on Cardiac Function in Patients With Transthyretin Amyloid Cardiomyopathy: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. JAMA Cardiol. 2024 Jan 1;9(1):25-34. doi: 10.1001/jamacardio.2023.4147. PMID: 37966817; PMCID: PMC10652219.<br><br>Garcia-Pavia P, Sultan MB, Gundapaneni B, Sekijima Y, Perfetto F, Hanna M, Witteles R. Tafamidis Efficacy Among Octogenarian Patients in the Phase 3 ATTR-ACT and Ongoing Long-Term Extension Study. JACC Heart Fail. 2024 Jan;12(1):150-160. doi: 10.1016/j.jchf.2023.08.032. Epub 2023 Nov 8. PMID: 37943223.<br><br>Elliott P, Gundapaneni B, Sultan MB, Ines M, Garcia-Pavia P. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. Eur J Heart Fail. 2023 Nov;25(11):2060-2064. doi: 10.1002/ejhf.2974. Epub 2023 Jul 26. PMID: 37434378.<br><br>Rozenbaum MH, Garcia A, Grima D, Tran D, Bhambri R, Stewart M, Li B, Heeg B, Postma M, Masri A. Health impact of tafamidis in transthyretin amyloid |

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| | cardiomyopathy patients: an analysis from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and the open-label long-term extension studies. Eur Heart J Qual Care Clin Outcomes. 2022 Aug 17;8(5):529-538. doi: 10.1093/ehjqcco/qcab031. PMID: 33895806; PMCID: PMC9382662.<br><br>**Real World Studies of Tafamidis**<br>Ghoneem A, Bhatti AW, Khadke S, Mitchell J, Liu J, Zhang K, Trachtenberg B, Wechalekar A, Cheng RK, Baron SJ, Nohria A, Lenihan D, Ganatra S, Dani SS. Real-World Efficacy of Tafamidis in Patients With Transthyretin Amyloidosis and Heart Failure. Curr Probl Cardiol. 2023 Jun;48(6):101667. doi: 10.1016/j.cpcardiol.2023.101667. Epub 2023 Feb 23. PMID: 36828040.<br><br>Bézard M, Kharoubi M, Galat A, Poullot E, Guendouz S, Fanen P, Funalot B, Moktefi A, Lefaucheur JP, Abulizi M, Deux JF, Gendre T, Audard V, El Karoui K, Canoui-Poitrine F, Zaroui A, Itti E, Teiger E, Planté-Bordeneuve V, Oghina S, Damy T. Natural history and impact of treatment with tafamidis on major cardiovascular outcome-free survival time in a cohort of patients with transthyretin amyloidosis. Eur J Heart Fail. 2021 Feb;23(2):264-274. doi: 10.1002/ejhf.2028. Epub 2020 Nov 9. PMID: 33094885.<br><br>Ochi Y, Kubo T, Baba Y, et al. Early experience of tafamidis treatment in Japanese patients with wild-type transthyretin cardiac amyloidosis from the Kochi amyloidosis cohort. *Circ J* 2022;86:1121–8. [PubMed] [Google Scholar]<br><br>Falk RH, Haddad M, Walker CR, Dorbala S, Cuddy SAM. Effect of Tafamidis on Serum Transthyretin Levels in Non-Trial Patients With Transthyretin Amyloid Cardiomyopathy. JACC CardioOncol. 2021 Oct 19;3(4):580-586. doi: 10.1016/j.jaccao.2021.08.007. PMID: 34729530; PMCID: PMC8543137. |

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| | Systematic reviews and meta-analyses:<br><br>Singh BM, Bohara N, Gautam K, Basnet M, Kc S, Kc B, Raut A, Phudong A, Gautam J. A Systematic Review of Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy. Cureus. 2021 Sep 23;13(9):e18221. doi: 10.7759/cureus.18221. PMID: 34703707; PMCID: PMC8541744.<br><br>Wang J, Chen H, Tang Z, Zhang J, Xu Y, Wan K, Hussain K, Gkoutos GV, Han Y, Chen Y. Tafamidis treatment in patients with transthyretin amyloid cardiomyopathy: a systematic review and meta-analysis. EClinicalMedicine. 2023 Aug 24;63:102172. doi: 10.1016/j.eclinm.2023.102172. PMID: 37662524; PMCID: PMC10474377. |
| **22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA696?** | Completed trial of stabiliser acoramdis:<br><br>Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, Grogan M, Hanna M, Hoffman J, Masri A, Maurer MS, Nativi-Nicolau J, Obici L, Poulsen SH, Rockhold F, Shah KB, Soman P, Garg J, Chiswell K, Xu H, Cao X, Lystig T, Sinha U, Fox JC; ATTRibute-CM Investigators. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024 Jan 11;390(2):132-142. doi: 10.1056/NEJMoa2305434. PMID: 38197816. |

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| **23. How do data on real-world experience compare with the trial data?** | Real World data support the randomised data from ATTR-ACT in that they show stabilisation of cardiac symptoms, echo parameters and circulating biomarkers. They also support data showing a reduction in mortality and hospitalisation (see Q21)<br><br>**Two ongoing trials of silencers:**<br><br>**CARDIO-TTRansform**<br>NCT04136171<br>Eplontersen (TTR silencer, antisense oligonucleotide)<br>Composite of CV mortality and recurrent CV clinical events up to week 140<br>Enrollment completed mid-2022<br><br>**HELIOS-B**<br>NCT04153149<br>Vutrisiran (TTR silencer, small interfering RNA)<br><br>Composite of all-cause mortality recurrent CV events (CV hospitalizations and urgent HF visits) at 30-36 mo<br>Enrollment completed August 2021 |
| **24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this** | ATTR-CM affects predominantly older individuals (> 60 years of age). People of black African ancestry are also at higher risk of ATTR-CM by reason of a high prevalence (3-4%) of a predisposing genetic variant (V142I). |

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| **treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | Therefore, failure to licence tafamidis has a disproportionate effect on these groups and may contravene equality legislation. |

NICE National Institute for Health and Care Excellence

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. ATTR-CM is easily diagnosed by cardiologists using readily available tests.
2. Untreated ATTR-CM is associated with a high mortality and poor quality of life.
3. Randomised trial and real world data show that tafamidis reduces mortality and slows disease progression resulting in fewer hospital admissions.
4. Tafamidis is safe and adherence to therapy is high.
5. Unavailability of tafamidis disproportionately affects older people and individuals of black African ancestry who carry a common genetic variant that predisposes to ATTR-CM

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]**

**Clinical expert statement**

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **26 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received, 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 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.**

Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

NICE National Institute for Health and Care Excellence

# Part 1: Treating transthyretin amyloidosis with cardiomyopathy and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

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| **1. Your name** | Prof Philip Hawkins |
| **2. Name of organisation** | National Amyloidosis Centre, London (Royal Free Hospital and UCL) |
| **3. Job title or position** | |
| **4. Are you (please tick all that apply)** | ☐ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with transthyretin amyloidosis?<br>☐ A specialist in the clinical evidence base for transthyretin amyloidosis or tafamidis?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☐ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☒ Other (I do not know if they submitted one.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ |

Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

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| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |
| **8. What is the main aim of treatment transthyretin amyloidosis with cardiomyopathy?**<br>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | Relieve symptoms, improve quality of life, inhibit further amyloid formation and further damage to the heart. It is now clear that therapies that very substantially inhibit ongoing amyloid formation can result to gradual recovery from the disease – reversal is now a realistic goal. |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | ATTR cardiomyopathy is a progressive disease, but it progresses at different rates among patients. With current therapies, which merely aim to slow down progression, it is thus not possible to define a clinically significant response in most newly diagnosed patients. However, serial monitoring of quality of life, cardiac symptoms, serum NT-proBNP, 6 minute walk test and diuretic usage / lack of intensification can suggest evidence of disease stability in some cases, and occasionally improvement. Worsening of NAC disease stage and various cut-offs for increases in NT-proBNP after 12 months follow-up are associated with significantly worse survival, potentially providing an indication to switch therapy. |
| **10. In your view, is there an unmet need for patients and healthcare professionals in transthyretin amyloidosis with cardiomyopathy?** | At present there are no therapies available in England that have potential to slow down progression of ATTR-CM. Tafamidis is licenced for this indication, and several other therapies are in late stage development, which all seem very promising. At present only a small percentage of patients with ATTR-CM are being diagnosed, and greater awareness and resources enabling diagnostic imaging are needed in the much wider heart failure population. |
| **11. How is transthyretin amyloidosis with cardiomyopathy currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals | There are various international guidelines, but I don't think any specific for the NHS population. Currently, patients receive only supportive medical care, i.e. no disease modifying therapy outside trials, but supportive pharmacological care has improved vastly of late including use of SGLT-2 inhibitors which appear to be having a very positive effect on patients' symptoms and survival. |

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| across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | Should tafamidis be approved for NHS use, it is likely that physicians will routinely wish to prescribe it to virtually all ATTR-CM patients in addition to current supportive care. |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | The characteristics of the currently diagnosed ATTR-CM population in England are very different to the patients who participated in the phase 3 trial of tafamidis.<br><br>Patients are now mostly diagnosed through imaging, not biopsies, and are treated with a far wider range of supportive pharmacology. A substantial proportion of patients are now diagnosed at an early stage of disease (i.e. NAC disease stage 1).<br><br>Whilst tafamidis has an excellent safety record, the challenge will be to determine effectiveness / response / stopping rules within the NHS. Crucially, there are thought to be ~20,000 ATTR-CM pts in England, most presently undiagnosed, requiring much more equitable access to diagnostic DPD scintigraphy and cardiac MRI (noting that DPD scintigraphy has lately become licenced for this clinical indication).<br><br>Misdiagnosis remains common (false positive diagnoses of ATTR-CM and failure to recognise cardiac AL amyloidosis requiring urgent chemotherapy), hence this technology must for some time be prescribed under specialist care. |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care? | It is not known what factors may determine responsiveness to the treatment, and whether some patients may benefit more than others. It is likely that length of life will be increased in some patients, though note that the average age at diagnosis is 77 years, and it has lately been shown that untreated patients diagnosed with NAC stage 1a disease have the same survival as age-matched non-amyloid controls. |

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| • Do you expect the technology to increase health-related quality of life more than current care? | I would anticipate that reduced deterioration of quality of life is likely, but the benefits of tafamidis have not been demonstrated over and above recent improvements in supportive care, particularly the emerging symptomatic and survival benefits associated with SGLT2 inhibitors. |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | It has not been studied in patients with a very early diagnosis of ATTR-CM, although it is possible that such patients might ultimately even benefit most.<br><br>The phase 3 trial excluded patients with:<br><br>• An NTproBNP concentration < 600 pg/mL<br>• 6-minute walk test < 100 meters<br>• NYHA class IV heart failure<br>• Additional heart failure not related to TTR amyloid cardiomyopathy (which is of course very common in older people)<br>• Creatinine clearance ≤ 25 mL/min<br>• History of heart or liver transplantation<br>• Implanted cardiac device (very common in ATTR-CM population)<br>• Liver transaminase levels exceeding two times the upper limit of normal<br>• Severe malnutrition<br>• Use of NSAIDs, calcium-channel blockers, or digitalis (all common) |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?** | Easy, as once daily table by mouth. |

| | |
|---|---|
| (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | Note the many exclusions in the seminal trial. I would hope that specialist clinical practice and ongoing monitoring (including for example, follow up cardiac MRI) will yield pointers to responders and non-responders, the latter likely to be very important given several very promising new technologies on the near horizon. |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | This treatment will always be in addition to current standard of care.<br><br>Musculoskeletal disorders have emerged as very frequent manifestations of ATTR amyloidosis but have been little studied as yet. These include carpal tunnel syndrome (which can recur after surgery), lumbar spinal canal stenosis causing neuropathy, tendinopathy and rupture, and diffuse skeletal muscle amyloid deposition. An excess of patients with ATTR amyloidosis require joint replacement for apparent osteoarthritis, but the nature of this latter association is not known as yet.<br><br>I am unclear if / how QoL measurements may have taken these issues into account. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | This technology does represent a step change, since it would be the first potentially disease modifying treatment to become available for patients with ATTR-CM. However, the lack of measurable / biological markers of response in terms of effect on reducing ATTR amyloid formation is frustrating. |

| | |
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| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Excellent adverse effect profile, but noting the exclusions of many commonly used medicines in the target (older) population. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | Patients are lately being treated with much improved supportive care (see Conventional heart failure therapy in cardiac ATTR amyloidosis. Ioannou A et al. Eur Heart J. 2023 Aug 14;44(31):2893-2907), with survival benefits associated with beta blockers and mineralocorticoid antagonists in various sub-groups.<br><br>Mortality and hospitalisation measured in the trial are very robust outcomes.<br><br>Real world tolerance and safety appear excellent, as per trial. |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA696?** | The results of a phase 3 trial in ATTR-CM of a second generation TTR stabiliser, acoramidis, have just been published raising the possibility of greater efficacy. (Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. Gillmore JD, N Engl J Med. 2024 Jan 11;390(2):132-142). In submission for approval. |
| **23. How do data on real-world experience compare with the trial data?** | Earlier diagnosis and better supportive care since the trial was conducted have greatly reduced mortality and hospitalization, making comparisons with the trial population difficult / impossible. |
| **24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into** | Perhaps not technically an equality issue in the legal sense, but ATTR-CM is almost certainly especially underdiagnosed / considered / recognised in women, |

| | |
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| **account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | in whom currently used diagnostic echocardiographic parameters are inappropriate.<br><br>Of course the greatest inequality is the failure to diagnose ATTR-CM in the estimated 80-90% of patients who currently have the disease without it having been detected. |

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## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. ATTR-CM is far more common than previously thought, with an estimated 20,000 patients in England, most undiagnosed.
2. Currently no potentially disease modifying therapies are available to NHS patients with ATTR-CM, hence there is a major unmet need.
3. Tafamidis is a plausible, evidently safe therapy that delayed progression of ATTR-CM in the phase 3 trial.
4. Many ATTR-CM patients are now diagnosed at an early stage and would not have been eligible to join the tafamidis phase 3 trial, but it is nevertheless highly likely that progression of their disease could be similarly delayed.
5. It is currently not possible to either identify upfront which patients are most / least likely to benefit from tafamidis therapy nor to determine response / benefit in the first year or two of treatment since there are no early biomarkers of response and because ATTR-CM progresses variably among different patients and, overall, is expected to continue to worsen despite this treatment.

Thank you for your time.

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Clinical expert statement

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

**Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]**

**Patient expert statement**

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

# Information on completing this form

In part 1 we are asking you about living with or caring for a patient with transthyretin amyloidosis with cardiomyopathy. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

## Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **26 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments, 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 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.**

Patient expert statement

# Part 1: Living with or caring for a patient with transthyretin amyloidosis with cardiomyopathy

**Table 1 About you, transthyretin amyloidosis with cardiomyopathy, current treatments and equality**

NICE National Institute for Health and Care Excellence

| | |
|---|---|
| **1. Your name** | **Ben Laryea** |
| **2. Are you (please tick all that apply)** | ☒ A patient with transthyretin amyloidosis with cardiomyopathy?<br>☐ A patient with experience of the treatment being evaluated?<br>☐ A carer of a patient with transthyretin amyloidosis with cardiomyopathy?<br>☐ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | **UK ATTR Amyloidosis Patients' Association (UKATPA)** |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☐ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☐ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☐x I am drawing from personal experience<br>☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: |

| | |
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| **6. What is your experience of living with transthyretin amyloidosis?**<br>**If you are a carer (for someone with transthyretin amyloidosis with cardiomyopathy, please share your experience of caring for them** | I am a patient living with the burden of hereditary ATTR Cardiac Amyloidosis, having been diagnosed with the condition two years ago.<br><br>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.<br><br>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 grand children. 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.<br><br>Breaking the news to my children was one of the worst days of my life.<br><br>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.<br><br>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. |

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| | 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. |

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| **7a. What do you think of the current treatments and care available for transthyretin amyloidosis with cardiomyopathy on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | **As far as I am aware there is no current treatment available for those patients with Transthyretin Amyloidosis with cardiomyopathy.**<br><br>**However those with Polyneuropathy can access drugs and treatments, which as I have stated above seems inequitable, when treatments can be available for all. Those that are lucky enough to be receiving treatment that I have spoken to and got to know, report stabilisation of their condition and improved quality of life.** |
| **8. If there are disadvantages for patients of current NHS treatments for transthyretin amyloidosis with cardiomyopathy (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | N/A |
| **9a. If there are advantages of tafamidis over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does tafamidis help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | **If there is no current treatment, then simply having Tafamidis available to those who can't access anything currently, will the benefit and advantage in itself.** |

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| **10. If there are disadvantages of tafamidis over current treatments on the NHS please describe these.**<br>**For example, are there any risks with tafamidis? If you are concerned about any potential side effects you have heard about, please describe them and explain why.** | I haven't heard of any potential side effects that would be a concern. |
| **11. Are there any groups of patients who might benefit more from tafamidis or any who may benefit less? If so, please describe them and explain why.**<br>**Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments.** | |

| | |
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| **12. Are there any potential equality issues that should be taken into account when considering transthyretin amyloidosis with cardipmyopathy and tafamidis? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | I believe that groups such as the African /Carribbean communities may be disproportionately and significantly disadvantaged by the current position of no treatment available unless you have polyneuropathy. This is because the variant that affects this particular group generally tends not to lead to polyneuropathy. Having Tafamidis to treat transthyretin amyloidosis with cardiomyopathy will help with any equalities issues in this regard. |
| **13. Are there any other issues that you would like the committee to consider?** | |

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal
# Guidance review following a period of managed access
# NHS commissioning expert statement
# Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

**Information on completing this expert statement**

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1. Your name | **Fiona Marley** |

| | |
|---|---|
| 2. Name of organisation | **NHS England** |
| 3. Job title or position | **Deputy Director, Clinical Commissioning (Highly Specialised Services)** |
| 4. Are you (please tick all that apply): | ☒ commissioning services for a CCG or NHS England in general?<br>☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology?<br>☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)?<br>☐ an expert in treating the condition for which NICE is considering this technology?<br>☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)?<br>☐ other (please specify): |
| **Current treatment of the condition in the NHS (outside of the managed access agreement [MAA])** | |
| 5. Are any clinical guidelines used in the treatment of the condition, and if so, which? | **Yes, there is information on the website for the National Amyloidosis Centre:**<br>Information for Referring Physicians \| Centre for Amyloidosis and Acute Phase Proteins - UCL – University College London |
| 6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across | **There is a single national centre (the Royal Free Hospital) that diagnoses patients with amyloidosis, and the pathway of care is well-defined. The national centre confirms diagnosis of all patients and then some treatments (like Tafamidis) are delivered locally.** |

| | |
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| the NHS? (Please state if your experience is from outside England.) | |
| **Experience of the technology during the managed access agreement [MAA]** | |
| 7. Have there been advantages of the technology and managed access agreement? What are they? | **Whilst not available on a managed access agreement, the treatment was available via the Early Access to Medicines Scheme. This was an opportunity to test out the service model and identify centres with expertise in the treatment of the condition.** |
| 8. Have there been disadvantages of the technology and managed access agreement? What are they? | **No disadvantages.** |
| **The use of the technology (after the managed access agreement [MAA])** | |
| 9. To what extent and in which population(s) will the | **In patients with a confirmed diagnosis of transthyretin amyloidosis with cardiomyopathy** |

| | |
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| technology be used in your local health economy? | |
| 10. Would you expect any changes to the pathway of care compared to what has been established as part of the managed access agreement? | **No** |
| 11. Would you expect any changes if the technology became part of routinely commissioned care? | **No** |
| • How does healthcare resource use differ between the technology and routinely commissioned care? | **It gives a treatment option for some patients where there is currently no treatment option** |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | **Specialist clinics** |

| | |
|---|---|
| • What investment is needed to introduce the technology into routine practice? (For example, for facilities, equipment, or training.)<br>• Will further centres need to be commissioned? | **All potentially eligible patients will need to be assessed (by a pharmacist and nurse) to confirm that they meet the diagnostic criteria. Homecare arrangements will then need to be put in place.**<br>**It is likely that the centres that treated patients during EAMS will primarily be those who will treat patients going forward.** |
| • If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned?<br>• If not, how would starting and stopping criteria be adapted? | **The rules for starting and stopping will be developed by the national centre and shared with the treating centres.** |
| 12. What is the outcome of any evaluations or audits of the use of the technology? | **There have not been any audits.** |
| **Equality** | |

| | |
|---|---|
| 13a. Are there any potential equality issues that should be taken into account when considering this treatment? | Black patients are much more likely to present with ATTR-CM amyloidosis but without polyneuropathy. Currently they are not eligible for the other commissioned therapies and receive only best supportive care. They may be eligible for tafamidis. The scope does not prejudice the care of any patient with other protected characteristics. |
| 13b. Consider whether these issues are different from issues with current care and why. | Yes – because black patients may be eligible for treatment going forward and this will potentially reduce inequities. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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# Tafamidis for transthyretin amyloid cardiomyopathy (review of TA696) [ID6327]

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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**Declared competing interests of the authors**

None.

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None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.



**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows:**

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**Contributions of authors**

Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, the company's economic evaluation and contributed to the writing of the report. Huiqin Yang also acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Mirre Scholte acted as health economics project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Willem Witlox, Andrea Fernández Coves and Xiaoyu Tian acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

**Abbreviations**

| | |
|---|---|
| AE | Adverse events |
| AIC | Akaike information criterion |
| ATTR-CM | transthyretin amyloid cardiomyopathy |
| BIC | Bayesian information criterion |
| BNF | British National Formulary |
| BNP | Brain natriuretic peptide |
| BSC | Best supportive care |
| CEA | Cost effectiveness analysis |
| CI | Confidence interval |
| CM | Cardiomyopathy |
| CMAD | Cardiac mechanical assist device |
| CS | Company submission |
| CV | Cardiovascular |
| DP | Decision problem |
| DSA | Deterministic sensitivity analysis |
| DSU | Decision Support Unit |
| EAG | Evidence Assessment Group |
| eMIT | Electronic market information tool |
| EPAR | European Public Assessment Report |
| EQ-5D | European Quality of Life-5 Dimensions |
| ESC | European Society of Cardiology |
| EUR | Erasmus University Rotterdam |
| FAD | Final appraisal document |
| FDA | Food and Drug Administration |
| FE | Fixing error |
| FV | Fixing value |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HT | Heart transplant |
| ICER | Incremental cost-effectiveness ratio |
| ITC | Indirect treatment comparison |
| ITT | Intention to treat |
| K-M | Kaplan-Meier |
| KSR | Kleijnen Systematic Reviews |
| KCCQ-QS | Kansas City Cardiomyopathy Questionnaire |
| LQ | Lower quartile |
| LTE | Long-term extension |
| LV | Left ventricular |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MJ | Matters of judgement |
| NA | Not applicable |
| NAR | Numbers at risk |
| NHB | Net health benefit |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| NR | Not reported |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| NT-proBNP | N-terminal pro-B type natriuretic peptide |
| NYHA | New York Heart Association |
| ONS | Office for National Statistics |
| OS | Overall survival |
| PAS | Patient access scheme |

| | |
|---|---|
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| QD | Once daily |
| QALY | Quality-adjusted life year |
| RCT | Randomised controlled trial |
| SD | Standard deviation |
| SE | Standard error |
| SLR | Systematic literature review |
| SoC | Standard of care |
| SR | Systematic review |
| STA | Single technology appraisal |
| TA | Technology assessment |
| TTD | Time to treatment discontinuation |
| TTR-FAP | Transthyretin familial amyloid polyneuropathy |
| UK | United Kingdom |
| UQ | Upper quartile |
| UMC+ | University Medical Center+ |
| WR | Win ratio |

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# 1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness), 4 (cost effectiveness) and 5 (cost effectiveness results) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

## *1.1 Overview of the EAG's key issues*

**Table 1.1: Summary of key issues**

| ID1457 | Summary of issue | Report Sections |
|---|---|---|
| 1 | Uncertainty as to whether the mixed polyneuropathy and cardiomyopathy part of the decision problem population is limited to only those where cardiomyopathy is predominant. | 2.1, 2.3, 3, 4.2.4 |
| 2 | Uncertainty regarding the appropriateness of the comparators for the whole cardiomyopathy population. | 2.3, 3 |
| 3 | No comparative clinical effectiveness data in the company submission. | 3 |
| 4 | No updated SLR for economic evaluations, resources/costs, or utilities | 4.1 |
| 5 | Continuation of the tafamidis treatment effect in patients who discontinued treatment. | 4.2.6 |
| 6 | Extrapolation of tafamidis OS. | 4.2.6 |
| 7 | Not using treatment-independent utility values for the NYHA IV health state. | 4.2.8 |
| 8 | Utility values being higher than the UK general population age-matched average. | 4.2.8 |
| 9 | Inconsistent PSA results. | 5.2 |

NYHA = New York Heart Association; OS = overall survival; PSA = probabilistic sensitivity analysis; SLR = systematic literature review; UK = United Kingdom

## *1.2 Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival, OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reduction of limitations in physical activity for tafamidis. Deterministic incremental QALYs gained for tafamidis versus best supportive care (BSC) were [redacted], of which [redacted] was gained in New York Heart Association (NYHA) health states NYHA I and II.
- Increased OS for tafamidis. Deterministic incremental life years gained for tafamidis versus BSC were [redacted].

Overall, the technology is modelled to affect costs by:

- Higher treatment costs for tafamidis. Deterministic incremental costs for tafamidis versus BSC were [redacted], of which [redacted] were treatment costs.

The parameters that have the greatest effect on the ICER (based on the company's deterministic sensitivity analyses) are:

- Discount rates of costs and QALYs
- NYHA class health state utilities
- Cardiovascular (CV)-related hospitalisation event rates.

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the overall indication net health benefit (NHB) were related to:

- Including the early diagnosis impact on costs
- Assuming no treatment usage in NYHA IV
- Extrapolation of tafamidis OS using log-logistic distribution.

### *1.3 The decision problem: summary of the EAG's key issues*

**Table 1.2: Key issue 1: Uncertainty as to whether the mixed polyneuropathy and cardiomyopathy part of the decision problem population is limited to only those where cardiomyopathy is predominant**

| **Report Section** | **2.1, 2.3, 3** |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The company excluded three comparators, patisiran, inotersen and vutisiran, that were listed in the NICE scope for the treatment of people with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy [TTR-FAP] and hereditary ATTR-CM). The basis of this was lack of evidence and licence for ATTR-CM. However, despite this, it is feasible that they are currently used in clinical practice for patients in this mixed phenotype subgroup, who might therefore also be eligible for tafamidis. However, in response to clarification, as well as reiterating the lack of evidence and license argument the company suggested that mixed phenotype patients might be subdivided by "*predominant*" presentation. This might mean that not all mixed phenotype patients would be eligible for tafamidis and those that were would not currently be treated with any of the three comparators. |
| **What alternative approach has the EAG suggested?** | The EAG suggested that the three comparators would be included at least for the mixed phenotype subgroup and that for this, a full systematic review be conducted. |

| Report Section | 2.1, 2.3, 3 |
|---|---|
| **What is the expected effect on the cost effectiveness estimates?** | Unknown. |
| **What additional evidence or analyses might help to resolve this key issue?** | The DP population could be narrowed to exclude patients of mixed phenotype who are currently treated with the three comparators. Alternatively, a full systematic review should be conducted to establish if there is sufficient evidence for a comparison between tafamidis and these comparators. |
| ATTR-CM = transthyretin amyloid cardiomyopathy; DP = decision problem; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; TTR-FAP = transthyretin familial amyloid polyneuropathy | |

**Table 1.3: Key issue 2: Uncertainty regarding the appropriateness of the comparators for the whole cardiomyopathy population**

| Report Section | 2.1, 2.3, 3. |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The company excluded diflunisal as comparator despite being included in the NICE scope. The company stated that this was because of lack of license and lack of evidence i.e.*:"…no randomised clinical trials (RCTs) investigating diflunisal in ATTR-CM."* However, they also indicated that it had in fact been used in the National Health Service (NHS), although they added that: *"patients diagnosed more recently with ATTR-CM are no longer initiated on diflunisal given that the drug is poorly tolerated, due to the negative side effect profile (typically associated with nonsteroidal anti-inflammatory drugs)"* (p. 39). This might indicate that diflunisal is no longer a comparator, but the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure recommend it: *"Off-label use of diflunisal may be considered in wtTTR-CA [ATTR-CM] in combination with a proton pump inhibitor."* (p. 3685) Therefore, the uncertainty as to comparator for the whole ATTR-CM population remains a key issue. |
| **What alternative approach has the EAG suggested?** | The EAG suggested a breakdown of all comparators used in the NHS and an SR and an ITC for each of them, but these were not provided. |
| **What is the expected effect on the cost effectiveness estimates?** | Unknown. |
| **What additional evidence or analyses might help to resolve this key issue?** | A breakdown of all comparators used in the NHS should be provided and an SR and ITC for each of them conducted. |
| ATTR-CM = transthyretin amyloid cardiomyopathy; DP = decision problem; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; SR = systematic review; TTR-FAP = transthyretin familial amyloid polyneuropathy | |

### *1.4 The clinical effectiveness evidence: summary of the EAG's key issues*

**Table 1.4: Key issue 3: No comparative clinical effectiveness data in the company submission**

| **Report Section** | **3.** |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The company stated that their intention for this CS was for it to be "abbreviated". They stated that this was agreed during the DP meeting and that this abbreviated document would contain no clinical effectiveness evidence but: *"New evidence which has become available since the original STA for tafamidis in ATTR-CM [TA6966] and where these data have been applied in the new economic base case"*. No systematic review was presented. Nor was any comparative evidence (tafamidis versus any form of standard of care): instead, only the Kaplan-Meier curves based on the latest overall survival and time to discontinuation data and limited safety data from patients treated with tafamidis in the long-term extension (LTE) study. |
| **What alternative approach has the EAG suggested?** | The EAG requested a full systematic review and comparative evidence from the tafamidis trial, which were not provided. |
| **What is the expected effect on the cost effectiveness estimates?** | Unknown. |
| **What additional evidence or analyses might help to resolve this key issue?** | The FAD for TA696 did conclude that the ATTR-ACT trials were appropriate for decision making and that, based on ATTR-ACT, tafamidis is more effective than placebo in both primary and secondary outcomes. However, it is not usual practice in an STA to not present comparative clinical effectiveness evidence. Therefore, the EAG would still recommend that this is done. |
| ATTR-CM = transthyretin amyloid cardiomyopathy; CS = company submission; DP = decision problem; EAG = Evidence Assessment Group; FAD = final appraisal document; LTE = long-term extension; STA = single technology appraisal; TA696 = technology appraisal 696 | |

### *1.5 The cost effectiveness evidence: summary of the EAG's key issues*

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

**Table 1.5: Key issue 4: No updated SLRs for economic evaluations, resources/costs or utilities**

| **Report Section** | **4.1.1** |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The company did not update their SLRs for economic evaluations, resources/costs or utilities. Therefore, it is possible that evidence relevant to the economic evaluation was overlooked. |
| **What alternative approach has the EAG suggested?** | The SLRs should be updated to incorporate the latest evidence available. |
| **What is the expected effect on the cost effectiveness estimates?** | Unknown |

| Report Section | 4.1.1 |
|---|---|
| **What additional evidence or analyses might help to resolve this key issue?** | See above. |
| EAG = Evidence Assessment Group; SLR = systematic literature review | |

**Table 1.6: Key issue 5: Extrapolation of tafamidis OS**

| Report Section | 4.2.6 |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The company used the generalised gamma curve for the extrapolation of tafamidis OS, in contrast to the committee's preferred curve in TA696 without sufficient arguments. |
| **What alternative approach has the EAG suggested?** | The EAG remains using the log-normal for the modelling of tafamidis OS in its base-case. |
| **What is the expected effect on the cost effectiveness estimates?** | Using the log-normal for the modelling of tafamidis OS resulted in an increased ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | Long-term (external) OS data to validate the clinical plausibility of the extrapolated OS data beyond the observed trial data. |
| EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; TA696 = technology appraisal 696 | |

**Table 1.7: Key issue 6: Continuation of the tafamidis treatment effect in patients who discontinued treatment**

| Report Section | 4.2.6 |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The company assumed an increasing proportion of surviving patients to discontinue tafamidis whilst continuing to accrue the benefits of treatment, without incurring any further treatment costs. The EAG considers this unlikely to be a reasonable assumption. |
| **What alternative approach has the EAG suggested?** | A scenario analysis assuming that all patients remain on treatment beyond the observed trial period and the treatment effect and costs are indefinitely applied.<br>A scenario analysis assuming that treatment discontinuation continued beyond the observed trial period and outcomes for the BSC arm were applied to tafamidis discontinuers. |
| **What is the expected effect on the cost effectiveness estimates?** | The company's current approach underestimates the ICER for tafamidis versus BSC. The EAG's exploratory scenario analyses resulted in an increased ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | Additional (long-term) evidence regarding the survival, CV-related hospitalisations, NYHA transitions and HRQoL in patients who discontinued tafamidis. |

| Report Section | 4.2.6 |
|---|---|
| BSC = best supportive care; CV = cardiovascular; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association | |

**Table 1.8: Key issue 7: Not using treatment-independent utility values for the NYHA IV health state**

| Report Section | 4.2.8 |
|---|---|
| **Description of issue and why the EAG has identified it as important** | As previously discussed in TA696, there is a substantial difference in utility values between arms in NYHA IV, while utility values for tafamidis and BSC in the other NYHA classes were similar. Moreover, these values were based on a low number of observations. |
| **What alternative approach has the EAG suggested?** | The EAG preferred using BSC utility values for the tafamidis arm (both in treatment and after treatment discontinuation) in the NYHA IV health state. |
| **What is the expected effect on the cost effectiveness estimates?** | Applying treatment independent utility values in NYHA class IV increased the ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | NA |
| BSC = best supportive care; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NA = not applicable; NYHA = New York Heart Association; TA696 = technology appraisal 696 | |

**Table 1.9: Key issue 8: Utility values being higher than the UK general population age-matched average**

| Report Section | 4.2.8 |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The utility values for the health state NYHA I in both arms (tafamidis: [redacted], BSC: [redacted]), and for the tafamidis arm in the NYHA II health state ([redacted]) were higher than those from the UK general population age-matched average (0.779). This lacks face validity as clinical experts in the TA696 technical engagement stated that "*it was not plausible that someone with ATTR-CM could have a better quality of life than someone of a similar age and sex from the general population*" |
| **What alternative approach has the EAG suggested?** | The EAG base-case included a cap for all the values higher than the utility value from the UK general population age-matched average. |
| **What is the expected effect on the cost effectiveness estimates?** | Applying a cap on utility values above the general population age-matched average increased the ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | NA |

| Report Section | 4.2.8 |
|---|---|
| BSC = best supportive care; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NA = not applicable; NYHA = New York Heart Association; TA696 = technology appraisal 696; UK = United Kingdom | |

**Table 1.10: Key issue 9: Inconsistent PSA results**

| Report Section | 5.2 |
|---|---|
| **Description of issue and why the EAG has identified it as important** | PSA results seemed inconsistent and are therefore deemed unreliable. |
| **What alternative approach has the EAG suggested?** | The EAG would like a justification for the inconsistency in PSA results and an updated economic model with a properly working PSA. |
| **What is the expected effect on the cost effectiveness estimates?** | Unknown. |
| **What additional evidence or analyses might help to resolve this key issue?** | An updated economic model with a properly working PSA, including an explanation of the issues and how they were resolved. |
| EAG = Evidence Assessment Group; PSA = probabilistic sensitivity analysis | |

### *1.6 Summary of the EAG's view*

The company submission (CS) base-case ICER (deterministic) for tafamidis versus BSC was [redacted]. The estimated EAG base-case ICER (deterministic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained. The most influential adjustment was assuming a different curve for the extrapolation of overall survival in the tafamidis arm. The ICER increased most in the scenario analyses with alternative assumptions regarding the outcomes of patients that discontinue tafamidis treatment.

## 2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

**Table 2.1: Statement of the decision problem (as presented by the company)**

| | Final scope issued by NICE | Decision problem addressed in the CS | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| **Intervention** | Tafamidis | As per final scope | Not applicable | No comment. |
| **Population** | People with transthyretin amyloid cardiomyopathy (ATTR-CM) | As per final scope | Not applicable | This includes the subgroup with transthyretin familial amyloid polyneuropathy [TTR-FAP] – see Comparators below. |
| **Comparator(s)** | People with ATTR-CM:<br>• Established clinical management without tafamidis (including diflunisal)<br>People with mixed phenotype transthyretin amyloidosis (that is, people presenting with both TTR-FAP and hereditary ATTR-CM)<br>• Patisiran<br>• Inotersen<br>• Vutrisiran | BSC (established clinical management without tafamidis) | We do not consider inotersen, patisiran, vutrisiran or diflunisal to be appropriate comparators as none of these medicines are licensed for the treatment of ATTR-CM.[1-4]<br>It is also important to note these medicines have higher list price to tafamidis and are either administered via disposable pre-filled injections/infusions[5] (list price of diflunisal not available via BNF):<br>Inotersen:<br>• List price per pack: £23,700<br>• Annual cost: £308,100<br>Patisiran:<br>• List price per dose: £7,676<br>• Annual cost: £399,176<br>Vutrisiran:<br>• List price per dose: £95,862<br>• Annual cost £383,449<br>Inotersen, patisiran, and vutrisiran licensed for hereditary transthyretin amyloidosis in adult patients with Stage 1 or 2 polyneuropathy,[2-4] have been included | Although inotersen, patisiran and vutrisiran are not licensed for ATTR-CM, they are licensed for TTR-FAP and, more importantly it is likely that they are SoC in UK clinical practice for the subgroup of mixed phenotype. The FAD for TA696 stated that there was insufficient evidence to consider inotersen or patisiran as comparators, but it was issued over two years ago, so the EAG requested a systematic review to include all comparators listed in the scope as well as any other used in UK clinical practice.[15] |

| | Final scope issued by NICE | Decision problem addressed in the CS | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | | | as comparators in the final scope, for the treatment of people with ATTR and a mixed phenotype, expressing symptoms of both cardiomyopathy and polyneuropathy.[6]<br>We agree there is a small UK population of hereditary ATTR patients with a mixed phenotype; estimated 16.6% presenting with polyneuropathy also suffer from ATTR-CM.[7] However, patisiran, inotersen and vutrisiran have not been satisfactorily evaluated in patients with heart failure:<br>(1) the safety and efficacy of these drugs has not been established in symptomatic ATTR-CM. Evidence from NEURO-TTR and APOLLO and HELIOS-A only support use of patisiran, inotersen and vutrisiran in patients with ATTR polyneuropathy. This is consistent with their marketing authorisations.[2-4] In contrast, the ATTR-ACT study was powered to compare all-cause mortality rates and rates of cardiovascular-related hospitalisations in patients receiving tafamidis versus placebo for ATTR-CM.[8]<br>(2) APOLLO and NEURO-TTR studies defined 'cardiac' subgroups on the basis of a measurement of the thickness of the heart wall. The echocardiogram criteria (LV wall thickness ≥13mm) used to define a cardiac (mixed phenotype) subpopulation in APOLLO and NEURO-TTR does not meet the consensus diagnostic criteria for ATTR-CM.[9] It is a structural finding and may be sub-clinical. A thickened heart wall does not imply cardiac deposition of TTR amyloid nor the presence of clinical heart failure.<br>(3) From a demographic perspective, the Val122Ile mutation found in Afro-Caribbean patients is causative | |

| | Final scope issued by NICE | Decision problem addressed in the CS | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | | | in 63% of cases of hereditary ATTR-CM in the UK.[10] This manifests with a predominant cardiac phenotype. Only 3 patients (1.7%) with Val122Ile mutation were enrolled in NEURO-TTR and a further 2 patients (0.9%) in APOLLO. Of the patients with hereditary ATTR-CM in ATTR-ACT, 61 (57.5%) had a causative Val122Ile mutation.<br>(4) The endpoints assessed in APOLLO, NEURO-TTR and HELIO-A were reflective of the disease burden of patients with ATTR-PN and did not include any clinical cardiac endpoints included in the scope for tafamidis. Thus, these studies do not provide sufficient evidence of safety or efficacy of treatment in a population with ATTR-CM.[11-13] These studies do not provide a valid indirect treatment comparison based on the lack of shared endpoints and distinct populations.<br><br>Patisiran<br>The FDA are assessing an application to approve patisiran for the treatment of ATTR-CM. This is based on data derived from an exploratory analysis of the APOLLO phase 3 trial.[14]<br><br>Diflunisal<br>Diflunisal is not licensed for the treatment of ATTR-CM.[1] To our knowledge, there are currently no RCTs investigating diflunisal in ATTR-CM. As per the comment from NHSE on the NICE Final Scope; "The National amyloidosis centre at the Royal Free NHS FT also use an unlicensed treatment, diflunisal for patients in the latter stages of the disease." Whereas tafamidis is | |

| | Final scope issued by NICE | Decision problem addressed in the CS | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | | | started in patients at NYHA class I to III. Therefore, diflunisal is not considered a relevant comparator. | |
| **Outcomes** | The outcome measures to be considered are:<br>• Overall survival<br>• Cardiovascular-related mortality<br>• Cardiac function (such as longitudinal strain or brain natriuretic peptide [BNP] level)<br>• Cardiovascular-related hospitalisation<br>• Functional exercise capacity<br>• Signs and symptoms of heart failure (such as breathlessness)<br>• Adverse effects of treatment<br>• Health-related quality of life | As NICE scope | Not applicable. | Only overall survival (OS) and adverse events (AEs) experienced by ≥30% patients (no grade reported) and only from the ATTR-ACT long-term extension (LTE) trial were presented. This therefore excludes any comparative data for any outcome for the comparators listed in the scope, which prompted the EAG to request this in the clarification letter. |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. | As NICE scope | Not applicable. | The economic analysis was in line with the NICE reference case. |

| | Final scope issued by NICE | Decision problem addressed in the CS | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and PSS perspective.<br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. | | | |
| **Other considerations** | If the evidence allows, the following subgroups will be considered:<br>• severity of heart failure (such as by New York Heart Classification class) | Not addressed, but HRs for mortality reported for NYHA classes I or II vs. III presented at a follow-up reported to be "Over ~5 years" (p. 23) | Not applicable. | The feasibility of such analyses versus all comparators was not explicitly considered in the CS and only very limited data for one outcome at a follow-up time that was unclear only vs. placebo was presented. |

| | Final scope issued by NICE | Decision problem addressed in the CS | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. | | | |

Based on Table 1, CS[16]

AE = adverse events; ATTR-CM = transthyretin amyloid cardiomyopathy; BNF = British National Formulary; BNP = brain natriuretic peptide; BSC = best supportive care; CS = company submission; EAG = Evidence Assessment Group; FAD = final appraisal document; FDA = Food and Drug Administration; HR = hazard ratio; LTE = long-term extension; NHSE = National Health Services England; NHS FT = National Health Service Foundation Trust; NICE = National Institute for Health and Care Excellence; NYHA = New York Heart Association; OS = overall survival; PSS = Personal Social Services; RCT = randomised controlled trial; SoC = standard of care; TA696 = technology appraisal 696; TTR-FAP = transthyretin familial amyloid polyneuropathy; UK = United Kingdom

### *2.1 Population*

The population defined in the scope issued by the National Institute for Health and Care Excellence (NICE) is:[6] people with transthyretin amyloid cardiomyopathy (ATTR-CM). The population in the company submission (CS) decision problem (DP) is stated to be the same.[16] However, the company excludes all comparators for the subgroup, which is stated in the scope i.e., people with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy (TTR-FAP) and hereditary ATTR-CM). The basis of this is lack of evidence for the treatment of heart failure and lack of license for cardiomyopathy, as opposed to neuropathy.[16]

**Evidence Assessment Group (EAG) comment:** Because the DP population includes the mixed phenotype subgroup and the comparators are different for this subgroup, the EAG requested analyses for this subgroup as well as the subgroup of only ATTR-CM for decision making, to which the company reiterated lack of evidence ("*no new major data"* (p. 3)) and lack of license for ATTR-CM treatment, as well as lack of National Institute for Health and Care Excellence (NICE) recommendation as reasons for not including the comparators excluded for the mixed phenotype subgroup.[17] However, they also cited *"anecdotal evidence from conversations with UK clinicians"* that they would be ruled out as comparators according to whether cardiomyopathy was the "*predominant*" presentation (p. 4). This would seem to imply that in clinical practice, not all mixed phenotype patients would be eligible for tafamidis, but only those where cardiomyopathy was "*predominant*". However, the company have not explicitly narrowed the DP population. Also, the 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure recommends patisiran and inotersen for this mixed phenotype subgroup, stating that they *"may be considered in those patients with combined hTTR polyneuropathy* [TTR-FAP] *and CA* [ATTR-CM]" (p. 3685).[18] Therefore, this is a key issue.

### *2.2 Intervention*

The intervention is in line with the scope.[6, 16] Tafamidis is a soft capsule for oral administration and the recommended dose is one tafamidis 61 mg capsule taken once a day. The company reported that *"Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis."* and that Vyndaqel 61 mg (tafamidis) corresponds to 80 mg tafamidis meglumine.[16]

**EAG comment:** The final appraisal document (FAD) for TA696 stated that the dose of tafamidis used in ATTR-ACT was different to the dose in the marketing authorisation for tafamidis, which is 61 mg, but that the marketing authorisation states that the relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at a steady state and therefore the committee concluded that the ATTR-ACT trials were appropriate for decision making.[15] The EAG are therefore satisfied that there is no issue regarding the dose of tafamidis.

### *2.3 Comparators*

The description of the comparators in the NICE scope is as follows:[6]

People with ATTR-CM:

- Established clinical management without tafamidis (including diflunisal)

People with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy (TTR-FAP) and hereditary ATTR-CM):

- Patisiran

- Inotersen
- Vutrisiran.

However, in the CS, the only comparator is best supportive care (BSC).[16] The company justifies this by stating that inotersen, patisiran, vutrisiran and diflunisal are not licensed for ATTR-CM and that *"…patisiran, inotersen and vutrisiran have not been satisfactorily evaluated in patients with heart failure"* (Table 1). They also argue that there is insufficient evidence for comparison to these four treatments, citing selected information regarding the trials of these three treatments, as well as stating that: *"To our knowledge, there are currently no randomised clinical trials (RCTs) investigating diflunisal in ATTR-CM."* (Table 1) No systematic review (SR) was presented.

**EAG comment:** Any treatment that is currently used in United Kingdom (UK) clinical practice should be a comparator, regardless of license, but the company presented no evidence as to whether this was the case. Lack of evidence cannot be used as a reason for not including these comparators without an SR. Therefore, the EAG requested that the company provided evidence as to what is standard of care (SoC) in the UK, and comparative clinical effectiveness and cost effectiveness evidence versus all relevant comparators, to which the company responded by restating the lack of evidence and license, see Section 2.1.[17]

Specifically, the company also did not provide a comparison with diflunisal, and it was not listed in the response to the clarification question regarding UK clinical practice.[17] The company restated the argument made in the CS that it should not be a comparator, as for the treatments for the mixed phenotype subgroup, because of lack of license and lack of evidence i.e.*:"…no randomised clinical trials (RCTs) investigating diflunisal in ATTR-CM."* (p. 39) However, they also restated that it has been used in the National Health Service (NHS) by *"The National amyloidosis centre at the Royal Free NHS FT also use an unlicensed treatment, diflunisal for patients in the latter stages of the disease."*" (p. 39). They then stated that *"diflunisal may have been prescribed in the past for ATTR-CM patients given the lack of any other treatments available for ATTR-CM"*, although they added that *"patients diagnosed more recently with ATTR-CM are no longer initiated on diflunisal given that the drug is poorly tolerated, due to the negative side effect profile (typically associated with nonsteroidal anti-inflammatory drugs)"* (p. 39). This might indicate that diflunisal is not a comparator, but it is not clear and made less clear by the reference that the company cited, the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, recommending it: *"Off-label use of diflunisal may be considered in wtTTR-CA [ATTR-CM] in combination with a proton pump inhibitor."* (p. 3685)[18] There has been an update to these guidelines in 2023, but with no mention of ATTR-CM, so it appears that this recommendation remains.[19] In response to the specific request for an SR and an indirect treatment comparison (ITC), the company referred to their response to the question regarding the DP and no SR or ITC was provided.[17] Therefore, the uncertainty as to comparator for the whole ATTR-CM population remains a key issue.

For the comparators for the mixed phenotype subgroup, the company also listed some of the outcomes in the trials for the three comparators in order to illustrate lack of comparability with the tafamidis trials generally. One exception was the composite outcomes that included all-cause mortality and cardiovascular (CV) hospitalisations in the patisiran trial, APOLLO-B, which the company stated "*…may be viewed as having strong clinical meaningfulness for ATTR-CM*" (p. 4).[17] The company went on to state that *"This is demonstrated by their inclusion as primary endpoints in the ATTR-ACT trial."* This might therefore be viewed as a reason for a comparison between tafamidis and patisiran. However, in response to the specific request for an SR and an ITC, the company referred to their response to the

question regarding the DP and no SR or ITC was provided. Note that the company reported the composite outcome results, which showed that the difference between patisiran and placebo was not found to be statistically significant (95% confidence interval (CI) overlapped the point of no difference of win ratio (WR) or hazard ratio (HR) of 1). This seemed to be part of the argument not to perform an ITC between tafamidis and patisiran, but the EAG would argue that the feasibility of an ITC should not depend on the results of the direct comparisons, but on the comparability of the trials. Of course, the EAG would argue that ITC feasibility should not be the basis for determining the appropriateness of comparators, but whether patients currently receiving patisiran or any of the other comparators listed in the scope might be eligible for tafamidis. As stated in Section 2.1, this remains unclear and therefore uncertainty as to the comparators for the mixed phenotype subgroup is a key issue.

### *2.4 Outcomes*

The NICE final scope lists the following outcome measures:[6]

- Overall survival
- CV-related mortality
- Cardiac function (such as longitudinal strain or brain natriuretic peptide (BNP) level)
- CV-related hospitalisation
- Functional exercise capacity
- Signs and symptoms of heart failure (such as breathlessness)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

However, of these outcomes the company presented only overall survival (OS) and adverse events (AEs) experienced by ≥30% patients (no grade reported) and only from the ATTR-ACT long-term extension (LTE) trial were presented.

**EAG comment:** To inform a decision as to whether an intervention is sufficiently effective, safe and cost effective, comparison with SoC is required. Therefore, the EAG requested that comparative evidence be presented, including ATTR-ACT trial data if tafamidis versus placebo or all outcomes listed in the scope, and indirect treatment comparisons versus all relevant comparators for:

- All-cause mortality and CV-related hospitalisations
- Overall survival
- CV-related hospitalisations
- CV-related mortality
- Mobility decline (6-minute walk test).

The company responded by stating that, other than OS, these outcomes were not collected for the LTE trial and referred to the "original submission" (TA696) for outcomes from ATTR-ACT.[17, 20] This lack of comparative evidence, which is generally required for decision making is therefore a key issue.

### *2.5 Other considerations*

The scope stated that if the evidence allows, the following subgroups will be considered:

- severity of heart failure (such as by New York Heart Association Classification (NYHA) class

This subgroup analysis was only presented in the CS for NYHA classes I or II versus III and only as hazard ratios versus placebo for mortality.[16]

**EAG comment:** The EAG did not request any further subgroup analyses by NYHA class in the clarification letter.

# 3. CLINICAL EFFECTIVENESS

## *3.1 Critique of the methods of review(s)*

The company stated that their intention for this CS was for it to be *"abbreviated"* (p. 4).[16] They stated that this was agreed during the DP meeting and that this abbreviated document would contain no clinical effectiveness evidence but: *"New evidence which has become available since the original single technology appraisal (STA) for tafamidis in ATTR-CM (TA696) and where these data have been applied in the new economic base case"* (p. 4) No SR was presented.[16]

**EAG comment:** The EAG requested in the clarification letter an SR to inform clinical and cost effectiveness analyses for comparison with all relevant comparators, to which the company responded by referring to the response to the question regarding the comparators in the DP (see Sections 2.1 and 2.3)[17] As stated in Sections 2.1 and 2.3, it is unclear whether diflunisal for the whole ATTR-CM population and the three comparators in the scope for the mixed phenotype (polyneuropathy and ATTR-CM) subgroup should be included. However, as also stated above, if they are currently being used to treat patients who are eligible for tafamidis then they should, and lack of evidence cannot be cited without the performance of an SR. Indeed, the company have shown a degree of comparability of outcomes for at least one of those three comparators, patisiran, in response to clarification i.e. the secondary outcomes from the APOLLO-B trial of patisiran included mortality and CV hospitalisations.[17] Therefore, lack of an SR would be part of the key issue regarding uncertainty in comparators.

### 3.1.1 Searches

Not applicable.

### 3.1.2 Inclusion criteria

Not applicable.

### 3.1.3 Critique of data extraction

Not applicable.

### 3.1.4 Quality assessment

Not applicable.

### 3.1.5 Evidence synthesis

A systematic review of clinical effectiveness was not conducted. Therefore, there was no relevant information on evidence synthesis.

## *3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)*

### 3.2.1 Study retrieval

### 3.2.2 Details of the included trial

Outcomes from only one trial was included, the ATTR-ACT long-term extension (LTE) trial.[16] This included some patients for longer term follow-up from the ATTR-ACT trial, which was a randomised controlled trial (RCT) with placebo as comparator. However, other than a subgroup analysis by NYHA class of OS (see Section 3.2.7), no outcomes from ATTR-ACT were reported in the CS, those having

been reported in TA696 for which NICE issued guidance in 2021.[16, 20] The company did present a comparison between the two trials, as shown in Table 3.1.

**Table 3.1: Summary of the trial methodology for ATTR-ACT and the ATTR-ACT LTE**

| Trial acronym (trial number): | ATTR-ACT (NCT01994889) | ATTR-ACT LTE (NCT02791230) |
|---|---|---|
| **Trial design** | Phase III, multicentre, international, double-blind, randomised placebo-controlled trial. | Phase III, multicentre, long-term extension study of ATTR-ACT with a 60-month treatment phase. |
| **Eligibility criteria for participants** | Patients between 18 and 90 years of age with ATTR-CM (wild-type or hereditary). | Cohort A: Patients who successfully completed 30 months of ATTR-ACT.<br>Cohort B: Patients diagnosed with ATTR-CM who had not participated in ATTR-ACT. |
| **Settings and locations where the data were collected** | Conducted at 48 sites worldwide (including 2 UK sites). The trial sites were secondary or tertiary care settings. | ATTR-ACT sites and additional sites worldwide. |
| **Trial drugs** | 2:1:2 ratio of 80 mg* of tafamidis meglumine (n=176), 20 mg of tafamidis meglumine (n=88) or placebo (n=177); oral QD for 30 months. | Cohort A: tafamidis meglumine (20 mg or 80 mg* QD). After Protocol Amendment 3 (20 July 2018) patients were assigned to open-label treatment of tafamidis free acid 61 mg (or if not available, tafamidis meglumine 80 mg*).<br>Cohort B: tafamidis free acid 61 mg QD (or if not available, tafamidis meglumine 80 mg*). |
| **Permitted and disallowed concomitant medication** | Patients could use non-prohibited supplements and medications during the study. Medications taken after the first dose of trial medication were documented as concomitant medications. This included prescription and over-the-counter medicines, vitamins, and herbal remedies.<br><br>Medications considered to be BSC were permitted and were to be stabilised for at least 4 weeks of therapy (other than diuretics) prior to baseline. Changes in diuretic dose were permitted within 4 weeks of the baseline visit.<br>The following medication was prohibited:<br>Any investigational therapy<br>Tauroursodeoxycholate and doxycycline | Patients could use non-prohibited supplements and medications during the study with the exception of those listed below:<br>Any investigational therapy<br>Diflunisal<br>Tauroursodeoxycholate and doxycycline<br>Digitalis and calcium channel blockers (e.g., verapamil, diltiazem) |

| Trial acronym (trial number): | ATTR-ACT (NCT01994889) | ATTR-ACT LTE (NCT02791230) |
|---|---|---|
| | Digitalis and calcium channel blockers. If used prior to randomisation, these medications were to be stopped at least 30 days before Baseline (Day 1)<br>Patients discontinued use of diflunisal at least 30 days prior to the Baseline visit (Day 1). All NSAIDs apart from the following permitted NSAIDs: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam and sulindac. | |
| **Randomisation and blinding** | An interactive web-based response system was used for randomisation. Blinding was achieved by means of a matching placebo. Patients and investigators were blinded to treatment allocation. | Cohort A: As described in the pivotal study, then open-label after Protocol Amendment. Patients initially randomised to placebo in ATTR-ACT were re-randomised 2:1 to 80 mg* and 20 mg, until the Protocol Amendment when all patients were switched to the higher dose.<br>Cohort B: All patients were assigned tafamidis free acid 61 mg (or if not available, tafamidis meglumine 80 mg*) treatment. |
| **Primary outcomes** | All-cause mortality and frequency of CV-related hospitalisation at Month 30 using the Finkelstein-Schoenfeld method | All-cause mortality<br>Incidence of treatment-emergent adverse events |
| **Other outcomes used in the economic model/specified in the scope** | **All-cause mortality**<br>**CV-related hospitalisation**<br>CV-related mortality<br>Cardiac function (6MWT, NT-proBNP, echocardiographic parameters)<br>**NYHA functional classification**<br>Transthyretin stabilisation<br>**Adverse effects of treatment**<br>**Health-related quality of life** (KCCQ-OS, **EQ-5D-3L**, EQ-5D-VAS)<br>All outcomes were pre-specified. An independent, endpoint adjudication committee, who were unaware of trial group assignments, determined whether investigator-reported events met the definition of disease-related efficacy end points, with the use of predefined endpoint criteria.<br>**Outcomes used in the economic modelling are shown in bold** | **All-cause mortality**<br>**Outcomes used in the economic modelling are shown in bold** |

| Trial acronym (trial number): | ATTR-ACT (NCT01994889) | ATTR-ACT LTE (NCT02791230) |
|---|---|---|
| **Pre-planned subgroups** | Stratification factors<br>*TTR* genotype (wild-type versus hereditary)<br>NYHA class at baseline (class I/II versus class III)<br>Dose analysis<br>Dose (20 mg vs. placebo, 80 mg vs. placebo) | *TTR* genotype (wild-type versus hereditary) |
| *Tafamidis (Vyndaqel) 61 mg corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.<br>Based on Table 4, CS[16]<br>6MWT = 6-minute walk test; ATTR-ACT = Tafamidis in transthyretin cardiomyopathy clinical trial; BSC = best supportive care; CS = company submission; CV: cardiovascular; EQ-5D: European Quality of Life-5 Dimensions; KCCQ-QS: Kansas City Cardiomyopathy Questionnaire; LTE: long-term extension; NSAID: non-steroidal anti-inflammatory drugs; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; QD: once daily; TTR = transthyretin; UK = United Kingdom; VAS = visual analogue scale | | |

**EAG comment:** The LTE trial does not provide any comparative data appropriate to the DP i.e., versus any of the comparators including BSC. The understanding of the EAG is that a full CS was required, which included an SR, as mentioned above and all comparative evidence. The EAG therefore requested this to which the company responded in the response to clarification letter by referring the EAG to Sections B.2.6.2 and B.2.10.1 in TA696 Document B for comparative evidence of tafamidis versus placebo associated with clinical effectiveness and safety, respectively.[16] It is true that the committee as reported in the FAD from TA696 concluded that the ATTR-ACT trials were appropriate for decision making and that, based on ATTR-ACT, tafamidis is more effective than placebo in terms of:[15]

- the primary outcome, a combined measure of all-cause mortality and CV-related hospitalisations, was assessed in a hierarchical analysis using the Finkelstein-Schoenfeld method. At month 30, 186 people (70.5%) were alive in the tafamidis group compared with 101 people (57.1%) in the placebo group. Of those alive at month 30, people who had tafamidis had fewer annual CV-related hospitalisations (0.297) on average than those who had placebo (0.455). Tafamidis statistically significantly reduced all-cause mortality and frequency of CV-related hospitalisations compared with placebo.
- the secondary outcomes: at month 30 compared with placebo, tafamidis was associated with statistically significant reductions in:
    - cardiovascular-related mortality
    - cardiovascular-related hospitalisations
    - mobility decline (assessed using the 6-minute walk test).
- quality of life. The Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score results showed that from baseline to month 30, people taking tafamidis had a slower decline in quality of life than people taking placebo (least squares mean difference compared with placebo, 13.65 ($p<0.0001$)).

However, it is not usual practice to not present all comparative (in this case versus placebo) clinical effectiveness evidence in a CS. Also, if an ITC is required (see Sections 2.1 and 2.3) and this would be via the placebo arm as common comparator then it would also be expected that all evidence versus placebo would be presented as part of the feasibility assessment. It should be noted that the EAG does not consider it appropriate to extract this evidence from TA696 as it is the role of the EAG to critique the evidence that is compiled by the company in the CS. The uncertainty as to whether this comparative evidence is required is therefore a key issue.

### 3.2.3 Statistical analysis of the included studies

The statistical analysis of the included studies was not reported in the CS.[16] The EAG notes that HRs of all-cause mortality were reported for the ATTR-ACT LTE trial in the CS.[16]However, no details of methods for estimating the HRs of all-cause mortality were provided in the CS. [16]The EAG requested the methods for estimating the HRs of all-cause mortality of the ATTR-ACT LTE trial.

In responding to EAG's request, the company made the following statement:

*"The hazard ratios observed in the ATTR-ACT LTE trial, inclusive of outcomes in patients who received placebo in ATTR-ACT and then tafamidis in ATTR-ACT LTE study (and therefore cannot be considered informative and were not used), were provided on page 23 (Section 6.3) of the current CS and referenced the reporting article, Elliott et al. (2023). Per this publication: 'all-cause mortality was assessed using a Cox proportional hazards model with treatment and genotype included in the model'".*[17]

Furthermore, the EAG requested the methods and results on the assessment of proportional hazards assumption for all-cause mortality for the ATTR-ACT LTE trial. In responding to EAG's request, the company states that "*There was no placebo arm in the ATTR-ACT LTE trial, therefore, assessment of the proportional hazards assumption for all-cause mortality was not feasible. In TA696 a Cox proportional hazards model was used to analyse time to all-cause mortality*."[17]

**EAG comment:**

- There were no details of methods and results on the assessment of proportional hazards assumptions for all-cause mortality of the ATTR-ACT LTE trial in the CS. The EAG requested the methods and results of the assessment of proportional hazards assumptions for these outcomes.
- In responding to the EAG's request, the company states that "*There was no placebo arm in the ATTR-ACT LTE trial, therefore, assessment of the proportional hazards assumption for all-cause mortality was not feasible."*[17] The EAG are satisfied with this response.

### 3.2.4 Baseline characteristics

No baseline characteristics were provided.[16]

**EAG comment:** The EAG requested the baseline characteristics, and the company presented a table in the clarification letter response, reproduced as Table 3.2.[17]

**Table 3.2: Patient characteristics at baseline by NYHA class – ATTR-ACT LTE**

| | NYHA class I/II | | NYHA class III | |
|---|---|---|---|---|
| | **Continuous tafamidis (n=121)** | **Placebo to tafamidis (n=114)** | **Continuous tafamidis (n=55)** | **Placebo to tafamidis (n=63)** |
| **Age, years** | | | | |
| Mean (SD) | 75(7.1) | 73 (6.5 ) | 76 (7.6) | 76 (6.8) |
| Medican (range) | 75 (56-88) | 74 (53-86) | 76 (46-87) | 76 (51-89) |
| Male sex, n (%) | 113 (93.4) | 105 (92.1) | 45 (81.8) | 52 (82.5) |
| **Race, n (%)** | | | | |
| White | 102 (84.3) | 94 (82.5) | 34 (61.8) | 52 (82.5) |
| Black | 9 (7.4) | 16 (14.0) | 17 (30.9) | 10 (15.9) |
| Asian | 8 (6.6) | 4 (3.5) | 3 (5.5) | 1 (1.6) |
| Other | 2 (1.7) | 0 | 1 (1.8) | 0 |
| **Transthyretin genotype, n (%)** | | | | |
| Wild-type | 99 (81.8) | 90 (78.9) | 35 (63.6) | 44 (69.8) |
| Variant | 22 (18.2) | 24 (21.1) | 20 (36.4) | 19 (30.2) |
| **NT-proBNP, pg/ml, median (UQ-LQ)** | 2,672 (1,722.0-4,235.6) | 2,816 (1,766.0-4,360.0) | 4,410 (2,625.0-7,166.0) | 4,079 (2,321.0-5,269.0) |
| **Troponin I[a], ng/ml, median (UG-LQ)** | 0.13 (0.08-0.18) | 0.13 (0.08-0.18) | 0.18 (0.13-0.30) | 0.14 (0.08- 0.22) |
| **6MWT distance, m, median (UQ-LQ)** | 383 (310-451) | 409 (327-475) | 256 (195-340) | 250 (80-333) |

| | NYHA class I/II | | NYHA class III | |
|---|---|---|---|---|
| | Continuous tafamidis (n=121) | Placebo to tafamidis (n=114) | Continuous tafamidis (n=55) | Placebo to tafamidis (n=63) |
| Patients continously treated with tafamidis meglumine 80 mg/free acid 61 mg, or placebo then tadamidis. n denotes number of patients.<br>[a]Troponin I level missing for one placeo-treated patient with NYHA I/II symptoms (n=113).<br>Based on Table 3, clarification letter response.[17]<br>6MWT = 6-min walk test; LQ = lower quartile; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association Functional Classification; SD = standard deviation; UQ = upper quartile | | | | |

Although no comparative evidence was reported, the baseline characteristics could be used to assess generalisability, which the EAG requested and to which the company responded with a comparison to a retrospective UK cohort (see Table 3.3).

**Table 3.3: Comparison of baseline characteristics in ATTR-ACT LTE and a UK cohort**

| | ATTR-ACT LTE[21] | | | | Untreated patients |
|---|---|---|---|---|---|
| | NYHA class I/II | | NYHA class III | | |
| | Continuous tafamidis | Placebo to tafamidis | Continuous tafamidis | Placebo to tafamidis | Gillmore et al. (2018)[22] |
| **Number of patients** | 121 | 114 | 55 | 63 | 869 |
| **Median age (range)** | 75 (56-88) | 74 (53-86) | 76 (46-87) | 76 (51-89) | NR |
| **Median age at diagnosis (range)** | NR | NR | NR | NR | 77 (41-95) |
| **Male sex, n (%)** | 113 (93.4) | 105 (92.1) | 45 (81.8) | 113 (93.4) | 737 (85) |
| **NYHA classification, n (%)[a]** | | | | | |
| Class I/II | 235 (67) | | | | 656 (75) |
| Class III | 118 (33) | | | | 205 (24) |
| Class IV | 0 | | | | 8 (1) |
| **TTR genotype, n (%)** | | | | | |
| Wild-type TTR | 99 (81.8) | 90 (78.9) | 35 (63.6) | 44 (69.8) | 553 (63.6) |
| Hereditary TTR | 22 (18.2) | 24 (21.1) | 20 (36.4) | 19 (30.2) | 316 (36.3) |
| Based on clarification letter response[17]<br>[a]NYHA class: I = without resulting limitations, II = slight limitation, III = marked limitation, IV = inability to carry on any physical activity without discomfort.<br>NR = not reported; NYHA = New York Heart Association; TTR = transthyretin | | | | | |

### 3.2.5 Risk of bias assessment

None was provided.[16]

### 3.2.6 Efficacy results of the included studies

Only OS and time to treatment discontinuation (TTD) results were reported.[16] These were an 84-month (August 2021 data cut) update to LTE data with tafamidis 61 mg once daily (QD) (no patients remained on placebo from the original RCT) presented in TA696 (August 2019 cut-off).

#### 3.2.6.1 Overall survival

The OS data were derived from the ATTR-ACT LTE trial, which was an extension trial of the ATTR-ACT trial. The company states that "*In TA696, overall survival (OS) data was derived from the ATTR-*

*ACT trial (NCT01994889) which was limited to 30 months post treatment initiation. ATTR-ACT was a Phase III, multicentre, international, three-arm, parallel design, placebo-controlled, randomised study with a 30-month double-blind treatment phase, to determine the efficacy of tafamidis meglumine administered orally as soft gel capsules compared to placebo, based on clinical outcomes in patients with wild-type or hereditary ATTR-CM. Patients treated with tafamidis showed statistically significant and clinically meaningful treatment benefits compared with the placebo group*." [16]

The company further states that "*As of September 2021, more recent tafamidis OS data from the ATTR-ACT LTE has become available and been incorporated into the updated economic analysis. Data now extends to 84 months of tafamidis treatment and substantially reduces uncertainty associated with OS extrapolations*." [16]

The results showed that at the data cut of August 2021 of the ATTR-ACT LTE trial, the Kaplan-Meier curve for patients who received continuous tafamidis treatment from the tafamidis meglumine 80 mg treatment arm of ATTR-ACT showed a trend towards decreasing hazards.[16] It should be noted that tafamidis (Vyndaqel) 61 mg (which was appraised in this STA) corresponds to 80 mg of tafamidis meglumine.[16]

Only the Kaplan-Meier (K-M) plot for OS was presented in the CS.[16] Figure 3.1 shows the K-M plot of overall survival for patients who received continuous tafamidis treatment from tafamidis meglumine 80 mg in ATTR-ACT to tafamidis free acid 61 mg in ATTR-ACT LTE.

**Figure 3.1: Kaplan-Meier plot of overall survival – 80 mg tafamidis meglumine in ATTR-ACT to tafamidis free acid 61 mg in ATTR-ACT LTE (August 2021 data cut)**

Based on Figure 1, CS.[16]
CMAD: cardiac mechanical assist device; HT: heart transplant; NAR: numbers at risk; OS: overall survival

### 3.2.6.2 Time to discontinuation

Time to treatment discontinuation data from ATTR-ACT LTE trial were reported in the CS.[16] The company states that "*time to treatment discontinuation (TTD) data included in economic analysis in TA696 was also derived from the ATTR-ACT clinical trial and limited to 30 months post treatment initiation. Similar to OS, data from the ATTR-ACT LTE (August 2019 cut-off date) was also used to validate goodness-of-fit statistics and assessment of visible fit for parametric distribution functions used to extrapolate overall survival beyond the observed period of ATTR-ACT."*[16]

The company further states that "*as of September 2021, more recent TTD data from the ATTR-ACT LTE has become available and been incorporated into the updated economic evaluation. Data now extends to 84 months."*[16]

Only the K-M plot was presented in the CS. Figure 3.2 shows the K-M curve for proportion of patients not discontinued the treatment among patients who received continuous tafamidis treatment from 80 mg tafamidis meglumine in ATTR-ACT to tafamidis free acid 61 mg in ATTR-ACT LTE trial.

**Figure 3.2: Proportion of patients not discontinued – 80 mg tafamidis meglumine in ATTR-ACT to tafamidis free acid 61 mg in ATTR-ACT LTE (August 2021 data cut)**

Based on Figure 2, CS.[16]
Abbreviations: CMAD: cardiac mechanical assist device; HT: heart transplant; NAR: numbers at risk.

**EAG comment:**

- Only OS and TTD data from the ATTR-ACT LTE trial were reported in the CS. However, neither the OS or TTD results provided any further information useful for decision making, given that there were no comparative data of OS or TTD between the intervention arm and the

control arm from the ATTR-ACT LTE trial. Other relevant outcomes from this trial were not reported.

- The company only provided data at the data cut of August 2021. The EAG requested further longer-term data from this ATTR-ACT LTE trial for all outcomes reported. The company states that further longer-term data from the ATTR-ACT LTE trial is not available. The company also states that the following outcomes were not collected within the ATTR-ACT LTE:[17]
    - CV-related mortality
    - cardiac function (such as global longitudinal strain or BNP level)
    - CV-related hospitalisation
    - functional exercise capacity
    - signs and symptoms of heart failure (such as breathlessness)
    - health-related quality of life (of patients and carers)

### 3.2.7 Subgrouping

Subgroup analyses of the ATTR-ACT LTE by NYHA classes I or II versus class III were presented.[16] This also included the hazard ratios versus placebo, reported to be "*Over ~5 years*" (p. 23).[16] Although no new comparative (versus placebo) data were presented, the original 30-month median follow-up data comparative data from the end of ATTR-ACT were represented by NYHA class to compare to the LTE data, which included the switch to tafamidis.

#### 3.2.7.1 Subgroup analysis based on NYHA classes

Subgroup analyses of the ATTR-ACT LTE by NYHA classes I or II versus NYHA class III were reported in the CS.[16]

For the subgroup analyses based on the NYHA classes, the company made the following statements:

- *"In TA696, there was uncertainty regarding tafamidis treatment reducing cardiovascular-related mortality in people with ATTR-CM classified as NHYA III (refer to Section 3.11 in FAD for TA696).*
- *The analysis integrates data on all-cause mortality from two groups were compared: (i) Continuous tafamidis group: patients who initially received tafamidis meglumine 80 mg in ATTR-ACT and ATTR-ACT LTE, followed by tafamidis free acid 61 mg after the protocol amendment.[21] (ii) Placebo to tafamidis group: patients who received placebo in ATTR-ACT and then tafamidis meglumine 80 or 20 mg in ATTR-ACT LTE, followed by tafamidis free acid 61 mg after the protocol amendment. Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT are not included in this analysis."*[16]

The company further states that over ~5 years, tafamidis treatment continued to improve patients' survival outcome.[16] The results of the interim analysis showed that, across NYHA classes I-III patients who received continuous tafamidis treatment continued to have better survival than those who received placebo in ATTR-ACT followed by tafamidis in the ATTR-ACT LTE trial: the HR of all-cause mortality for the subgroup of NYHA class I/II was 0.50 (95% CI, 0.346–0.727), exploratory P=0.0003.[16] Furthermore, the HR of all-cause mortality for the subgroup of NYHA class III was 0.64 (95% CI, 0.408–0.992), exploratory P=0.0460.[16]

The all-cause mortality over ~5 years' treatment with tafamidis by NYHA class at baseline of the ATTR-ACT LTE trial at the August 2021 data cut is presented in Table 3.4 below.

**Table 3.4: All-cause mortality over ~5 years' treatment with tafamidis by NYHA class at baseline (ATTR-ACT LTE August 2021 data cut)**

| | NYHA class I or II at baseline | | NYHA class III at baseline | |
|---|---|---|---|---|
| **At end of ATTR-ACT** | **Tafamidis meglumine 80 mg** | **Placebo** | **Tafamidis meglumine 80 mg** | **Placebo** |
| Median months' follow-up | 30 | 30 | 30 | 30 |
| All-cause mortality, n/n (%) | 25/121 (20.7) | 37/114 (32.5) | 29/55 (52.7) | 39/63 (61.9) |
| HR | 0.635 (0.382-1.055) | | 0.769 (0.473-1.250) | |
| **ATTR-ACT LTE data cut (1 August 2021)** | **All patients receiving tafamidis receive tafamidis free acid 61mg†** | | | |
| | **Continuing from tafamidis meglumine 80 mg** | **Placebo to tafamidis** | **Continuing from tafamidis meglumine 80 mg** | **Placebo to tafamidis** |
| Median months' follow-up | 61 | 60 | 60 | 56 |
| All-cause mortality, n/n (%) | 49/121 (40.5) | 70/114 (61.4) | 35/55 (63.6) | 51/63 (81.0) |
| HR | 0.502 (0.346-0.727)* | | 0.636 (0.408-0.992)* | |

Based on Table 5, CS.[16]
*P<0.05.
†Patients completing ATTR-ACT could enrol in ATTR-ACT LTE to receive up to 60 additional months of tafamidis treatment (NCT02791230). Patients receiving tafamidis meglumine (80 mg or 20 mg) in ATTR-ACT initially continued this dose in ATTR-ACT LTE. Those who had received placebo in ATTR-ACT were randomised 2:1 to tafamidis meglumine 80 or 20 mg, stratified by genotype. Following a protocol amendment in July 2018, all patients transitioned to the approved tafamidis dosage of once-daily tafamidis free acid 61 mg.
HR presented with 95% CI.
CI = confidence interval; CS = company submission; HR = hazard ratio; NYHA = New York Heart Association

The company argued that these results show the benefit of starting tafamidis as early as possible.

### 3.2.7.2. Subgroup analysis based on ATTR genotype

The data of subgroup analysis based on ATTR genotype (wild-type versus hereditary) of the ATTR-ACT LTE trial were not reported in the CS.[16] The EAG requested the results of subgroup analysis based on ATTR genotype (wild-type versus hereditary) of the ATTR-ACT LTE trial. In responding to EAG's request, the company provided the subgroup analysis results relating to the two subgroups.[17]

Compared with patients switching from placebo to tafamidis, there was a significant reduction in the risk of all-cause mortality in the subgroup of patients with wild-type ATTR-CM (HR 0.61, 95% CI 0.43–0.87; P=0.006) among patients who received continuous tafamidis treatment.[17] Furthermore, compared with patients switching from placebo to tafamidis, there was a borderline significant reduction in the subgroup of patients with hereditary ATTR-CM (HR 0.57, 0.33–0.99; P=0.05) among patients who received continuous tafamidis treatment. [17]

**EAG comment:**

- As concluded in the FAD, tafamidis seems to be more effective than placebo and regardless of NYHA class in terms of OS, albeit with some overlap of the 95% CI.

- The results of subgroup analyses from ATTR-ACT LTE trial were generally consistent for the all-cause mortality outcome between the NYHA I/II and NYHA III subgroups.
- The EAG requested the results of subgroup analysis based on ATTR genotype (wild-type versus hereditary) of the ATTR-ACT LTE trial. In responding to EAG's request, the company provided the results relating to these subgroup analyses.[17] The results showed that there were generally consistent results for all-cause mortality between the subgroup of patients with wild-type ATTR-CM and the subgroup of patients with hereditary ATTR-CM of the ATTR-ACT LTE trial. The EAG recognises that the ATTR-ACT LTE is powered on primary outcome measure and lacks the statistical power for genotype subgroup analysis.
- The company only provided data of subgroup analysis at the data cut of August 2021. Further longer-term follow-up data are not available.

### 3.2.8 Adverse events

As with efficacy, only results with tafamidis were reported in the CS, and only for the most common ones (experienced by at least 30% of patients) (Table 3.5).[16]

**Table 3.5: Most common adverse events – 80 mg tafamidis meglumine to 61 mg tafamidis in ATTR-ACT LTE (August 2021 data cut)**

| n (%) | Continuous tafamidis n=110 |
|---|---|
| **Any adverse event in the ATTR-ACT LTE** | **108 (98.2)** |
| **System organ classes where ≥30% of patients had an adverse event** | |
| Cardiac disorders | 79 (71.8) |
| Infections and Infestations | 64 (58.2) |
| Injury, poisoning, and procedural complications | 57 (51.8) |
| Respiratory, thoracic, and mediastinal disorders | 55 (50.0) |
| General disorders and administration site conditions | 54 (49.1) |
| Nervous system disorders | 51 (46.4) |
| Gastrointestinal disorders | 50 (45.5) |
| Musculoskeletal and connective tissue disorders | 49 (44.5) |
| Metabolism and nutrition disorders | 43 (39.1) |
| Skin and subcutaneous tissue disorders | 42 (38.2) |
| Renal and urinary disorders | 35 (31.8) |

Based on Table 6, CS.[16]
Events coded per Medical Dictionary for Regulatory Activities v 24.0.
CS = company submission

**EAG comment:** The EAG requested on treatment-related adverse events from the ATTR-ACT LTE trial, which have been provided by the company in clarification letter response, as shown in Table 3.6.[17]

**Table 3.6: Adverse events - ATTR-ACT LTE August 2021 (Tafamidis 80 mg/tafamidis 61 mg free acid)**

| Patients, n (%) | Continuous tafamidis |
|---|---|
| Any adverse effect in the LTE | 108 (98.2) |

| Patients, n (%) | Continuous tafamidis |
|---|---|
| **Cardiac disorders** | 79 (71.8) |
| Cardiac failure | 28 (25.5) |
| Atrial fibrillation | 21 (19.1) |
| Ventricular tachycardia | 13 (11.8) |
| Cardiac failure (acute) | 11 (10.0) |
| Cardiac failure (congestive) | 9 (8.2) |
| Pericardial effusion | 7 (6.4) |
| **Infections and infestations** | 64 (58.2) |
| Cellulitis | 17 (15.5) |
| Urinary tract infection | 14 (12.7) |
| Pneumonia | 13 (11.8) |
| Upper respiratory tract infection | 8 (7.3) |
| Bronchitis | 7 (6.4) |
| Nasopharyngitis | 7 (6.4) |
| **Injury, poisoning, and procedural complications** | 57 (51.8) |
| Fall | 31 (28.2) |
| Skin abrasion | 9 (8.2) |
| Contusion | 7 (6.4) |
| Skin laceration | 7 (6.4) |
| **Respiratory, thoracic, and mediastinal disorders** | 55 (50.0) |
| Dyspnoea | 20 (18.2) |
| Cough | 18 (16.4) |
| Pleural effusion | 18 (16.4) |
| Epistaxis | 9 (8.2) |
| **General disorders and administration site conditions** | 54 (49.1) |
| Oedema (peripheral) | 16 (14.5) |
| Fatigue | 12 (10.9) |
| Asthenia | 9 (8.2) |
| Chest pain | 8 (7.3) |
| **Gastrointestinal disorders** | 50 (45.5) |
| Constipation | 11 (10.0) |
| Nausea | 11 (10.0) |
| Ascites | 9 (8.2) |
| Diarrhoea | 8 (7.3) |
| Dysphagia | 7 (6.4) |
| **Nervous system disorders** | 51 (46.4) |
| Dizziness | 15 (13.6) |

| Patients, n (%) | Continuous tafamidis |
|---|---|
| Balance disorder | 9 (8.2) |
| **Musculoskeletal and connective tissue disorders** | 49 (44.5) |
| Arthralgia | 21 (19.1) |
| Pain in extremity | 12 (10.9) |
| Back pain | 9 (8.2) |
| Osteoarthritis | 8 (7.3) |
| Muscle spasms | 7 (6.4) |
| Muscular weakness | 7 (6.4) |
| **Metabolism and nutrition disorders** | 43 (39.1) |
| Hypokalaemia | 12 (10.9) |
| Gout | 10 (9.1) |
| Hyponatraemia | 8 (7.3) |
| Decreased appetite | 7 (6.4) |
| **Skin and subcutaneous tissue disorders** | 42 (38.2) |
| Pruritus | 11 (10.0) |
| Skin ulcer | 8 (7.3) |
| **Renal and urinary disorders** | 35 (31.8) |
| Acute kidney injury | 18 (16.4) |
| Renal failure | 8 (7.3) |

Based on Table 5 of the clarification letter response.[17]
Patients continuously treated with tafamidis meglumine 80 mg or free acid 61 mg. Includes system organ classes where ≥30% of patients in the study had an adverse event, and within these, MedDRA Preferred Terms in ≥6% of patients. Adverse events reported up to 28 days after the patient's last dose of tafamidis.
Data from the interim ATTR-ACT LTE (August 2021 data cut). Events coded per MedDRA v24.0.
MedDRA = Medical Dictionary for Regulatory Activities

The EAG also asked the company to compare to the expected AEs with BSC and explain if the AEs expected to be related to treatment with tafamidis. As there was no placebo (BSC) arm in the ATTR-ACT LTE, the company response using the findings from ATTR-ACT to compare adverse events profiles of tafamidis and BSC, where the safety outcomes of tafamidis 80 mg, tafamidis 20 mg, and placebo are shown to be similar.[17] The company also responded that incidence and types of AEs were similar, or lower, than that with pooled tafamidis (80 mg and 20 mg) or placebo in ATTR-ACT, and no new safety concerns emerged in patients treated with tafamidis 80 mg or tafamidis 61 mg free acid in the ATTR-ACT LTE.

The EAG requested the company to elaborate whether the 51.8% of patients with "injury, poisoning and procedural complications" expected to be related to treatment with tafamidis. The company explained that a large portion of the "injury, poisoning and procedural complications" category is comprised of the "fall" adverse event 28.2%, which may happen among elderly individuals, where the ATTR-ACT and ATTR-ACT LTE study populations have a large proportion of elderly individuals.[17] There were similar occurrences of these events in the participants who received a placebo in the study.

These AE data provide no further information relevant for decision making given the lack of comparison to any SoC, either as BSC or any other treatment. This is therefore part of the key issue regarding lack of comparative data in this CS.

### *3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

No ITC was conducted.[16]

**EAG comment:** As stated in Section 3.1, the EAG requested in the clarification letter an SR to inform clinical and cost effectiveness analyses for comparison with all relevant comparators, to which the company responded by referring to the response to the question regarding the comparators in the DP (see Sections 2.1 and 2.3)[17] As stated in Sections 2.1 and 2.3, it is unclear whether diflunisal for the whole ATTR-CM population and the three comparators in the scope for the mixed phenotype (polyneuropathy and ATTR-CM) subgroup should be included. However, as also stated above, if they are currently being used to treat patients who are eligible for tafamidis then they should, and lack of evidence cannot be cited without the performance of SR. Indeed, the company have shown comparability of outcomes for at least one of those three comparators, patisiran, in response to clarification.[17] Therefore, as already stated, lack of an SR would be part of the key issue regarding uncertainty in comparators.

### *3.4 Critique of the indirect comparison and/or multiple treatment comparison*

No ITC was conducted.[16]

**EAG comment:** As stated in Sections 2.1 and 2.3, it is unclear whether diflunisal for the whole cardiomyopathy (CM) population and the three comparators in the scope for the mixed phenotype (polyneuropathy and CM) subgroup should be included. However, as also stated above, if they are currently being used to treat patients who are eligible for tafamidis then they should, and lack of evidence cannot be cited without the performance of SR and, depending on the findings of the SR, the feasibility of an ITC should be assessed. Indeed, the company have shown comparability of outcomes for at least one of those three comparators, patisiran, in response to clarification.[17] Therefore, lack of an ITC would be part of the key issue regarding uncertainty in comparators.

### *3.5 Additional work on clinical effectiveness undertaken by the EAG*

None undertaken.

### *3.6 Conclusions of the clinical effectiveness section*

The company stated that their intention for this CS was for it to be "abbreviated" (p. 4).[16] They stated that this was agreed during the DP meeting and that this abbreviated document would contain no clinical effectiveness evidence but: *"New evidence which has become available since the original STA for tafamidis in ATTR-CM (TA696) and where these data have been applied in the new economic base case"* (p. 4). No SR was presented.[16] The EAG requested in the clarification letter an SR to inform clinical and cost effectiveness analyses for comparison with all relevant comparators, to which the company responded by referring to the response to the question regarding the comparators in the DP (see Sections 2.1 and 2.3)[17] As stated in Sections 2.1 and 2.3, it is unclear whether diflunisal for the whole CM population and the three comparators in the scope for the mixed phenotype (polyneuropathy and CM) subgroup should be included. However, as also stated above, if they are currently being used to treat patients who are eligible for tafamidis then they should, and lack of evidence cannot be cited without the performance of SR. Indeed, the company have shown comparability of outcomes for at least

one of those three comparators, patisiran, in response to clarification.[17] Therefore, lack of an SR would be part of the key issue regarding uncertainty in comparators.

The only clinical efficacy evidence that was presented was OS and TTD results.[16] These were an 84-month (August 2021 data cut) update to LTE data with tafamidis 61 mg QD (no patients remained on placebo from the original RCT) presented in TA696 (August 2019 cut-off) only in the form of K-M curves, except for a representation of 30-month NYHA class subgroup comparative (versus placebo) data for OS.

The only safety data that were presented were for the most commonly experienced AEs (at least 30% of patients) who received tafamidis.[16] No comparative data were presented.

Overall, the CS presented no clinical effectiveness evidence in a form that was suitable for decision making i.e., that was comparative (compared to any kind of SoC). This is therefore a key issue.

# 4. COST EFFECTIVENESS

## *4.1 EAG comment on company's review of cost effectiveness evidence*

No systematic literature review (SLR) was performed for this CS. The SLRs from TA696 were used in the current CS. Please refer to TA696 for the SLRs on 1) cost effectiveness analysis (CEA) studies (TA696 CS Appendix G); 2) HRQoL studies (TA696 CS Appendix H); 3) costs and healthcare resource use studies (TA696 CS Appendix I).

### 4.1.1 Searches performed for cost effectiveness section

No literature searches were conducted for the current CS.

### 4.1.2 Inclusion/exclusion criteria

No SLR was conducted for the current CS.

### 4.1.3 Conclusions of the cost effectiveness review

No SLR was conducted for the current CS.

**EAG comment:** It is unclear to the EAG why the company did not include the usual SLRs for economic evaluations, resources/costs and utilities as part of the CS. It is therefore possible that evidence relevant to the de novo economic evaluation was overlooked.

## *4.2 Summary and critique of company's submitted economic evaluation by the EAG*

### 4.2.1 NICE reference case checklist

**Table 4.1: NICE reference case checklist**

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| **Perspective on outcomes** | All direct health effects, whether for patients or, when relevant, carers | Health gains accrued by patients are valued in terms of QALYs gained. Impacts on caregivers are not included. |
| **Perspective on costs** | NHS and PSS | The analysis adopts an NHS and PSS perspective. |
| **Type of economic evaluation** | Cost utility analysis with fully incremental analysis | The results of the company's base-case analysis are presented in terms of the incremental cost per QALY gained for tafamidis versus BSC. |
| **Time horizon** | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | The model adopts a 26.67-year time horizon. At this timepoint, more than 99.6% of patients in the model have died. |
| **Synthesis of evidence on health effects** | Based on systematic review | All of the clinical inputs to the model are derived from the ATTR-ACT trial and its long-term extension study.[8 21] This was the key study included in the company's systematic |

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| | | review of clinical evidence in TA696.[20] The systematic literature review was not updated for the current submission. |
| **Measuring and valuing health effects** | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | Health state utility values are based on EQ-5D-3L data collected in ATTR-ACT, valued using the UK tariff.[8] |
| **Source of data for measurement of health-related quality of life** | Reported directly by patients and/or carers | Yes |
| **Source of preference data for valuation of changes in health-related quality of life** | Representative sample of the UK population | Yes |
| **Equity considerations** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | No additional equity weighting is applied to estimated QALY gains. |
| **Evidence on resource use and costs** | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | Resource costs include those relevant to the NHS and PSS. Unit costs were valued at 2021/2022 prices. |
| **Discounting** | The same annual rate for both costs and health effects (currently 3.5%) | Costs and health effects are discounted at a rate of 3.5% per annum. |

BSC = best supportive care; EAG = Evidence Assessment Group; EQ-5D: European Quality of Life-5 Dimensions; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

### 4.2.2 Model structure

The company submitted an update of the health economic model previously developed by the EAG in TA696.[23] This Excel model was updated with new data and enhanced user functionality elements. No changes were made to the model structure in the original company submission TA696. More information about the model structure can be found in Sections 5.2.2 and 5.2.3 of the TA696 EAG report.[23] Two issues regarding the model structure and implementation were identified by the EAG in TA696.[23] The first issue regarding the complexity of the model implementation (Section 5.3.3(1) of the TA696 EAG report[23]) was resolved in the current implementation of the model. The second issue regarding model structure (Section 5.3.3(2) of the TA696 EAG report[23]) remained unresolved, however the committee decided that it "*had concerns about the New York Heart Association (NYHA) classification system, but concluded that because there was no available alternative the company's model could be considered for decision making*".[15]

**EAG comment:** The company adopted the same model structure as in TA696[23], but updated the model with new data (up to 84 months) and enhanced user functionality elements. No issues were identified by the EAG.

### 4.2.3 Population

Consistent with the NICE scope, the population considered in the CS (CS Table 1) was people with ATTR-CM. The marketing authorisation indication is the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with ATTR-CM. The phase 3 trial evidence for tafamidis came from the ATTR-ACT trial and its long-term extension study (ATTR-ACT-LTE).[8, 21] ATTR-ACT focused on patients between 18 and 90 years of age with ATTR-CM (wild-type or hereditary). In the ATTR-ACT-LTE, patients who successfully completed 30 months of ATTR-ACT (cohort A) and patients diagnosed with ATTR-CM who had not participated in ATTR-ACT (cohort B) were included. The current submission did not provide details about the baseline demographic characteristics included in the health economic model, but according to the original EAG report Section 5.2.4 and Table 9[23] they are informed by the intention-to-treat (ITT) population of the ATTR-ACT trial. In their clarification response, the company provided the baseline demographics included in the model and confirmed that they were the same as in TA696.[17] The EAG report of TA696 identified an issue regarding a subgroup analysis conducted by the company (Section 5.3.3(3c) of the TA696 EAG report[23]), which was resolved after technical engagement, where the viewpoint of the EAG was adopted by the company: *"The company agrees that it would not be clinically appropriate for patients in NYHA III to not be eligible to start treatment but for NYHA I/II patients to remain on treatment upon progression to NYHA III".*[24]

**EAG comment:** The EAG notes that the population in the economic model is consistent with the NICE scope.

### 4.2.4 Interventions and comparators

The intervention considered in the model is tafamidis, administered orally at a dose of 61 mg QD. This is in line with the marketing authorisation for the ATTR-CM indication.[25] In the ATTR-ACT trial, patients received tafamidis meglumine 20 mg, 80 mg or placebo in a 1:2:2 ratio. In the ATTR-ACT LTE, all patients switched to tafamidis free acid 61 mg after protocol amendment. The CS stated that tafamidis free acid 61 mg has been shown to be bioequivalent to 80 mg tafamidis meglumine.[16] In addition, patients are also assumed to receive a range of concomitant medications as part of BSC, see the TA696 EAG report Section 5.2.1.[23]

The comparator considered was BSC, see the TA696 EAG report Section 5.2.1.[23]

The NICE scope listed established clinical management (including diflunisal) as BSC for the ATTR-CM population. For people with mixed phenotype transthyretin amyloidosis (i.e., people presenting with both TTR-FAP and hereditary ATTR-CM), patisiran, inotersen and vutrisiran are listed as comparators. These comparators were not included in the CS (see also Section 2.3 and key issue 1 of this report).

**EAG comment:** The main concerns of the EAG relate to: a) lack of comparators, and b) diflunisal not included in BSC.

a) Inotersen, patisiran and vutrisiran were not included as comparators in the economic model. As stated in Sections 2.1 and 2.3, it remains unclear whether patients currently receiving patisiran or any of the other comparators listed in the scope might be eligible for tafamidis. The EAG suggests that the three comparators would be included for (at least) the mixed phenotype subgroup. The impact on the incremental cost-effectiveness ratio (ICER) for tafamidis (in this specific subgroup) is unknown.

b) As opposed to the NICE scope, diflunisal was not incorporated as one of the treatments in BSC. As stated in Section 2.3, it remains unclear whether diflunisal is a comparator to tafamidis for the whole ATTR-CM population. Inclusion of diflunisal has an unknown impact on the ICER of tafamidis.

### 4.2.5 Perspective, time horizon and discounting

The analysis was performed from the NHS and Personal Social Services (PSS) perspective. Details on discount rates and cycle length are described in the TA696 EAG report Sections 5.2.1 and 5.2.2 and associated issues relating to cycle length in the model can be found in Section 5.3.3(1).[23] Relating to these issues, the EAG stated: "*Whilst the EAG considers the company's approach to be unconventional, this issue is unlikely to have a material impact on the ICER for tafamidis."*

**EAG comment:** The approach is in concordance with the NICE reference case.

### 4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence to inform the treatment effectiveness of tafamidis and BSC were the ATTR-ACT trial and its long-term extension study (ATTR-ACT LTE), respectively.[8, 21] Within the economic model, treatment efficacy was captured via the estimation of health state occupancy, OS, TTD, and CV-related hospitalisation.

Following TA696,[20] the company provided updates regarding the modelling of tafamidis and BSC OS, and tafamidis TTD.

#### 4.2.6.1 Extrapolation of tafamidis and BSC OS

In the economic model, tafamidis OS was estimated based on fully parametric survival curves that were fitted to the observed data in the ATTR-ACT LTE trial with excess non-disease related survival hazard from the Office for National Statistics (ONS, 2018-2020) applied. The company stated that the most appropriate parametric survival curve (exponential, Weibull, log-logistic, log-normal, Gompertz, and generalised gamma were considered) for the modelling of tafamidis OS was selected based on NICE Decision Support Unit (DSU) guidance,[26] including ranking distributions based on statistical fit (Akaike information criterion, AIC, and Bayesian information criterion, BIC), visual inspection of the observed versus the predicted data, and assessment of the hazard profiles in the parametric models versus the observed data. The company selected the generalised gamma curve in its base-case for the modelling of tafamidis OS. This was based on the fact that the generalised gamma showed the most rapid reduction in excess hazard, matching well the gradient of the observed hazard during the third year. The company additionally argued that the generalised gamma had the lowest AIC of all candidate parametric survival models. Next to that, the company discussed a peak hazard at 24 months followed by a decline towards a rising general population hazard based on non-parametric hazard profiles and suggested that the log-logistic, log-normal and generalised gamma models were the only models capable of predicting such a local peak hazard. Hence, the log-logistic and log-normal curves were explored in scenario analyses.

In line with committee preferences in the FAD for TA696,[15] the company selected the Weibull curve to extrapolate the observed BSC OS data from ATTR-ACT as no new data for the placebo arm in ATTR-ACT were available.

#### 4.2.6.2 Relative risk of death by any cause per NYHA class

A different proportion of patients within each NYHA class moved to the death state depending on an estimated relative risk. For each health state, the company provided updated disaggregated Cox proportional hazard models of death by any cause for the tafamidis arm in ATTR-ACT LTE (CS Table 8). The hazards associated with BSC were not updated due to the lack of new data.

#### 4.2.6.3 Extrapolation of tafamidis TTD

The fitting and selection process for the tafamidis TTD curves was in line with the fitting and selection process for the tafamidis and BSC OS curves. Discontinuation event data were analysed using death as a competing risk, and censoring was applied to patients with heart transplant, cardiac mechanical assist device (CMAD) implantation, and loss to follow-up. In addition, patients who discontinued treatment proximate to death and patients who discontinued treatment as they gained access to commercial tafamidis were censored. A scenario analysis was explored where patients were censored at the time of their first assessment as NYHA IV. For patients who discontinued from tafamidis, an indefinite tafamidis treatment effect was assumed without incurring any further treatment costs.

The company used the exponential curve in its base-case for the modelling of tafamidis TTD (as per the EAG's preferred assumption in TA696 [23]), given its low AIC and BIC and the degeneration of multi-parameter models to the exponential form.

**EAG comment:** The main concerns of the EAG relate to: a) the extrapolation of tafamidis OS, and b) continuation of the tafamidis treatment effect in patients who discontinued treatment.

a) The company fitted the generalised gamma curve to the updated observed ATTR-ACT LTE trial data (with extended follow-up of 84 months) for the extrapolation of tafamidis OS based on its numerical advantage on AIC, and its agreement with the non-parametric hazard profile estimated to 84 months follow-up. The EAG notes that the candidate parametric survival models are fairly similar in terms of their statistical and visual fit to the observed ATTR-ACT LTE trial data. In line with TA696, the AIC of the company's selected generalised gamma curve was similar to the log-normal curve, but the generalised gamma was the worst fitting curve according to the BIC values. The EAG was unable to validate the extrapolated tafamidis OS beyond the observed trial data, as no long-term external data was provided by the company due to availability issues. The 10 years OS rates in Table 42 of the clarification response, as well as the plotted OS curves in Figure 5 of the CS demonstrate that the company's selected generalised gamma curve gives the highest tafamidis OS estimation beyond the observed ATTR-ACT LTE trial data compared to the other candidate parametric survival models. The EAG does not consider the company's arguments for the selection of this curve as sufficient. Hence, in line with the committee's preferred curve in TA696, the EAG remains using the log-normal (similar AIC compared to generalised gamma and second best BIC overall) for the modelling of tafamidis OS in its base-case.
b) The company assumed an indefinite tafamidis treatment effect after discontinuation. Thus, an increasing proportion of surviving patients are assumed to discontinue tafamidis whilst continuing to accrue the benefits of treatment, without incurring any further treatment costs. This issue was extensively discussed in the EAG report and the technical engagement and appraisal consultation document (ACD) responses in TA696. The committee concluded that assuming continued treatment benefits without a cost was overly optimistic and would lead to an underestimated ICER. In TA696, the EAG presented two exploratory scenario analyses; one in which it was assumed that all patients remain on treatment beyond the observed trial period and the treatment effect is indefinitely applied, and one in which it was assumed that treatment discontinuation continued beyond the observed trial period and outcomes for the BSC arm were applied to tafamidis discontinuers (i.e., survival, CV-related hospitalisations, NYHA transitions and HRQoL). Although the EAG acknowledges the limitations as discussed in TA696 (i.e., assuming no discontinuation beyond the observed trial period in scenario 1 and assuming that the tafamidis treatment effect is immediately lost after patients discontinue in scenario 2, the EAG's concerns regarding the problems of the company's approach remain unchanged and hence these scenario analyses are also presented to quantify the uncertainty surrounding this issue in the current appraisal.

### 4.2.7 Adverse events

The evidence on treatment AEs used for intervention and comparators was ATTR-ACT,[8] as in the original CS.[20] In the TA696 EAG report,[23] more information about the treatment-related AEs can be found in Sections 5.2.2 and 5.2.4. Associated issues can be found in Sections 5.3.3(8) regarding the AE costs being high and from outdated sources. The company applied lower AE costs values, which were deemed more appropriate by the EAG in TA696.[23]

**EAG comment:** The updated CS did not include additional or altered information on the AEs.

### 4.2.8 Health-related quality of life

#### 4.2.8.1 Health-related quality of life data identified in the review

The SLR from TA696 was used in the current CS, an update was not performed. Please check TA696 CS Document B Section 3.4.3 for more information on the SLR of the HRQoL studies.[20]

#### 4.2.8.2 Health state utility values

The utility values were estimated for the following health states: NYHA I, NYHA II, NYHA III, and NYHA IV. Health-related quality of life data was collected in study ATTR-ACT using European Quality of Life-5 Dimensions (EQ-5D-3L).[8] No EQ-5D-3L was collected in the extension study ATTR-ACT LTE.[21] Therefore, the updated model used the same health state utility values as the previous submission TA696. Table 4.2 includes a summary of all utility values per health state used in the cost effectiveness analyses. For the complete description of the HRQoL data and health state utility values, please check Sections 5.2.3, and 5.2.4, and associated issues can be found in Section 5.3.3(7) from the original EAG report for TA696.[23] The main concerns of the EAG regarding HRQoL assumptions in TA696 were: 1) NYHA IV health state utility value being derived from limited observations; 2) ATTR-ACT EQ-5D-3L data being restricted to the on-treatment period; 3) treatment-dependent utilities being inconsistent with assumed stopping rule; and 4) utilities not being age-adjusted.

The updated company base-case resolved issues 3 and 4 above.[16] Issue 3 was resolved by incorporating continuation of treatment in NYHA IV, as the committee agreed that "*it was not appropriate to model a stopping rule based on the NYHA classification*". Issue 4 was resolved by applying age-adjusted utility decrements after month 30 because the committee concluded that "*using age-adjusted utility values was appropriate*". Regarding issues 1 and 2, the committee agreed that it "*had concerns about using treatment-dependent health state utility values from relatively few observations [in NYHA IV] and the potential for informative censoring to bias these estimates. It concluded that the treatment-dependent utility values were reasonable in NYHA class 1 to 3, and that the best supportive care utility value should be applied in the NYHA class 4 health state"*. However, in the updated economic model provided by the company, utility values for NYHA IV were still treatment dependent. In the clarification response, the company clarified that patients in the NYHA IV health state in the tafamidis arm would be assigned a utility of [redacted] until they discontinued to BSC in which they would switch to a utility value of [redacted].[17]

**Table 4.2: Health state utility values**

| Health state | Tafamidis | | Tafamidis (discontinued) | | BSC | | Reference |
|---|---|---|---|---|---|---|---|
| | Utility value | SE | Utility value | SE | Utility value | SE | ATTR-ACT |
| NYHA I | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| NYHA II | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| NYHA III | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| NYHA IV | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

BSC = best supportive care; NYHA = New York Heart Association; SE = standard error

#### 4.2.8.3 Disutility values

Disutilities associated with AEs and CV-related hospitalisations were not included, as in the original CS, in which those were assumed to be already captured within NYHA state specific utility values.[16] The critique of the lack of disutility values for the CV-related hospitalisations can be found in Section 5.3.3(7) of the original EAG report in TA696. However, the EAG concluded that including this disutility would have a limited impact on the ICER.

**EAG comment:** The main concerns of the EAG relate to: a) not having treatment independent utility values for NYHA IV, b) assuming the same utilities for patients on treatment and discontinuations in the tafamidis arm, and c) utility values higher than the general population age-matched average.

a) The updated CS stated that treatment-independent utilities were implemented in the NYHA IV health state in the new base-case, as preferred by the committee[15]. However, each arm had a different utility value in the updated model (tafamidis: [redacted], tafamidis discontinued: [redacted], BSC: [redacted]). In clarification response B13, the company specified that tafamidis patients in the health state NYHA IV would have the utility value of tafamidis ([redacted]) and would only be assigned the utility value of BSC ([redacted]) after discontinuing the treatment.[17] This contradicts the statements made by the company in the CS, as the utility values of NYHA IV are not treatment independent by definition. The company argued that the committee decision was made in the "*context of an economic model assuming that patients entering NYHA IV would discontinue from tafamidis, and where the only scenarios that had been presented enforcing treatment independent utilities did so under this assumption*".[17] The FAD states *"The committee agreed that it had concerns about using treatment-dependent health state utility values from relatively few observations and the potential for informative censoring to bias these estimates. It concluded that the treatment-dependent utility values were reasonable in NYHA class 1 to 3, and that the best supportive care utility value should be applied in the NYHA class 4 health state."*.[15] However, it was unclear based on what context the committee took this decision. Nevertheless, the following considerations still hold: 1) there is little data available for patients on tafamidis in NYHA IV as the EQ-5D data was only collected during the on-treatment period, and most people in the trial stopped before progression to NYHA IV; 2) both treatment groups had a small number of observations (tafamidis group, n=[redacted] observations; placebo group, n=[redacted] observations); and 3) there is a substantial difference in utility values between arms in NYHA IV, while utility values for tafamidis and BSC in the other NYHA classes were similar. Therefore, now that patients can continue treatment in NYHA IV, the EAG believes the

committee's considerations should apply to all utility values in NYHA IV, i.e., the tafamidis utility value in NYHA IV should be [redacted] to obtain truly treatment-independent utility values.

b) Patients who discontinued treatment in the NYHA I-III health states in the tafamidis arm were assigned the same utilities as those who were still on treatment (Table 4.2). The validity of this assumption is unclear to the EAG, as EQ-5D-3L data collection was restricted to the on-treatment period only.[27] Therefore, no information on patient utility values after treatment discontinuation is available. In addition, during the committee meeting for TA696, the committee stated that "*the mechanism underlying tafamidis' proposed [extended ]benefit [was] unclear*"[15]. Consequently, the EAG considers that tafamidis utility values for health states NYHA I-III would only be appropriate for those patients who are still on treatment. The EAG included a scenario analysis in which patients discontinuing treatment with tafamidis were assigned BSC outcomes, including BSC utility values, instead of tafamidis outcomes.

c) In the updated base-case, the baseline age of the population was 74 years old. In the UK, the average utility value of the general population age-matched average (65-74) is 0.779.[28] However, as shown in Table 4.2, the health state utilities for patients in the NYHA I (tafamidis: [redacted], BSC:[redacted]) and NYHA II (tafamidis: [redacted], BSC:[redacted]) were higher than (or just below) the general population utility value for the general population age-matched average. The company justified this by arguing that patients in the NYHA I and NYHA II health states have either no or slight limitation of their physical activity, and, given that the general population in this age group may suffer from other illnesses and/or have physical limitations, it would be reasonable to assume higher health state utility values for patients with ATTR-CM than the general population.[17] However, this lacks face validity as "*the clinical experts involved in technical engagement explained that it was not plausible that someone with ATTR-CM could have a better quality of life than someone of a similar age and sex from the general population*".[15] Despite being asked in clarification question B12, the company did not provide an updated economic model applying a cap to the utility values higher than those from the general population.[17] Therefore, the EAG base-case included a cap for the health states with utility values higher than those from the age-matched general population. The EAG implemented this analysis by capping all utility values above the general population utility values already implemented in the economic model.

### 4.2.9 Resources and costs

The cost categories included in the model were drug acquisition, CV-related hospitalisations, disease management, management of AEs, and end of life care costs.[16] An extensive description of the cost categories can be found in the original EAG report of TA696, Section 5.2.4.[23] The EAG critique can be found in the same document in Section 5.3.3(8), and it entailed: 1) use of high and outdated AE costs, 2) potential underestimation of NYHA IV health state costs, 3) high unit costs for concomitant medication, 4) including wastage costs for tafamidis, and 5) early diagnosis benefits attributable to tafamidis. The EAG considered the first three points resolved by the company or had limited impact on the ICER. The committee agreed that drug wastage costs for tafamidis should be included as "*it was likely to happen in practice"*, and that "*the company's early diagnosis assumptions [were] not appropriate for decision making because there was not enough evidence to support them".*[15] The company updated its base-case accordingly to include drug wastage costs and remove the early diagnosis benefits attributable to tafamidis.[16] In addition, after technical engagement, the EAG criticised the stopping rule applied by the company in which "*people in the NYHA class 1 to 3 health states who stop treatment with tafamidis [were] assumed to benefit from treatment indefinitely without any treatment costs*". Hence, the committee agreed that "*it was unrealistic to assume continued treatment benefits without a cost".* In the CS base-case BSC treatment costs are assumed for patients who discontinue tafamidis.[16]

The CS Table 9 shows the updated costs in the economic model.[16] Costs were updated based on 2022 electronic market information tool (eMIT) database costs,[29] 2021/2022 NHS reference costs,[30] and 2021/2022 Personal Social Services Research Unit (PSSRU) unit costs.[31] End of life costs were inflated using PSSRU Health Services inflation index.[32]

#### 4.2.9.1 Resource use and costs data identified in the review

The SLR on UK relevant resource use and cost information from TA696 was used in the current CS, and was not updated. For more details on the SLR conducted in TA696, please refer to Document B of TA696.[20]

#### 4.2.9.2 Treatment costs (with patient access scheme)

The company updated the patient access scheme (PAS) from [redacted] ([redacted] per pack) to [redacted] ([redacted] per pack).

#### 4.2.9.3 Health state costs

Table 4.3 summarises the changes in health state costs per month from the original CS to the updated CS.[16]

**Table 4.3: Health state costs per cycle**

| Health state | TA696 | Updated CS |
|---|---|---|
| **NYHA I** | [redacted] | [redacted] |
| **NYHA II** | [redacted] | [redacted] |
| **NYHA III** | [redacted] | [redacted] |
| **NYHA IV** | [redacted] | [redacted] |
| Based on CS original model (Costs!D46:D49), and CS updated model (Clinical Preproc!E153:E156).<br>CS = company submission; NYHA = New York Heart Association | | |

**EAG comment:** The EAG had no concerns with the updated resource use and costs provided by the company. The EAG had a slight concern that relates to incorporating AE costs as a one-off cost in the first model cycle. This lacks face validity as AEs were recorded to happen after the first month of treatment in the ATTR-ACT trial. Furthermore, this cost calculation strategy can never include the AEs from patients in the NYHA IV health state, as there were no patients in this health state during the first cycle. The EAG acknowledges that the impact of this assumption on the ICER is likely to be small, however the economic model could be improved by applying the costs of AEs in line with the nature of incidence observed in the trial and to include the AEs costs for patients in the NYHA IV health state.

### 4.2.10 Severity

In response to the clarification letter, the company provided the results of their disease severity assessment. Age-adjusted utilities for the general population from Ara and Brazier (2011)[33] were used to calculate quality-adjusted life years (QALYs) in the sex- and age-matched general population.

In the company's base-case analysis, with a mean age at baseline of 74.34 and a proportion of males at 90%, the absolute shortfall estimate is [redacted] and the proportional shortfall estimate is [redacted], resulting in a severity modifier of [redacted].

**EAG comment:** The EAG has no comments.

### 4.2.11 Uncertainty

Key areas of uncertainty were not explicitly discussed by the company.

**EAG comment:** Although the company did not explicitly address key areas of uncertainty, the company's assessment of the key sources of uncertainty would be informative to the EAG.

# 5. COST EFFECTIVENESS RESULTS

## *5.1 Company's cost effectiveness results*

The CS base-case cost effectiveness results (probabilistic) indicated that tafamidis is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than best supportive care amounting to an ICER of [redacted] per QALY gained (Table 5.1). The probability of tafamidis being cost effective, at a threshold of £30,000 per QALY gained, compared to BSC is approximately [redacted]. There were slight differences between the probabilistic results reported by the company and the results that were produced when the EAG ran the model with the company's default settings.

**Table 5.1: Probabilistic CS base-case results**

| Intervention | QALYs | Costs (£) | Incremental QALYs | Incremental Costs | ICER (£/QALY) | NHB (QALYs) |
|---|---|---|---|---|---|---|
| **BSC** | [redacted] | [redacted] | | | | |
| **Tafamidis** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BSC = best supportive care; CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year | | | | | | |

Overall, the technology is modelled to affect QALYs by:

- Reduction of limitations in physical activity for tafamidis. Deterministic incremental QALYs gained for tafamidis versus BSC were [redacted], of which [redacted] was gained in health states NYHA I and II.
- Increased OS for tafamidis. Deterministic incremental life years gained for tafamidis versus BSC were [redacted].

Overall, the technology is modelled to affect costs by:

- Higher treatment costs for tafamidis. Deterministic incremental costs for tafamidis versus BSC were [redacted], of which [redacted] were treatment costs.

**EAG comment:** The EAG has no comments.

## *5.2 Company's sensitivity analyses*

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's DSAs) are:

- Discount rates of costs and QALYs
- NYHA class health state utilities
- CV-related hospitalisation event rates.

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the overall indication net health benefit (NHB) were related to:

- Including the early diagnosis impact on costs
- Assuming no treatment usage in NYHA IV
- Extrapolation of tafamidis OS using log-logistic distribution.

**EAG comment:** The main concern of the EAG relates to inconsistencies in the PSA results. The company's PSA outcomes reported in the CS[16] are different from the results that were produced when the EAG ran the model with the company's default settings. Moreover, when the EAG implemented scenarios the PSA results seemed inconsistent. First of all, the scenario analysis in which utilities were adjusted (EAG analyses 3), resulted in different total costs for BSC (probabilistic value). Moreover, the scenario proposed by the EAG in TA696 (EAG analysis 5), does not seem to be responsive when switched off. So, after the PSA was run with EAG scenario 5 and the results were again set to the default settings, the results were different from default PSA results and thus do not seem to incorporate changes in these settings properly. It is unclear to the EAG what exactly causes these problems, and hence justification and correction by the company is requested. Therefore, the EAG analyses were limited to deterministic base-case and sensitivity analyses.

### *5.3 Model validation and face validity check*

The company's economic model in the original CS was validated by an independent consultant and cell-by-cell verification was undertaken in order to verify the model calculations. In addition, the EAG performed double-programming of the deterministic version of the company's economic model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.

Following TA696,[20] the company provided a comparison of clinical trial outputs versus modelled outputs in CS Appendix D as a face validity assessment. The company stated the model outputs closely represent the outcomes observed during ATTR-ACT LTE.

**EAG comment:** The main concern of the EAG relates to the mismatch between the modelled OS and TTD outcomes reported in Table D1 of Appendix D, Tables 42 and 43 of the clarification response, and the economic model. For example, the modelled 5-year tafamidis OS in Table D1 of Appendix D ([redacted]) does not match with the reported modelled 5 year tafamidis generalised gamma OS in Table 42 of the clarification response ([redacted]), nor the 5 year tafamidis OS in the economic model ([redacted]). Further justification for these mismatches should be provided, and if applicable, corrections in the tables and/or economic model should be provided. This issue was resolved after the factual inaccuracy check. The company has explained the differences between the tables and explained that the [redacted]% in Table D1 of Appendix D should be corrected to [redacted]%.

# 6. EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

## *6.1 Exploratory and sensitivity analyses undertaken by the EAG*

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. (2020):[34]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al. (2016)):[35]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

### 6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as a starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case.

#### 6.1.1.1 Fixing errors

The EAG was unable to make adjustments for the error in the PSA that was identified.

#### 6.1.1.2 Fixing violations

There were no violations found that needed fixing.

#### 6.1.1.3 Matters of judgement

1. Modelling a log-normal survival curve for the extrapolation of overall survival for tafamidis (Section 4.2.6)
   The EAG modelled a log-normal survival curve for the extrapolation of tafamidis overall survival instead of a generalised gamma curve as was chosen by the company.
2. Modelling treatment independent utility values in NYHA class IV (Section 4.2.8)

The EAG modelled treatment independent utility values in NYHA class IV based on the BSC utility value ([redacted] for both BSC and tafamidis) instead of treatment dependent utility values ([redacted] for BSC and [redacted] for tafamidis).

3. Applying a cap on utility values above the general population age-matched average (Section 4.2.8)
   The EAG modelled a cap on utility values that were above the general population age-matched average.

### 6.1.2 EAG exploratory scenario analyses

The EAG performed the following scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

#### 6.1.2.1 Exploratory scenario analyses

4. Modelling a tafamidis discontinuation plateau after the observed period while the treatment effect is applied indefinitely (Section 4.2.6)
   The EAG modelled a discontinuation plateau after the observed period and the treatment effect is applied indefinitely instead of extrapolating tafamidis TTD over time whilst assuming an indefinite tafamidis treatment effect.
5. Modelling tafamidis treatment discontinuation by extrapolating TTD after the observed period and outcomes for the BSC arm were applied to tafamidis discontinuers (Section 4.2.6)
   The EAG modelled tafamidis treatment discontinuation by extrapolating TTD after the observed period and outcomes for the BSC arm were applied to tafamidis discontinuers instead of assuming an indefinite tafamidis treatment effect.

### 6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

**Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)**

| Key issue | Section | Source of uncertainty | Alternative approaches | Expected impact on ICER[a] | Resolved in EAG base-case[b] | Required additional evidence or analyses |
|---|---|---|---|---|---|---|
| **No updated SLRs for economic evaluations, resources/costs or utilities** | 4.1 | Methods | The SLRs should be updated to incorporate the latest evidence available. | **+/-** | No | The SLRs should be updated to incorporate the latest evidence available. |
| **Uncertainty whether patisiran, inotersen and vutrisiran are comparators to tafamidis in the mixed phenotype population.** | 4.2.4 | Transparency and unavailability | The EAG suggested to include the three comparators at least for the mixed phenotype subgroup. | +/- | No | Conduct a full SLR and economic evaluation including the three comparators. Alternatively, the population could be narrowed down to exclude patients with mixed phenotype. |
| **Continuation of the tafamidis treatment effect in patients who discontinued treatment** | 4.2.6 | Methods | The EAG has modelled two exploratory scenarios: 1) discontinuation plateau and 2) BSC outcomes after discontinuation | + | Explored in EAG analysis 4 and 5 | Additional (long-term) evidence regarding the survival, CV-related hospitalisations, NYHA transitions and HRQoL in patients who discontinued tafamidis. |
| **Extrapolation of tafamidis OS** | 4.2.6 | Methods | The EAG preferred to use a log-normal curve to extrapolate overall survival | Increased by [redacted] | Yes, EAG analysis 1 | None |
| **Not using treatment-independent utility values for the NYHA IV health state** | 4.2.8 | Bias and indirectness | The EAG preferred to use treatment independent utility values in NYHA class IV | Increased by [redacted] | Yes, EAG analysis 2 | None |
| **Utility values being higher than the UK general population** | 4.2.8 | Bias and indirectness | The EAG preferred to cap utility values above the UK | Increased by [redacted] | Yes, EAG analysis 3 | None |

| Key issue | Section | Source of uncertainty | Alternative approaches | Expected impact on ICER[a] | Resolved in EAG base-case[b] | Required additional evidence or analyses |
|---|---|---|---|---|---|---|
| | | | general population age-matched average | | | |
| **Inconsistent PSA results** | 5.2 | Methods | The EAG would like a justification for the inconsistency in PSA results and, if applicable, updated economic model with a properly working PSA. | No influence on deterministic results, only PSA results are affected in an unknown way. | No | An updated economic model with a properly working PSA. |

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored

BSC = best supportive care; CV = cardiovascular; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; NYHA = New York Heart Association; OS = overall survival; PSA = probabilistic sensitivity analysis; SLR = systematic literature review; UK = United Kingdom

### *6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. Table 6.3 shows the exploratory scenario analyses conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

**Table 6.2: Deterministic EAG base-case**

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | NHB (£30,000 threshold) |
|---|---|---|---|---|---|---|
| **CS base-case** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG Analysis 1: log-normal instead of generalised gamma overall survival curve** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 2: treatment independent utility values in NYHA IV** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 3: cap on utility values above the general population age-matched average** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG base-case** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

BSC = best supportive care; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; NYHA = New York Heart Association; QALY = quality-adjusted life year

**Table 6.3: Deterministic scenario analyses (conditional on EAG base-case)**

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | NHB (£30,000 threshold) |
|---|---|---|---|---|---|---|
| **EAG base-case** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 4: discontinuation plateau with indefinite treatment effect** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 5: BSC outcomes for tafamidis discontinuers** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | NHB (£30,000 threshold) |
|---|---|---|---|---|---|---|
| BSC = best supportive care; EAG = external assessment group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality adjusted life year | | | | | | |

### *6.3 EAG's preferred assumptions*

The estimated EAG base-case ICER (deterministic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained. Probabilistic EAG base-case analyses could not be generated due to inconsistencies in the PSA. The most influential adjustments were applying a cap on the utility values above the general population age-matched average utility value and assuming a log-normal curve for the extrapolation of OS. The ICER increased most in the scenario analysis 5, with alternative assumptions regarding the outcomes for patients who discontinue tafamidis treatment.

### *6.4 Conclusions of the cost effectiveness section*

The company's cost effectiveness model largely complied with the NICE reference case. The only deviation from the reference case was that the synthesis of evidence was based on a literature review conducted for a previous submission (TA696) and was therefore outdated.[20] The most prominent issues highlighted by the EAG are shown in the key issue tables in Section 1.5.

The first important limitation was that inotersen, patisiran and vutrisiran were not included as comparators in the economic model and diflunisal was not included as one of the treatments in the BSC arm, while these were listed as relevant comparators in the NICE scope. It is plausible that inotersen, patisiran and vutrisiran are relevant comparators to tafamidis for (at least) the mixed phenotype subgroup. The impact of including these treatments on the ICER is unknown. Second, while this was determined unrealistic in TA696[15], the company assumed an increasing proportion of surviving patients to discontinue tafamidis whilst continuing to accrue the benefits of treatment, without incurring any further treatment costs. The EAG explored two alternative assumptions in its scenario analyses. In particular the scenario where BSC outcomes were assumed for tafamidis discontinuers had a substantial impact on the ICER. Next to that, a generalised gamma curve for the extrapolation of tafamidis OS was chosen by the company, in contrast to the committee's preferred curve in TA696,[15] without sufficient arguments. In addition, treatment-dependent utility values in NYHA class IV seemed unjustified due to the low number of observations and the lack of plausibility of the large difference between the values obtained for the tafamidis and BSC arms. Last, the PSA results seemed inconsistent and are therefore deemed unreliable by the EAG. Therefore, the EAG only performed deterministic base-case and sensitivity analyses.

The CS base-case ICER (deterministic) for tafamidis versus BSC was [redacted]. The estimated EAG base-case ICER (deterministic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained. The most influential adjustment was assuming a different curve for the extrapolation of OS in the tafamidis arm. The ICER increased most in the scenario analyses with alternative assumptions regarding the outcomes of patients that discontinue tafamidis treatment.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of tafamidis. The main sources of non-quantifiable uncertainty are potential subgroups in the tafamidis population, the relevance of comparators included in the NICE scope, and the outcomes of patients that discontinue tafamidis. Partly this can be resolved by the company by conducting further analyses. This includes providing a model including all comparators included in the NICE scope for the right population, a proper implementation of the PSA, and additional supporting clinical evidence on the

outcomes of tafamidis discontinuers. Therefore, the EAG believes that neither the CS or the EAG report contains an unbiased ICER of tafamidis compared with the relevant comparators.

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The company has responded to the concerns of the EAG regarding inconsistencies in the PSA and provided a health economic model with updated PSA.

The issues included:

- The company's PSA outcomes reported in the CS are different from the results that were produced when the EAG ran the model with the company's default settings.
- Scenario analysis in which utilities were adjusted (EAG analyses 3), resulted in different total costs for BSC (probabilistic value).
- Scenario proposed by the EAG in TA696 (EAG analysis 5), does not seem to be responsive when switched off. So, after the PSA was run with EAG scenario 5 and the results were again set to the default settings, the results were different from default PSA results and thus do not seem to incorporate changes in these settings properly.

The EAG has reviewed this updated health economic model and confirms that all issues relating to the PSA are now resolved. The EAG confirms obtaining the same PSA results when running the company base case. In its report, the EAG did not run their analyses probabilistically as these provided inconsistent results. To complete the set of analyses for the upcoming ACM, the EAG has now ran probabilistic sensitivity analyses for all EAG analyses, see Tables 1 and 2 below.

**Table 1: Probabilistic EAG base-case**

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | NHB (£30,000 threshold) |
|---|---|---|---|---|---|---|
| **CS base-case** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG Analysis 1: log-normal instead of generalised gamma overall survival curve** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 2: treatment independent utility values in NYHA IV** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 3: cap on utility values above the general population age-matched average** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG base-case** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

BSC = best supportive care; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; NYHA = New York Heart Association; QALY = quality-adjusted life year

**Table 2: Probabilistic scenario analyses (conditional on EAG base-case)**

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | NHB (£30,000 threshold) |
|---|---|---|---|---|---|---|
| **EAG base-case** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 4: discontinuation plateau with indefinite treatment effect** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG analysis 5: BSC outcomes for tafamidis discontinuers** | | | | | | |
| BSC | [redacted] | [redacted] | | | | |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

BSC = best supportive care; EAG = external assessment group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality adjusted life year

**Questions for the clinical expert (priority in bold)**

*Population*

1) The ATTR-CM population consists of several patient subgroups. Could you please elaborate on the percentages of patients with wildtype ATTR-CM, hereditary ATTR-CM and patients with a mixed phenotype (i.e. patients who also have familial polyneuropathy) in the UK ATTR-CM population?

According to NAC database (which is likely to underestimate total since there will be patients who have not been referred to NAC out there) as of Oct 2023

| Characteristic | N | Notes |
|---|---|---|
| Patients with ATTR-CM who are alive and live in England | 1747 | Excludes Scotland, NI, Republic Ireland, Wales |
| Proportion wild-type (estimate) | 90% | |
| Proportion hereditary (estimate) | 10% | |
| Number in trials | ~600 | Trials will not exclude tafamidis use |
| NYHA IV (2.5%) | 43 | |
| **Eligible population** | **1704** | Eligible population right now |
| | | |

*Intervention and comparator*

2) **Please elaborate on the standard of care in UK clinical practice for both the whole ATTR-CM population and for the transthyretin familial polyneuropathy and hereditary ATTR-CM subgroup.**

   FOR TTR-CM without cardiomyopathy the SoC is heart failure management. The unit offers entry to clinical trials for an eligible patients. Difflunasil is only available to legacy patients now (so we cannot offer to new diagnosis)

   For hTTR-CM the treatment options are the same unless they have evidence of neuropathy and are eligible for gene silencing therapies under CCPs

a) **Are the treatments listed in Table 1 considered standard of care for the ATTR-CM population?**

More or less, the unit published a recent retrospective review of treatment of heart failure in TTR-CM this August (Ioannou A, Massa P, Patel RK, Razvi Y, Porcari A, Rauf MU, Jiang A, Cabras G, Filisetti S, Bolhuis RE, Bandera F, Venneri L, Martinez-Naharro A, Law S, Kotecha T, Virsinskaite R, Knight DS, Emdin M, Petrie A, Lachmann H, Wechelakar A, Petrie M, Hughes A, Freemantle N, Hawkins PN, Whelan C, McMurray JJV, Gillmore JD, Fontana M. Conventional heart failure therapy in cardiac ATTR amyloidosis. Eur Heart J. 2023 Aug 14;44(31):2893-2907. doi: 10.1093/eurheartj/ehad347. PMID: 37216684; PMCID: PMC10424879.)

'beta-blockers were prescribed in in 55.4%, angiotensin-converting enzyme inhibitors (ACEis)/angiotensin II receptor blockers (ARBs) in 57.4%, and mineralocorticoid receptor antagonists (MRAs) in 39.0% of cases.
During a median follow-up of 27.8 months (interquartile range 10.6–51.3), 21.7% had beta-blockers discontinued, and 32.9% had ACEi/ARBs discontinued. In contrast, only 7.5% had MRAs discontinued.
A propensity score-matched analysis demonstrated that treatment with MRAs was independently associated with a reduced risk of mortality in the overall population [hazard ratio (HR) 0.77 (95% confidence interval (CI) 0.66–0.89), P < .001] and in a pre-specified subgroup of patients with a left ventricular ejection fraction (LVEF) >40% [HR 0.75 (95% CI 0.63–0.90), P = .002]; and treatment with low-dose beta-blockers was independently associated with a reduced risk of mortality in a pre-specified subgroup of patients with a LVEF ≤40% [HR 0.61 (95% CI 0.45–0.83), P = .002]. No convincing differences were found for treatment with ACEi/ARBs.'

There is a paper from our centre in press reporting benefit of SGLT2-i in heart failure and cardiac amyloidosis across EF range of HFrEf and HFpEF

'SGLT2-i treatment in ATTR-CM patients was well tolerated and associated with reduction in worsening of symptoms, NT-proBNP and eGFR, lower diuretic requirement over time. SGLT2-i treatment was also associated with reduced risk of HF hospitalization, cardiovascular and all-cause mortality. These preliminary findings merit prospective randomized controlled trials of SGLT2-i in ATTR-CM.'

**b) Is diflunisal part of current clinical care for any of these patients?**
No it is not available for new patients

**c) How is the transthyretin familial polyneuropathy and hereditary ATTR-CM subgroup treated?**
**See above**

**Table 1. Non-disease modifying therapy for ATTR-CM – BSC in the UK**

| Therapy | Considerations in ATTR-CM patients |
|---|---|

| | |
|---|---|
| **Loop diuretics** | Recommended, especially bioavailable loop diuretics (e.g., furosemide) to avoid diuretic resistance in advanced cardiomyopathy |
| **Aldosterone antagonists** | Consider addition of low dose spironolactone 12.5 mg every other day |
| **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers** | Usually poorly tolerated due to risk of symptomatic hypotension as disease progresses |
| **Beta-blockers** | Risk of symptomatic hypotension, given fixed stroke volume and reliance of higher heart rate to maintain cardiac output |
| **Calcium channel blockers** | Contraindicated<br>May lead to high-degree heart block and profound negative inotropic effect with resulting cardiogenic shock |
| **Digoxin** | Relatively contraindicated<br>Hypersensitivity may lead to abrupt cardiac rhythm disturbances and sudden death |

Source: Adapted from Castano et al. 2015

3) **For the transthyretin familial polyneuropathy and hereditary ATTR-CM subgroup, patisiran, inotersen and vutrisiran might be new treatment options next to tafamidis. Please elaborate on whether or not these are considered relevant treatment options for this specific subgroup of patients (and therefore comparators to tafamidis)?**

Gene silencing agents and CISPAR 9 gene editing have been trialed in cardiac TTR amyloid and in theory and, in line with what is understood about amyloidogenisis and treatment of amyloid in general, knock down of the fibril precursor by the levels demonstrated would be expected to result in decreased amyloid formation and better patient outcomes. A recent modeling study (McGirr K, Sarkar S, Subramanian K. Quantitative modeling of approved and emerging therapeutics for modifying TTR levels in patients with Transthyretin Amyloid Cardiomyopathy. CPT Pharmacometrics Syst Pharmacol. 2023 Nov 6.) suggests that genetic silencers reduced tetrameric flux more than small molecule stabilizers and that combining both approaches might have further benefit.

Patisiran in the APOLLO B trial (Maurer M, et al. Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis N Engl J Med 2023) was shown to preserve functional capacity, from analysis of a 12-month double blind period with a smaller decline in the 6-min walking distance than the placebo group (Hodges–Lehmann estimate of median difference 14.69 m, 95% CI 0.69–28.69 m, P = 0.02). Quality of life and health status improved in the patisiran group (as indicated by an increase in KCCQ-OS score), whereas in the placebo group, the score declined (least-squares mean difference 3.7 points, 95% CI 0.2–7.2, P = 0.04). But there was no significant differences in the secondary composite end point of death from any cause, cardiovascular events, and change from baseline in the 6-min walking distance.

HELIOS-B Phase 3 study of vutrisiran should produce early results in 2024 and is expected to be very similar in action to Parisian. The expectation in the cardiology commentary is that analysis of longer follow up data will produce evidence of protective effects which match or exceed that of stabilizers such as tafamadis (which was analyzed at 30 months and may have recruited patients with more advanced disease). At the moment these data are just lacking but my best guess is that in the future they will be part of the therapeutic options.

*Treatment effectiveness*

4) **For the extrapolation of tafamidis overall survival (OS) and time to treatment discontinuation (TTD) over the lifetime time horizon of the economic model (modelled patient starting age is 74 years), the company fitted fully parametric survival curves to the observed ATTR-ACT LTE trial data (disease related survival with excess non-disease related survival from the Office for National Statistics (ONS)). More details can be found in sections 7.2 to 7.5 in the company submission. Could you please complete the table below by providing us estimates of the expected median OS and TTD for tafamidis and BSC, as well as the expected percentage of patients alive (OS) and on treatment (TTD) at 2, 5 and 10 years ?**

**Table 2: Expected OS and TTD for tafamidis and BSC**

| | **Tafamidis** | **BSC** |
|---|---|---|
| OS median (months) | [redacted] | [redacted] |
| OS(%) 2 years | [redacted] | [redacted] |
| OS (%) 5 years | [redacted] | [redacted] |
| OS (%) 10 years | [redacted] | [redacted] |
| TTD median (months)‡ | [redacted] | [redacted] |
| TTD (%) 2 years | | |

| | | |
|---|---|---|
| TTD (%) 5 years | | |
| TTD (%) 10 years | | |

This is complicated depending on the stage of disease at presentation – see summary table below of biomarker based staging and prognosis in ATTR amyloid cardiomyopathy and is reflected in wildly different data from 3 cohorts one of which is the model.

I suspect real world data will be towards the less favorable survival outcomes compared to trial populations but the 'baseline' is shifting as increasing awareness and recognition that early diagnosis may allow access to therapy is changing the diagnostic pathways and thus the patient population may be shifting to earlier stage disease.

| Model | Type | Biomarker, cut-off | Stages | Estimated median OS (months) |
|---|---|---|---|---|
| Kristen *et al.*[57] | ATTRwt and ATTRv | NT-proBNP >2584 ng/L (or BNP >195 ng/L)<br>TnT >50 ng/L (or TnI >580 ng/L) | A: 2 >cut-offs | 40% alive[a] |
| | | | B: 2 <cut-offs | 98% alive[a] |
| | | | C: 1 >cut-off | 80% alive[a] |
| Grogan *et al.*[58] | ATTRwt | NT-proBNP ≥3000 ng/L<br>TnT ≥50 ng/L | I: both below the cut-offs | 66 |
| | | | II: 1 above the cut-off | 40 |
| | | | III: both above the cut-offs | 20 |
| Gillmore *et al.*[56] | ATTRwt and ATTRv | NT-proBNP >3000 ng/L<br>eGFR <45 mL/min/1.73 $m^2$ | I: both below the cut-offs | 69 |
| | | | II: 1 above the cut-off | 47 |
| | | | III: both above the cut-offs | 24 |

*Gilmore, J.D., et al. Analysis of disease progression in patients with transthyretin cardiac amyloidosis. Orphanet J Rare Dis 10 (Suppl 1), O10 (2015)

+Gonzalez-Lopez E, et al Prognosis of Transthyretin Cardiac Amyloidosis Without Heart Failure Symptoms. JACC CardioOncol. 2022

^Elliott P, et al. Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy. Circ Heart Fail. 2022 (company model)

5) **Is it reasonable to assume that treatment benefit with tafamidis will be maintained indefinitely after treatment is stopped? If not, after treatment is stopped how would the magnitude of treatment benefit from tafamidis change in relation to BSC and over what time period? In other words what would the disease progression look like after treatment is discontinued?**

I don't think it is reasonable to assume the benefit of TTR stabilizers will persist after therapy is discontinued and I would anticipate that once treatment has discontinued circulating TTR would revert to baseline propensity to form amyloid. Whether clinical disease progression would be in parallel with BSC of care (from a more favorable baseline) or not is impossible to predict.

*Health-related quality of life*

6) **The company modelled patient health based on different health state utility values using the EQ-5D-3L data from the ATTR-ACT trial. Table 3 contains a summary of these health state utility values. In the model developed by the company, the baseline age of the population was 74 years old. In the UK, the utility value of the general population in this age group (65-74) is 0.779. However, as showed in table 3, the health state utilities for patients in the NYHA I and NYHA II states were higher (or just above) than the general population utility value for the same age group. The company justified this by arguing that patients in these health states (i.e., NYHA I and NYHA II) have either no or slight limitation of their physical activity, and, given that the general population in this age group may suffer from other illnesses and/or have physical limitations, it would be reasonable to assume higher health state utility values for patients with transthyretin amyloid cardiomyopathy than the general population.**

a) **Would you expect patients with ATTR-CM to have higher utility values than the general population in the same age-group, based on your experience with ATTR-CM?**

**No – I wonder if this is a trial artifact. In general patients who have presented with cardiomyopathy have a health related poor quality of life. There may be a specific issue with patients picked incidentally/early on CMRI or nuclear medicine testing who are pre or pauci symptomatic. The difficulty is that so far tafamidis seems most beneficial in early disease and in preventing progression to symptomatic disease (which is associated with a severe and irreversible deterioration in health state utility values) – so it would be rational to target treatment at individuals before their HSUV is significantly compromised.**

b) **Please elaborate on the appropriateness on applying a cap to the utility values used in the model, so that they do not exceed the general population utility values.**

See above – on first principles from an understanding of the natural history of cardiac TTR amyloidosis with relentless progression and the evidence of most benefit from treating earlier stage disease with tafamidis I think modeling on an aim of preserving HSUV would be rational.

Table 3. Health state utility values used in the model per state.

| Health state | Tafamidis | BSC | Reference |
|---|---|---|---|
| NYHA I | [redacted] | [redacted] | ATTR-ACT |
| NYHA II | [redacted] | [redacted] | |
| NYHA III | [redacted] | [redacted] | |
| NYHA IV | [redacted] | [redacted] | |

Abbreviations: BSC: Best supportive care, CS: Company submission; NYHA: New York Heart Association.

7) Table 3 shows a slight difference in utility values between the tafamidis and BSC arms for health states NYHA I-III, and a bigger difference in NYHA IV.

a) In your experience, do patients in the same health state experience differences in quality of life depending on their treatment arm (for example in a patient on BSC in NYHA class III and a patient on tafamidis in NYHA class III)?

Yes patients reported symptomatic improvement and this is supported by trial evidence

b) The company argue that the significant difference in the NYHA IV health state is due to the fact that patients continuing treatment are likely to be healthier than those who have discontinued, even if they are in the same NYHA class. In your practice, would you expect a higher utility value in patients in the NYHA IV health state that are being treated with tafamidis, in comparison with those treated with BSC?

The London practice would not be to add in tafamadis at this point as there is little evidence of benefit. We do not have stopping rules, have few patients with advanced disease on tafamidis and very few patients have discontinued as it is so well tolerated so I can not answer directly answer this question. As NYHA class IV is defined as severe limitations, experiences symptoms even while at rest and most patients are bedbound I would ask if the difference between the calculated HSUVs is clinically meaningful at these low levels?

**Single Technology Appraisal**

**Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 6 December 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

**Issue 1 Reproducing EAG analysis 3**

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr>
<td>Page 57, Table 6.2, Section 6.2<br><br>The EAG base-case is a product of various changes to the company base-case, these include:<br><br>• EAG analysis 1: log-normal instead of generalised gamma overall survival curve<br><br>• EAG analysis 2: treatment independent utility values in NYHA IV<br><br>• EAG analysis 3: cap on utility values above the general population age-matched average<br><br>The company has been able to reproduce EAG</td>
<td>Please update the results as following Table 6.2 and throughout the EAG report:<br><br>
<table>
<tr><td colspan="6">EAG analysis 3: cap on utility values above the general population age-matched average</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>Tafamidis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="6">EAG base-case</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>Tafamidis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>The ICERs associated with EAG analysis 3 and the EAG base-case need to be factually accurate.</td>
<td>Not a factual inaccuracy. The suggested analysis by the company still results in utility values above the general population age-matched average in subsequent cycles (i.e. when patients are above 75 years of age).</td>
</tr>
</table>

| | | | |
|---|---|---|---|
| analysis 1 and 2, however, when the company has capped utilities the results from EAG analysis 3 have been not reproduced. To reproduce EAG scenario 3, the company has capped utility values above the general population age-matched average (0.779) values in the 'Utilities' sheet. Utilities which were capped include:<br>• NYHA I in both arms (tafamidis: 0.845, BSC: 0.876),<br>• NHYA II in the tafamidis arm (0.787)<br>The resultant ICER was [redacted] instead of [redacted], this led to a lower EAG base-case ICER of [redacted] instead of [redacted]. | | | |

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| ***Note:*** age-adjusted utility decrements have already been implemented in the economic model submitted by the CS and are encompassed in this ICER. | | | |

**Issue 2 Scope of EAG report**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Multiple instances within the EAG report.<br><br>The current CS (ID6237) is an abbreviated submission, as agreed upon with NICE at the decision problem meeting. The scope was to address the evidence gap that resulted in a negative recommendation in the assessment of the initial CS (TA696). The intention was not to reiterate previously resolved issues raised by the EAG in initial assessment of TA696. We believe the | Items outside of scope of the abbreviated submission should be clearly marked as such. | Evidence that has already been reviewed by an EAG does not require re-assessment with this submission – only new evidence, the scope for which was agreed with NICE, requires assessment. Wording within the EAG report should reflect the scope of the current evidence assessment and not imply a paucity of evidence, when this evidence has already been assessed | Not a factual inaccuracy. The EAG produced a critique in the context of the scope for this appraisal, ID6327. |

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| discrepancy in scope between the abbreviated CS and the EAG's assessment remit has resulted in the associated report highlighting 'errors by omission', for example:<br><br>"*The understanding of the EAG is that a full CS was required, which included an SR, as mentioned above and all comparative evidence. The EAG therefore requested this to which the company responded in the response to clarification letter by referring the EAG to Sections B.2.6.2 and B.2.10.1 in TA696 Document B for comparative evidence of tafamidis versus placebo associated with clinical effectiveness and safety, respectively*." – Page 29<br><br>"*it is not usual practice to not present all comparative (in this case versus placebo)* | | and the critique is available to all parties. | |

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| *clinical effectiveness evidence in a CS.*<br><br>*It should be noted that the EAG does not consider it appropriate to extract this evidence from TA696 as it is the role of the EAG to critique the evidence that is compiled by the company in the CS.*" – Page 29<br><br>It is hoped that clarity can be obtained between NICE and the EAG on this matter, and that these "issues" will be marked as outside of scope of the current evidence assessment. | | | |

**Issue 3 Dose interchangeability**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 22, Section 2.2.<br>The description of the intervention omits the sentence included in Table 2 of the CS describing dose interchangeability: "*Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.[1]"* | The sentence reflecting that tafamidis and tafamidis meglumine are not interchangeable on a per mg basis should be added. | Clarity on active forms and comparison between technologies. | Text added. |

**Issue 4 Comparison of trial endpoints**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 25, EAG comment on Section 3.1.<br>The EAG state: *"Indeed, the company have shown comparability of outcomes for at least one of those three comparators, patisiran, in response to clarification."* The company | The company propose the EAG report be amended to include the following statement: *"In the response to clarification questions, the company provided an overview of different primary and secondary clinical endpoints in completed phase 3 clinical trials for patisiran, inotersen, vutrisiran and tafamidis (Table 1 in the response to clarification questions).* | Although Table 1 in the company's response to CQs compared endpoints across trials, the language used in the EAG report suggests that tafamidis and patisiran have comparable and similar effects on all outcomes, from statistical and clinical perspectives. While patisiran | Further clarification has been provided. |

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| believe this statement is worded ambiguously and could be misconstrued. | *The company highlighted that it would not be appropriate make comparisons, as the primary endpoints differed markedly. In the case of patisiran, secondary endpoints could be compared, however, patisiran did not meet significance in these endpoints."* | met the primary and the first secondary endpoint at Month 12 in the APOLLO-B, it did not meet significance in its other endpoints, including measures of mortality and hospitalisation which may be viewed as having strong clinical meaningfulness for ATTR-CM and which were included as the primary endpoints in the ATTR-ACT trial. Therefore, while the company believes outcomes may be compared, this is not to say that they compare well and are similar, which is how the current statement may be interpreted. | |

## Issue 5 Supplementing evidence from TA696

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 25, Section 3.2.2.<br><br>The EAG report reads: "*Outcomes from only one trial was included, the ATTR-ACT long term extension (LTE) trial…no outcomes from ATTR-ACT were reported in the CS, those having been reported in TA696 for which NICE issued guidance in 2021*."<br><br>The company feels that this may be misleading; as agreed during the DP meeting, the present submission is intended to represent an abbreviated document that should update, supplement, and expand on TA696, and therefore it should be considered that the evidence submitted as part of TA696 should be considered as informative to the current appraisal. The current wording implies a paucity of evidence.<br><br>***Note***: To aid the EAG's evaluation the company also | The EAG report should be amended to reflect the relationship between the present submission and TA696. We suggest:<br><br>*"In addition to evidence already submitted as part of TA696 (for which NICE issued guidance in 2021), which remains relevant to and should inform the present submission, the company added newly available data on outcomes from the ATTR-ACT long term extension (LTE) trial. This included some patients for longer term follow-up from the ATTR-ACT trial, which was a randomised controlled trial (RCT) with placebo as comparator. A subgroup analysis from ATTR-ACT by NYHA class of OS (see Section 3.2.7) was also included, additional to the outcomes from ATTR-ACT reported as part of TA696. The company did present a comparison between ATTR-ACT and ATTR-ACT LTE, as shown in Table 3.1."* | The company feel the current wording is possibly misleading and implies that there is a relative paucity of evidence being submitted for consideration. Because there have been no additional therapies approved for use in ATTR-CM in the UK since the negative recommendation in 2021, tafamidis still represents a paradigm shift in a disease with significant unmet need. The evidence submitted in 2021 should be reconsidered in addition to the new evidence that has become available (as agreed upon in the DP meeting). | This is not a factual inaccuracy. The EAG critiqued the company submission for this appraisal, which, as stated above, was undertaken in response to the scope for this appraisal. |

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| provided a complete version of the previous submission (ID1531 for TA696). | | | |

**Issue 6 Specifying outcomes used in the economic model**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 27, Table 3.1, Row: "other outcomes used in the economic model/specified in the scope".<br><br>In the CS, outcomes used in the economic modelling are shown in bold, and a statement to this end is included in the EAG report. However, appropriate formatting has been lost; the EAG report does not show which outcomes are used in the associated economic model. | Formatting of text in bold included in the Table 4 in the CS should be incorporated into Table 3.1 of the EAG report.<br><br>The following outcomes should be formatted in bold: all-cause mortality (both trials), CV-related hospitalisation, NYHA functional classification, adverse effects of treatment, health related quality of life (EQ-5D-3L). | Formatting allows for ease of reference to outcomes used in the economic model. | Amended. |

**Issue 7 All-cause mortality as a statistically significant secondary endpoint in ATTR-ACT**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 29, EAG comment on Section 3.2.2.<br>In the second bullet point, all-cause mortality has been missed as a statistically significant secondary endpoint from ATTR-ACT. Despite all-cause mortality being assessed in combination with CV-related hospitalisations as a primary endpoint, it was also assessed independently as a secondary endpoint in ATTR-ACT. | Add all-cause mortality to the list of statistically significant secondary endpoints from ATTR-ACT. | Factual accuracy: document should reflect accurate clinical trial information. | Not a factual inaccuracy. This was not mentioned in the FAD nor did the company submit it in their company submission. |

**Issue 8 Proportional hazards in ATTR-ACT LTE**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG report |
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| Page 30, EAG comment on Section 3.2.3. | The company recommends this statement be removed. It may be replaced with: *"Due to treatment cross-* | It is clear that under the assumption of any non-zero treatment effect of tafamidis | This has been amended to remove the criticism. |

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| The EAG states: *"it was unclear whether these estimated HRs were supported by underlying assumptions of proportional hazards."* After treatment crossover, proportional hazards may only be maintained under degenerate conditions, i.e. if there is no treatment effect. It should be clear that there is no assumption of proportional hazards underlying the Cox hazard ratios presented, but this is an observation of a weighted average hazard ratio over follow-up, with the non-trivial weighting scheme given by the estimation of the Cox model.[2] Under the condition of non-proportional hazards, Cox testing loses power[3] and so significant p-values require a larger number of events to achieve; the observation of significant OS benefit to | *over on the placebo arm, proportional hazards would not be assumed to hold through ATTR-ACT LTE. This violation of proportionality of hazards would be expected to reduce the power of the Cox test to detect a significant hazard ratio between the two arms; therefore, whilst the presented hazard ratios are confounded by this cross-over, the observation of a statistically significant effect in favour of tafamidis has not been positively impacted by this violation of proportional hazards and remains significant. The confounded hazard ratios were not used to inform estimates of treatment effectiveness within the submission."* | that proportional hazards could not be maintained between the tafamidis 80 mg-tafamidis and placebo-tafamidis crossover arms through ATTR-ACT LTE. This violation of proportional hazards has a known biasing effect on the estimated hazard ratio which is not in favour of tafamidis, and tends to reduce the power of the Cox model to detect statistically significant differences in hazard. The numerical value of the hazard ratios were not used to inform estimates of actual treatment effectiveness at any time and are provided for completeness. Claiming that this is unclear prejudices against the evidence of tafamidis' benefit presented by the company. | |

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| those randomised to tafamidis in ATTR-ACT despite placebo arm cross-over is achieved in spite of non-proportional hazards and derives no benefit from this violation. | | | |

**Issue 9 Brackets in table of adverse events in ATTR-ACT LTE**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 37, Table 3.5, Column “continuous tafamidis n = 110”.<br>In the EAG report the % values do not appear in closed parentheses; the initial bracket is not included as in the CS, which may lead to errors in interpretation. | The brackets should be added to clarify the relationship between absolute number and percentage e.g., 79 (71.8) instead of 79 71.8). | This will avoid errors in interpretation of the presented data. | Amended. |

**Issue 10 Tafamidis treatment effect post discontinuation**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 45, Section 4.2.6.3.<br>The EAG report states: "*for patients who discontinued from tafamidis, an indefinite tafamidis treatment effect was assumed without incurring any further treatment costs. The company assumed an indefinite tafamidis treatment effect after discontinuation".*<br>These statements are misleading and factually incorrect. It implies that outcomes due to tafamidis treatment were purposefully overinflated in the company base case. However, it fails to recognise that overall survival (now observed up to 84 months) includes patients whilst on and off treatment and therefore, reflects the impact of treatment | The statements may be re-worded to reflect the following: *"patients who discontinued from tafamidis continued to be modelled according to extrapolative models based upon observed outcomes (with 84 month follow up) in patients initially assigned to treatment with tafamidis in the ATTR-ACT trial but who have subsequently discontinued study treatment, without incurring any further treatment costs."* | The models used in the company base case includes outcomes due to patients who had discontinued from tafamidis; any ongoing treatment effect implied is due to that observed in the intention to treat population with tafamidis and is not conditional upon active treatment.<br>This statement provided by the EAG, is not substantiated considering the additional 54 months of data has been presented. This additional data accurately reflects both overall survival and treatment discontinuation extrapolated from the previous appraisal. Therefore, a continued assertion that an indefinite treatment effect being | Not a factual inaccuracy. |

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| discontinuation. Direct utilisation of observed overall survival and discontinued data in the model does not constitute an assumption of indefinite treatment benefits after discontinuation.<br><br>In TA696, the EAG also raised a similar concern. However, the advent of long-term follow up data from ATTR-ACT LTE has now shown that our previously proposed generalised Gamma model (suggested in company base case in TA696) was a very strong predictor of the additional observed data (refer to Figure 1 below – dark blue line [G. gamma + LT – ATTR-ACT). Therefore, providing further evidence suggesting the company approach predicts an indefinite benefit with no cost is inappropriate when the approach has been ratified | | modelled is factually incorrect.<br><br>Furthermore, the company has also shown that the previous EAG's concern regarding this topic in TA696 has been ratified with substantial additional long-term data (refer to Figure 1). | |

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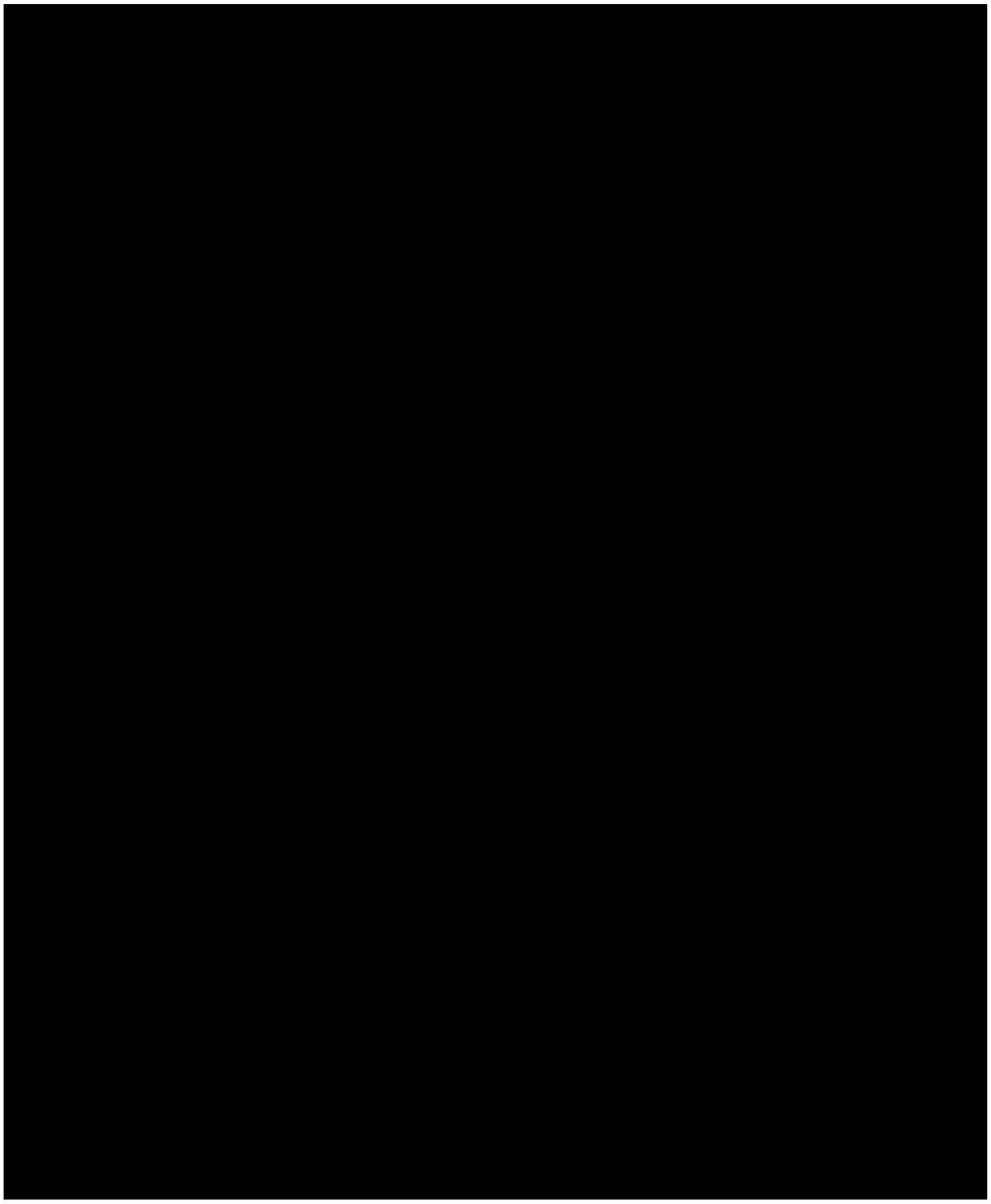
| with substantial additional long-term data. | | | |

**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) + Company's generalised Gamma model from TA696 (ATTR-ACT)**



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).
Source: Pfizer data on file.

**Issue 11 Extrapolation of tafamidis OS**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 45, EAG comment on Section 4.2.6.3.<br>The EAG states: *"the EAG does not consider the company's arguments for the selection of this curve as sufficient."*<br>The company has approached these data according to best practice according to the NICE decision support unit. As of TA696, there was negligible difference between the log-normal and generalised Gamma models, as evidenced by the near-0 value of the Q parameter of the generalised Gamma, and therefore the preference of the log- | The EAG should provide arguments sufficient to support the selection of their curve. This should not appeal to decisions made on superseded data, and should be considerate that the generalised Gamma model is the most flexible of the limited number of candidate models, and that the reason it provides outcomes at an extreme of the candidate range is due to its ability to respond to changes in the hazard function that the lognormal is unable to. It should be considered that the log-normal is a degenerate form of the generalised Gamma, and so it is not a structural imposition of the generalised Gamma model that produces higher mean survival estimates, but the data themselves. | The company has followed best practice for model selection and considers that the EAG's decision to find the arguments insufficient may have been biased due to decisions on now superseded data.<br>The company feel that the generalised Gamma model is the most appropriate model for evaluating the uncertainty in the hazard function for the following reasons:<br>• Generalised gamma distribution displayed best fit for new long-term follow up data from ATTR-ACT LTE; model predicts closest to the contemporary value of | Not a factual inaccuracy. |

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| normal over the generalised Gamma was justified. With increased follow-up, the higher flexibility of the generalised Gamma model represents a greater than 2-point improvement in log-likelihood, causing it to rank highest by AIC, whilst the BIC so heavily penalises additional degrees of freedom that the highest ranking model is the exponential, despite this reflecting no aspect of the observed hazard profile of the trial data.<br><br>The EAG's justification for the use of the log-normal model as presented is due to outdated precedent and the fact the generalised Gamma reflects an extreme of the small number of models considered under the DSU TSD 14 algorithm, which is to be expected given that the flexibility afforded to this model allow | | the KM estimate (Figure 5 in CS)<br>• Generalised Gamma had the lowest AIC of candidate models; indicated highest log-likelihood by greater than 2 units (Figure 5 in CS)<br>• The generalised Gamma model showed the most rapid reduction in excess hazard, matching well the gradient of the observed hazard during the third year whilst peak hazard was higher than other models (Figure 6 in CS)<br>• Within PSA, the generalised Gamma model generates results fully overlapping those of the log-normal model.<br><br>Given the reasons listed above, the company believes it is not appropriate for the EAG to conclude insufficient reasoning for the selection of this model | |

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| it to follow the observed hazard profile far closer than any other candidates.<br><br>Furthermore, it should be noted that the generalised Gamma model contains within its parameter space the log-normal model, and within PSA generates results fully overlapping those due to the log-normal model. Therefore, it should be considered whether uncertainty in the hazard function may be more appropriately explored in PSA in this instance.<br><br>The company considers the EAG's statement to lack sufficient justification given the importance of this modelling decision. | | and should provide further rationale for the selection of log-normal apart from outdated EAG opinion from TA696. | |

**Issue 12 Mismatch in tafamidis OS data**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 52, EAG comment on Section 5.3.<br><br>The EAG requests: *"further justification for these mismatches [in tafamidis OS data in the CS and the response to CQs] should be provided, and if applicable, corrections in the tables and/or economic model should be provided".* | The discrepancies between Table D1 in the CS and Table 42 of the response to CQs may be clarified by noting that in the clarification response, as noted in the table footnotes, a baseline hazard according to the marginal hazard of the general population matched to the ATTR-ACT population was used; this differs from the baseline hazard due to English life tables used for the predictions in the economic model. The ATTR-ACT population was considered more appropriate for the clarification response as the layout of the table suggested that comparisons may be drawn between the models with respect to their error against the trial data, therefore prediction over the population of the trial was most appropriate.<br><br>In addition, Table D1 may be corrected for the identified typographical error – the value [redacted] should be replaced by [redacted]. | The main discrepancy is easily identified by consideration of the populations to which the relative survival model is applied.<br><br>The company thanks the EAG for highlighting a typographical error, which may be fixed. | The EAG thanks the company for explaining the differences between the tables. A sentence has been added to the EAG report, stating: "This issue was resolved after the factual inaccuracy check. The company has explained the differences between the tables and explained that the [redacted]% in Table D1 of Appendix D should be corrected to [redacted]%." |

**Issue 13 Inconsistent PSA results**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 52, EAG comment on Section 5.2.<br>The EAG states: *"the main concern of the EAG relates to inconsistencies in the PSA results. […] "It is unclear to the EAG what exactly causes these problems, and hence justification and correction by the company is requested."*<br>The EAG also lists several "problems" identified.<br>1) Reproduction of the company submitted PSA results<br>2) Implementation of EAG scenario analysis 3 resulting in different probabilistic total BSC costs | Please could the EAG provide further information regarding inconsistencies and problems experienced with the PSA so that the company can work on resolving these issues. | The company requires further information to address the potential issues identified. | Not a factual inaccuracy. The company correctly summarized the issues: 1) reproduction of the company submitted PSA results was not possible, 2) EAG analysis 3 resulted in different BSC costs, while the scenario only impacted utilities, and 3) after running the PSA with EAG scenario 5, and thereafter setting all model inputs to default and again running the PSA, the results are not similar to the default PSA results (neither the company's results or our default PSA results). The EAG ran |

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| 3) "The company's worst case scenario (EAG analysis 5), does not seem to be responsive when switched off."<br>4) After PSA run of scenario 5, results were set to default, and differed from default PSA settings.<br>The company has not been able to replicate these errors in the PSA when running the model provided by the EAG and comparing results with the previous version of the model. | | | these analyses on two separate computers to make sure it was not a local issue. |

**Issue 14 Wording associated with scenario analysis**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 52, EAG Comment on Section 5.2.<br>The EAG refers to EAG analysis 5 as: "*the company's worst case scenario"*.<br>The company would like to clarify that this scenario is in fact the EAG's worst case scenario from TA696 rather than the company's and was provided to the current EAG for completeness and transparency. | The scenario should be referred to as *"the worst case scenario proposed by the EAG in TA696".* | Reflect an accurate account of information from TA696. | Amended to "the scenario proposed by the EAG in TA696". |

**Issue 15 EAG exploratory scenario analyses**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG comment |
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| Page 54, Section 6.1.2.1, and Page 57 Section 6.2. | The EAG should provide mention of the evidence included in CS Section 7.6 and consider that these scenario | The company has provided evidence as to why these exploratory scenarios are not | Not a factual inaccuracy. |

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| The EAG have carried out two exploratory scenario analyses which were also carried out by the previous EAG in TA696:<br>• EAG analysis 4: discontinuation plateau with indefinite treatment effect<br>• EAG analysis 5: BSC outcomes for tafamidis discontinuers<br>The presentation of these analysis does not appear to consider the new evidence highlighting why these specific scenario analyses from TA696 were not appropriate for decision making considering new long-term data from ATTR-ACT LTE (Section 7.6). | analyses are not appropriate for decision making considering new long-term data from ATTR-ACT LTE (Figures 9 and 10, Section 7.6 in CS). | appropriate for decision making considering new long-term data from ATTR-ACT LTE (Figures 9 and 10, Section 7.6 in CS) and feel this should be considered. | |

| **Location of incorrect marking** | **Description of incorrect marking** | **Amended marking** |
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| N/A | N/A | N/A |

**References**:


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2. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. Stat Med. 2009 Aug 30;28(19):2473-89. doi: 10.1002/sim.3623.

3. Royston, P., Parmar, M.K. Augmenting the logrank test in the design of clinical trials in which non-proportional hazards of the treatment effect may be anticipated. *BMC Med Res Methodol* 16, 16 (2016). https://doi.org/10.1186/s12874-016-0110-x