NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission summary** from Pfizer

2. **Company responses to clarification questions**

3. **Patient group, professional group and NHS organisation submission** from:
   a. UK ATTR Amyloidosis Patients' Association (UKATPA)

4. **Expert personal perspectives** from:
   a. Dr Marianna Fontana, Associate Professor Honorary Consultant Cardiologist – clinical expert, nominated by the British Cardiovascular Society (BCS)
   b. Professor Philip Hawkins, Professor of Medicine – clinical expert, nominated by the University College London Hospital NHS Foundation Trust
   c. David Gregory – patient expert, nominated by UK ATTR Amyloidosis Patients Association
   d. Paul Pozzo – patient expert, nominated by UK ATTR Amyloidosis Patients Association
   e. Ayesha Ali, Medical Advisor, Highly Specialised Services – commissioning expert, nominated by NHS England

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

6. **Evidence Review Group response to Factual Accuracy Check**

7. **Technical report**

Post-technical engagement documents

8. **Technical engagement response from company**
   a. Main response
   b. Appendix to response

9. **Technical engagement responses from experts:**
   a. Professor Philip Hawkins, Professor of Medicine – clinical expert,

nominated by the University College London Hospital NHS Foundation Trust

10. Technical engagement responses from consultees and commentators:
a. Royal College of Physicians
b. NHS England
c. NHS England – additional response

11. Evidence Review Group critique of company response to technical engagement prepared by School of Health and Related Research (ScHARR)

12. 1-page summary about earlier diagnosis provided by the company

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 [ID1531]

Document B

Company evidence submission

September 2019

File name	Version	Contains confidential information	Date
ID1531_Tafamidis_DocumentB_28APR19[Redacted]	v1.0	No	28th April 2020

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 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: • Established clinical management without tafamidis People with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy (TTR-FAP) and hereditary ATTR-CM) • Patisiran • Inotersen	Best supportive care (established clinical management without tafamidis)	Inotersen and patisiran, both licensed for hereditary transthyretin amyloidosis in adult patients with Stage 1 or 2 polyneuropathy [1,2], have been included as relevant comparators in the Final Scope, for the treatment of people with ATTR and a mixed phenotype, expressing symptoms of both cardiomyopathy and polyneuropathy.[3] We agree there is a small UK population of hereditary ATTR patients with a mixed phenotype (B.1.3.2, Figure 4). However, we do not believe that these two comparators are relevant to this appraisal for the reasons provided below. Further evidence to support the inappropriateness of this comparison can be found in a tabulated summary of key differences in the populations studied (Section B.1.3.6.1, Table 7). 1) **Neither patisiran or inotersen have been evaluated in patients with heart failure.** The safety and efficacy of neither drug has, therefore, been established in symptomatic ATTR-CM. Evidence from NEURO-TTR and APOLLO only support use of patisiran and inotersen in patients with ATTR polyneuropathy. This is consistent with their marketing authorisations. Furthermore, these studies excluded patients with significant cardiac disease at baseline (Table 7). In contrast, the ATTR-ACT study mandated

			a history of hospitalisation for heart failure or clinical evidence of heart failure in the inclusion criteria. (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.[4] 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. (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. 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. (4) The remaining cases (37%) of non-Val122Ile hereditary ATTR-CM in the UK are caused by a multitude of ultra-rare mutations, each associated with a predominant phenotype. When patients are diagnosed (and treatment decisions made), they typically present with a dominant phenotype, but may develop additional symptoms during their lifetime (mixed phenotype). (5) The endpoints assessed in APOLLO and NEURO-TTR 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, neither study provides evidence of safety or efficacy of treatment in a population with ATTR-CM.[5-8] Neither study permits a valid indirect treatment comparison based on the lack of shared endpoints and distinct populations.

Outcomes	The outcome measures to be considered are: • Overall survival • Cardiovascular-related mortality • Cardiac function (such as longitudinal strain or brain natriuretic peptide [BNP] level) • Cardiovascular-related hospitalisation • Functional exercise capacity • Signs and symptoms of heart failure (such as breathlessness) • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered are: • All-cause mortality • Cardiovascular-related mortality • Cardiac function (6MWT, NT-proBNP, echocardiographic parameters) • Transthyretin stabilisation • Frequency of cardiovascular-related hospitalisation • NYHA classification • Adverse effects of treatment • Health-related quality of life	Not applicable
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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.

	outcomes between technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • severity of heart failure (such as by New York Heart Classification class) 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 (NYHA I/II)	Not applicable
Special considerations including issues related to equity or equality	Not specified	Not applicable	

Abbreviations: 6MWT: 6-minute walk test; ATTR-CM; transthyretin amyloid cardiomyopathy; ATTR-PN: hereditary transthyretin amyloid polyneuropathy; HF: heart failure; NA: not applicable; NAC: National Amyloidosis Centre; NYHA: New York Heart Association; QALY: quality-adjusted life year; Val122Ile: valine replaced by isoleucine at position 122.

B.1.2 Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2. The draft Summary of Product Characteristics (SmPC) is presented in Appendix C. The European Public Assessment Report (EPAR) is not yet available at the time of submission.

Table 2. Technology being appraised

UK approved name and brand name	Tafamidis (Vyndaqel®)
Mechanism of action	Tafamidis is a specific stabiliser of transthyretin (TTR).[9] 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 (Section B.1.3.1).[10-12] The dissociation of TTR tetramers to monomers is the rate limiting step in the pathogenesis of ATTR-CM.[13] Tafamidis binds to the native tetrameric form of transthyretin, preventing its dissociation into monomers and reducing amyloid formation.
Marketing authorisation/CE mark status	On 16 November 2011, the European Commission granted marketing authorisation under exceptional circumstances for tafamidis meglumine 20 mg capsule for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy (ATTR-PN) to delay peripheral neurologic impairment.[9] The polyneuropathy indication will not be considered in this submission. Tafamidis does not yet have a marketing authorisation for the treatment of transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) in the European Union. The anticipated dose/ formulation is tafamidis free acid 61 mg QD. The European Medicines Agency (EMA) timelines are shown below: EMA regulatory milestones **Milestone** / **Date** **Marketing Authorisation Application** / [redacted] **CHMP opinion** / [redacted] **Marketing Authorisation** / [redacted]
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	The proposed indication for tafamidis is "[redacted]", aligned with the indication in this appraisal.
Method of administration and dosage	*Method of administration:* Tafamidis is a soft capsule for oral administration *Dosage:* The proposed treatment dose in the EMA Line Extension Application is tafamidis 61 mg (equivalent to tafamidis meglumine 80 mg).

	Bioequivalence was demonstrated in healthy volunteers at steady state concentration,[14] and in a bioavailability/food effect study.[15]
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.[4]
List price and average cost of a course of treatment	**List price:** £10,685 per pack of 30 capsules **Annual cost:** £130,089.88 per patient at list price **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
Patient access scheme (if applicable)	[redacted]

Abbreviations: ATTR-PN: transthyretin amyloid polyneuropathy; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; TTR: transthyretin.

B.1.3 Health condition and position of the technology in the treatment pathway

Summary

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare, progressive and ultimately fatal disease, characterised by the deposition of amyloid fibrils in the heart muscle (myocardium), leading to heart failure.[16]
- UK patients with ATTR-CM have significant unmet need as there are no approved pharmacological disease-modifying treatments available. Current treatment aims to manage the symptoms of heart failure (e.g. with diuretics), and prevent complications of heart rhythm abnormalities.[17,18]
- The number of new diagnoses has risen sharply in the last decade due to greater use of non-invasive diagnostic imaging and awareness of the disease. The National Amyloidosis Centre (NAC) recorded approximately 180 new diagnoses in 2016.[19]
- Patients with ATTR-CM experience progressive deterioration in physical function and health-related quality of life (HRQoL).[20,21] Significant caregiver burden has also been reported, with negative impact on physical and emotional well-being.[22]
- The prognosis of people with ATTR-CM is poor: median survival of patients recieiving best supportive care (BSC) in the UK varies between 2.3 and 5.8 years from diagnosis.[19,23-25]
- Delayed diagnosis is thought to be a major reason for shortened survival.[26,27,28-30] On average, patients experience >3 years delay in reaching a diagnosis from the onset of cardiac symptoms.[30]
- Tafamidis is a novel stabiliser of transthyretin (TTR): it inhibits the rate-limiting step in the process of amyloid formation.
- Tafamidis has been shown to significantly reduce all-cause mortality and cardiovascular-related hospitalisations in ATTR-CM.[31] Furthermore, statistically significant and clinically meaningful treatment effects favouring tafamidis in functional capacity and HRQoL were observed, compared to placebo.[31]

B.1.3.1 Disease overview

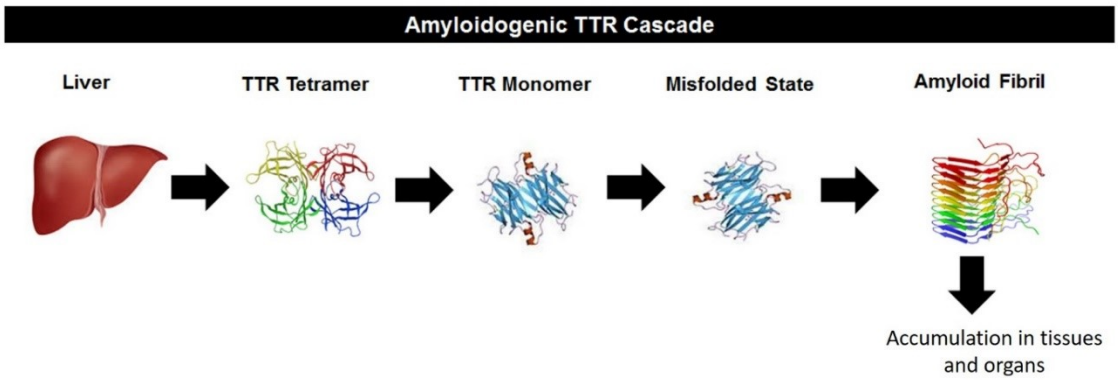
Transthyretin amyloid cardiomyopathy (ATTR-CM) is a fatal disease, characterised by the deposition of transthyretin (TTR) amyloid fibrils in the heart muscle (myocardium). Build-up of amyloid damages the myocardium, resulting in stiff heart muscle walls (restrictive

cardiomyopathy) which in turn leads to an inability to pump an adequate supply of blood through the circulatory system (heart failure).[12,16]

TTR is synthesised primarily in the liver and is made up of four identical subunits called monomers.[32] Its function is to serve as a secondary carrier to transport Vitamin A (retinol) and a thyroid hormone (thyroxine). Alterations in the structure of the TTR protein, caused by ageing or an inherited mutation, increase its tendency to break down into its constituent monomers, which misfold and aggregate forming insoluble amyloid fibrils which accumulate in tissues and organs (Figure 1).[10-12]

Insoluble amyloid fibrils can deposit in any of the cardiovascular structures of the heart including the myocardium, conduction system or valvular tissues.[16] Infiltration of the myocardium typically results in progressive thickening and stiffening of the left and right ventricular walls, ultimately leading to restrictive cardiomyopathy and heart failure.[16]

Figure 1. Pathogenesis of ATTR



Source: Adapted from Castano et al. 2015[10]

There are two forms of the disease:

- Wild-type ATTR-CM

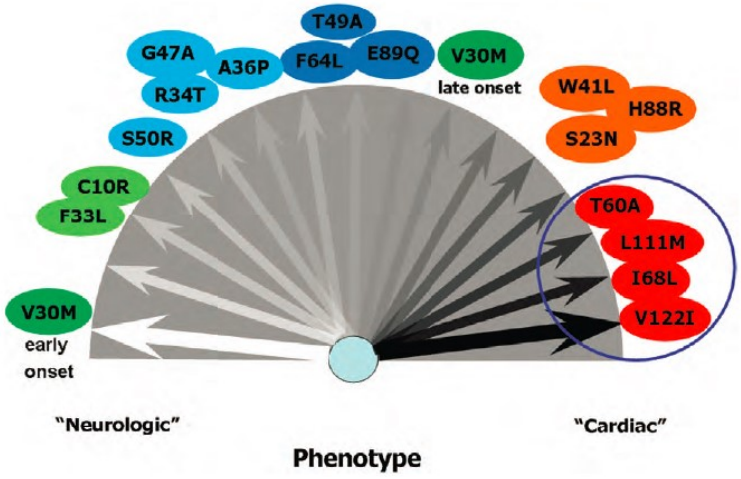
Wild-type ATTR-CM is the more common form. It is not inherited, but is associated with ageing[25,33] and predominantly affects the heart.[25,34]

- Hereditary ATTR-CM

Hereditary ATTR-CM is inherited in autosomal dominant fashion and is caused by a mutation in the transthyretin (TTR) gene. Hereditary ATTR-CM can therefore devastate multiple generations in a family.[35] Hereditary ATTR amyloidosis may present with predominant symptoms of either cardiomyopathy or polyneuropathy. A genotype-phenotype correlation has been reported for hereditary ATTR amyloidosis, with some mutations more commonly

presenting with polyneuropathy and others typically presenting with cardiomyopathy (Figure 2).[36,37]

Figure 2. Possible spectrum of genotype-phenotype correlations in hereditary ATTR



Mutations associated with a predominant or exclusive cardiac phenotype are circled in blue.
Reproduced from Rapezzi et al. 2012.[36]

B.1.3.2 Epidemiology

The availability of a disease-modifying treatment will increase disease awareness and index of suspicion among physicians, leading to higher rates of diagnosis

- Wild-type ATTR-CM accounts for approximately 69% of ATTR-CM cases in the UK.[19] It predominantly affects males, who account for 94% of cases.[23] It is strongly associated with ageing, with an average age at diagnosis of 78 years.[23]
- Hereditary ATTR-CM accounts for approximately 31% of ATTR-CM cases in the UK.[19] On average individuals are diagnosed at 73 years of age,[38] again with men more likely to be affected than women.[23]

B.1.3.2.1 Incidence

Increasing use of a non-invasive diagnostic algorithm, and greater physician awareness, has led to growth in the number of patients diagnosed with ATTR-CM

Diagnostic data from 2000 to 2008 at the NAC suggests an incidence rate of 0.03 per 100,000 for wild-type ATTR-CM.[30] In the following decade the total number of cases of ATTR-CM (wild-type and hereditary) diagnosed at the NAC increased 30-fold.[23] While growth in new cases of hereditary ATTR-CM have plateaued, new diagnoses of wild-type ATTR-CM have risen sharply, with approximately [redacted] new cases in 2016 alone (Figure 3).[19]

Figure 3. New diagnoses of ATTR-CM at the NAC between 2000 and 2016

Note: DPD refers to the introduction of 99mTechnetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid nuclear scintigraphy, see Section B.1.3.3 for further details.
Source: Communication from National Amyloid Centre, adapted from Lane et al. 2019.[19]

B.1.3.2.2 Prevalence

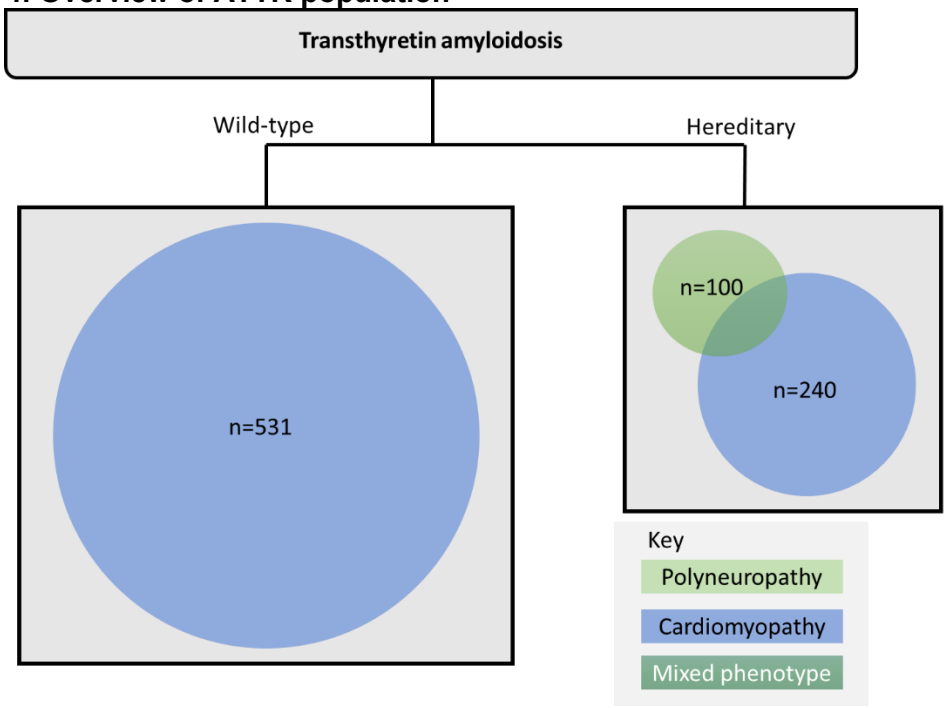
The prevalence of ATTR-CM in the UK remains unknown. Case series from the NAC provide information on the number of patients for whom data is available, but do not report on the number alive at any given time. The largest UK study of ATTR-CM reported on 711 patients with wild-type ATTR-CM and 323 patients with hereditary ATTR-CM seen between 2000 and 2017.[19]

Among patients with hereditary ATTR-CM, Val122Ile is the most common mutation in the UK and is causative in 63% of cases.[19] Among all patients with Val122Ile ATTR-CM (205) seen at the NAC between 2000 and 2017, <5% had co-existing symptomatic polyneuropathy suggestive of a mixed phenotype.[19,24] Disease in this group of patients with Val122Ile hereditary ATTR-CM is therefore considered to manifest in a predominantly cardiac phenotype. Several non-Val122Ile mutations make up the remaining 37% of hereditary ATTR-CM and these ultra-rare mutations cause a spectrum of disease ranging from predominantly cardiac phenotypes to mixed phenotype (with neurological and cardiac symptoms) (Figure 2).[36]

Prevalence estimates for ATTR-CM have been based on the number of new diagnoses described in Figure 3, and the survival estimates provided separately for wild-type ATTR-CM, and hereditary ATTR-CM (non-Val122Ile and Val122Ile) in a contemporary report from the NAC.[19] With a reported median survival of 4.8 years, the number of cases of wild-type ATTR-

CM diagnosed in the 4.8 years from last available data was estimated to be 531. Corresponding values for Val122Ile hereditary ATTR-CM (median survival 2.6 years) and non-Val122Ile hereditary ATTR-CM (median survival 5.8 years) are 108 and 132, respectively (Figure 4). In the last 3 years for which there are data available, 121 patients have been diagnosed with Val122Ile ATTR-CM alone (cardiac phenotype) (Figure 3). The remaining patients with hereditary ATTR-CM will include those with a predominant cardiac phenotype, and those with a mixed phenotype (Figure 4).

Figure 4: Overview of ATTR population



Source: Extrapolated from communication from National Amyloid Centre in Figure 3, and survival analyses from Lane et al. 2019.[19]

B.1.3.3 Diagnostic pathway

Patients in the UK experience > 3-year delay from cardiac symptoms to diagnosis, by which time many will have progressed to advanced disease

ATTR-CM is frequently overlooked as a cause of heart failure and is often delayed in its recognition. In the UK, the average diagnostic delay from first presentation with cardiac symptoms is 39 months in patients with wild-type, and 25 months in those with hereditary ATTR-CM.[19] Some 40% of patients with wild-type ATTR-CM wait >4 years for a diagnosis.[19] By the time a diagnosis is made, many patients will have progressed to advanced heart failure, missing any opportunity for early intervention to alter the course of the disease. The reasons for missed and delayed diagnosis are multifactorial and include disease-, clinician- and system-related factors.[28] The previously perceived rarity of the disease, overlap of symptoms

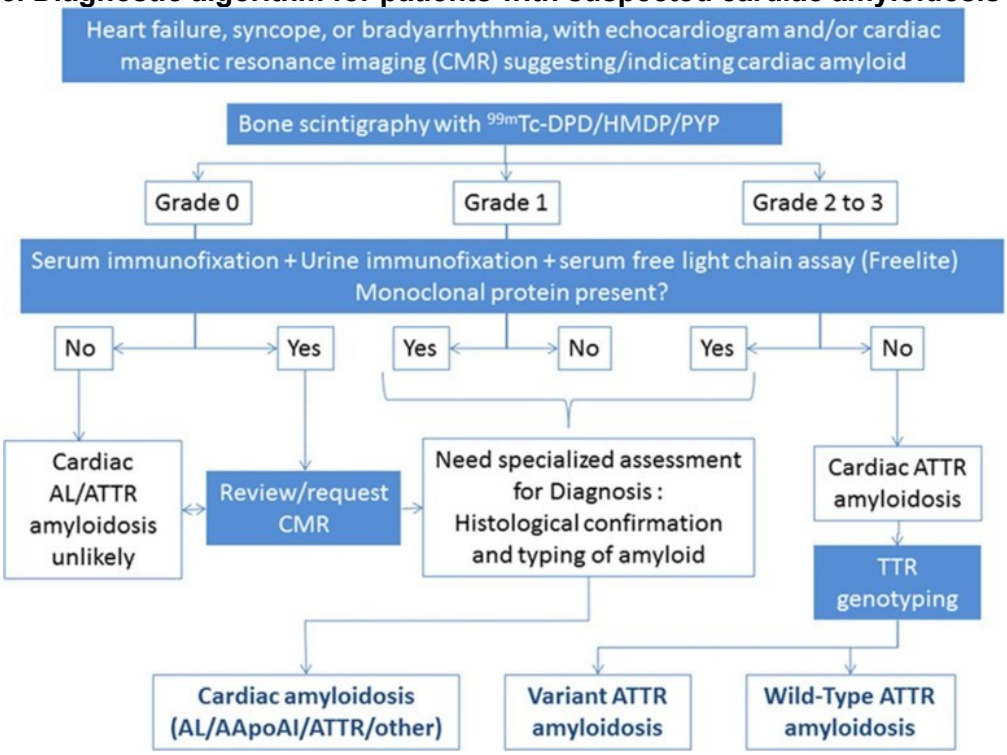
with other conditions and the absence of a disease-modifying treatment have likely held back awareness of the disease among clinicians, including heart failure specialists.[29,39]

A non-invasive diagnostic algorithm for suspected cardiac amyloidosis has led to an increase in new diagnoses

Endomyocardial biopsy (EMB) with histological testing was previously considered the gold-standard method of diagnosing ATTR-CM. In 2016, specialist centres across Europe (including the NAC in the UK) and the United States published a consensus non-invasive diagnostic pathway involving nuclear scintigraphy imaging. This convenient and relatively inexpensive imaging modality has reduced procedural risks to patients and minimised delays associated with the historical requirement for EMB.[4,40] When combined with a screen for abnormal proteins in the blood and urine, nuclear scintigraphy imaging offers 100% specificity and positive predictive value for detecting ATTR-CM.[4] Once a diagnosis is confirmed, genotyping of the *TTR* gene is used to detect the presence of mutations, differentiating the more common wild-type disease from hereditary ATTR-CM.[4] Identifying eligible patients for treatment with tafamidis does not require any additional investigations beyond those already considered standard of care in the UK. Figure 5 shows the non-invasive diagnostic algorithm that includes nuclear scintigraphy imaging.

A disease-modifying treatment, in combination with the non-invasive diagnostic pathway, will lead to earlier diagnosis and improve patient outcomes

Figure 5. Diagnostic algorithm for patients with suspected cardiac amyloidosis



Abbreviations: AL: amyloid light chain; ATTR: transthyretin amyloidosis; CMR: cardiac magnetic resonance.
Source: Gillmore et al. 2016[4]

B.1.3.4 Burden of disease

B.1.3.4.1 Mortality

Patients with ATTR-CM have a poor life expectancy

Median survival among patients with ATTR-CM in the UK ranges from 2.3 to 6.1 years, depending on genotype (Table 3). In contemporary cohorts, patients with Val122Ile hereditary ATTR-CM have the poorest overall survival - less than half that of patients with wild-type ATTR-CM. Longitudinal studies have shown that advanced NYHA class, elevated cardiac biomarkers (NT-proBNP, Troponin), age and reduced renal function (eGFR) are all independently associated with premature mortality in ATTR-CM.[23,41,42]

Table 3. Median survival of ATTR-CM patients in the UK

Population	Median age (range) at diagnosis (years)	Median survival (years)[a]
ATTR-CM (wild-type and hereditary) attending NAC[19] (n = 1,034)	Wild-type: 79 (73-83) Hereditary Val122Ile: 77 (72-80) Hereditary non-Val122Ile: 67 (62-71)	5.8 2.6 4.7
ATTR-CM (wild-type and hereditary) attending NAC[23] (n = 869)	77 (41-95)	Overall: 4.8 (from baseline[b]) NAC Stage I[c]: 5.8 NAC Stage II[c]: 3.9 NAC Stage III[c]: 2.0
Afro-Caribbean patients with hereditary Val122Ile ATTR-CM attending HF clinic[24] (n = 211)	71 (54-77)	Val122Ile: 2.3
Wild-type ATTR-CM at NAC[25] (n = 102)	73 (69.5-78.2)	2.7 (from diagnosis) 6.1 (from onset of HF symptoms)

[a]From diagnosis unless otherwise stated
[b]Date of baseline was the same as the date of diagnosis in >95% of patients and was within 1 month of diagnosis in nearly all remaining patients
[c]NAC ATTR Disease Stage, based on NT-proBNP and eGFR, p<0.0001 for between-group differences.
Abbreviations: ATTR-CM: transthyretin amyloid cardiomyopathy; HF: heart failure; NAC: National Amyloidosis Centre; Val122Ile: valine replaced by isoleucine at position 122.

B.1.3.4.2 Symptom burden

Patients with ATTR-CM endure progressive functional disability

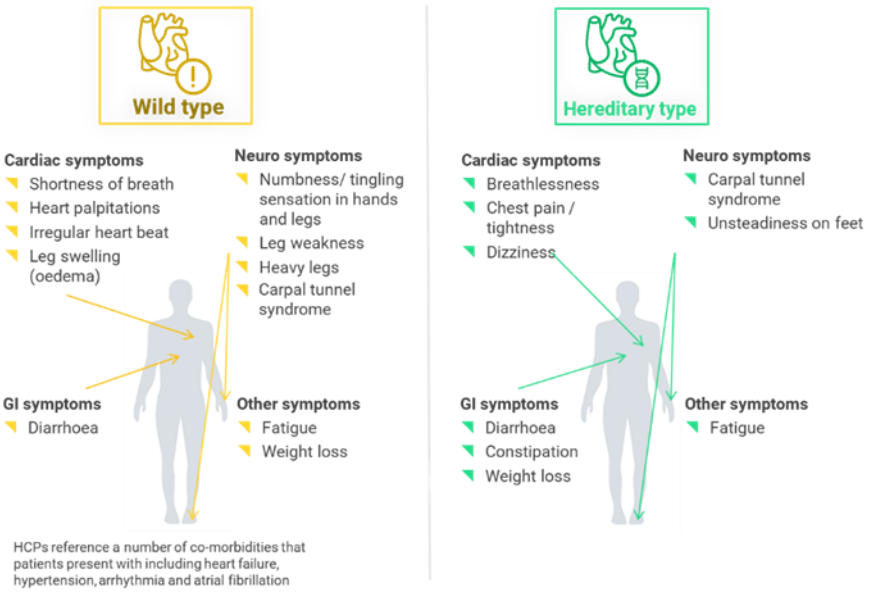
Heart failure causes shortness of breath, fatigue and functional limitation. Patients frequently report pain (which worsens with advancing NYHA class)[43] and gastrointestinal symptoms

(caused by poor intestinal blood flow, gut wall oedema and hepatic congestion).[44] Late-stage heart failure is highly symptomatic and has a comparable symptom burden to advanced cancer.[45-47]

Observational studies of patients with ATTR-CM report progression of symptoms and functional decline as measured by NYHA class and walking distances, respectively.[19,48] A high frequency of hospitalisations is characteristic, most frequently for exacerbation of heart failure.[48]

Although ATTR-CM commonly presents with symptoms of heart failure or arrhythmias, amyloidosis is a systemic disease and can cause non-cardiac symptoms, particularly in hereditary ATTR-CM (Figure 6).[49-51]

Figure 6. Common symptoms of ATTR-CM in wild-type and hereditary patients

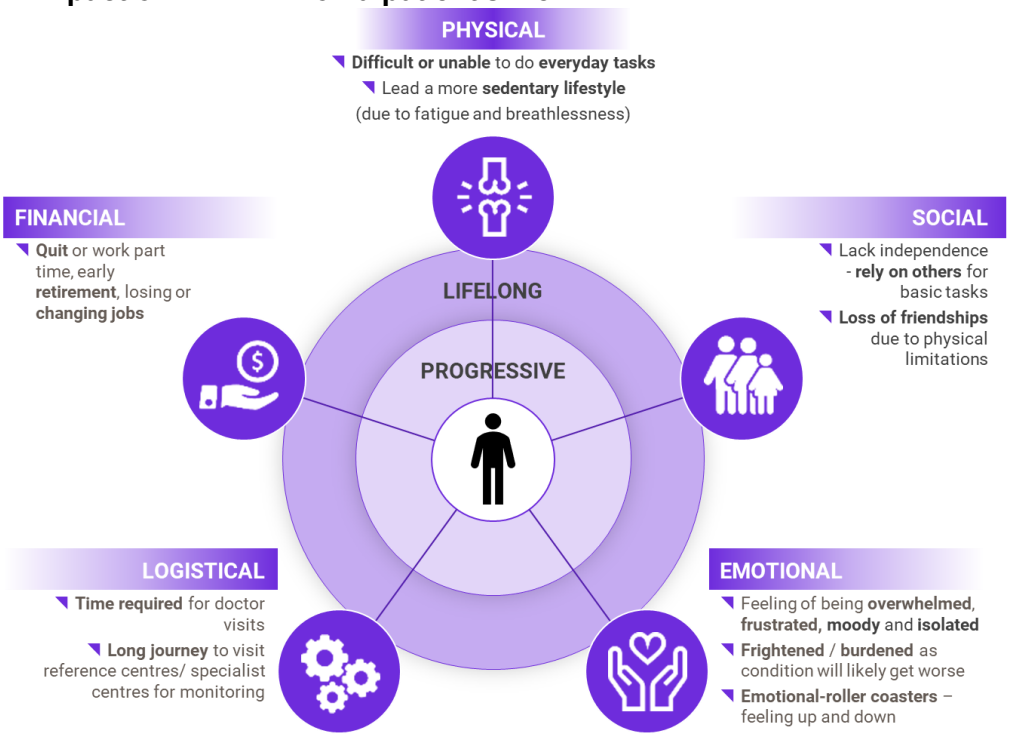


Source: Pfizer data on file[21]

Progressive functional disability significantly impairs HRQoL

The symptom burden and functional disability associated with ATTR-CM impacts all aspects of a patient's quality of life (Figure 7) [52].

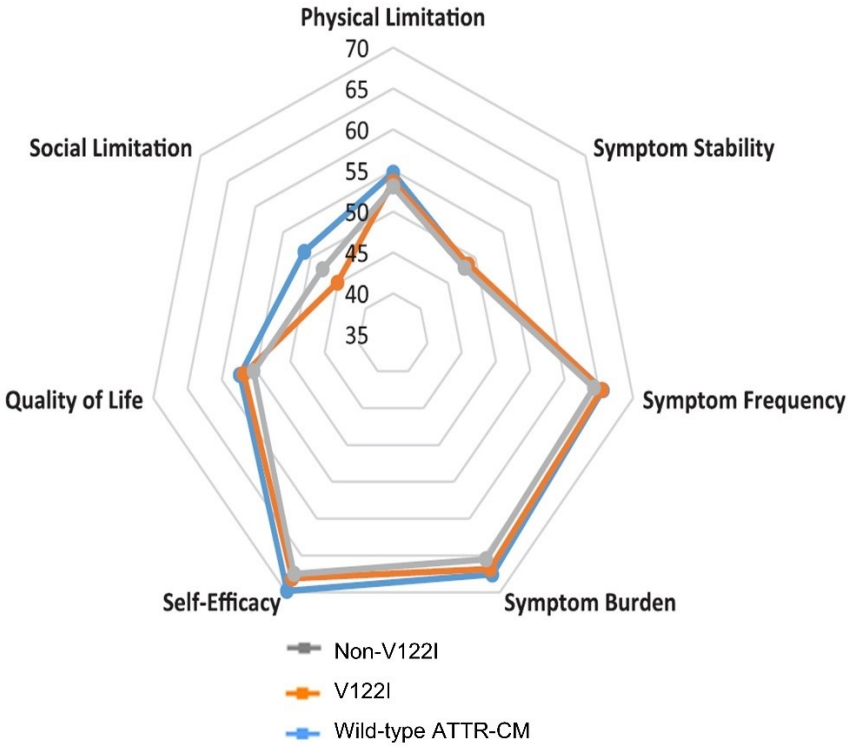
Figure 7. Impact of ATTR-CM on a patient's life



Source: Pfizer data on file [21]

Among patients seen at the NAC, poor HRQoL was observed in both wild-type and hereditary ATTR-CM.[19] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a valid, reliable and prognostically important measure of patient's health status in heart failure.[53,54] The lowest scoring (lower scores indicate worse impairment) domains in KCCQ (Figure 8) were physical limitation, social limitation and symptom stability. In both forms of the disease, deterioration was observed in all 12 domains of the KCCQ.

Figure 8. Kansas City Cardiomyopathy Questionnaire scores within the first 12 months of diagnosis



A score of 100 indicates perfect health and the range in KCCQ is 0-100 although the scale in this figure is limited to 70. Domains of self-efficacy and symptom burden and symptom frequency are therefore significantly impaired in this population. Lower scores indicate worse impairment. N = 158 respondents
Source: Lane et al. 2019.[19]

Carer and family burden

In addition to patients, carers of those affected by ATTR-CM experience a significant impact on their physical and emotional well-being.[22] In a cross-sectional survey that enrolled patients with ATTR-CM and their carers through patient advocacy groups in the United States, caregivers reported substantial burden, including poor mental health and work impairment, with a level of burden similar to that reported by caregivers of patients with Alzheimer's disease, as assessed by the Zarit Burden Interview.[22] Living with ATTR-CM can permanently change family dynamics, as patients become more dependent on family members for their care. In a Patient Experience Study, 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".*[21]

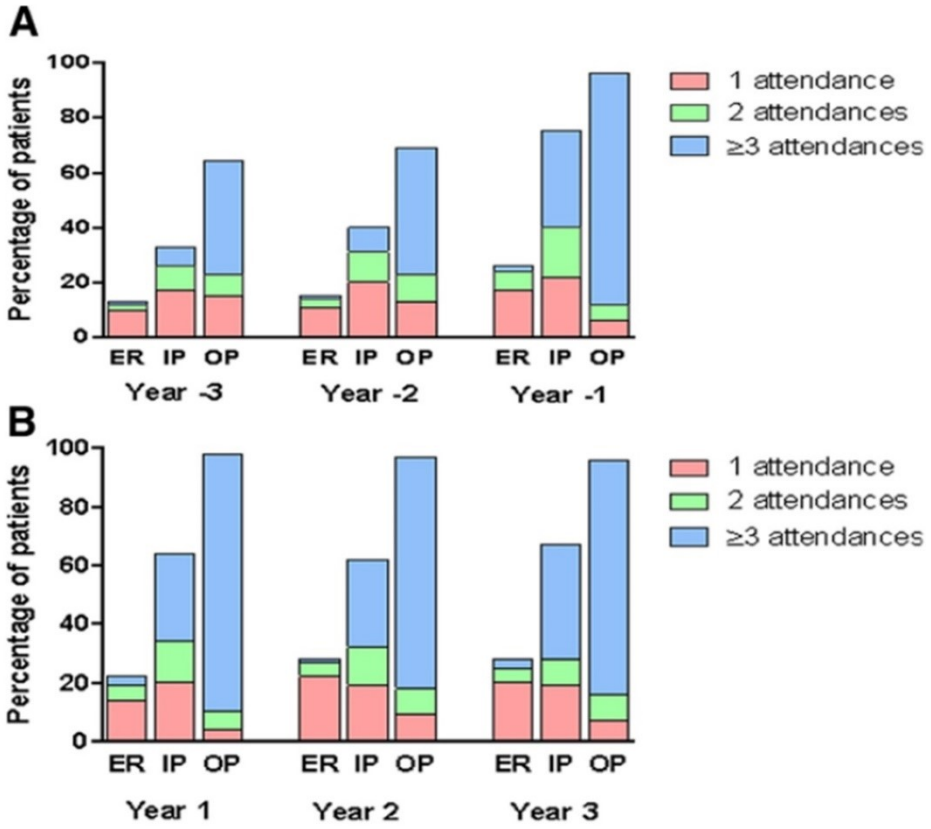
Hereditary forms of the disease can devastate multiple generations of a family,[35] and caregivers may themselves be affected by ATTR.[22] *TTR* variants are inherited as an autosomal dominant trait, meaning that children of a person with the gene have a 50% chance of inheriting the disease.[55] The penetrance of many *TTR* mutations (i.e. the probability that

they will manifest clinically) is poorly understood, including that of Val122Ile, the commonest cause of hereditary ATTR-CM in the UK.[56-60] This uncertainty as to whether or not symptoms will manifest, coupled with the relatively late presentation of cardiac manifestations (generally over the age of 40 years) may lead to anxiety, depression and psychological distress among family members.[61]

B.1.3.4.3 Economic burden

In the UK, ATTR-CM patients experience an average >3-year delay to diagnosis with 42% waiting >4 years after presentation with cardiac symptoms.[19] During this period they can expect to attend 17 hospital outpatient appointments or inpatient admissions.[19] The breakdown of hospital usage before and after diagnosis is displayed in Figure 9A and B, respectively. In the year following a diagnosis, patients will experience two inpatient admissions and eight outpatient attendances on average.[19]

Figure 9. English NHS hospital services usage A) before and B) after diagnosis of ATTR-CM



A. English NHS hospital services usage covering ER, IP and OP in the 3 years before diagnosis. B. English NHS hospital services usage, covering ER, IP, and OP during the first 3 years after diagnosis of ATTR-CM (percentages adjusted for surviving patients at each time point).
Abbreviations: ER: emergency room; IP: inpatient admission; OP: outpatient services.
Source: Lane et al. 2019.[19]

Applying NHS reference costs to the median 3 inpatient stays (£2,537[62]) and assuming the remaining 14 consist of 12 hospital outpatient appointment (£163 first; £128 subsequent[62])

and 2 emergency room visits (£211), the total cost over the 3 years of these resources leading up to diagnosis is approximately £9,605 per patient. This approximation can be considered an underestimate of the true cost prior to diagnosis, given that it does not include the fourth, fifth and additional years prior to diagnosis (42% of patient were waiting >4 years for diagnosis[19]), patients that have been mis/undiagnosed (increasing those with >4 year diagnosis), and the cost of investigations and treatments that are often unnecessary such as cardiac MRI (£389 per test), repeated echocardiograms (£189) and ECGs (£120),[62] Therefore, the true cost could be in excess of £20,000 per patient.

Data from the NAC suggest that a third of patients are diagnosed in <6 months.[19] It is therefore feasible that widespread adoption of the non-invasive diagnostic pathway in combination with greater disease awareness could result in an average delay to diagnosis of approximately 6 months. This improvement in time to diagnosis brought about by the implementation of the non-invasive pathway across a network of UK centres and the availability of a disease modifying treatment would yield significant cost savings for the NHS (explored in scenario analysis; Section B.3.8.3).[19]

There are further potential savings from nationwide implementation of the non-invasive diagnostic pathway incorporated in the Early Access to Medicines Scheme (EAMS), which has created equity of access to diagnostic services, eliminating the requirement for lengthy initial assessments and annual follow-up at the NAC for most patients (explored in scenario analysis; Section B.3.8.3). Despite this it is acknowledged that complex patients will require ongoing assessments at the NAC.

B.1.3.5 Disease staging

The NYHA classification measures the severity of symptoms and functional capacity of patients with heart failure

NYHA classification is a patient-reported measure and therefore aligns closely with patient symptoms and functional capacity (Table 4). It is a statistically significant predictor of both HRQoL and survival.[63] [64,65] Guidelines from both NICE and the European Society of Cardiology use the NYHA classification to stratify patients with heart failure by disease severity in order to guide treatment recommendations.[66,67]

Table 4. New York Heart Association functional classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: American Heart Association, 2017.[68]

Two disease-specific prognostic staging systems have been developed using biomarkers in patients with ATTR-CM.[23,41] The first was published by the Mayo Clinic in 2016 and uses thresholds of troponin and NT-proBNP to stratify patients with wild-type ATTR-CM into 3 stages.[41] Another, the NAC staging system, was published in 2018 and combines eGFR and NT-proBNP, separating patients with either wild-type or hereditary disease into 3 stages.[23] Table 5 shows NAC ATTR disease stage-specific survival adjusted for a number of confounding factors.[19]

Table 5. Survival by NAC ATTR disease stage using a multivariable model

Stage	Parameters	Median survival (years)	Hazard ratio for death [a,b]
I	NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min	5.7	Reference
II	Patients not covered by stage I or III	3.5	2.05 (95% CI: 1.35-3.10)
III	NT-proBNP >3000 ng/L and eGFR <45 ml/min	2.2	3.71 (95% CI: 2.31-5.93)

[a] p<0.001 for between-group differences
[b] Multivariable model combining age, NAC ATTR Disease Stage, LVEF, genotypic subgroup and 6MWT distance at the time of diagnosis. P=0.001 and p<0.001 for stage II and III in comparison to stage I, respectively).
Abbreviations: 6MWT: 6-minute walk test; CI: confidence interval; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NAC: National Amyloidosis Centre; NT-proBNP: N-terminal pro-B-type natriuretic peptide.
Source: Lane et al. 2019.[19]

To best represent health states, a staging system must discriminate disease severity, utility and length of survival. Of the three systems, only NYHA functional classification has demonstrated a relationship with severity, survival and utility. [63-65,69,70] The Mayo Disease Stage and NAC ATTR Disease Stage have only demonstrated a relationship with survival.

Additionally, to be effective, the disease staging system must be easily implemented in clinical practice. UK clinicians advised that NYHA classification is commonly used in heart failure clinics in the UK for ongoing patient assessment. This is because it can be used irrespective of the cause of heart failure, is simple to derive and best reflects patients' symptom burden.

B.1.3.6 Clinical pathway of care

There are currently no approved pharmacological disease-modifying treatments for ATTR-CM. There is a significant unmet medical need for an effective and well- tolerated treatment that can slow the progression of the disease

There are currently no UK treatment guidelines or approved disease-modifying pharmacological treatments for ATTR-CM. Symptomatic management of heart failure is the mainstay of BSC in the UK. Liver transplantation (to remove the primary source of mutant TTR in hereditary cases) and heart transplantation have been reported but are rarely used in the UK (discussed in the following section).

In the UK, a single centre (NAC) currently provide diaganotic and management advice services for the national case load of ATTR-CM patients.

A 2019 consensus recommendation from the Heart Failure Association of the European Society of Cardiology suggests that tafamidis should be considered in patients with symptomatic heart failure due to confirmed transthyretin amyloidosis in order to improve exercise capacity and quality of life, and to reduce CV hospitalisations and mortality.[71]

B.1.3.6.1 Current pharmacological treatment

In the existing paradigm, the main aims of treatment are to relieve symptoms of congestive heart failure and prevent arrhythmic/thromboembolic events (Table 6).[17,18,72]

- Diuretics, including aldosterone antagonists and bioavailable loop diuretics, are the main strategy to manage heart failure symptoms in ATTR-CM.[72]
- The use of some conventional heart failure and anti-arrhythmic medications in ATTR-CM may actually cause harm,[18,72] adding to the difficulty in managing the disease.

Patisiran and inotersen are not considered appropriate comparators for the reasons outlined in Section B.1.1. Neither medicine has been evaluated in patients with ATTR-CM, therefore their efficacy and safety has not been established in this population. This is consistent with the marketing authorisation for both which does not include treatment of patients with ATTR-CM. A summary of the key differences in the study populations of patisiran (APOLLO), inotersen (NEURO-TTR) and tafamidis (ATTR-ACT) is shown in Table 7.

Table 6. Non-disease-modifying therapy for ATTR-CM

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 May lead to high-degree heart block and profound negative inotropic effect with resulting cardiogenic shock
Digoxin	Relatively contraindicated Hypersensitivity may lead to abrupt cardiac rhythm disturbances and sudden death

Source: Adapted from Castano et al. 2015.[72]

Table 7. Key differences in the APOLLO, NEURO-TTR and ATTR-ACT study design and populations

Trial number (acronym)	NCT01960348 (APOLLO; Patisiran)[5]	NCT01737398 (NEURO-TTR; Inotersen)[8]	NCT01994889 (ATTR-ACT; Tafamidis)[31,73]
Inclusion criteria for participants	Adult patients with ATTR-PN and a Neuropathy Impairment Score (NIS) of 5-130	Adult patients with stage 1 or 2 ATTR-PN	Adult patients with ATTR-CM (wild-type or hereditary) and a history of heart failure (prior hospitalisation for HF or clinical evidence of HF)
Cardiac exclusion criteria	(NYHA III/IV, history acute coronary syndrome, uncontrolled arrhythmia, unstable angina).	NYHA III/IV, history acute coronary syndrome	NYHA IV
Pre-planned cardiac subgroups	Cardiac sub-population defined by left ventricular wall thickness ≥13mm (no clinical evidence of heart failure)	Cardiomyopathy subgroup defined by left ventricular wall thickness ≥13mm (no clinical evidence of heart failure	N/A (clinical evidence of heart failure an eligibility criteria)
Diagnostic criteria for ATTR-CM	No diagnostic criteria met (echocardiogram findings alone)	No diagnostic criteria met (echocardiogram findings alone)	TTR amyloid deposits on biopsy or cardiac nuclear scintigraphy with IVST >12mm
Primary Outcome	Change from baseline in modified NIS	Change from baseline in modified NIS and Norfolk Quality of Life-Diabetic Neuropathy questionnaire	Combination of all-cause mortality and cardiovascular-related hospitalisations
Pre-defined cardiac outcomes	None	Secondary outcome measure: global longitudinal strain	Primary outcome measure: combination of all-cause mortality and frequency of CV-related hospitalisation Secondary outcome measure(s): 6MWT, KCCQ-OS, CV-related mortality
Median age at baseline, range	62 (range 24-83)	59 (SD 13)	75 (range 46-89)
Presence of heart failure	Not reported	Not reported	441 (100%)
Median NT-proBNP, IQR (pg/ML)	837 (292, 2354) in cardiac subgroup	Not reported	2966 (1752, 4862) in tafamidis arm, 3161 (1864, 4825) in placebo arm

Abbreviations: 6MWT: 6-minute walk test; ATTR-ACT: Tafamidis in transthyretin cardiomyopathy clinical trial; CMAD, transplantation/cardiac mechanical assist device; CV: cardiovascular; EQ-5D: EuroQoL-5 Dimensions; IVST: interventricular septum thickness; KCCQ-QS: Kansas City Cardiomyopathy Questionnaire; NSAID: Nonsteroidal anti-inflammatory drugs; NYHA: New York Heart Association; PGA: patient global assessment; QD: once daily.

Implantable cardiac devices

There is a high incidence of cardiac autonomic dysfunction and progressive conduction disease in ATTR-CM patients, which may require pacemaker implantation.[72] However, pacemaker implantation carries a risk in ATTR-CM patients,[72] and was not associated with a significant change in the risk of death or time to death in a retrospective study of elderly patients with ATTR-CM. Implantable cardioverter-defibrillators (ICD) are generally not suitable for ATTR-CM patients, and careful risk/benefit analysis is recommended in specific patients for whom this therapy may be beneficial.[72]

Organ transplantation

Organ transplantation is the only disease-modifying treatment strategy currently available. As the liver is the primary site of TTR protein production, liver transplantation may be helpful for patients with hereditary ATTR-CM, as the donor liver produces normal instead of mutant TTR protein.[72] Thus, the aim of liver transplantation is to reduce the supply of abnormal TTR protein and prevent the formation of further amyloid deposition in organs.[72] Liver transplantation can lead to stabilisation of ATTR-CM, with the highest success rate for patients early in the course of disease before there has been extensive damage to the nervous system or cardiac tissue.

In practice, liver transplant for ATTR-CM is almost never performed in the UK. It is normally reserved for younger patients with the Val30Met mutation, which is extremely rare in the UK.[74,75] In patients with mutations other than Val30Met, cardiac disease may progress unabated further following liver transplantation.[75]

Combined heart-liver transplantation or heart transplantation in isolation have been suggested as a potential alternative for selected patients. These procedures are also rarely performed in the UK, due to the advanced age of eligible patients and the scarcity of donor organs.[76]

B.1.4 Equality considerations

The Val122Ile mutation is found almost exclusively in people of Afro-Caribbean origin, where its prevalence is 3-4%.[38,58,77] Its clinical penetrance is unknown; when it does manifest clinically patients experience symptoms of heart failure.[19,24] It was the fourth most common cause of all heart failure (11.8%) among 1,392 Afro-Caribbean patients seen at a general heart failure clinic in a London hospital.[24]

Patients with this mutation have a poorer prognosis compared to Afro-Caribbean patients with other causes of heart failure.[24]. Furthermore, 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]

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

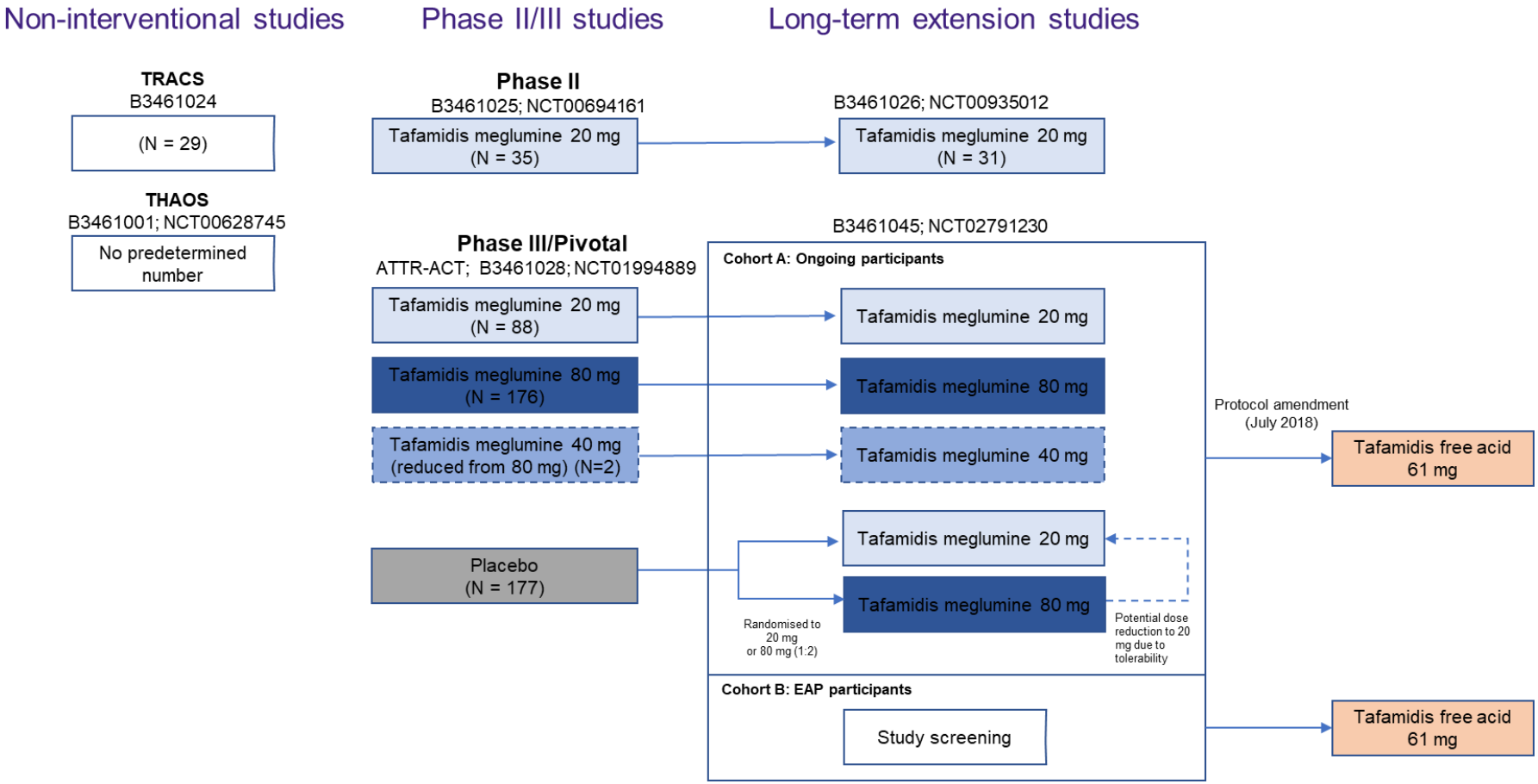
A systematic literature review (SLR) was undertaken in August 2018 and updated in May 2019 to identify evidence for the clinical effectiveness of interventions in the treatment of ATTR-CM. Full details of the SLR methodology are summarised in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR undertaken in August 2018 identified 1,861 publications. On review, 1,844 were excluded leaving 16 studies eligible for data extraction. The SLR update (August 2018 to May 2019) identified an additional 54 studies for review and 4 additional studies were identified for data extraction (Appendix D).

The SLR did not identify any other interventional studies beyond the pivotal Phase III ATTR-ACT and the Phase II trial, with their respective extension studies (Figure 10).

Figure 10. Studies in the tafamidis ATTR-CM clinical development programme



Abbreviations: ATTR-ACT: Tafamidis in transthyretin cardiomyopathy clinical trial; EAP: expanded access protocol; THAOS: Transthyretin-Associated Amyloidosis Outcomes Survey; TRACS: Transthyretin Amyloidosis Cardiac Study.

1. ATTR-ACT Phase III RCT and extension study

ATTR-ACT (tafamidis in transthyretin cardiomyopathy clinical trial, NCT01994889)[31] was an international, double blind, placebo-controlled RCT evaluating the efficacy, safety and tolerability of daily oral dosing of tafamidis in comparison to placebo in patients with ATTR-CM (Table 8). The primary analysis used a hierarchical combination of all-cause mortality and the frequency of cardiovascular (CV)-related hospitalisations.[31] Patients who completed ATTR-ACT (Cohort A) were eligible for enrolment in an ongoing long-term extension study (NCT02791230) alongside patients who had not participated in ATTR-ACT (Cohort B).[78] Further information on these studies is available from the following sources:

- ATTR-ACT: Maurer et al. 2018[31] and the Clinical Study Report (CSR)[73]
- ATTR-ACT extension study: data from the cut-off date of 15 February 2018[79]

2. Phase II trial and extension study

Tafamidis was evaluated in a Phase II trial (NCT00694161)[80] and a subsequent open-label long-term extension study (NCT00935012)[81]. Neither trial was used to populate the economic model, as these were single-arm studies. Supportive long-term safety and efficacy data are however presented in Section B.2.6.4 and Section B.2.10.3, respectively. Further information on these trials is available from the following sources:

- Phase II study: Maurer et al. 2015[80] and Sultan et al. 2017[82]
- Phase II extension study: data from the cut-off date of 01 August 2017 [83]

3. Non-interventional studies

Two non-interventional studies have been conducted. The objectives of THAOS (B3461001) and Transthyretin Amyloidosis Cardiac Study (TRACS) were:

- **THAOS:** A global, multicentre longitudinal observational survey of patients with documented ATTR amyloidosis, with the aim to characterise the natural history. The survey was initially limited to patients with ATTR-PN but has subsequently expanded to include patients with ATTR-CM; Coelho et al. 2013[84]
- **TRACS:** A prospective, longitudinal, natural history study to assess the morbidity and mortality of patients with ATTR-CM followed up every six months for two years; Ruberg et al. 2012.[48]

Table 8. Clinical effectiveness evidence from ATTR-ACT and ATTR-ACT extension study

Study	ATTR-ACT (NCT01994889)[31]	ATTR-ACT extension NCT02791230)[78]
Study design	Phase III, multicentre, international, double-blind, randomised placebo-controlled trial with a 30-month treatment phase	Phase III, multicentre, long-term extension study with a 60-month treatment phase
Population	Patients between 18 and 90 years of age with transthyretin amyloid cardiomyopathy (wild-type ATTR-CM or hereditary ATTR-CM)	Cohort A: Patients who completed 30 months of ATTR-ACT Cohort B: Patients diagnosed with ATTR-CM who did not previously participate in ATTR-ACT
Intervention(s)	Tafamidis meglumine (20 or 80 mg QD)	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 61 mg tafamidis (or if not available, tafamidis meglumine 80 mg). Cohort B: Tafamidis free acid 61 mg QD (or if not available, tafamidis meglumine 80 mg).
Comparator(s)	Placebo	None
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	Used for validation of extrapolated outcomes but not as a primary data source.
Rationale for use/non-use in the model	The study provides direct evidence evaluating the efficacy of tafamidis versus placebo, in addition to best supportive care in ATTR-CM patients.	Data are only available on tafamidis use, not BSC without tafamidis, as all patients in the extension received tafamidis. [redacted] (see B.2.3.3.4).
Reported outcomes specified in the decision problem	• All-cause mortality • Cardiac function (6MWT, NT-proBNP, Troponin, NYHA, echocardiographic variables) • CV-related hospitalisation	• All-cause mortality • Incidence of treatment-emergent adverse events

Study	ATTR-ACT (NCT01994889)[31]	ATTR-ACT extension NCT02791230)[78]
	• CV-related mortality • Transthyretin stabilisation • Adverse effects of treatment • Health-related quality of life • Duration of treatment	
All other reported outcomes	• All-cause hospitalisation	None specified

Abbreviations: ATTR-ACT: Tafamidis in transthyretin cardiomyopathy clinical trial; BSC: Best Supportive Care; CV: cardiovascular; EQ-5D: EuroQoL-5 Dimensions; KCCQ-QS: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; PGA: patient global assessment; QD: once daily.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the methodology used in ATTR-ACT and the ATTR-ACT extension study is presented in Table 9.

Table 9. Summary of the trial methodology for ATTR-ACT and the ATTR-ACT extension study

Trial number (acronym)	NCT01994889 (ATTR-ACT)[31,73]	NCT00935012 (ATTR-ACT extension)[79]
Trial design	ATTR-ACT was a Phase III, multicentre, international, double-blind, placebo-controlled trial to evaluate the efficacy, safety and tolerability of tafamidis in patients with ATTR-CM.	Ongoing Phase III, open-label, long-term extension safety study. Cohort A: Patients who completed 30 months of ATTR-ACT Cohort B: Patients diagnosed with ATTR-CM who did not previously participate in ATTR-ACT.
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.
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). 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. Medications considered to be BSC were permitted and were to be stabilised for at least 4 weeks of therapy (other	Patients could use non-prohibited supplements and medications during the study with the exception of those listed below: • Any investigational therapy • Diflunisal • Tauroursodeoxycholate and doxycycline • Digitalis and calcium channel blockers (e.g. verapamil, diltiazem)

	than diuretics) prior to baseline. Changes in diuretic dose were permitted within 4 weeks of the baseline visit. The following medication was prohibited: • Any investigational therapy • Tauroursodeoxycholate and doxycycline • Digitalis and calcium channel blockers. If used prior to randomisation, these medications were to be stopped at least 30 days before Baseline (Day 1) • 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. • 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 Details of outcome measures and timings of assessment for all relevant outcomes (primary and other) are provided in B.2.3.1.5.	• All-cause mortality • Incidence of treatment-emergent adverse events
Other outcomes used in the economic model/specified in the scope	• **All-cause mortality** • **CV-related hospitalisation** • CV-related mortality	None

	• Cardiac function (6MWT, NT-proBNP, echocardiographic parameters) • **NYHA functional classification** • Transthyretin stabilisation • **Adverse effects of treatment** • **Health-related quality of life (**KCCQ-OS, **EQ-5D-3L**, EQ-5D-VAS**)** 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. **Outcomes used in the economic modelling are shown in bold**	
Pre-planned subgroups	Stratification factors • *TTR* genotype (wild-type versus hereditary) • NYHA class at baseline (class I/II versus class III) Dose analysis • Dose (20 mg vs. placebo, 80 mg vs. placebo)	• *TTR* genotype (wild-type versus hereditary)

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; NSAID: Nonsteroidal anti-inflammatory drugs; NYHA: New York Heart Association; PGA: patient global assessment; QD: once daily.

B.2.3.1 ATTR-ACT

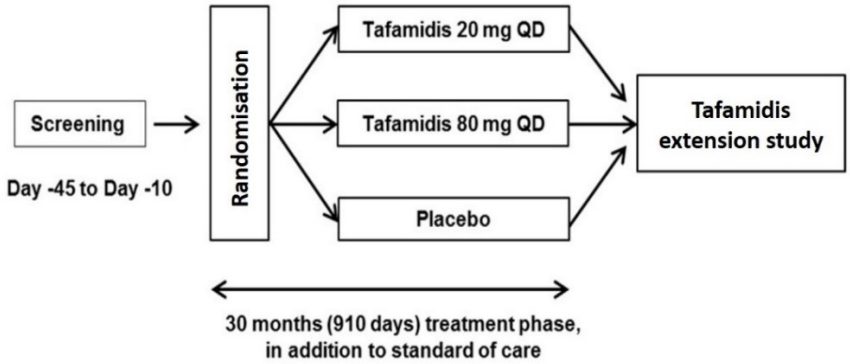
B.2.3.1.1 Study design

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.[31] In addition, the safety and tolerability of tafamidis were assessed.

Treatment assignment was stratified by *TTR* genotype (wild-type or hereditary) and by baseline severity (NYHA class I or combined NYHA class II and III).[31]

Patients were randomly assigned in a 2:1:2 ratio to receive placebo (4 x placebo capsules), tafamidis 20 mg (1 x 20 mg tafamidis meglumine plus 3 x placebo capsules) or tafamidis 80 mg (4 x 20 mg capsules of tafamidis meglumine) in a blinded fashion for 30 months in addition to BSC (e.g. diuretics) (Figure 11).[31] The 20 mg dose of tafamidis meglumine was used in the Phase II study[80].

Figure 11. Schematic diagram of ATTR-ACT



Source: Clinical Study Report (B3461028).[73]

B.2.3.1.2 Eligibility criteria

The inclusion and exclusion criteria for ATTR-ACT are listed in Table 10.

Table 10. Inclusion and exclusion criteria in ATTR-ACT

Inclusion criteria	Exclusion criteria
• Age between 18 and 90 years • Wild-type or hereditary ATTR-CM confirmed by the presence of amyloid deposits on analysis of biopsy specimens obtained from cardiac or noncardiac sites (e.g. fat aspirate, gastrointestinal sites, salivary glands, or bone marrow) and, in patients without hereditary ATTR-CM, by the presence of transthyretin precursor protein confirmed on immunohistochemical analysis, scintigraphy, or mass spectrometry • Evidence of cardiac involvement (demonstrated by echocardiography, with an end diastolic interventricular septal wall thickness exceeding 12 mm) • Medical history of heart failure with at least one prior hospitalisation for heart failure or clinical evidence of heart failure • NT-proBNP concentration ≥600 pg/mL • 6MWT >100 metres.	• Heart failure that was not due ATTR-CM • NYHA class IV heart failure • Presence of light chain amyloidosis • Prior liver or heart transplantation or implanted cardiac mechanical assist device • Previous treatment with tafamidis • eGFR of <25 mL/min/1.73 m^2 • Liver transaminase levels exceeding two times the upper limit of the normal range • mBMI of less than 600 • Receiving concurrent treatment with NSAIDs (other than those permitted), tauroursodeoxycholate, doxycycline, calcium channel blockers (e.g. verapamil, diltiazem) or digitalis.

Abbreviations: 6MWT: 6-minute walk test; eGFR: estimated glomerular filtration rate; mBMI: modified body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association.
Source: Maurer et al. 2018.[31]

B.2.3.1.3 Settings and locations where the data was collected

The study was conducted at 48 centres in 13 countries: Belgium (1), Brazil (1), Canada (1), Czech Republic (3), France (2), Germany (2), Italy (3), Japan (3), Netherlands (1), Spain (2), Sweden (2), United Kingdom (2), and United States (25). UK sites included St George's Hospital and St Bartholomew's Hospital, London.

B.2.3.1.4 Study drugs and concomitant medications

Patients were randomised in a 2:1:2 ratio to one of the following three treatment arms:

- 80 mg of tafamidis meglumine (n=176), orally QD (blinded)
- 20 mg of tafamidis meglumine (n=88), orally QD (blinded)
- placebo (n=177); orally QD (blinded)

Randomised patients received continuous dosing of study treatment for 30 months from the date of first dosing or until one of the following criteria was met (whichever occurred first):

- Patient died

- Protocol violation
- Lost to follow up
- No longer willing to participate in the study
- Discontinued due to an adverse event
- Received a heart and/or liver transplantation, or CMAD

Drug adherence

Dosing adherence was defined as the proportion of patients who took their 4 capsules of study medication per day on at least 80% of days of study participation. Subjects with less than 80% dosing adherence were excluded from the per-protocol analysis.

B.2.3.1.5 Outcomes used in the economic model or specified in the scope

The primary endpoint was assessed using a hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations (defined as the number of times a patient was hospitalised for CV-related morbidity), applying the Finkelstein-Schoenfeld method.[31,85] The primary analysis compared the results of pooled tafamidis (20 mg and 80 mg) treatment group with the placebo group. In secondary analyses, the two components of the Finkelstein-Schoenfeld analysis, all-cause mortality and frequency of CV-related hospitalisation, were also analysed as separate endpoints.[73]

The secondary endpoints of all-cause mortality, CV-related hospitalisation, 6MWT distance and KCCQ-OS were selected based on observations in the observational Transthyretin Amyloidosis Cardiac Study (TRACS)[48] and the Phase II study,[80] conducted prior to ATTR-ACT to characterise the natural history of ATTR-CM. Cause of death and hospitalisations were adjudicated by a committee of external experts to determine if they were CV-related.

Study endpoints and assessment points are summarised in B.2.3.3.3.

Table 11. Summary of ATTR-ACT study endpoints

Endpoint	Definition	Time point (months)
Primary endpoint	Hierarchical assessment of all-cause mortality and frequency of CV-related hospitalisations (defined as the number of times a patient was hospitalised [i.e. admitted to a hospital] for CV-related morbidity using the Finkelstein-Schoenfeld method)	Up to 30
All-cause mortality	Death due to any cause. Heart transplantation and CMAD were treated as deaths	Up to 30

CV-related mortality	Death due to heart failure, arrhythmia, myocardial infarction, sudden cardiac death, stroke, and other CV causes. Heart transplantation and CMAD were treated as deaths.	Up to 30
All-cause hospitalisation	A non-elective admission to an acute care setting for medical therapy that resulted in at least a 24-hour stay (or a date change if the time of admission/discharge was not available). Hospitalisation did not include admission to rehabilitation facilities, hospice facilities, respite care, skilled nursing facilities, nursing homes, routine emergency room admissions (less than 24 hours) or same day surgeries	Up to 30
CV-related hospitalisation	Any hospitalisation due to a cardiovascular reason for hospitalisation including heart failure, arrhythmia, myocardial infarction, transient ischemic attack or stroke, and other CV causes	Up to 30
6MWT	An exercise test that measures the distance walked by an individual over a span of 6 minutes, providing information on functional limitation. The 6MWT was conducted in accordance with guidelines established by the American Thoracic Society.[86]	Baseline, 6, 12, 18, 24 and 30 (Month 30 was key secondary endpoint)
NYHA	Patients were assigned to a baseline NYHA functional classification. For definitions see Section B.1.3.5, Table 4	Baseline, 6, 12, 18, 24 and 30
TTR stabilisation	Whole blood samples were collected to measure TTR stabilisation	Baseline, 1, 6, 12, 18, 24, and 30
KCCQ-OS	A 23-item self-administered instrument quantifying various domains of health status and HRQoL in cardiomyopathy.[54] Patients are assessed in 8 domains; physical limitation, symptom stability, symptom frequency, symptom burden, total symptom, self-efficacy, quality of life and social limitation. Lower scores denoted poorer quality of life.[54]	Baseline, 6, 12, 18, 24 and 30 (Month 30 was key secondary endpoint)
EQ-5D-3L and VAS	A self-administered generic HRQoL instrument consisting of two parts.[87] In the first part, respondents were asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having three levels of function (1=no problem, 2=some problem, and 3=extreme problem). The second part is a participant's self-rating of current health state on a visual analogue scale (EQ-5D-3L VAS) with endpoints labelled 'best imaginable health state' (score of 100) and 'worst imaginable	Baseline, 6, 12, 18, 24 and 30

	health state' (score of 0). The scores from the 5 dimensions were used to calculate a single index value, also known as a utility score	
Echocardiographic parameters	A 2-D doppler echocardiogram was performed to assess specified parameters	Baseline, 6,18 and 30
NT-proBNP	Blood samples were collected to measure NT-proBNP concentration	Baseline, 12 and 30
Adverse effects	Described in Section B.2.10.	

Abbreviations: 6MWT: 6-minute walk test; AE: adverse event; CV: cardiovascular; HRQoL: health-related quality of life; mBMI: modified body mass index; EQ-5D-3L: EuroQoL-5 Dimensions; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire; LV: left ventricle; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PGA: patient global assessment; TTR: transthyretin; VAS: visual analog scale.
Source: Clinical Study Report (B3461028).[73]

B.2.3.2 Baseline characteristics

The baseline characteristics of patients in ATTR-ACT are shown in Table 12. Overall, the baseline characteristics were similar across the pooled tafamidis and placebo groups. The mean age in the pooled tafamidis and placebo group was 75 and 74 years respectively. Patients were predominantly male (>88%) in both groups.[31]

At baseline, the number of patients with no functional limitation (NYHA Class I) or slight limitation (NYHA Class II) were 9.1% and 61.4% in the placebo arm compared to 7.3% and 57.1% in the pooled tafamidis arm. The proportion of patients with marked functional limitation (NYHA Class III) was 29.5% and 35.6%, in the pooled tafamidis and placebo arms respectively.[31]

The proportion of patients receiving renin angiotensin system agents, beta blockers, diuretics and antithrombotic agents was similar across the pooled tafamidis and placebo arms. Few patients (<7%) had a permanent pacemaker or ICD, and the proportion was similar across the two treatment groups.[31]

Most patients had wild-type ATTR-CM. The proportion of patients with wild-type and hereditary ATTR-CM was comparable between the groups: 76.1% were wild-type in the pooled tafamidis group and 75.7% in the placebo group.[31]

Among patients with hereditary ATTR-CM in the UK, the two most common causative TTR mutations are [redacted] and [redacted].[38] In ATTR-ACT, [redacted] and [redacted] were also the most common mutations, present in [redacted]% and [redacted]% of 106 patients with hereditary ATTR-CM, respectively.[73]

Table 12. Baseline characteristics of patients across treatment groups in ATTR-ACT

	ATTR-ACT[31]			
	Tafamidis 20 mg (N=88)	**Tafamidis 80 mg (N=176)**	**Pooled Tafamidis (N=264)**	**Placebo (N=177)**
Mean age (SD), years	[redacted]	[redacted]	74.5 (7.2)	74.1 (6.7)
Sex, n (%)	[redacted]	[redacted]		
Male	[redacted]	[redacted]	241 (91.3)	157 (88.7)
Female	[redacted]	[redacted]	23 (8.7)	20 (11.3)
Race, n (%)	[redacted]	[redacted]		
White	[redacted]	[redacted]	211 (79.9)	146 (82.5)
Black	[redacted]	[redacted]	37 (14.0)	26 (14.7)
Asian	[redacted]	[redacted]	13 (4.9)	5 (2.8)
Other	[redacted]	[redacted]	3 (1.1)	0
NYHA classification, n (%)[a]	[redacted]	[redacted]		
NYHA Class I	[redacted]	[redacted]	24 (9.1)	13 (7.3)
NYHA Class II	[redacted]	[redacted]	162 (61.4)	101 (57.1)
NYHA Class III	[redacted]	[redacted]	78 (29.5)	63 (35.6)
NYHA Class IV	[redacted]	[redacted]	0	0
TTR genotype, n (%)	[redacted]	[redacted]		
Wild-type TTR	[redacted]	[redacted]	201 (76.1)	134 (75.7)
Hereditary TTR	[redacted]	[redacted]	63 (23.9)	43 (24.3)
Val122Ile	[redacted]	[redacted]	[redacted]	[redacted]
Thr60Ala	[redacted]	[redacted]	[redacted]	[redacted]
V30M	[redacted]	[redacted]	[redacted]	[redacted]
Mean mBMI (SD)[b]	[redacted]	[redacted]	1058.8 (173.8)	1066.4 (194.4)
Mean creatinine clearance (SD), mL/min	[redacted]	[redacted]	58.8 (17.9)	56.5 (20.4)
Median NT-proBNP (Q1, Q3), pg/ml	-	-	2995.9 (1751.5, 4861.5)	3161.0 (1864.4, 4825.0)
Median troponin I (Q1, Q3), ng/ml	[redacted]	[redacted]	0.14 (0.09, 0.20)	0.14 (0.08, 0.19)
Echocardiographic variables				
Mean left ventricular ejection fraction (SD), %	-	-	48.4 (10.3)	48.6 (9.5)
Mean interventricular wall thickness, mean (SD), mm	-	-	16.7 (3.8)	16.2 (3.5)

	ATTR-ACT[31]			
	Tafamidis 20 mg (N=88)	**Tafamidis 80 mg (N=176)**	**Pooled Tafamidis (N=264)**	**Placebo (N=177)**
Mean left atrial anterior-posterior diameter size (SD), mm	-	-	43.8 (7.0)	43.7 (6.1)
Mean left ventricular stroke volume (SD), ml	-	-	45.8 (16.1)	45.1 (16.9)
Mean global longitudinal strain (SD), %	-	-	-9.3 (3.5)	-9.4 (3.6)
Baseline medication, n (%)[c]	-	-		
Agents acting on RAS	-	-	69 (26.1)	48 (27.1)
Beta blockers	-	-	76 (28.8)	53 (29.9)
Diuretics	-	-	175 (66.3)	123 (69.5)
Antithrombotic agents	-	-	105 (39.8)	72 (40.7)
Permanent pacemaker, n (%)	-	-	13 (4.9)	12 (6.8)
ICD, n (%)	-	-	16 (6.1)	9 (5.1)
6MWT (SD), m	[redacted]	[redacted]	350.6 (121.3)	353.3 (126.0)
Mean KCCQ (SD)	[redacted]	[redacted]	67.3 (21.4)	65.9 (21.7)

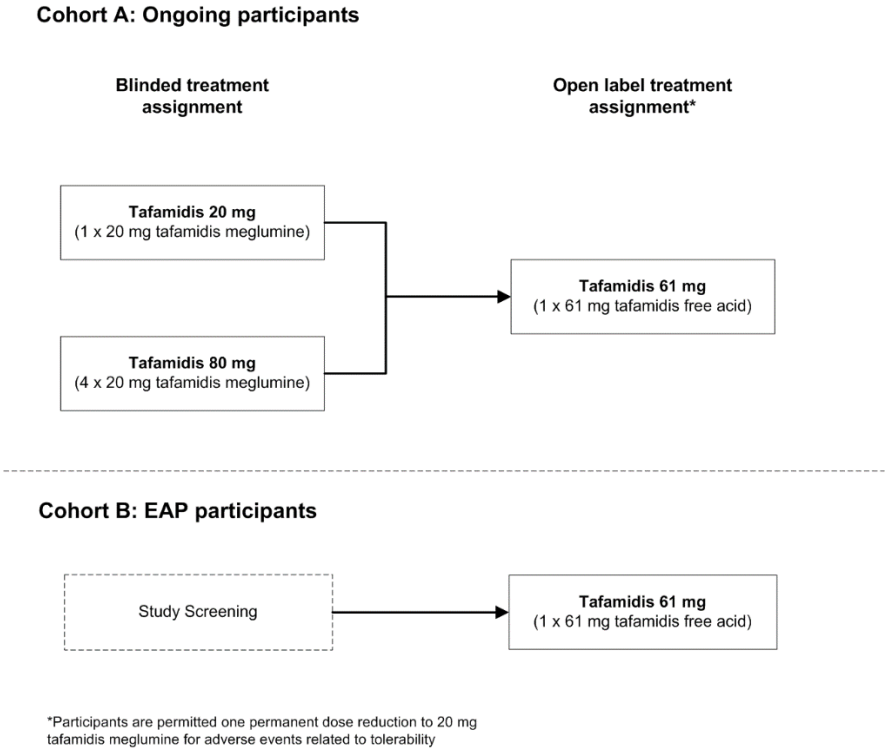
[a] NYHA class: I = without resulting limitations, II = slight limitation, III = marked limitation, IV = inability to carry on any physical activity without discomfort. Given the very low number of enrolled patients in ATTR-ACT with a baseline classification of NYHA Class I, the baseline groupings used for efficacy analyses were changed from 'NYHA Class I and NYHA Classes II and II combined' to NYHA Classes I and II combined and NYHA Class III'.
[b] The modified BMI (mBMI) is calculated by multiplying the body mass index [weight (kg)/height (meters squared)] by serum albumin concentration (g/L).
[c] Patients may be taking >1 medication in a class, each medication is only counted once per patient.
Abbreviations: 6MWT: 6-minute walk test; ICD: implantable cardioverter-defibrillator; KCCQ: Kansas City Cardiomyopathy Questionnaire; mBMI: modified body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; NR: not reported; NYHA: New York Heart Association; RAS: renin angiotensin system; SD: standard deviation; TTR: transthyretin. " – " denotes data not available
Source: Maurer et al. 2018[31]; Clinical Study Report (B3461028).[73]

B.2.3.3 ATTR-ACT extension study

B.2.3.3.1 Study design

The Phase III multicentre, long-term extension safety study is evaluating the long-term safety of daily oral dosing of tafamidis in addition to BSC (e.g. diuretics) in patients with ATTR-CM. The study continues to collect data until the patient has access to tafamidis via a prescription, whichever occurs first. This ongoing study is open to patients completing ATTR-ACT and patients with a diagnosis of ATTR-CM.[79]

Figure 12. Schematic diagram of the expanded access Protocol Amendment in the ATTR-ACT extension study



After Protocol Amendment 3, dated 20 July 2018, patients who had previously participated in ATTR-ACT were now known as Cohort A, and were assigned to open-label treatment of 61 mg tafamidis.
Abbreviation: EAP: expanded access protocol.
Source: B3461045 (Data on file).[79]

Patients who completed ATTR-ACT were initially treated as follows[79]:

- Patients who received 20 mg or 80 mg in ATTR-ACT continued the same dosage in the extension study.
- Patients who received placebo in ATTR-ACT were re-randomised 1:2 to blinded 20 mg or 80 mg tafamidis in the extension study. Those who were assigned to placebo in

ATTR-ACT and randomised to 80 mg tafamidis were permitted one blinded dose reduction to 20 mg for AEs relating to tolerability.[79]

Following Protocol Amendment 3, dated 20 July 2018, patients who had previously participated in ATTR-ACT were known as Cohort A, and were assigned to open-label treatment.[79] Patients receiving tafamidis meglumine 20 mg or 80 mg were assigned to tafamidis free acid 61 mg, once daily, in addition to BSC (e.g. diuretics) for up to 60 months.[79]

[redacted] patients completed ATTR-ACT but did not enrol into the extension study. Reasons for not enrolling reflected [redacted] in [redacted] cases and patient decision in [redacted] cases.[73]

The ATTR-ACT extension study protocol has been amended to include an additional cohort of patients, known as Cohort B (EAP) who have not previously participated in ATTR-ACT.[79] [redacted]. Patients in Cohort B are permitted to be enrolled and assigned to open-label tafamidis 61 mg once daily, in addition to BSC, for up to 60 months.[79] One dose reduction to tafamidis meglumine 20 mg is permitted for AEs related to tolerability.

B.2.3.3.2 Eligibility criteria

For Cohort A, patients were eligible if they completed 30 months of the study treatment in ATTR-ACT.[79] Patients were ineligible to participate in the study if any of the following key criteria were met:[79]

- Chronic use of diflunisal, tauroursodeoxycholate, doxycycline, digitalis, calcium channel blockers, investigational drug(s) or other experimental interventions, other than tafamidis, independently or as part of a study within 30 months prior to enrolment.
- Use of certain NSAIDs
- Liver and/or heart transplant, or implanted cardiac mechanical assist device
- Require initiation of treatment with calcium channel blockers.

For Cohort B, patients are required to have documentation of:[79]

- Genetic testing for transthyretin amyloidosis (ATTR)
- Diagnosis of ATTR-CM and the diagnostic criteria used, including documentation that immunoglobulin light chain (AL) amyloidosis has been evaluated and ruled out

- Information on current medical status including documentation of NYHA functional classification.

B.2.3.3.3 Study endpoints

The primary endpoints of the ATTR-ACT extension study are safety as measured by all-cause mortality and incidence of TEAEs. Study endpoints are summarised in Table 13.

Table 13. Summary of ATTR-ACT extension study endpoints

Endpoint	ATTR-ACT extension study
Primary endpoint	Safety as measured by: • All-cause mortality • Incidence of TEAEs
Other key endpoints	• CV-related mortality • Frequency of all-cause hospitalisation • Frequency of CV-related hospitalisation (including heart failure, arrhythmia, myocardial infarction, stroke and other CV-related events) • Change from baseline at each visit in KCCQ-OS and domain scores (physical limitation, symptom stability, symptoms, self-efficacy, social limitation, and quality of life) and domain summary scores (functional summary and clinical summary) • NYHA classification at each visit

Abbreviations: CV: cardiovascular; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; TEAE: treatment-emergent adverse events.
Source: Clinical Study Protocol (B3461045)[79]

A summary of the statistical methods used in the ATTR-ACT extension study is presented in B.2.4.

B.2.3.3.4 Use of ATTR-ACT extension study data in the economic model

Data from the ATTR-ACT extension study were used to validate extrapolated outcomes but were not used as a primary data source in the economic model, for the following reasons:

- Data are only available to describe tafamidis use and not BSC, as all patients in the extension study received tafamidis.
- [redacted].[73]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical methodology for ATTR-ACT and the ATTR-ACT extension study is provided below.

B.2.4.1 ATTR-ACT

B.2.4.1.1 Analysis sets

The main analysis sets in the ATTR-ACT study are defined below:[73]

- **Safety analysis set**: all randomised patients who received at least 1 dose of study drug.[73]
- **Intention-to-treat (ITT) analysis set**: all patients in the safety analysis set who had at least 1 post-baseline efficacy evaluation (i.e. post-baseline hospitalisation, study visit, or date of death). The ITT population was used for the primary analysis.[73]
- **Per protocol (PP) analysis set**: all patients in the ITT population who did not violate inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis.[73]

Patients who discontinued for transplantation (i.e. heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the primary analysis in the same manner as death.[73]

B.2.4.1.2 Statistical methods

In the primary analysis, a hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations was assessed using the Finkelstein-Schoenfeld method.[85] The Finkelstein-Schoenfeld test increases the sensitivity and power of the analysis while also preserving the importance of the all-cause mortality endpoint. This is important for a disease with relatively low prevalence. The test is based on the principle that each patient in the study is compared to every other patient within each stratum (based on TTR genotype and NYHA baseline classification) in a pairwise manner.[11]

The pairwise comparison proceeds in hierarchical fashion using all-cause mortality first, assigning +1 to the “better” patient and -1 to the “worse” patient (Table 14). If both patients are dead, then the patient with a longer survival time is assigned +1 and the one with the shorter survival time -1. If one patient is alive and the other is not, the alive patient receives a

+1 and the deceased one -1. If both patients are alive, the comparison uses CV-related hospitalisation to assign scores. The patient with the fewer CV-related hospitalisations (frequency) receives +1 while the other receives -1. In short, the score for the pair (i,j) indicates whether patient i has the more favourable outcome than patient j. The test statistic is based on the sum of these scores.[11] The "CV-related hospitalisation" in all analyses, unless otherwise specified, combines hospitalisations adjudicated by external experts as CV-related with hospitalisations adjudicated as indeterminate.[11]

Table 14. Finkelstein-Schoenfeld scoring algorithm

Scenario	Mortality	Survival time	CV hospitalisation frequency	Score
1	Dead	…	…	-1
	Alive	…	…	+1
2	Dead	Low	…	-1
	Dead	High	…	+1
3	Dead	Tied	High	-1
	Dead	Tied	Low	+1
4	Dead	Tied	Tied	0
	Dead	Tied	Tied	0
5	Alive	…	High	-1
	Alive	…	Low	+1
6	Alive	…	Tied	0
	Alive	…	Tied	0

In each scenario, a pairwise comparison of patients is made by first taking mortality into account. If there is a clear difference (scenario 1), then a score is assigned. If both participants died (scenario 2), then survival time is considered, and a score is assigned if there is a difference between the patients. If there is no difference between the 2 patients in survival time, then the frequency of CV-related hospitalisation (scenario 3) is considered, and a score is assigned. If there is no difference in CV-related hospitalisation frequency between the 2 patients (scenario 4), then a score of 0 is assigned. If both participants are alive, then the frequency of CV-related hospitalisation (scenario 5) is considered, and a score is assigned. If there is no difference in CV-related hospitalisation (scenario 6), then a score of 0 is assigned.
Abbreviations: CV: cardiovascular.
Source: Maurer et al. 201711

Statistical methods in the ATTR-ACT study are summarised in Table 15 for the primary and other endpoints.

Table 15. Summary of statistical analyses in ATTR-ACT

Objective	To assess the efficacy of an oral dose of 20 mg or 80 mg tafamidis meglumine soft gel capsules based on all-cause mortality and frequency of CV-related hospitalisations, in addition to an assessment of safety and tolerability in comparison to placebo.

Statistical analysis of primary endpoint (Hierarchical assessment of all-cause mortality and frequency of CV-related hospitalisations at Month 30)	• The primary analysis assessed a hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations using the Finkelstein-Schoenfeld method[85] (see Section B.1.2.4.1 for detailed endpoint definition). ITT and PP analysis sets were used in the analysis of the primary endpoint. The ITT analysis was the primary analysis. • 20 mg and 80 mg groups (including patients in the 80 mg group that may have had a dose reduction to 40 mg) were pooled into one group for comparison to placebo. • Finkelstein-Schoenfeld analysis was applied by strata (based on TTR genotype and NYHA baseline classification) and combined to produce the overall test statistic. As a result, patient to patient pairwise comparisons were performed among similar patients and then combined.
Statistical analysis of key secondary endpoints (Change from baseline in 6MWT and KCCQ-OS at Month 30)	• ITT and PP analysis sets were used in the assessment of all secondary endpoints. The ITT analysis was the primary analysis. • Secondary endpoints were evaluated using a mixed model repeated-measures (MMRM) analysis of covariance (ANCOVA). • Centre and patient-within-centre were treated as random effects, and treatment, visit, TTR status (wild-type or hereditary) and visit-by-treatment interaction were treated as fixed effects, with the baseline value as a covariate. • A pre-specified hierarchical testing order (6MWT, followed by the KCCQ-OS) provided multiplicity protection against type 1 error (alpha level at 0.05). The multiplicity procedure was applied to the ITT analysis set only.
Statistical analysis of further secondary endpoints (all-cause mortality, CV-related mortality, CV-related hospitalisation and TTR stabilisation at Month 1)	• ITT analysis set was used in the analysis of all further secondary endpoints. • Time to CV-related mortality and time to all-cause mortality were analysed using cox proportional hazards models. Frequency of CV-related hospitalisations was analysed using Poisson regression analyses. These analyses, in addition to the primary endpoint and key secondary endpoints, were additionally presented by TTR genotype (wild-type or hereditary), NYHA baseline classification, as well as dose (randomised dose group) in an exploratory analysis. • The proportion of patients who achieved TTR stabilisation in each treatment group at Month 1 was compared using a Cochran-Mantel-Haenszel test. A similar test of proportion was performed for TTR stabilisation at all other time points and was considered exploratory. No subgroup analyses were performed at these other time points.

	• Except for the analyses by dose group, all analyses of the secondary endpoints compared the pooled tafamidis group with the placebo group. • Further secondary endpoints were not adjusted for multiplicity.
Statistical analysis of exploratory endpoints (all-cause hospitalisation, NYHA classification, EQ-5D-3L and VAS scores, echocardiographic characteristics and NT-proBNP)	• ITT analysis set was used in the analysis of all exploratory endpoints. • The frequency of all-cause hospitalisation was analysed using Poisson regression analyses. The number of CV-related days hospitalised, and the number of all-cause days hospitalised were analysed using an ANOVA. • The change from baseline in NYHA functional classification was presented using descriptive statistics, reporting the number and percentage of patients in each classification at each visit. • The following endpoints were evaluated at each time point post-baseline using ANCOVA (MMRM). – Change from baseline in EQ 5D 3L Index Score and visual analogue scale (VAS) scores – Change from baseline in echocardiographic parameters – Change from baseline in NT-proBNP concentration
Safety endpoints	• A 3-tier approach was used to summarise AEs: – Tier 1: pre-specified events of clinical importance: analysed using the Chang and Zhang method[88] who inverted two 1-sided tests at half the significance level each for calculating p values and CIs. – Events not in tier-1 but were common: both proportion and 95% CIs were generated using an asymptotic approach (Proc Binomial). – Events that were neither tier-1 or tier-2: simple proportions were presented. • No adjustment for multiple comparisons or stratification factors in the analyses.

Sample size, power calculation	The study was powered to show a difference between the pooled tafamidis group and the placebo group. The sample size requirement for the primary comparison of interest of the pooled tafamidis 20 mg and 80 mg treatment group versus placebo was based on the observational study B346102473 (TRACS)[48], an understanding of current clinical assumptions in ATTR-CM patients and the uncertainty of assumptions from these limited data. A sample size of 400 patients was estimated to give the trial approximately 90% power for the primary analysis. This calculation assumed a 30% reduction in mortality with tafamidis, a reduction in CV-related hospitalisations for the tafamidis group (1.5 CV-related hospitalisations for the tafamidis group and 2.5 CV-related hospitalisations for the placebo group), a treatment duration of 30 months and a significance level (alpha) of 0.05 (two-side test).
Data management, patient withdrawals	No imputation was done for missing patients in the primary analysis based on the Finkelstein-Schoenfeld method. Information on vital status, transplant and cardiac assist device was collected at 30 months for patients who discontinued early. This information was included in the primary analysis. A sensitivity analysis (of the primary analysis) using multiple imputation that imputes missing CV-related hospitalisation data was performed. Supplemental analyses of the two key secondary variables grouped the patients based on their dropout or missing data patterns using a pattern mixture model. For all analyses using MMRM, no imputation of missing values was done.
Censoring	In the survival analysis of the ITT population, patients who received a CMAD or heart transplant were treated the same as those who died and were not censored. A sensitivity analysis was performed that did not include CMAD or heart transplant events as death.

Abbreviations: 6MWT: 6-minute walk test; AE: adverse event; ANCOVA: analysis of covariance; ANOVA: analysis of variance; CI: confidence interval; CMAD, cardiac mechanical assist device; CV: cardiovascular; ITT: intention-to-treat; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire; mBMI: modified body mass index; MMRM: mixed model repeated-measures; NYHA: New York Heart Association; PP: per protocol; TRACS: Transthyretin Amyloidosis Cardiac Study; TTR: transthyretin.
Source: Clinical Study Report (B3461028)[73], Maurer et al. 2018.[31]

B.2.4.2 ATTR-ACT extension study

Statistical methods planned for the ongoing ATTR-ACT extension study are summarised in Table 16 for the primary and other endpoints.

Table 16. Summary of statistical analyses in the ATTR-ACT extension study

Objective	• To obtain additional, long-term, safety data for tafamidis in ATTR-CM patients. • To provide tafamidis to ATTR-CM patients who completed 30 months of blinded treatment in ATTR-ACT.

Statistical analysis of primary endpoint	• All-cause mortality will be analysed using cox proportional hazards model by integrating data from ATTR-ACT. • Kaplan-Meier survival curves for each treatment group along with median survival times (if applicable) will be presented. • Patients who discontinue for transplantation (i.e. heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, will be handled in the same manner as death. • Incidence of TEAE: The incidence of TEAEs will be tabulated by treatment group and by system organ class. AEs are classified into 1 of 3 tiers.
Statistical analysis of other endpoints	• CV-related mortality will be analysed using cox proportional hazards model. • Kaplan-Meier survival curves and median survival times for each treatment group will be presented. • KCCQ will be analysed using a MMRM with an unstructured covariance matrix (or as appropriate) with patients as a random effect and treatment, visit, TTR genotype and visit-by-treatment interaction, as fixed effects and baseline score as covariate. • Frequency of hospitalisation (all-cause and CV-related), NYHA classification, electrocardiogram parameters will be summarised descriptively.
Sample size, power calculation	No formal sample size calculation.
Data management, patient withdrawals	Not reported.

Abbreviations: AE: adverse event; CV: cardiovascular; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; mBMI: modified body mass index; MMRM: mixed model repeated-measures; TEAE: treatment-emergent adverse event; TTR: transthyretin.
Source: Data on file (B3461045)[79]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of ATTR-ACT was performed using the Cochrane Collaboration's tool,[89] and was determined to be at low risk of bias across the different domains that were assessed. See Appendix D 3 for full details of the quality assessment for ATTR-ACT.

B.2.6 Clinical effectiveness results of the relevant trials

The results of ATTR-ACT are presented below for the ITT population. The ATTR-ACT extension study is ongoing; available results are presented after the main study, in Section B.2.6.2.

B.2.6.1 Patient disposition (ITT population)

A total of 548 patients were screened for entry into ATTR-ACT, and 441 were randomised into treatment. The most common reasons that screened patients were not admitted to the trial were closure of enrolment (for wild-type patients), clinical instability, and ineligibility on the grounds of cardiac biomarker concentration (NT-proBNP) or renal function (eGFR levels).[31] 88 patients were randomised to the tafamidis 20 mg group, 176 to the tafamidis 80 mg group and 177 to the placebo group.[31] The CONSORT diagram is presented in Appendix D and patient disposition is described in Table 17.

All patients that had been randomised received at least one dose of the study drug (safety analysis set). Two patients in the tafamidis 80 mg group and four in the placebo group received a blinded dose reduction.[73]

Of the 441 patients, 58.5% completed the study and 24.0% discontinued. Fewer patients in the pooled tafamidis group (19.7%) discontinued compared to the placebo arm (30.5%). Discontinuation due to AEs was infrequent and was comparable between the tafamidis (6.4%), and the placebo group (6.2%).[73]

Table 17. Patient disposition in ATTR-ACT (ITT population)

Number (%) of patients	Tafamidis 20 mg n (%)	Tafamidis 80 mg n (%)	Pooled tafamidis n (%)	Placebo n (%)
Assigned to study treatments	88	176	264	177
Treated:	[redacted]	[redacted]	264 (100.0)	177 (100.0)
Completed[a]	[redacted]	[redacted]	173 (65.5)	85 (48.0)
Discontinued[b]**:**	[redacted]	[redacted]	52 (19.7)	54 (30.5)
Protocol violation	[redacted]	[redacted]	1 (0.4)	1 (0.6)
Lost to follow-up	[redacted]	[redacted]	1 (0.4)	0
No longer willing to participate in study	[redacted]	[redacted]	25 (9.5)	37 (20.9)
Other:	[redacted]	[redacted]	[redacted]	[redacted]
Organ transplantation	[redacted]	[redacted]	6 (2.3)	5 (2.8)
Cardiac mechanical assist device implantation	[redacted]	[redacted]	2 (0.8)	0
Discontinuation due to adverse events[c]:	[redacted]	[redacted]	17 (6.4)	11 (6.2)
Related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]
Not related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Analysed for efficacy:				
Intention-to-treat analysis set	[redacted]	[redacted]	264 (100.0)	177 (100.0)
Per protocol analysis set	[redacted]	[redacted]	[redacted]	[redacted]
Analysed for safety[d]**:**	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events[e]	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory data[f]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The number of patients completed is derived from the patient summary electronic case report form.
[b]All assessments where the relation to study drug was not defined. Discontinued from study other than death.
[c]Relationship is determined by investigator's assessment of relationship to study treatment on the adverse event CRF page. It includes all patients who died or had transplantation or cardiac mechanical assist device.
[d]Analysed for safety tabulates the number of patients treated.
[e]Adverse events tabulates the number of patients who have reported an adverse event.
[f]Laboratory data tabulates the number of patients who have at least 1 lab result.
Source: Clinical Study Report (B3461028)[73]

B.2.6.2 Results (ATTR-ACT pivotal study)

Overall, 441 participants were randomised and all met the criteria for the ITT and the safety analysis sets. The results of ATTR-ACT are presented below for the ITT population. ATTR-ACT demonstrates that tafamidis is a breakthrough treatment on many levelsregards as it is the first time a medical treatment has been shown to:

- Reduce mortality and morbidity in ATTR-CM.[90]
- Reduce all-cause mortality and CV-related hospitalisations in patients with HFpEF.[91]
- Be effective on endpoints of all-cause mortality and CV-related hospitalisation through acting centrally (on the myocardium), rather than acting peripherally or by neurohormonal modulation[92]

Overview of ATTR-ACT efficacy results

- Patients treated with tafamidis showed statistically significant and clinically meaningful treatment benefits compared with the placebo group:
  - In the primary analysis (all-cause mortality and the frequency of cardiovascular hospitalisations) (p=0.006)
  - For both all-cause mortality (HR, 0.70; 95% CI, 0.51 to 0.95; p=0.0259) and CV-related hospitalisation (RR, 0.67 95% CI, 0.56, 0.81; p<0.0001) when analysed separately.
- Tafamidis was also associated with statistically significant benefits in key secondary and exploratory endpoints:
  - CV-related mortality (HR 0.69, 95% CI, 0.4, 0.98; p=0.0383)
  - Cardiac function measured by change from baseline to Month 30 in 6MWT (76 metre difference; p<0.0001) and NT-proBNP ([redacted])
  - Change from baseline to Month 30 in health-related quality of life by KCCQ-OS score ([redacted]), EQ-5D-3L index score ([redacted]) and EQ-5D VAS ([redacted])
  - TTR stabilisation at Month 1 ([redacted])
- Patients treated with tafamidis were more likely to maintain or improve their NYHA class than the placebo group. It is a statistically significant predictor of both HRQoL and survival.[63] [64,65]

- Patients treated with tafamidis in ATTR-ACT and then continued tafamidis treatment in the extension study experienced a greater than [redacted]% reduction in death compared to those in the placebo arm of ATTR-ACT who switched to tafamidis in the extension study.

B.2.6.2.1 Primary analysis

A summary of the key outcomes from ATTR-ACT is provided in Table 18. Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisations in the overall ITT population showed a significant treatment effect favouring tafamidis (p=0.0006).

Table 18. ATTR-ACT: Mortality, CV-related hospitalisations, and Finkelstein-Schoenfeld analysis of all-cause mortality and CV-related hospitalisations

	Pooled Tafamidis (N=264)	Placebo (N=177)
All-cause mortality		
Number of all-cause mortality[a], n (%)	78 (29.5)	76 (42.9)
Hazard ratio[b] (95% CI)	0.70 (0.51, 0.96)	-
p-value	0.0259	-
CV-related mortality		
Number of CV-related events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	-
p-value	[redacted]	-
CV-related hospitalisations		
Total number of patients with CV-related	138 (52.3)	107 (60.5)
Frequency of CV-related hospitalisation (95%	0.48 (0.42, 0.54)	0.70 (0.62, 0.80)
Relative risk ratio (95% CI)	0.68 (0.56, 0.81)	-
p-value	<0.0001	-
Finkelstein-Schoenfeld analysis[c]		
Number of patients alive, n (%)	186 (70.5)	101 (57.1)
Average frequency of CV-related	0.297	0.455
p-value	0.0006	-

[a] Heart transplantation and combined heart and other organ transplantation or for implantation of a cardiac mechanical assist device are handled in the same manner as death.
[b] Hazard ratio from a Cox proportional hazards model with TTR genotype and NYHA baseline classification in the model.
[c] The Finkelstein-Schoenfeld test is a hierarchical comparison of mortality and frequency of CV-related hospitalisations. The primary comparison tests if at least 1 and possibly both all-cause mortality and frequency of CV-related hospitalisations are different between the tafamidis and placebo treatment groups.
Abbreviations: CI: confidence interval; CV: cardiovascular; N: total number of patients; n: number of patients; SD: standard deviation.
Source: Clinical Study Report (B3461028).[73]

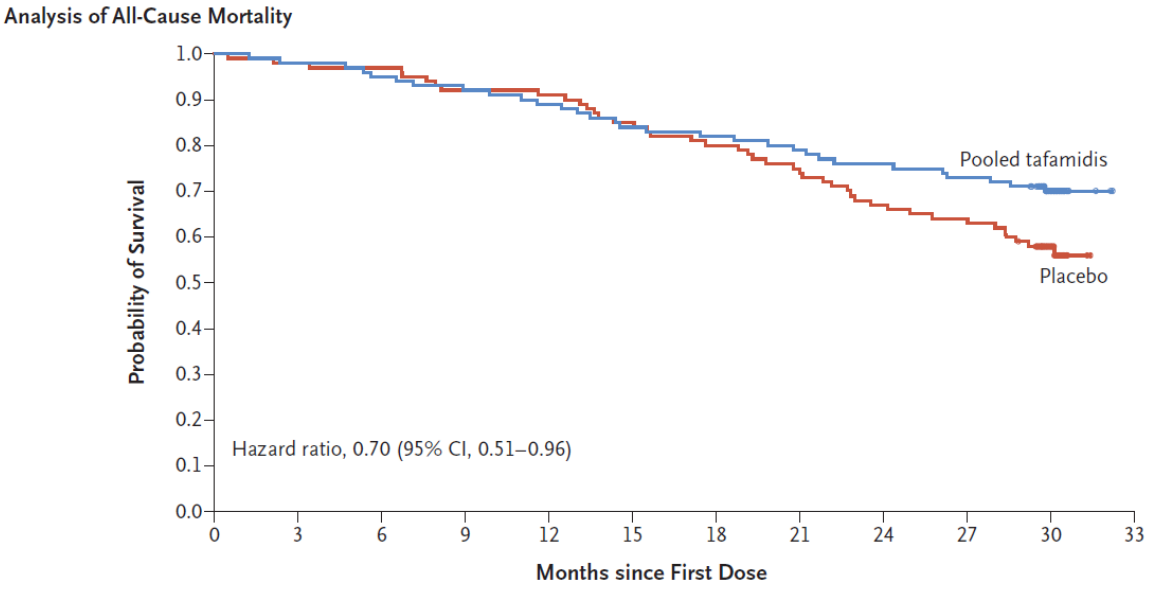
B.2.6.2.2 All-cause mortality, CV-related mortality and CV-related hospitalisation

All-cause mortality

The two components of the Finkelstein-Schoenfeld analysis, all-cause mortality and frequency of CV-related hospitalisation were analysed separately (secondary endpoints).

Overall, all-cause mortality events were observed in 78 (29.5%) and 76 (42.9%) participants for the pooled tafamidis and placebo groups, respectively. There were 186 (70.5%) and 101 (57.1%) participants in the pooled tafamidis and placebo groups, respectively, censored because they were alive at the time of analysis. The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis was 0.698 (95% CI 0.508, 0.958), indicating a 30.2% reduction in the risk of death relative to the placebo group (p=0.0259). The observed effect on overall survival emerged after approximately 18 months of treatment (Figure 13).

Figure 13. ATTR-ACT: Kaplan-Meier plot of CV-related mortality in patients receiving pooled tafamidis or placebo (ITT population)



Source: Maurer et al. 2018

CV-related mortality

Overall, cardiovascular-related mortality for pooled tafamidis and placebo groups was observed in [redacted] ([redacted]) and [redacted] ([redacted]) partcipants, respectively. There were [redacted] ([redacted]) and

[redacted] ([redacted]) participants in the pooled tafamidis and placebo groups, respectively, who were censored. Participants in the pooled tafamidis and placebo groups were censored because they were alive at the time of analysis (186 [70.5%] and 101 [57.1%] participants, respectively) and deaths for all other reasons ([redacted] [redacted] and [redacted] [redacted] participants, respectively). The hazard ratio from the cardiovascular-related mortality Cox-proportional hazard model was [redacted] (95% CI [redacted], [redacted]), indicating a [redacted] reduction in the risk of cardiovascular-related death in the pooled tafamidis group relative to the placebo group (p[redacted]).

Figure 14. ATTR-ACT: Kaplan-Meier plot of CV-related mortality in patients receiving pooled tafamidis or placebo (ITT population)

[redacted]

Source: Clinical Study Report (B3461028)[73]

CV-related hospitalisations

In the overall ITT population, the treatment difference (relative risk ratio) between the pooled tafamidis and placebo groups was 0.676, indicating a 32.4% reduction in the risk of CV-related hospitalisation in the tafamidis group relative to placebo (p<0.0001) (Table 18).[73]

B.2.6.2.3 Cardiac function

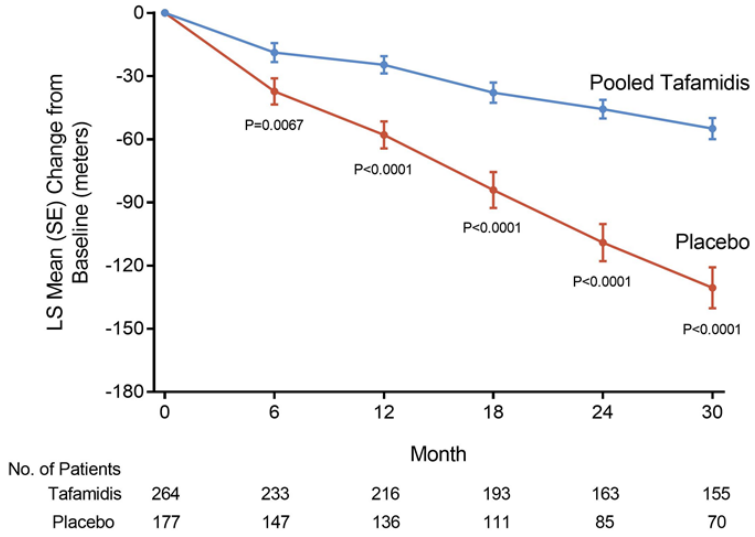
6MWT

Functional capacity was assessed using the 6MWT. The 6MWT was tested first in a pre-specified sequence (with KCCQ-OS score tested second) to maintain an overall bound on Type I error probability of 0.05.[31]

A significant treatment effect favouring tafamidis was observed from the first assessment at Month 6 and remained significant through Month 30 in all patients (Figure 15). Table 19 shows,

at Month 30, tafamidis reduced the decline in the 6-minute walk test distance compared to placebo (75.7 meters [SE=9.2, P<0.0001]); these significant results were first observed at Month 6.[73]

Figure 15. ATTR-ACT: Change from baseline in distance walked during the 6MWT (ITT population)



Note: Shows the least squares (LS) mean (±SE) change from baseline to Month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. I bar indicate standard errors.
Source: Clinical Study Report (B3461028)

Table 19. ATTR-ACT: Change from baseline to Month 30 in the distance walked during the 6MWT baseline classification (ITT population)

	Pooled Tafamidis (N=264)	Placebo (N=177)
Distance walked at baseline in metres, mean (SD)	350.6 (121.3)	353.3 (126.0)
Change from baseline to Month 30 in metres, mean	-30.5 (87.9)	-89.7 (105.2)
LS[a] mean (SE) difference (versus placebo)	75.7 (9.2)	
p-value	<0.0001	

Least squares mean is from an ANCOVA (MMRM) model with an unstructured covariance matrix.
Abbreviations: 6MWT: 6-minute walk test; LS: least squares; N: total number of patients; n: number of patients; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).[73]

NYHA Classification

Overall, a greater percentage of patients in the tafamidis group improved upon or remained in their respective NYHA baseline classifications compared with those in the placebo group.

In the pooled tafamidis group, [redacted], [redacted], and [redacted] patients remained at their NYHA baseline classification of NYHA Class I, II, and III, respectively, at Month 30. In

the placebo group, [redacted], [redacted], and [redacted] patients remained at their NYHA baseline classification of NYHA Class I, II, and III, respectively at Month 30 (Figure 16).

For participants in the pooled tafamidis group with a baseline classification of Class II, [redacted] participants improved to Class I and [redacted] worsened to Class III at Month 30. For participants in the placebo group with a baseline classification of Class II, [redacted] participants improved to Class I, while [redacted] and [redacted] participants worsened to Class III and IV, respectively at Month 30.

Figure 16. ATTR-ACT: NYHA classification shift from baseline to Month 30 (ITT population)

Note: Green cells indicates the proportion of patients that improved or remained in their respective NYHA classification. Blue cells indicate the proportion of patients that worsened in their NYHA classification at Month 30. N is the number of patients with both baseline and post-baseline visit results.
Source: Clinical Study Report (B3461028).[73]

NT-proBNP

Elevated concentrations of NT-proBNP are unfavourable in patients with heart failure, and have been shown to independently predict mortality in ATTR-CM.[23,73]In the overall ATTR-ACT ITT population, patients receiving tafamidis experienced a significant treatment benefit in NT-proBNP concentration compared to the placebo group. The LS mean Month 30 change from baseline difference from the placebo group was [redacted] for the pooled tafamidis group. (Table 21).

Table 20. ATTR-ACT: Change from baseline to Month 30 in NT-proBNP (ITT population)

NT-proBNP (pmol/L)	Pooled Tafamidis (N=264)	Placebo (N=177)
Baseline		
n	264	177
Mean (SD)	[redacted]	[redacted]
Month 30		
n	170	80
Mean (SD)	[redacted]	[redacted]
Month 30 - change from baseline		
n	170	80
Mean (SD)	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]
LS mean (SE) difference from placebo	[redacted]	
95% CI of difference	[redacted]	
p-value	[redacted]	

Abbreviations: CI: confidence interval; ITT: intention-to-treat; LS: least squares; N: total number of participants; n: number of participants; NT-proBNP: N-terminal pro-brain natriuretic peptide; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).[73]

Echocardiographic parameters (ITT population)

In the overall ITT population, directionally positive treatment effects favouring tafamidis were observed at Month 18 in global longitudinal strain [redacted] and at Month 30 in 2-dimensional left ventricular stroke volume [redacted], circumferential mid global strain [redacted] and radial mid-global strain [redacted]. The change from baseline in left ventricular end diastolic interventricular septal wall thickness, left ventricular posterior wall thickness, and left ventricular ejection fraction were similar across the two groups.[73] Echocardiographic findings are summarised in Table 21.[73]

Table 21. ATTR-ACT: Change in echocardiography measures from baseline to Month 30

Echocardiography measure	Pooled Tafamidis (N = 264)	Placebo (N = 177)
Left ventricular end diastolic interventricular septal wall thickness — mm		
Baseline, mean (SD)	16.7 (3.8)	16.2 (3.5)
Change from baseline to Month 30, LS mean (SE)	-0.11 (0.24)	0.33 (0.34)
LS mean (SE) difference from placebo	-0.44 (0.34)	
95% CI of difference	-1.11 to 0.23	
p-value	[redacted]	
Left ventricular posterior wall thickness — mm		
Baseline, mean (SD)	17.0 (3.9)	16.7 (4.1)
Change from baseline to Month 30, LS mean (SE)	0.92 (0.36)	1.19 (0.44)
LS mean (SE) difference from placebo	-0.27 (0.65)	
95% CI of difference	-1.55 to 1.01	
p-value	[redacted]	

Echocardiography measure	Pooled Tafamidis (N = 264)	Placebo (N = 177)
Left ventricular ejection fraction — %		
Baseline, mean (SD)	48.4 (10.3)	48.6 (9.5)
Change from baseline to Month 30, LS mean (SE)	-2.82 (0.85)	-4.34 (1.10)
LS mean (SE) difference from placebo	1.51 (1.06)	
95% CI of difference	-0.57 to 3.60	
p-value	[redacted]	
Left ventricular stroke volume — ml		
Baseline, mean (SD)	45.8 (16.1)	45.1 (16.9)
Change from baseline to Month 30, LS mean (SE)	-5.38 (0.99)	-11.66 (2.09)
LS mean (SE) difference from placebo	6.28 (2.20)	
95% CI of difference	1.96 to 10.59	
p-value	[redacted]	
Circumferential mid global strain — %		
Baseline, mean (SD)	-16.4 (8.6)	-16.8 (9.6)
Change from baseline to Month 30, LS mean (SE)	-0.77 (0.65)	1.91 (0.65)
LS mean (SE) difference from placebo	-2.67 (0.78)	
95% CI of difference	-4.20 to -1.15	
p-value	[redacted]	
Radial mid global strain — %		
Baseline, mean (SD)	17.8 (11.0)	17.6 (10.4)
Change from baseline to Month 30, LS mean (SE)	0.25 (0.77)	-3.28 (1.18)
LS mean (SE) difference from placebo	3.53 (1.29)	
95% CI of difference	1.00 to 6.06	
p-value	[redacted]	
Global longitudinal strain — %		
Baseline, mean (SD)	-9.3 (3.5)	-9.4 (3.6)
Change from baseline to Month 30, LS mean (SE)	1.46 (0.28)	2.16 (0.33)
LS mean (SE) difference from placebo	-0.70 (0.37)	
95% CI of difference	-1.43 to 0.02	
p-value	[redacted]	

Abbreviations: CI: confidence interval; LS: least square; SD: standard deviation; SE: standard error.
Source: Maurer et al. 2018[31], Clinical Study Report (B3461028)[73]

B.2.6.2.4 TTR stabilisation

In the overall ATTR-ACT population (ITT), pharmacodynamic testing at Month 1 showed stabilisation of the TTR protein in [redacted] of patients in the pooled tafamidis group and [redacted] of those in the placebo group [redacted], as shown in Figure 17.[73] This pattern remained consistent through to Month 30 [redacted].[73]

Figure 17. ATTR-ACT: TTR stabilisation at Month 1

Abbreviations: TTR: transthyretin.
Source: Clinical Study Report (B3461028)[73]

B.2.6.2.5 Health-related quality of life

KCCQ-OS

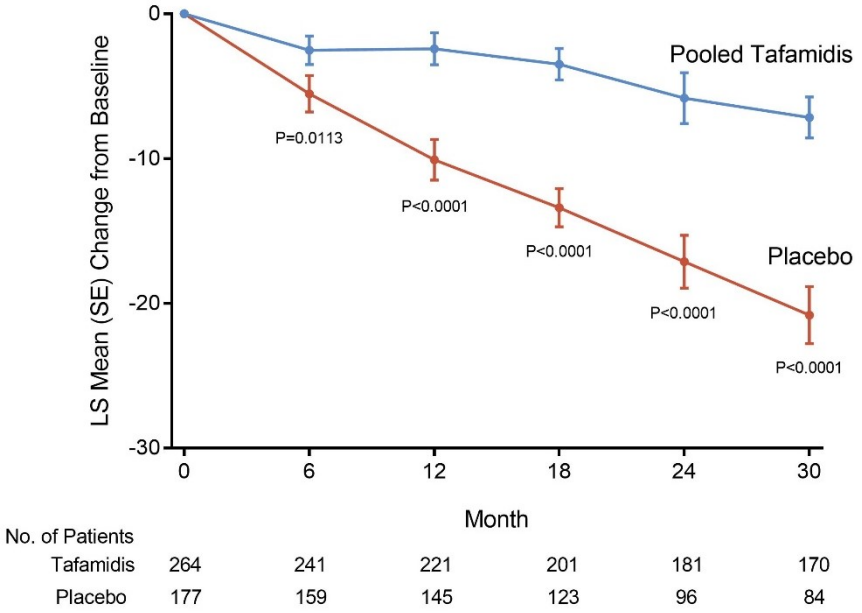
Change from Baseline to Month 30 in the KCCQ-OS score for the ITT analysis set is provided in Table 22 and Figure 18, which show tafamidis reduced the decline at Month 30 compared to placebo (LS mean difference 13.7 [SE=2.1, P<0.0001]). Significant results were first observed at Month 6 and remained significant through Month 30.

Table 22. ATTR-ACT: Change from baseline to Month 30 in the KCCQ-OS

	Pooled Tafamidis (N=264)	Placebo (N=177)
KCCQ-OS at baseline[a]	67.3 (21.4)	65.9 (21.7)
Change from baseline to Month 30 in KCCQ-	-3.9 (19.3)	-14.6 (21.4)
LS[b] mean (SE) difference (versus placebo)	13.65 (2.13)	
p-value	<0.0001	

Least squares mean is from an ANCOVA (MMRM) model with an unstructured covariance matrix.
Abbreviations: 6MWT: 6-minute walk test; LS: least squares; N: total number of patients; n: number of patients; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).[73]

Figure 18. ATTR-ACT: Change from baseline in KCCQ-OS (ITT population)



Abbreviations: LS = least squares; SE = standard error.
Source: Clinical Study Report (B3461028).[73]

B.2.6.2.6 EQ-5D-3L index score and VAS scores

In the overall ITT population, patients treated with tafamidis experienced [redacted] in EQ-5D-3L index scores over 30 months, compared to patients treated with placebo (Table 23).[73] [redacted].[73]

Patients treated with tafamidis [redacted] in EQ-5D-3L VAS scores over 30 months compared with the placebo group (Table 23).[73] [redacted].[73]

Table 23. ATTR-ACT: Change from baseline to Month 30 in the EQ-5D-3L and VAS scores (ITT population)

	Pooled tafamidis (N=264)	Placebo (N=177)
EQ-5D-3L index score		
Baseline		
n		
Mean (SD)		
Month 30		
n		
Mean (SD)		
Month 30 - change from baseline		
n		
Mean (SD)		
LS mean (SE)		
LS mean (SE) difference from placebo		
95% CI of difference		
p-value		
EQ-5D-3L VAS score		
Baseline		
n		
Mean (SD)		
Month 30		
n		
Mean (SD)		
Month 30 - change from baseline		
n		
Mean (SD)		
LS mean (SE)		
LS mean (SE) difference from placebo		
95% CI of difference		
p-value		

Abbreviations: CI: confidence interval; EQ-5D-3L: EuroQoL-5 Dimensions 3-level; ITT: intention-to-treat; LS: least squares; N: total number of participants; n: number of participants; NYHA: New York Heart Association Classification; SD: standard deviation; SE: standard error; VAS: visual analog scale.
Source: Post-hoc analysis

B.2.6.3 Results (ATTR-ACT extension study)

Available data from the ongoing ATTR-ACT extension study included all-cause mortality, reported from a 15 February 2018 cut-off date. The extension study demonstrates evidence of a [redacted] in the 12 months of additional follow-up beyond the 30-month ATTR-ACT study period. This separation was observed through to the data cut-off for the extension study analysis.[79]

In a pooled analysis combining the parent and extension studies, for a median additional 6 month follow-up period (total of 36 months) patients who received tafamidis in the original study and continued to receive tafamidis in the extension study (i.e. the tafamidis/tafamidis group) had a [redacted]% reduction in risk of death (all-cause mortality) compared to patients who

had received placebo in ATTR-ACT and switched to tafamidis 20 mg or 80 mg in the extension study (placebo/tafamidis group) (p=[redacted]). Results are summarised in Table 24 and the Kaplan-Meier plot is shown in Figure 19.[79]

Table 24. Combined all-cause mortality of ATTR-ACT and ATTR-ACT extension study

	Pooled tafamidis (N=264)	Placebo (N=177)
Number of all-cause mortality[a]	88 (33.3)	89 (50.3)
Number of deaths	[redacted]	[redacted]
Number of heart transplants	[redacted]	[redacted]
Number of cardiac mechanical assist devices	[redacted]	[redacted]
Number censored	[redacted]	[redacted]
Reason for censoring:		
Alive at time of analysis	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]
Versus placebo		
Hazard ratio[a]	0.64	
95% confidence interval of hazard ratio	[0.47, 0.85]	
Log-rank test p-value[c]	[redacted]	

[a] Hazard ratio from a Cox proportional hazards model with treatment and ATTR-CM genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in a model.
[b] Reasons related to breach of eligibility criteria, and patient/family decision to discontinue.
[c] 2-sided maximum likelihood p-value from a Cox proportional hazards model with treatment and ATTR genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in a model.
Patients who discontinue for transplantation (i.e. heart or any heart-combo transplantation) or for implantation of a cardiac mechanical assist device were handled in the same manner as death.
Source: B3461045 (data on file).[79]

Figure 19. Kaplan-Meier plot of all-cause mortality- combined ATTR-ACT and ATTR-ACT extension study

Source: B3461045 (data on file).[79]

B.2.6.4 Further supporting evidence for tafamidis

B.2.6.4.1 Phase II study

Data from the Phase II study[80] were not used in the economic model but provide supportive evidence of efficacy and safety and have been provided for completeness.

Tafamidis was assessed in an open-label, multicentre, single-treatment, 12-month Phase II study (NCT00694161).[80] The study determined TTR stabilisation (primary endpoint), safety and tolerability, and other clinical outcomes in patients with ATTR-CM receiving tafamidis. Patients with wild-type ATTR-CM (n = 31) or hereditary ATTR-CM (Val122Ile; n = 4) were enrolled and treated with 20 mg tafamidis QD for 6 weeks, then continued taking daily oral tafamidis 20 mg for up to 12 months.[80]

Participants had a median age of 76 years and median disease duration of 5 years. Most participants (94%) had a baseline NYHA classification of I or II at enrolment. [80]

- Tafamidis effectively stabilised TTR in 97.1% of ATTR-CM patients (both wild-type and hereditary) at Week 6, with approximately 88% stabilised throughout the 12 months.[80]
- In the course of 12 months treatment with tafamidis, in addition to receiving BSC, 2/35 patients (6%) died, 9/35 (26%) experienced at least 1 CV-related hospitalisation, and 9/35 (26%) experienced the composite endpoint of death or CV-related hospitalisation.[80]
- Overall, patients reported preserved health related quality of life was preserved with minimal changes in KCCQ, PGA and Short Form 36 scores. Change in functional walking ability as determined by the 6MWT was minimal with the mean distance walked decreasing by 8.9 metres from baseline to Month 12.[80]
- 20/28 (71%) of patients with available data demonstrated preserved NYHA classification status.
- NT-proBNP levels did not increase significantly over time and no consistent clinically relevant changes were seen in echocardiographic cardiac assessments.[80]

B.2.6.4.2 Post-hoc analysis: Phase II versus TRACS

Patients from the Phase II study were compared with patients in the observational, non-interventional TRACS study in a combined post-hoc analysis (baseline characteristics shown in Figure 32).[82]

Patients in TRACS with wild-type ATTR-CM (n = 18) and hereditary ATTR-CM (Val122Ile; n = 11) were treated with BSC only and served as a control group. The analysis was restricted to include patients with NYHA Class I/II only, to improve comparability of the two cohorts.[82]

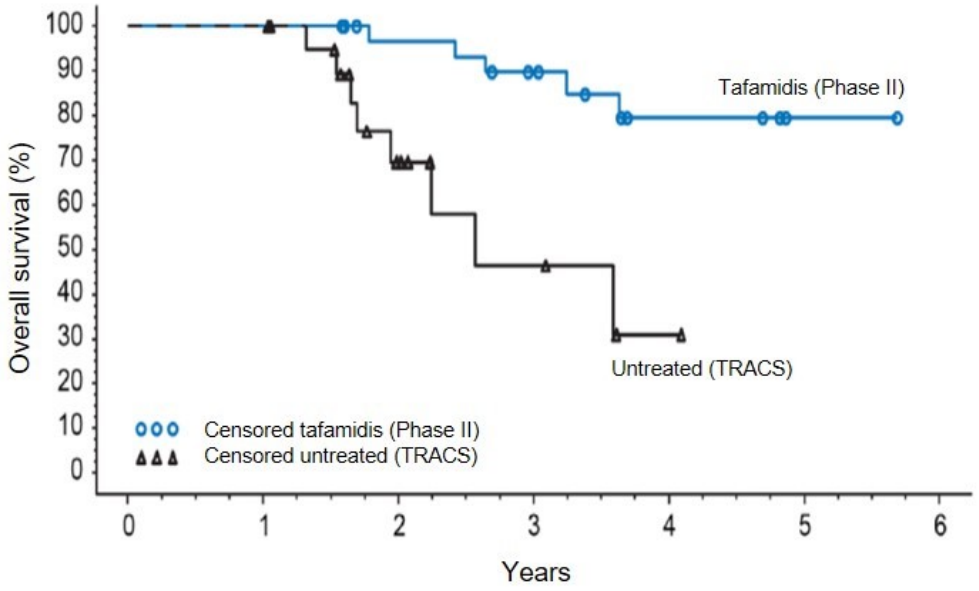
- There was a significant improvement (p=0.0004) in survival for patients treated with tafamidis compared with BSC over the long-term follow-up (Figure 20).[82]
- Improvements in additional outcomes over 12 months were also observed in patients treated with tafamidis in the Phase II compared to patients in the TRACS study. These observations included fewer CV-related hospitalisations, stabilisation of cardiac function (as assessed by cardiac biomarkers), more favourable results from echocardiographic and cardiac MRI testing, and better functional status.
- These results suggest that tafamidis slows disease progression and improves survival compared with BSC among patients in an early stage of disease defined by NYHA I/II functional status.

Table 25. Baseline characteristics of patients in Phase II study and TRACS

	Phase II (N=35)[80]		TRACS (N=29)[48]	
	Wild-type (n=31)	Hereditary (Val122Ile) (n=4)	Wild-type (n=18)	Hereditary (Val122Ile) (n=11)
Mean age (SD), years	76.9 (4.6)	72.8 (3.4)	75.5 (5.6)	71.1 (5.0)
Mean age at TTR-CM symptom onset (SD), years	73.6 (5.3)	69.3 (2.5)	72.7 (5.4)	69.5 (5.6)
Mean age at TTR-CM diagnosis (SD), years	75.0 (4.9)	71.5 (3.1)	74.8 (5.7)	70.3 (5.6)
Sex, n (%) male	93.5	75.0	100.0	81.8
Race, n (%) African American	0.0	75.0	0.0	100.0
NYHA functional classification ≥III, n (%)	1 (3.2)	1 (25.0)	4 (22.2)	3 (27.3)
Duration of TTR-CM–related symptoms (SD), months	94.8 (97.5)	74.5 (34.2)	35.4 (33.6)	21.6 (17.8)
Mean NT-pro-BNP (SD), pg/mL	4910 (4465)	5318 (343) n=2	4524 (2958) n=11	4762 (4117) n=10
Mean left ventricular posterior wall thickness (SD), mm	20.3 (3.5) n=30	19.5 (3.1)	19.3 (3.3)	18.0 (2.6)
Left ventricular ejection fraction, n (%)	47.8 (13.9) n=30	39.0 (15.0)	59.0 (11.5)	50.4 (12.3)

Note: Sample sizes are provided where patient data are missing.
Abbreviations: NT-pro-BNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; TRACS: Transthyretin Amyloidosis Cardiac Study; TTR-CM: transthyretin cardiomyopathy; Val122Ile: valine to isoleucine substitution at position 122.
Source: Sultan et al. 2017.[82]

Figure 20. Time to mortality for patients (NYHA Class I or II) treated with tafamidis in addition to BSC or BSC alone



Source: Sultan et al. 2017[82]

B.2.6.4.3 Phase II extension study

The Phase II extension study is an open-label study designed to obtain additional, long-term, safety data for tafamidis in patients with ATTR-CM, and to continue to provide 20 mg oral tafamidis to patients who completed the Phase II study.[83] Adverse events and concomitant medication use are collected at each 6-month clinic visit. ECGs are performed every 12 months.[83]

The study was initiated in September 2009. Of the 31 patients enrolled, 5 were ongoing as of the cut-off date of 15 February 2018. These patients had advanced disease, and the available efficacy data were limited and descriptive.[83]

As of 01 August 2017, [redacted] deaths had occurred in the Phase II extension study.[83] [redacted]

[redacted][83]

B.2.7 Subgroup analysis

Summary

- Pre-specified subgroups in ATTR-ACT were TTR genotype (wild-type versus hereditary) and baseline NYHA class (I or II versus III).
- Additional pre-specified analyses compared 20 mg tafamidis and placebo, and 80 mg tafamidis and placebo.
- The difference in all-cause mortality, CV mortality and CV-related hospitalisation favoured tafamidis over placebo across all pre-specified subgroups, except in patients with NYHA class III at baseline, among whom the rates of CV-related hospitalisations were higher in the tafamidis group relative to placebo.[73] This is thought to relate to a greater number of patients living in a more advanced disease state in the tafamidis group as a result of the survival benefit.
- Tafamidis reduced the decline in distance walked during the 6MWT and the KCCQ-OS score in all pre-specified subgroups compared with placebo.[73]

Pre-planned subgroup analyses for the ATTR-ACT trial were performed to assess the effect of TTR genotype (wild-type and hereditary) and NYHA baseline classification (class I and II combined and class III). Importantly:

- Subgroups were not powered to assess the effect of each subgroup on the study endpoints and, therefore, all analyses undertaken were exploratory and not controlled for Type 1 errors.[73]
- For TTR genotype and NYHA class, comparisons were made between pooled tafamidis (20 mg and 80 mg combined) and placebo for each subgroup.[73]

This section describes subgroup analyses related to stratification factors, NYHA baseline classification and TTR genotype (wild-type and hereditary). Dosing analyses comparing 20 mg tafamidis and placebo, and 80 mg tafamidis and placebo, are also presented.

B.2.7.1 Stratification factors

B.2.7.1.1 Primary analysis

NYHA baseline classification

Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisations in the NYHA I/II patients [redacted] (p=0.78) [redacted] Table 26, Figure 21).[73]

Table 26. ATTR-ACT: Finklestein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisations by NYHA baseline classification

	NYHA class I/II (N=300)		NYHA class III (N=141)	
	Pooled tafamidis (N=186)	Placebo (N=114)	Pooled tafamidis (N=78)	Placebo (N=63)
Number of patients alive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Average frequency of CV-related hospitalisations during 30 months (per year) among those alive at Month 30.	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		0.78	

Abbreviations: NYHA: New York Heart Association; N: total number of patients; n: number of patients.
Source: Clinical Study Report (B3461028).73

TTR genotype

In the primary analysis, a significant treatment effect favouring tafamidis was observed in wild-type patients ([redacted]). A significant treatment effect was not observed between pooled tafamidis and placebo among patients with hereditary ATTR-CM (p=0.30) although this was directionally favourable in the tafamidis group (Table 27).[73] The patient numbers in the hereditary subgroup were small and so caution should be applied in interpreting the results.

Table 27. ATTR-ACT: Finklestein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisations by TTR genotype

	Wild-Type (N=335)		Variant (N=106)	
	Pooled tafamidis (N=201)	Placebo (N=134)	Pooled tafamidis (N=63)	Placebo (N=43)
Number of patients alive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Average frequency of CV-related hospitalisations during 30 months (per year) among those alive at Month 30.	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		[redacted]	

Abbreviations: NYHA: New York Heart Association; N: total number of patients; n: number of patients.
Source: Clinical Study Report (B3461028).73

B.2.7.1.2 All-cause mortality and CV-related hospitalisations

The difference in all-cause mortality and frequency of cardiovascular-related hospitalisations favoured tafamidis over placebo across all pre-specified subgroups, including those based on TTR status (wild-type vs. hereditary) and NYHA class (I or II vs. III) (Figure 21). The exception was in patients with NYHA III baseline classification, among whom the rates of cardiovascular-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo (Figure 21). This finding may be explained by the fact that patients with a more advanced stage of disease (such as NYHA class III heart failure) who received tafamidis (for whom a subgroup analysis indicated a benefit with respect to mortality) had a longer period of time in which to incur hospitalisations than patients who received placebo.

NYHA baseline classification

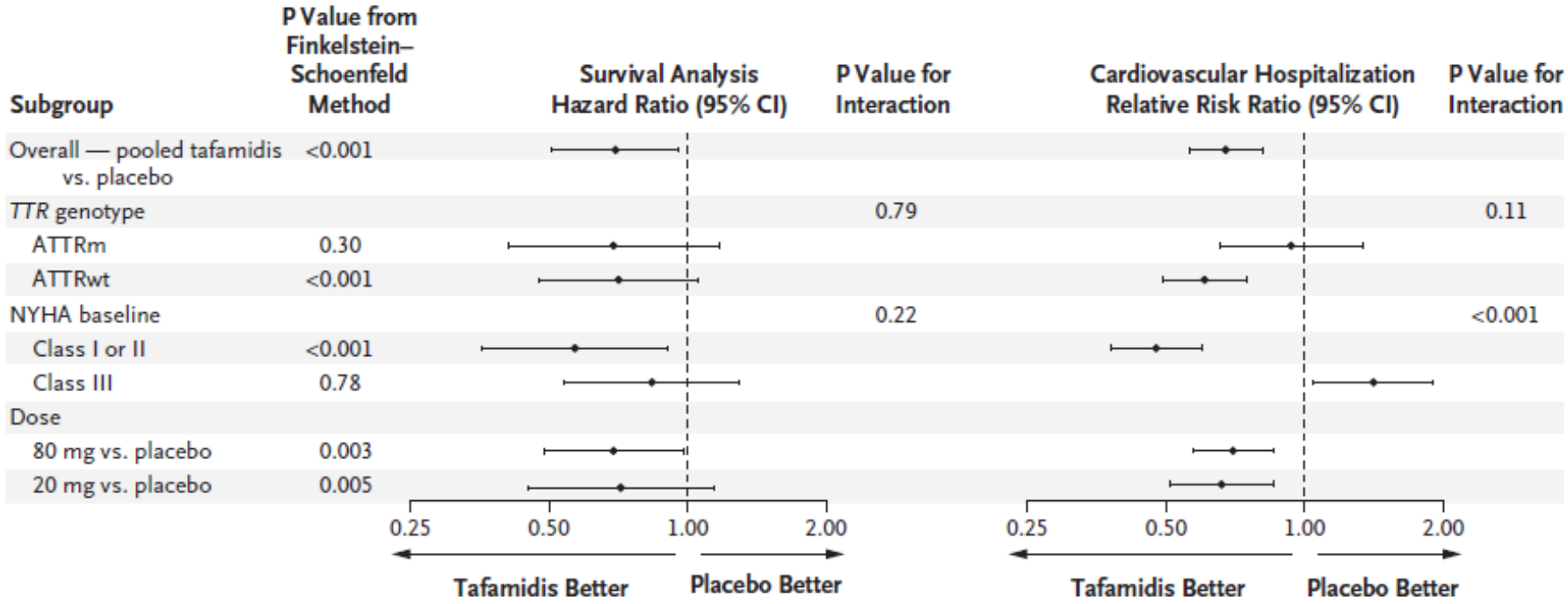
Patients with NYHA Class I/II baseline classification treated with tafamidis had significantly lower all-cause mortality at Month 30 compared to the placebo group ([redacted] vs. [redacted]). The hazard ratio indicated a 43.0% reduction in the risk of death with tafamidis relative to placebo (HR, 0.57; 95% CI, 0.36 to 0.90; P=0.017)**.**[31,73] Patients with NYHA III baseline classification treated with tafamidis also had lower all-cause mortality at Month 30 compared to the placebo group ([redacted] vs. [redacted], (HR, [redacted]; 95% CI, [redacted]; [redacted]**.**[31,73]

The relative risk ratios for CV-related hospitalisation between NYHA I/II and NYHA III participants in the pooled tafamidis group and the placebo group were [redacted] (95% CI [redacted]) and [redacted] (95% CI [redacted]), respectively ([redacted] and [redacted], respectively).

TTR genotype

When analysed separately, differences in all-cause mortality and CV-related hospitalisation favoured tafamidis over placebo in all subgroups by TTR genotype. The hazards ratios from the all-cause mortality Cox-proportional hazard model for variant and wild-type TTR genotype participants in the pooled tafamidis group were 0.690 (95% CI 0.408, 1.167) and 0.706 (95% CI 0.474, 1.052), respectively (p=[redacted] and [redacted], respectively). The relative risk ratios for CV-related hospitalisation between variant and wild-type TTR genotype participants in the pooled tafamidis group and the placebo group were [redacted] (95% CI [redacted]) and [redacted] (95% CI [redacted]), respectively (p=[redacted] and [redacted], respectively).

Figure 21. Overall and subgroup results as calculated with the use of the Finkelstein-Schoenfeld method, all-cause mortality and cardiovascular-related hospitalisations



All-cause mortality was evaluated with the use of a Cox proportional hazards model, with treatment and stratification factors treated as covariates. The survival analysis interaction terms are based on a post-hoc analysis. The frequency of cardiovascular-related hospitalisations was assessed with the use of a Poisson regression model. ATTRm denotes disease that results from an inherited autosomal dominant trait that is caused by pathogenic mutations in TTR (also referred to as hereditary ATTR-CM), ATTRwt disease that results from the deposition of wild-type transthyretin protein (also referred to as wild-type ATTR-CM), and NYHA New York Heart Association.
Source: Maurer et al. 2018.[31]

B.2.7.1.3 Cardiac Function (6MWT)

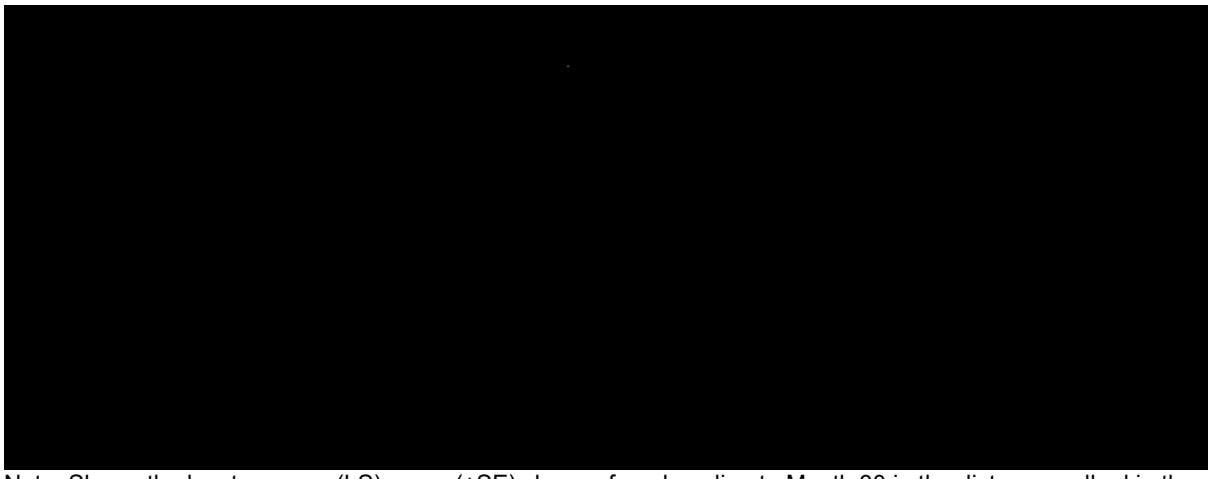
NYHA baseline classification

A significant treatment effect favouring tafamidis was observed from the first assessment at Month 6 and remained significant through Month 30 in patients with NYHA Class I/II baseline classification (Figure 22).[73] In patients with NYHA Class I/II baseline classification, at Month 30, tafamidis reduced the decline in the 6-minute walk test distance ([redacted] meters [SE=[redacted], P[redacted]]); these significant results were first observed at Month 6.[73] A significant treatment effect was observed only at Month 24 ([redacted]) for participants with NYHA Class III baseline classification; however, results were directionally positive at Month 12 through Month 30 (Figure 23).

Figure 22. ATTR-ACT: Change from baseline in distance walked during the 6MWT in patients with NYHA I/II baseline classification (ITT population)

Note: Shows the least squares (LS) mean (±SE) change from baseline to Month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. I bar indicate standard errors.
Source: Clinical Study Report (B3461028)[73]

Figure 23. ATTR-ACT: Change from baseline in distance walked during the 6MWT in patients with NYHA III baseline classification (ITT population)

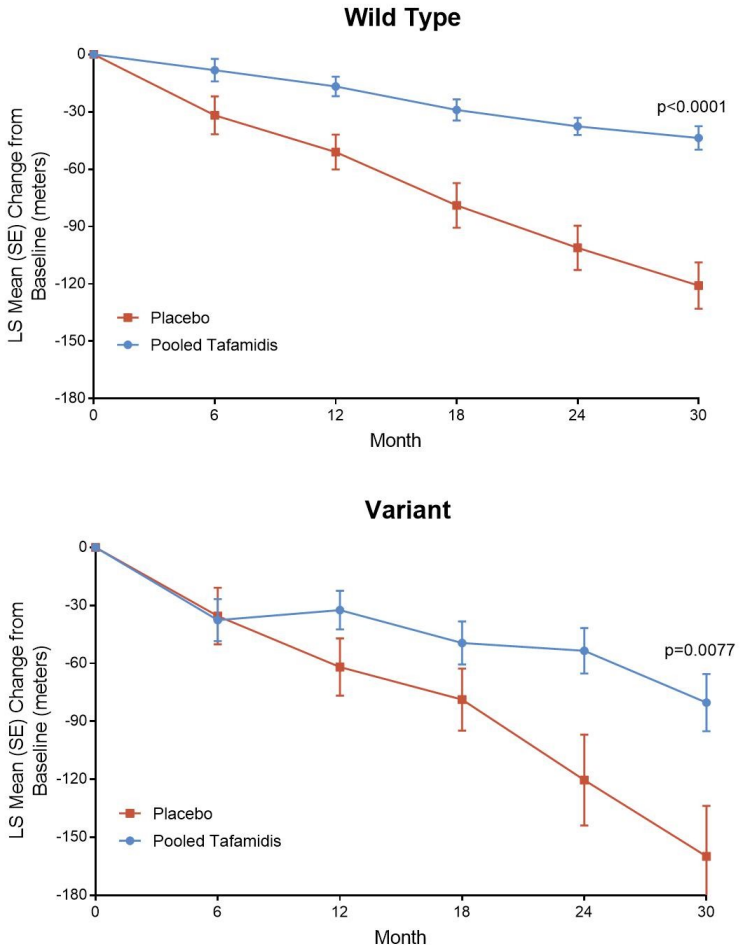


Note: Shows the least squares (LS) mean (±SE) change from baseline to Month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. I bar indicate standard errors.
Source: Clinical Study Report (B3461028)[73]

TTR genotype

In subgroup analysis by genotype, significant treatment effects were first observed at 6 months among wild-type ATTR-CM patients and at 12 months in those with hereditary ATTR-CM, both remained significant through Month 30 (Figure 24).

Figure 24. ATTR-ACT: Change from baseline in distance walked during the 6MWT for patients with wild-type and hereditary ATTR-CM (ITT population)



Note: Shows the least squares (LS) mean (±SE) change from baseline to Month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. I bars indicate standard errors.
Source: Clinical Study Report (B3461028)[73]

B.2.7.1.4 TTR stabilisation

NYHA baseline classification

Both wild-type ATTR-CM and variant ATTR-CM patients who received tafamidis demonstrated significantly greater TTR stabilisation than those who received placebo. At Month 1, a significantly greater proportion of patients in the tafamidis group with NYHA I/II ([redacted]%) or NYHA III ([redacted]%) demonstrated TTR stabilisation than was observed in the placebo group ([redacted]% and [redacted]%, respectively p[redacted]).[93]

TTR genotype

Across TTR genotype subgroups, TTR stabilisation was achieved in a significantly greater proportion of patients receiving tafamidis compared to placebo at Month 1.[73] Both wild-type

ATTR-CM and variant ATTR-CM patients who received tafamidis demonstrated significantly greater TTR stabilisation than those who received placebo. At Month 1, a significantly greater proportion of patients in the tafamidis group with variant ([redacted]) or wild-type ([redacted]) demonstrated TTR stabilisation than was observed in the placebo group ([redacted] and [redacted], respectively [redacted]).[73]

B.2.7.1.5 Health-related quality of life (KCCQ-OS)

NYHA baseline classification

Change from Baseline to Month 30 in the KCCQ-OS score for the ITT analysis set by NYHA baseline classification is provided in Table 28. A significant treatment effect favouring patients with NYHA Class I/II baseline classification was first observed at Month 6 ([redacted]) and remained significant through Month 30 (Figure 25). Significant treatment effects were observed for participants with NYHA Class III baseline classification at months 18 and 30 (p=[redacted] and [redacted], respectively) and were directionally favourable in the tafamidis group from Month 12 through Month 30 (Figure 26).

Table 28. ATTR-ACT: Change from baseline to Month 30 in the KCCQ-OS stratified by NYHA baseline classification

	NYHA class I/II (N=300)		NYHA class III (N=141)	
	Pooled tafamidis (N=186)	Placebo (N=114)	Pooled tafamidis (N=78)	Placebo (N=63)
KCCQ-OS at baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Month 30 in KCCQ-OS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS[b] mean (SE) difference (versus placebo)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

[a]Overall score is calculated as the mean of physical limitation, symptom frequency, symptom burden, quality of life, and social limitation scores.
Least squares means are from an ANCOVA (MMRM) model with an unstructured covariance matrix.
Abbreviations: KCCQ-OS: Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS: least squares; N: total number of participants; n: number of participants; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).[73]

Figure 25. ATTR-ACT: Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary for patients with NYHA Class I/II baseline classification (ITT population)

Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; LS = least squares; MMRM = Mixed Model Repeated Measure; NYHA = New York Heart Associations; SE = standard error; TTR = transthyretin.
Source: Clinical Study Report (B3461028).[73]

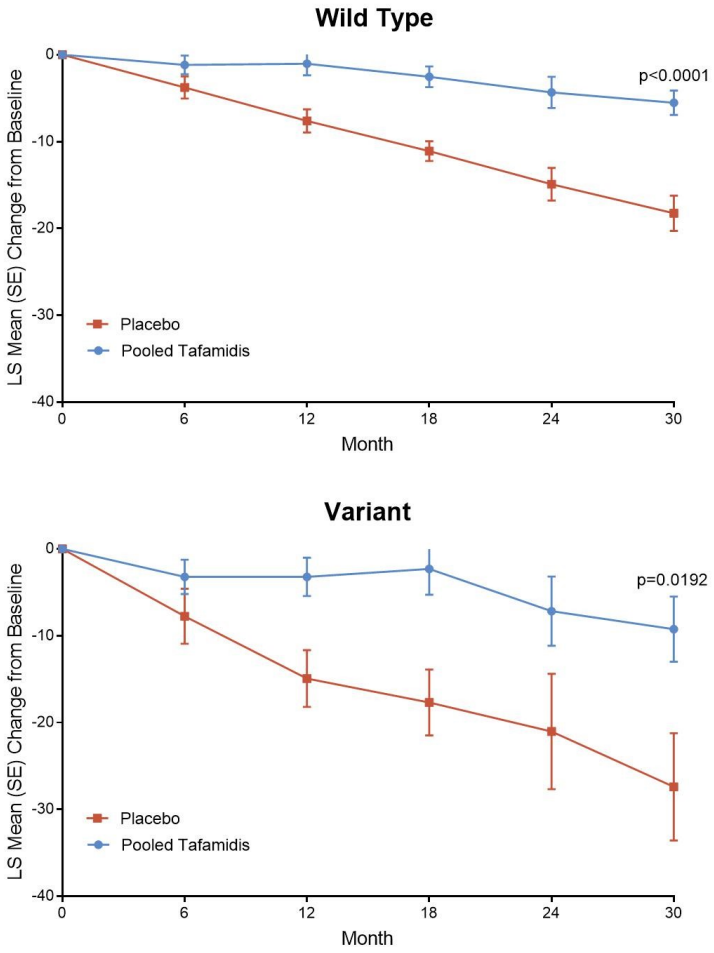
Figure 26. ATTR-ACT: Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary for patients with NYHA Class I/II baseline classification (ITT population)

Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; LS = least squares; MMRM = Mixed Model Repeated Measure; NYHA = New York Heart Associations; SE = standard error; TTR = transthyretin.
Source: Clinical Study Report (B3461028).[73]

TTR genotype

In subgroup analysis by genotype, significant treatment effects were first observed at 12 months in both wild-type and variant ATTR-CM patients, both remained significant through Month 30 (Figure 27).

Figure 27. ATTR-ACT: Change from baseline in KCCQ-OS for patients with wild-type and hereditary ATTR-CM (ITT population)



Abbreviations: LS = least squares; SE = standard error.
Source: Clinical Study Report (B3461028).[73]

B.2.7.2 Dose analysis

ATTR-ACT was powered to assess the safety, efficacy and tolerability of the pooled tafamidis meglumine 20 mg or 80 mg groups in comparison to placebo. It was not powered for dose response; however, a consistent treatment benefit for both doses compared to placebo was observed across all clinical endpoints (described further in this section). A consistent safety profile was also observed between the 2 dose groups that is comparable to placebo.[79]

Differentiation favouring the higher dose was seen post-hoc in ATTR-ACT by greater degree of TTR tetramer stabilisation and reduction in levels of NT-proBNP (accepted prognostic indicator for mortality in ATTR-CM[23,41]) for tafamidis meglumine 80 mg compared with 20 mg.[93] Additionally, [redacted] (further details in

this section).[79] Following CHMP Opinion, any further information to support the submission will be provided.

B.2.7.2.1 Primary analysis

The primary analysis demonstrated a significant treatment benefit with tafamidis across both the 20mg and 80mg doses (p=0.0048 and 0.0030, respectively) (Table 29).

Table 29. ATTR-ACT: Finklestein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisations by tafamidis dose

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Placebo (N=177)
Number of participants alive at Month 30, n (%)	[redacted]	[redacted]	[redacted]
Average CV-related hospitalisations during 30 months (per year) among those alive at Month 30	[redacted]	[redacted]	[redacted]
p-value	0.0048	0.0030	

Abbreviations: CV: cardiovascular; N: total number of patients; n: number of patients.
Source: Clinical Study Report (B3461028).[73]

B.2.7.2.2 All-cause mortality and CV-related hospitalisation

The [redacted] (all-cause mortality: [redacted] reduction for 20 mg dose arm and [redacted] reduction for 80 mg dose; CV-related hospitalisation: [redacted] reduction and [redacted] reduction, respectively).[73]

B.2.7.2.3 Cardiac function (6MWT)

A significant treatment effect favouring both the 20 mg and 80 mg tafamidis doses were first observed at Month 6 ([redacted] and [redacted], respectively) and remained significant through Month 30. The LS mean (SE) differences from placebo for the 20mg and 80 mg tafamidis doses were [redacted] and [redacted] meters, respectively ([redacted] for each dose).

Figure 28. ATTR-ACT: Change from baseline in distance walked during 6MWT by tafamidis dose

Note: Shows the least squares (LS) mean (±SE) change from baseline to Month 30 in the distance walked in the 6-minute walk test in the 20 mg and 80 mg tafamidis subgroups as compared with the placebo group. I bar indicate standard errors.

Source: Clinical Study Report (B3461028)

B.2.7.2.4 Cardiac biomarkers

Results from analyses of NT-proBNP and troponin I levels differentiate between the tafamidis meglumine 20 mg and 80 mg doses.[94] The tafamidis meglumine 20 mg group had a LS mean difference in change from Baseline to Month 30 from placebo of -1417.02 pg/mL (p=0.0571), while the tafamidis meglumine 80 mg group had a larger LS mean difference from placebo of -2587.54 pg/mL (p<0.0001).[94] Further, the LS mean difference between the 20 mg and 80 mg doses was 1170.51 pg/mL which was statistically significant (p=0.0468), favouring the 80 mg dose group.

For troponin I, tafamidis meglumine 20 mg group had a LS mean difference in change from Baseline to Month 30 from placebo of -0.06 ng/mL (p=0.2246), while the tafamidis meglumine 80 mg group had a larger LS mean difference from placebo of -0.10 ng/mL (p<0.0001).[94] The LS mean difference between the 20 mg and 80 mg doses for troponin I was 0.05 (p=0.2479), which was not statistically significant but numerically favoured the 80 mg dose group. These findings suggest an incremental benefit with use of the 80 mg dose over 20 mg.

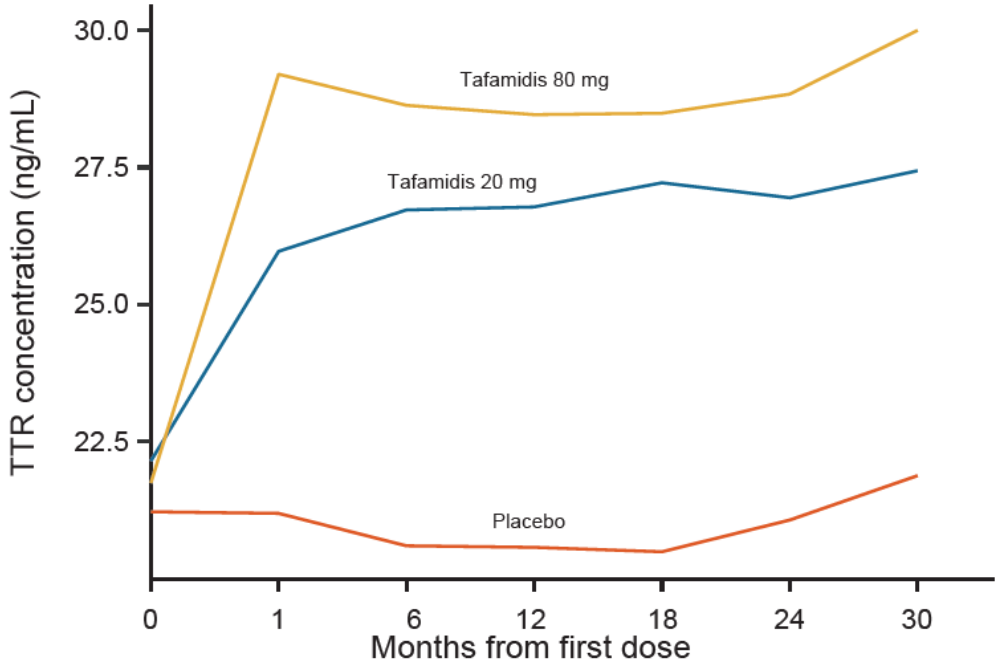
B.2.7.2.5 TTR stabilisation

[redacted] and [redacted] of patients achieved TTR stabilisation in the 20 mg and 80 mg tafamidis groups respectively, compared to [redacted] of placebo-treated patients ([redacted] for both groups).[73] Mean TTR stabilisation percentage was higher with tafamidis 80 mg at Month 12 month ([redacted]) compared with 20 mg ([redacted]) and was consistently higher throughout the duration of the study.[93] Mean TTR concentrations were also higher in the 80 mg treatment

group starting at Month 1 and continuing up to 30 months compared with the 20 mg treatment group.[93]

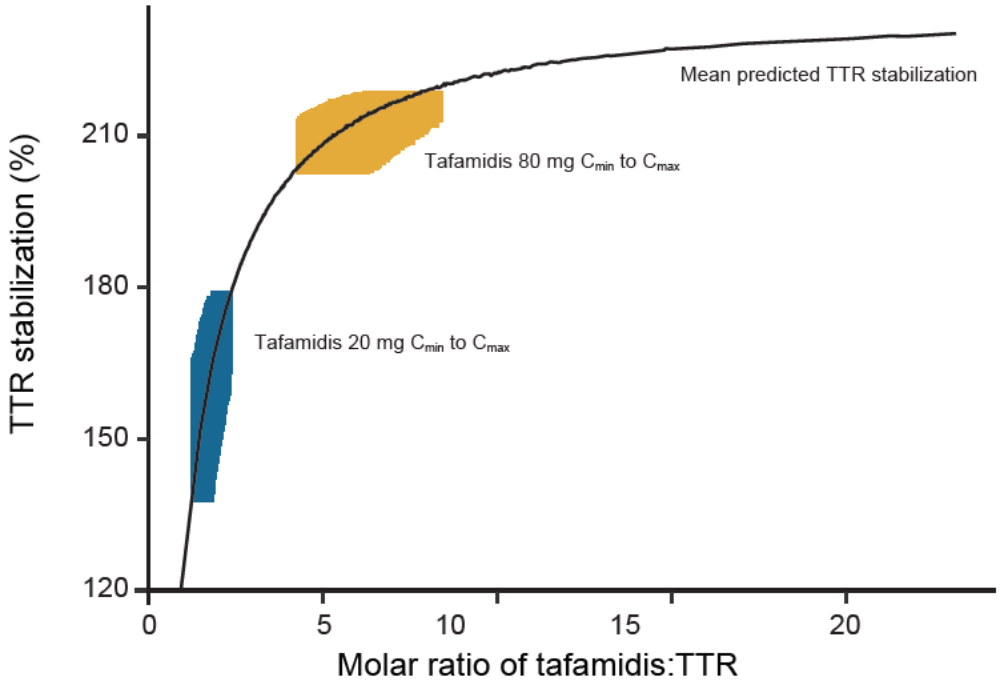
Figure 29 displays the higher mean TTR concentrations in the 80 mg treatment group compared with the 20 mg treatment group, and both were higher than placebo throughout the duration of the study, suggesting the high dose results in more TTR being conserved in its tetramer structure and less dissociated transthyretin being consumed in the amyloidogenic cascade.[94] Figure 30 shows the corresponding greater degree of TTR tetramer stabilisation in 80 mg vs 20 mg in ATTR-ACT.[94]

Figure 29. Mean TTR concentrations in ATTR-ACT



Higher TTR concentrations with tafamidis 80 mg vs 20 mg and vs placebo (and with tafamidis 20 mg vs placebo) suggest the high dose results in more TTR being conserved in its tetramer structure and less dissociated TTR being consumed in the amyloidogenic cascade.
Source: ePharm Artifact ID: RA16368647
Abbreviations: TTR = transthyretin

Figure 30. TTR tetramer stabilisation in ATTR-ACT



The black line represents the mean percentage TTR stabilization in patients with ATTR-CM. The orange-shaded region demonstrates the percentage stabilization expected over the geometric mean steady-state C_{min} to C_{max} following daily administration of tafamidis 80 mg. This approaches the plateau considered to be the target for stabilization. The blue shaded region demonstrates the tafamidis 20 mg steady-state exposures and is well below the stabilization plateau.
Source: ePharm Artifact ID: RA16368647
Abbreviations: C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration.

B.2.7.2.6 Health-related quality of life

A significant treatment effect favouring the 80 mg tafamidis dose was first observed at Month 6 (p=[redacted]) and remained significant through Month 30 (Figure 31). For the 20 mg tafamidis dose, a significant treatment effect favouring tafamidis dose was first observed at Month 12 (p=[redacted]) and remained significant through Month 30. The LS mean (SE) differences from placebo for the 20 mg and 80 mg tafamidis doses were [redacted] and [redacted], respectively ([redacted] for each dose) (Table 33).[73]

Table 30. ATTR-ACT: Change from baseline to Month 30 in the KCCQ-OS stratified by dose

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Placebo (N=177)
KCCQ-OS at baseline[a]	[redacted]	[redacted]	65.9 (21.7)
Change from baseline to Month 30 in KCCQ-OS, mean (SD)	[redacted]	[redacted]	-14.6 (21.4)
LS[b] mean (SE) difference (versus placebo)	[redacted]	[redacted]	-
p-value	[redacted]	[redacted]	-

[a]. Overall score is calculated as the mean of physical limitation, symptom frequency, symptom burden, quality of life, and social limitation scores.
Least squares means are from an ANCOVA (MMRM) model with an unstructured covariance matrix.
Abbreviations: KCCQ-OS: Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS: least squares; N: total number of participants; n: number of participants; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).[73]

Figure 31. ATTR-ACT: Change from baseline in KCCQ-OS by tafamidis dose

Abbreviations: LS = least squares; SE = standard error.
Source: Clinical Study Report (B3461028).[73]

B.2.8 Meta-analysis

The placebo group in ATTR-ACT was treated as BSC, which is reflective of practice in the UK as there are currently no licensed disease-modifying pharmacological treatments for the condition. Direct evidence for the comparative efficacy of tafamidis (in addition to BSC) versus placebo can be drawn from ATTR-ACT so no meta-analysis or indirect comparison were required.

B.2.9 Indirect and mixed treatment comparisons

The only relevant comparator in this appraisal is BSC symptomatic management (i.e. established clinical management without tafamidis). Therefore, no indirect or mixed treatment comparison is required. However, a post-hoc analysis compared survival of patients from the

open-label Phase II study (N=35) with patients from the natural history ATTR-CM study, TRACS (N=29)[82], as described in Section B.2.10.3.1.

B.2.10 Adverse reactions

Summary

- In ATTR-ACT, tafamidis treatment with either 20mg or 80mg doses was safe and well-tolerated, with a similar safety profile to placebo.[31]
- The frequency of TEAEs and serious TEAEs (both treatment-related and non-related) was similar between tafamidis-treated patients and placebo, and between the tafamidis dosing groups.[73]
- Dose reductions were infrequent, occurring in 2 patients receiving tafamidis (0.8%) and 4 patients receiving placebo (2.3%).[31]
- Most treatment-related TEAEs were mild or moderate in severity. The most frequently reported treatment-related TEAEs were diarrhoea, nausea and urinary tract infection (UTI), which were reported in a similar proportion of participants in the tafamidis and placebo groups.[73]
- A greater proportion of deaths were observed in the placebo group compared with the tafamidis group. None of the deaths were related to study treatment, and most were considered to be the result of the disease under study.[73]

Evidence on the safety of tafamidis for the treatment of ATTR-CM is available from the following studies:

- Phase III ATTR-ACT study [31,73]
- Phase III ATTR-ACT extension study: data from the cut-off date of 15 February 2018[79]
- Phase II study[80]
- Phase II extension study: data from the cut-off date of 01 August 2017[83]

B.2.10.1 ATTR-ACT

The safety analysis population (N=441) consisted of all participants who were enrolled in this study and who had taken at least 1 dose of study medication.

B.2.10.1.1 Exposure data and dosing compliance

Duration of treatment and total tafamidis exposure for ATTR-ACT are summarised in Table 31. In the pooled tafamidis group, [redacted] of patients were treated for 24 months or longer, with mean exposure duration of 24.0 months.[73]

Dosing compliance was similar across the treatment groups; [redacted] of patients in the pooled tafamidis group had compliance of [redacted].[73] Dose interruptions due to adverse events were reported in 53 patients (20.1%) in the pooled 20 mg + 80 mg tafamidis group and in 46 patients (26.0%) in the placebo group.[73] Requests for dose reductions due to adverse events were infrequent, and occurred more often in the placebo group (4 patients, 2.3%) than in the pooled tafamidis group (2 patients, 0.8%).[73] Actual dose reductions due to adverse events occurred in [redacted] in the tafamidis 80 mg group, and were for moderate AEs: urinary tract pain and moderate headache, occurring 15 and 113 days after first dose of blinded study medication respectively.

Table 31. ATTR-ACT: Study drug exposure and dosing compliance (safety analysis set)

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Pooled tafamidis (N=264)	Placebo (N=177)
Duration of treatment (months)[a]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Duration category (months) n (%)				
<6 month	[redacted]	[redacted]	[redacted]	[redacted]
6 - <12 month	[redacted]	[redacted]	[redacted]	[redacted]
12 - <18 month	[redacted]	[redacted]	[redacted]	[redacted]
18 - <24 month	[redacted]	[redacted]	[redacted]	[redacted]
24 - <30 month	[redacted]	[redacted]	[redacted]	[redacted]
30 - <36 month	[redacted]	[redacted]	[redacted]	[redacted]
Total amount of Tafamidis (mg)[b]				
Mean (SD)	[redacted]	[redacted]	[redacted]	
Median (range)	[redacted]	[redacted]	[redacted]	
Dosing compliance[c]				
Overall				
<80%	[redacted]	[redacted]	[redacted]	[redacted]
80 – <90%	[redacted]	[redacted]	[redacted]	[redacted]
≥90%	[redacted]	[redacted]	[redacted]	[redacted]

[a]Duration of treatment = (last date of study drug dosing – first date of study drug dosing + 1)/30.4375.
[b]Total amount of tafamidis (mg) = duration of treatment (days)* 20 mg/80 mg. Placebo patients did not receive tafamidis and therefore this variable is not applicable for this group.
[c]Compliance is defined as the total number of tablets actually taken by a subject divided by the number of tablets expected to be taken over treatment period times 100%. Only those safety analysis participants for whom adherence data was available and calculable are used in generating adherence statistics.
Source: Clinical Study Report (B3461028)73

B.2.10.1.2 Summary of adverse events

A summary of AEs is described in Table 32. The incidence of TEAEs in the tafamidis 20 mg, tafamidis 80 mg and placebo groups was similar overall. A higher proportion of patients in the placebo arm (50.8%) reported treatment-related TEAEs than patients in the tafamidis 20 mg ([redacted]) and tafamidis 80 mg arm ([redacted]).[73] The proportion of patients reporting serious TEAEs was moderately higher in the placebo compared to the tafamidis treatment arms.[73] There were no dose reductions due to serious TEAEs in placebo or tafamidis-treated patients. The most frequently reported serious TEAEs (≥15%)[73] were:

- Tafamidis 20 mg: [redacted]
- Tafamidis 80 mg: [redacted]
- Placebo: [redacted]

Table 32. Treatment-emergent adverse events (safety analysis set)

	Tafamidis 20 mg (N=88) n (%)	Tafamidis 80 mg (N=176) n (%)	Pooled tafamidis (N=264) n (%)	Placebo (N=177) n (%)
Treatment-emergent AEs (all causalities)				
Number of TEAEs	[redacted]	[redacted]	3174	2463
Patients with TEAEs	[redacted]	[redacted]	260 (98.5)	175 (98.9)
Patients with treatment-emergent SAEs	[redacted]	[redacted]	199 (75.4)	140 (79.1)
Patients with severe TEAEs	[redacted]	[redacted]	164 (62.1)	114 (64.4)
Patients discontinued drug due to TEAEs	[redacted]	[redacted]	56 (21.2)	51 (28.8)
Patients with dose reduced due to TEAEs	[redacted]	[redacted]	2 (0.8)	4 (2.3)
Patients with temporary discontinuation due to TEAEs	[redacted]	[redacted]	53 (20.1)	46 (26.0)
Treatment-emergent AEs (treatment-related)				
Number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with treatment-emergent SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with severe TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients discontinued drug due to TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with dose reduced due to TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with temporary discontinuation due to TEAEs	[redacted]	[redacted]	[redacted]	[redacted]

Note: Percentages are based on the number of patients in the Safety Analysis Set. Includes events occurring up to 28 days after last dose of study drug. Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 coding dictionary applied.
Abbreviations; N: total number of patients; n: number of patients; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: Clinical Study Report (B3461028)[73]

B.2.10.1.3 All-causalities adverse events

A summary of the incidence of TEAEs (all-causality) is provided in Table 33.

Table 33. ATTR-ACT: Summary of TEAEs events by MedDRA System Organ Class, Preferred Term (All Causalities) with PT ≥5% Incidence (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Placebo N=177 n (%)
[redacted]			

Note: Percentages are based on the number of patients in the safety analysis set. Multiple occurrences of the same adverse event in a subject at the preferred term level or system organ class level are counted as 1 adverse event per treatment in each row. Includes events occurring up to 28 days after last dose of study drug. MedDRA Version 20.1 coding dictionary applied.
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; N: total number of patients; n: number of patients; TEAE: treatment-emergent adverse event.
Source: Clinical Study Report (B3461028)[73]

B.2.10.1.4 Common adverse events

The most commonly reported all-causality TEAEs (≥20%) were cardiac failure, dyspnoea, dizziness, fall, diarrhoea and nausea. The most commonly reported treatment-related TEAEs (≥5%) were diarrhoea, nausea, and urinary tract infection (UTI); summarised in Table 34.[73]

Table 34. ATTR-ACT: Summary of common adverse events

	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Pooled tafamidis N=264 n (%)	Placebo N=177 n (%)
Most frequent all-causality TEAEs (>20% in any treatment group)				
Cardiac failure	[redacted]	[redacted]	76 (28.8)	60 (33.9)
Diarrhoea	[redacted]	[redacted]	32 (12.1)	39 (22.0)
Nausea	[redacted]	[redacted]	29 (11.0)	36 (20.3)
Fall	[redacted]	[redacted]	70 (26.5)	41 (23.2)
Dizziness	[redacted]	[redacted]	42 (15.9)	37 (20.9)
Dyspnoea	[redacted]	[redacted]	50 (18.9)	54 (30.5)
Most frequent treatment-related TEAEs (>5% in any treatment group)				
Diarrhoea	[redacted]	[redacted]	16 (6.1)	18 (10.2)
Nausea	[redacted]	[redacted]	11 (4.2)	10 (5.6)
UTI	[redacted]	[redacted]	9 (3.4)	8 (4.5)

Patients are counted only once per treatment in each row.
MedDRA v20.1 coding dictionary applied.
Serious Adverse Events - according to the investigator's assessment.
In ATTR-ACT, there was a provision for patients to request a blinded dose reduction for adverse events related to tolerability.
Abbreviations: N: number of patients; TEAE: treatment-emergent adverse event; UTI: urinary tract infection.
Source: Clinical Study Report (B3461028)[73]

Adverse events of special interest

Adverse events of special interest in ATTR-ACT were diarrhoea, urinary tract infections (UTI) and abdominal pain. These AEs were observed with tafamidis use in a previous ATTR-PN clinical study.[95] In addition, important potential risks included hypersensitivity, hepatotoxicity and thyroid dysfunction. In general, adverse events were similar across the tafamidis and placebo groups, except for diarrhoea, UTIs and hypersensitivity, which were more prevalent into the placebo group (Table 35).[73]

Table 35. ATTR-ACT: Incidence proportion of adverse events of special interest

Event of special interest*	Tafamidis 20 mg (N=88) n (%)	Tafamidis 80 mg (N=176) n (%)	Placebo (N=177) n (%)
Abdominal pain	[redacted]	[redacted]	[redacted]
Diarrhea-related	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Vaginal infection	[redacted]	[redacted]	[redacted]
Hypersensitivity-related	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]
Thyroid dysfunction	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report (B3461028)[73] and B3461028 (data on file)[93]

B.2.10.1.5 Deaths

In ATTR-ACT, there were 144 deaths reported at the 30-month vital status assessment; 72 (50.0%) deaths in the placebo group, [redacted] in the tafamidis 20 mg, and [redacted] in the tafamidis 80 mg treatment groups.[73] Of the 144 deaths, [redacted] occurred up to 28 days after last dose. Of the total patients, [redacted], [redacted] and [redacted] in the placebo,

tafamidis 20 mg and tafamidis 80 mg groups respectively, died up to 28 days after last dose. The majority of deaths in the study were considered the result of underlying disease: [redacted], [redacted], and [redacted] in the placebo, tafamidis 20 mg, and tafamidis 80 mg groups, respectively.[73] No death was assessed as related to study treatment.

B.2.10.1.6 Laboratory parameters

In patients with normal laboratory parameter baseline values, a similar proportion of patients in the tafamidis 20 mg and tafamidis 80 mg arms ([redacted] and [redacted]) experienced abnormal laboratory tests compared with the placebo arm ([redacted]).[73]

Thyroxine values for the tafamidis 80 mg group were proportionally higher than those in the tafamidis 20 mg and placebo groups.[73] No clinically meaningful shifts in free thyroxine or thyrotropin values were observed, and no corresponding signal in thyroid dysfunction was observed in the analysis of TEAEs, suggesting that normal thyroxine function was maintained.[73] No meaningful impact of tafamidis was observed on haemoglobin, platelet, leukocytes and lymphocytes counts.[73]

B.2.10.2 ATTR-ACT extension study

Safety data from the ATTR-ACT extension study was pooled with ATTR-ACT data (n=[redacted] tafamidis 20 mg and n=[redacted] tafamidis 80 mg).

As of cut-off date of 15 February 2018, the mean duration of exposure was [redacted] months for [redacted] patients in the tafamidis 20 mg group, and [redacted] months for [redacted] patients in the tafamidis 80 mg group.[79] Up to 42 months of exposure has been observed in [redacted]% and [redacted]% of tafamidis-treated patients in the 20 mg and 80 mg groups, respectively.[79] Dose interruptions due to adverse events in the broad ATTR-CM Cohort (ATTR-ACT and ATTR-ACT extension study) occurred at similar rates across the tafamidis 20 mg ([redacted]) and 80 mg treatment groups ([redacted]).[79] Further safety data for the ATTR-ACT extension study are not yet available.

B.2.10.3 Supporting safety evidence for tafamidis

B.2.10.3.1 Phase II study

Safety data from the Phase II study are shown in Table 13. All 35 patients experienced ≥1 AE during the study. The most frequent AEs included dyspnoea, congestive cardiac failure and dizziness. Of the 35 patients, 20.0% (7 patients) reported an AE of diarrhoea.[80]

Fifteen patients (42.9%) experienced ≥1 serious adverse events (SAE). The most common SAEs were cardiac events, such as cardiac failure (10 patients, 28.6%) and atrial fibrillation

(3 patients, 8.6%). Four patients experienced SAEs that were assessed as possibly related to tafamidis which included ataxia, falls, heart failure, a fall induced haemorrhagic stroke and syncope.[80]

Two of the 35 patients died during the study: one patient died of a haemorrhagic stroke after a fall approximately 4 months after study start. The other patient was diagnosed with immunoglobulin light chain (AL) amyloidosis approximately 11 months after starting the study.[80]

In summary, the AEs reported during this Phase II study reflect the study populations' underlying cardiac disease, elderly status and burden of comorbidities. There were no apparent safety concerns related to drug therapy, suggesting that an oral daily dose of 20 mg tafamidis was well tolerated in ATTR-CM patients over 12 months.

Table 36. Phase II study: Summary of adverse events

Event, n (%)	ATTR-CM (N=35)
Summary of AEs	
Patients with ≥1 AE	35 (100)
No. of patients with ≥1 SAE	15 (42.9)
Patients who discontinued because of an AE	1 (2.9)
Serious adverse events[a]	
Cardiac failure	10 (28.6)
Atrial fibrillation	3 (8.6)
Fall	3 (8.6)
Syncope	2 (5.7)

[a]Only those SAEs occurring in ≥2 patients are listed. Any patient with multiple incidences is counted only once per category.
Abbreviation: AE: adverse event; SAE: serious adverse event.
Source: Maurer et al. 2015[80]

B.2.10.3.2 Phase II extension study

In the ongoing Phase II extension study, as of 01 August 2017, all 31 patients enrolled into this study experienced at least one TEAE.[83] A total of [redacted] SAEs were reported in 28 patients. The most frequently reported SAEs were congestive cardiac failure ([redacted]), cardiac failure and fall (each reported for [redacted]), cellulitis and disease progression (each reported for [redacted]).[83]

B.2.10.3.3 The Transthyretin Amyloidosis Outcomes Survey (THAOS) (B3461001)

THAOS is an international, multicentre disease registry, initiated in 2007, that collects long-term, observational data on disease progression in patients with ATTR amyloidosis (with phenotypes ranging from ATTR-CM to ATTR-PN).[84] No UK centres have contributed patient

data to THAOS, which collects information on patient's medical and family history, physical and neurologic examinations, ambulatory status, genotype, laboratory assessments, electrocardiograms and echocardiograms, histories of hospitalisations, death, transplants, and quality of life. The THAOS study has also been designed to collect safety information related to the use of tafamidis and, therefore, has become a source of data to better characterise the safety profile of tafamidis.[84]

As of 15 February 2018, [redacted] patients ([redacted] males, [redacted] females) received tafamidis while participating in THAOS.[96] The safety population represents ATTR amyloidosis patients (n=[redacted]) with any tafamidis treatment exposure from the time they were enrolled into THAOS, excluding time during clinical trial participation. The overall mean (±SD) duration of exposure in the safety population is [redacted] years.[96] Overall, [redacted] patients experienced at least 1 TEAE and [redacted] reported at least 1 SAE.[96] [redacted] patients experienced TEAEs leading to permanent discontinuation of tafamidis.[96] [redacted] patients experienced AEs associated with a fatal outcome. All [redacted] reports were determined by investigators to be unrelated to tafamidis treatment.[96]

B.2.11 Ongoing studies in ATTR-CM population

The ATTR-ACT and the Phase II long-term extension studies are currently ongoing. Accordingly, the ATTR-ACT extension study protocol was amended to include an additional cohort of patients (i.e. an early access programme) who have not previously participated in the ATTR-ACT study. ATTR-ACT sites that are centres of excellence for the management of ATTR-CM will enrol patients in this cohort. No UK sites will enrol new patients in the ATTR-ACT extension study as early access in the UK will be provided through the Early Access to Medicine Scheme.

B.2.12 Innovation

Tafamidis is a breakthrough treatment for ATTR-CM

ATTR-ACT demonstrates that tafamidis is a breakthrough treatment on many levels as it is the first time a medical treatment has been shown to:

- Reduce mortality and morbidity in ATTR-CM.[90]
- Reduce all-cause mortality and CV-related hospitalisations in patients with HFpEF.[91]
- Be effective on endpoints of all-cause mortality and CV-related hospitalisation through acting centrally (on the myocardium), rather than acting peripherally or by neurohormonal modulation[92]

Tafamidis is expected to generate greater than [redacted] incremental QALYs (undiscounted). As such, it represents a paradigm shift in the management of the disease. This contrasts with previous NICE recommendations to treat heart failure with reduced ejection fraction (HFrEF), sacubitril valsartan and ivabradine, which only generated incremental QALYs of 0.33 and 0.28, respectively.[97,98]

It is the first and only treatment option that moves beyond symptomatic management to slow disease progression and slow the decline in physical functioning and quality of life. This paradigm shift in the treatment of the disease will reduce some of the substantial burden of ATTR-CM on patients, caregivers and healthcare systems in an area of significant unmet need.[22]

Tafamidis has a convenient once daily oral administration, thereby not increasing the burden on patients to have to travel for treatment. This is especially important given the average age of ATTR-CM patients who may experience difficulty in securing transportation and who often must cope with polypharmacy.

Benefits not fully captured in the economic analysis

There are several key benefits of tafamidis that are not fully captured in the economic model by the cost and QALY assessment:

- **Tafamidis will deliver service transformation for patients - improving outcomes and producing significant cost savings:** Delayed diagnosis is thought to be a major reason for shortened survival of patients with cardiac amyloidosis.[33,99] On average, patients experience more than three years delay in reaching a diagnosis from the onset of symptoms, by which time many will have progressed to advanced heart failure.[33] Furthermore, during this 3-year delay, patients in the UK attend hospital 17 times on average, including 3 inpatient admissions.[19]
  - The absence of a disease-modifying treatments for ATTR-CM has held back awareness of the disease among clinicians,[27,29] and contributed to the significant under-diagnosis of the disease in the UK, supported by a range of evidence from screening studies,[100,101] autopsy data,[102] and national trends in new cases.[19]
  - Given the rapidly progressive nature of ATTR-CM, significant delays in diagnosis mean that many patients can expect to have advanced disease at the point of treatment initiation,[23,24,30] with a missed opportunity for delaying disease progression should tafamidis become available.

- UK data suggest that >20% of patients with wild-type ATTR-CM are already in NYHA classification III or IV heart failure at diagnosis.[23] The corresponding figure for patients with Val122Ile hereditary ATTR-CM is 40%, suggesting these patients have more advanced disease at diagnosis.
- With expanded use of non-invasive nuclear scintigraphy,[4] the availability of tafamidis (subject to NICE recommendation) is likely to promote the identification of ATTR-CM before advanced cardiac damage has occurred. At an earlier stage, patients may derive the optimal benefit from tafamidis: longer survival, fewer hospitalisations and improved quality of life.
- Significant cost savings in reduced outpatient and inpatient attendances can be achieved through earlier diagnosis. Once a diagnosis is given (and treatment initiated), unnecessary investigations and cycling through secondary care services can be limited (explored in scenario analysis [Section B.3.8.3]. With an average delay to diagnosis of 6 months instead of 3 years, cost savings are estimated to be in excess of £20,000 per patient [Section B.1.3.4.3]).
- A system shift may also address significant mis/undiagnosed patients, which is likely to result in additional outcomes (QoL/survival) and economic benefits for the NHS.

- **Impact on carers and family:** ATTR-CM is a progressive and debilitating disease with poor prognosis (life expectancy of 2.3 - 5.8 years), which currently lacks UK-approved disease-modifying treatments. As such, a diagnosis of ATTR-CM can be devastating. Hereditary ATTR-CM carries an additional impact on multiple generations of a family because TTR variants are inherited as an autosomal dominant trait.[35] The availability of a treatment that can delay disease progression, extend and improve quality of life, and would give people with the disease reassurance that it was treatable – both for themselves and for family members who may be affected in the future.
- **Reduction in carer burden:** Carers of patients with ATTR-CM report a significant impact on their physical and emotional well-being due to the enduring progressive functional disability from ATTR-CM.[22] By reducing the decline in functional capacity and quality of life, tafamidis has the potential to help relieve the carer burden associated with this progressive disease.
- **The introduction of tafamidis aligns with a key priority in the NHS Long-Term Plan**: if recommended, tafamidis can help frail and older people stay healthy and independent for longer.[103]

Promising Innovative Medicine designation, Early Access to Medicines Scheme and other designations

Based on the innovative nature of tafamidis, it was granted a Promising Innovative Medicine (PIM) designation by the MHRA in December 2018. tafamidis subsequently received an Early Access to Medicines Scheme (EAMS) positive scientific opinion from the MHRA for the treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation. The tafamidis Early Access to Medicines Scheme EAMS is currently enrolling patients at 20 sites across the UK.

In addition to the cost savings discussed through shortening the time to diagnosis. There are further potential savings from nationwide implementation of the EAMS, which is widening the number of specialised centres, removing the requirement for annual appointment for all patients at the NAC (explored in scenario analysis; Section B.3.8.3).

Furthermore, tafamidis has recently (May 2019) been approved by the US Food and Drug Administration (FDA) where it had Orphan Drug, Fast Track and Breakthrough Therapy designations. In addition, tafamidis has been approved in Japan after receiving Orphan Drug and Sakigake designation. In the EU, tafamidis has Orphan Drug Designation.

Summary

Tafamidis is a convenient once daily oral medication, that is the first and only treatment option that moves beyond symptomatic management to reduce mortality and morbidity in ATTR-CM;[37] reduce all-cause mortality and CV hospitalisations in HFpEF;[38] and does so by acting directly on the myocardium (rather than peripherally or by neurohormonal modulation).[92]

Given the stabilisation of disease and prolonged survival observed in ATTR-ACT, tafamidis is expected to generate greater than [redacted] incremental QALYs (undiscounted). As such, it represents a paradigm shift in the management of a rare, progressive and fatal disease with a significant unmet need. This contrasts with previous NICE recommendations to treat heart failure with reduced ejection fraction (HFrEF), sacubitril valsartan and ivabradine, which only generated incremental QALYs of 0.33 and 0.28, respectively[97,98].

This innovation offers key benefits in several health outcomes and cost savings that are not captured within the current cost-effectiveness estimate, including those for carers' and families of those affected. In conjunction with widespread adoption of the non-invasive diagnostic pathway, access to tafamidis could reduce the average UK delay to diagnosis from 3 years to 6 months. Significant cost savings (potentially in excess of £20,000 per patient, explored in

scenario analysis; Section B.1.3.4.3) would result from reduced hospital admissions/ attendances, minimising unnecessary investigations and addressing mis/undiagnosed patients. Improved outcomes would be achieved by treating patients before the onset of advanced heart failure.

Tafamidis received a Promising Innovative Medicine designation from the MHRA and patients are currently receiving tafamidis across 20 UK cardiology centres through EAMS.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence

The primary clinical evidence supporting use of tafamidis for ATTR-CM derives from the pivotal randomised controlled trial, ATTR-ACT. Supportive evidence is available from the ATTR-ACT extension study, Phase II and the Phase II extension study.

Pivotal study (ATTR-ACT)

ATTR-ACT is a placebo-controlled randomised Phase III trial which demonstrated that tafamidis significantly reduced all-cause mortality and CV-related hospitalisation in ATTR-CM patients. The primary analysis used a hierarchical combination of all-cause mortality and the frequency of cardiovascular (CV)-related hospitalisations over the duration of the trial, applying the method of Finkelstein-Schoenfeld.

- A statistically significant and clinically meaningful treatment effect favouring patients treated with tafamidis (pooled) compared to those treated with placebo (p=0.0006) was demonstrated.[31] Additionally, the two components of the primary analysis were analysed separately and the pooled tafamidis group demonstrated a 30.2% reduction in risk of death for patients in this group compared to placebo (hazard ratio [HR], 0.70; 95% CI 0.51 to 0.96; p=0.03) and a 32.4% reduction in the frequency of CV-related hospitalisation compared to placebo-treated patients (RR, 0.68; 95% CI, 0.56 to 0.81; p<0.0001).[31,73]
- The two key secondary endpoints demonstrated statistically significant and clinically meaningful differences favouring the pooled tafamidis-treated group versus the placebo-treated group on measures of functional capacity (6MWT) and quality of life (KCCQ-OS): the pooled tafamidis LS mean (SE) change from Baseline to month 30 difference from placebo in the 6MWT was 75.7 (9.2) metres (p<0.0001), and the pooled tafamidis LS mean (SE) change from Baseline to Month 30 difference from placebo in the KCCQ-OS score was 13.7 (2.1) points (p<0.0001).[31,73] In addition, for both the 6MWT and KCCQ-OS, a statistically significant treatment effect favouring tafamidis was first observed at Month 6 (6MWT [redacted], KCCQ-OS [redacted]) and remained significant through Month 30.[31]

- Tafamidis-treated patients also had a 30.9% reduction in the risk of CV-related death relative to placebo-treated patients ([redacted]).[73] In addition, significantly more patients in the pooled tafamidis group ([redacted]) demonstrated TTR stabilisation at Month 1 than was observed for patients in the placebo group ([redacted]) ([redacted]).[73]
- The benefit of tafamidis was observed for all subgroups of the patient population in ATTR-ACT, indicating that tafamidis can be used in the treatment of a broad range of patients with ATTR-CM. Consistent directional all-cause mortality benefit of tafamidis was observed across all *TTR* genotype and NYHA baseline classification subgroups. In the NYHA class I and II combined subgroup, tafamidis-treated patients experienced a meaningful reduction in risk of mortality. Further, a consistent directional CV-related hospitalisation benefit favouring tafamidis was observed across all subgroups except the NYHA class III subgroup. The significantly higher hospitalisation rate observed in this cohort may be attributable to a longer survival during a more severe period of disease. This highlights the importance of early diagnosis and treatment of this progressive disease.[82]

Supportive data from the long-term ATTR-ACT extension study demonstrates additional evidence of a continued survival benefit, with separation of the survival curve persisting for approximately 12 months following the 30-month period of ATTR-ACT through to the data cut-off for the ATTR-ACT extension analysis.[79]

Supportive data from the single-treatment, 12-month Phase II study also demonstrated TTR stabilisation in addition to an absence of clinically significant changes in electrocardiographic parameters suggesting a reduction in cardiac disease progression.[80] Further, post-hoc analyses with untreated patients from the TRACS study demonstrated increased survival benefits of tafamidis.[82]

Safety of tafamidis

Tafamidis treatment was safe and well tolerated in the patient population in ATTR-ACT, with few dose reductions (two patients receiving tafamidis [0.8%] and 4 patients receiving placebo [2.3%]) and a similar frequency of TEAEs and serious TEAEs between the treatment groups; the safety profile was similar to placebo.[73] Most TEAEs were mild or moderate in severity.[31] The most frequently reported TEAEs with the highest severity (severe) between treatment groups were congestive cardiac failure and cardiac failure, which were reported in a similar proportion of participants in the tafamidis 20 mg and 80 mg treatment groups and the placebo group.[73] The rate of discontinuation from the study due to an adverse event was low and similar between all groups.[73] A greater proportion of deaths were observed in the placebo

group compared with the tafamidis group. None of the deaths were related to study treatment, and most were considered as a result of the disease under study.[73]

Summary

As demonstrated by its robust efficacy results and a clinical safety profile comparable to that of placebo, tafamidis has a favourable benefit-risk profile that supports the proposed indication and addresses the unmet medical needs of this fatal disease.

B.2.13.2 Strengths and limitations of the clinical evidence base

B.2.13.2.1 Limitations of study evidence

In the clinical evidence base, there is no direct RCT evidence for the 61 mg tafamidis formulation. However, the 61 mg formulation has been shown to be bioequivalent to the 80 mg tafamidis meglumine dose (4 x 20 mg tafamidis meglumine capsules) used in the trial. The 61 mg dose was formulated upon emerging evidence from clinical studies suggesting benefit of the 80 mg tafamidis meglumine dose (bioequivalent to 61 mg tafamidis) over the 20 mg dose. The 61 mg dose is available as a single oral capsule for improved patient convenience in a primarily elderly population often dealing with polypharmacy.

In ATTR-ACT, certain endpoints were only measured at restrictive timepoints. Two biomarkers that are associated with survival – NT-proBNP (biomarker of heart failure) and troponin I (biomarker of myocardial injury) – were measured at baseline, Month 12 and Month 30. Determining the change from baseline at an earlier timepoint in the trial (e.g. Month 3) would have been of interest to establish if an earlier clinical effect of tafamidis over placebo was present. However, more frequent measurement of these biomarkers, in addition to other scheduled activities, might have negatively affected patient participation.

The trial did not recruit patients with NYHA class IV classification at baseline, who experience severe cardiac heart failure symptoms.[68] Inclusion of these patients in the trial would have provided a more complete understanding of the effect of treatment with tafamidis on ATTR-CM. However, given the limited life expectancy of an ATTR-CM, NYHA class IV patient and the 30-month trial definition, it was thought not to be feasible.

However, these limitations should be viewed within the context of the study strengths and the high unmet need in this patient population.

B.2.13.2.2 Strengths of study evidence

Critical appraisal of ATTR-ACT was performed using the Cochrane Collaboration's tool,[89] and was determined to be at low risk of bias across the different domains that were assessed. ATTR-ACT provides direct comparative evidence on the clinical efficacy of tafamidis versus placebo (BSC). In clinical practice, BSC is the current treatment option for these patients, therefore the trial provided a direct, relevant comparison. The size of the trial (264 and 177 in the pooled tafamidis and placebo arms, respectively) was large considering the rare status of the disease. In addition, patient-reported outcomes were captured by two different tools: a cardiomyopathy-specific instrument (KCCQ)[54] and also the EQ-5D, the latter providing utility estimates which are directly attributable to tafamidis treatment.

B.2.13.3 Relevance of the evidence base to the decision problem

This submission presents four relevant studies, one of which is a placebo-controlled randomised trial evaluating the efficacy of tafamidis in ATTR-CM patients (wild-type and hereditary ATTR-CM), in line with the decision problem. Currently ATTR-CM patients are managed with BSC which mirrors the treatment of patients in the placebo arm of ATTR-ACT, therefore providing a direct comparison of tafamidis to the comparator.[4] Thus, the clinical evidence base is directly relevant to the decision problem. Further, outcomes considered in this submission mirror the decision problem set out by NICE. Patisiran and Inotersen were included in the appraisal scope but are not considered appropriate comparators for the reasons stated in Table 1.

The evidence base presented within this submission represents the best available evidence and is directly relevant to the decision problem.

B.2.13.4 External validity of study results to patients in routine clinical practice

In ATTR-ACT, four patients were enrolled from the UK; most patients were enrolled from the USA (n=279).[31] However, ATTR-ACT patients 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 NAC (n=869), a national diagnostic and advisory service for amyloidosis[23]. A larger NAC cohort published by Lane et al.[19] did not report NYHA class, so the cohort reported by Gillmore et al. [23] is the most informative for comparison of patient characteristics. Of note, baseline characteristics in Gillmore et al. [23] are reported at diagnosis, whereas those in ATTR-ACT are reported at randomisation, which could have been months or years after diagnosis.

- Male patients predominate in both groups, and the proportion of male patients is similar. Age is also comparable, with both groups representing a predominantly elderly population
- Most patients in both groups were in NYHA class II at diagnosis/randomisation
    - The NAC cohort had more patients in NYHA class II (75%) and fewer in NYHA class III (24%) than ATTR-ACT (NYHA II: 57% and 61%, placebo and tafamidis, respectively; NYHA III 35% and 30%)
    - A small proportion (<10%) of ATTR-ACT patients were in NYHA class I, but NYHA I was not represented in the NAC cohort
- The NAC cohort had a higher proportion of hereditary patients than in ATTR-ACT (36% vs. 24%). Regardless, tafamidis was associated with a benefit in both wild-type and hereditary subgroups[73]
- The proportions of patients fitted with a pacemaker, and baseline levels of the cardiac biomarker NT-proBNP, were similar between the groups
- The proportions of patients in each NAC disease stage at baseline were broadly similar across ATTR-ACT and the NAC dataset

Background care in ATTR-ACT is also comparable with current care in the UK; patients receive individualised symptomatic management in both groups. The NAC publication does not report baseline medication

For the NAC cohort, median overall survival from diagnosis was 4.8 years (57 months, 95% CI 49.1-60.4 months).[23] In ATTR-ACT, median overall survival was not reached during the study period; at Month 30, 57.1% of patients in the placebo arm were alive.[31] In the ATTR-ACT extension study, patients in the placebo/ tafamidis arm had a median survival of approximately [redacted] months. When comparing the two cohorts, it is important to note that reported survival in ATTR-ACT was time from trial randomisation, whereas the NAC study reported survival from diagnosis. This potential for lead-time bias (i.e. reporting of survival from an earlier starting point in the NAC group than in the trial) should be considered in any comparison of time-to-event outcomes.

Table 37. Comparison of baseline characteristics in ATTR-ACT and a UK cohort

	ATTR-ACT[31]		Untreated
	Tafamidis	**Placebo**	**Gillmore et al. 2018[23]**
Number of patients	264	177	869
Median age at randomisation (range), years	75 (46-88)	74 (51–89)	NR
Median age at diagnosis, years	NR	NR	77 (41-95)
Sex, n (%)			
Male	241 (91.3%)	157 (88.7)	737 (85)
Female	23 (8.7%)	20 (11.3)	132 (15)
NYHA classification, n (%)[a]			
Class I	24 (9.1)	13 (7.3)	0
Class II	162 (61.4)	101 (57.1)	656 (75)
Class III	78 (29.5)	63 (35.6)	205 (24)
Class IV	0	0	8 (1)
TTR genotype, n (%)			
Wild-type TTR	201 (76.1)	134 (75.7)	553 (63.6)
Hereditary TTR	63 (23.9)	43 (24.3)	316 (36.3)
Val122Ile	[redacted]	[redacted]	201 (23.1)
Permanent pacemaker	13 (4.9)	12 (6.8)	39 (4.5)

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

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify cost-effectiveness studies for the treatment of ATTR-CM. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) were conducted in August 2018 and subsequently updated in May 2019; further, searches were conducted for HTA submissions, including NICE, Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG). The search was extended to include models of cardiomyopathy, due to the low number of expected studies for ATTR-CM. Full details of the process and methods of the SLR are provided in Appendix G.

There were no economic evaluations identified for ATTR-CM. However, one study was identified for non-ischemic cardiomyopathy. This study was not considered relevant to the decision problem as it evaluated implantable cardiac devices in non-ischemic cardiomyopathy patients, which lies outside the current scope.

B.3.2 Economic analysis

The economic case presented in this submission was based on conventional cost-utility analysis, assessing the use of tafamidis plus BSC versus BSC alone (based on placebo from ATTR-ACT) for the treatment of adult patients with ATTR-CM. A de novo model was developed to determine cost-effectiveness, as there were no pre-existing models identified in this indication. Although no ATTR-CM or cardiomyopathy HTAs were identified in the SLR outlined above, several HTAs describing therapies for cardiovascular diseases, such as heart failure (e.g. ivabradine [TA267][97] and sacubitril valsartan [TA388][98]), were identified and used to inform development and population of the model inputs, where relevant. The model development was also informed by clinician opinion, to ensure that the model had face validity and provided an appropriate approximation of clinical practice in the UK.

B.3.2.1 Patient population

In the base case, the economic analysis evaluates the overall population, which aligns with the final scope and the primary analysis of ATTR-ACT. (see Section B.1.1).

B.3.2.2 Model structure

The model developed to evaluate the cost-effectiveness of tafamidis was a discrete time cohort-level Markov state-transition model. During model conceptualisation, other model types were considered. A partitioned survival model was considered, where state

membership is based on the area under parametric survival curves. A multi-state model was also considered that would allow simulated patients free transition between all NYHA states, treatment states, and death, in continuous time. However, a Markov model was considered most appropriate for the reasons outlined in Table 38.

Table 38. Justification for the Markov model structure

Feature	Justification
Allows for all possible transition permutations, between a given set of health states	A Markov model structure allows for the specification of transition probabilities capable of representing all possible health state transitions. In the case of ATTR-CM, clinical opinion and observed trial data both indicate that, while a decline in NYHA class status is generally observed, temporary improvements are possible and noted. To adequately reflect this, a model structure capable of simulating both forward and backwards transitions is required.
Allows for simple incorporation of the available data	A Markov model structure allows for easy incorporation of discrete time-dependent disease progression rates (as time-dependent within-trial transition matrices were employed).
Allows for explicit modelling of the relationship between disease progression and clinical outcomes	A partitioned survival approach estimates progression and survival endpoints independently of each other. As it was expected that clinical events (i.e., death) will be influenced by disease progression rates, as determined by NYHA class health state occupancy and transitions, a Markov model was deemed appropriate
Allows for the accurate representation of clinical outcomes, without additional model complexity	A Markov model structure reflects clinical outcomes without the additional complexity that alternative model structures, such as a multi-state model, would entail. A more complex model structure would have required additional transition rates to be estimated from low observation counts, increasing uncertainty in the estimated values. Therefore, a simpler Markov model was preferred. Further, during ATTR-ACT, NYHA class was observed at six-monthly intervals, whereas OS was observed continuously which could be accurately captured in a simpler Markov framework.

Abbreviations: NYHA: New York Heart Association; OS: overall survival.

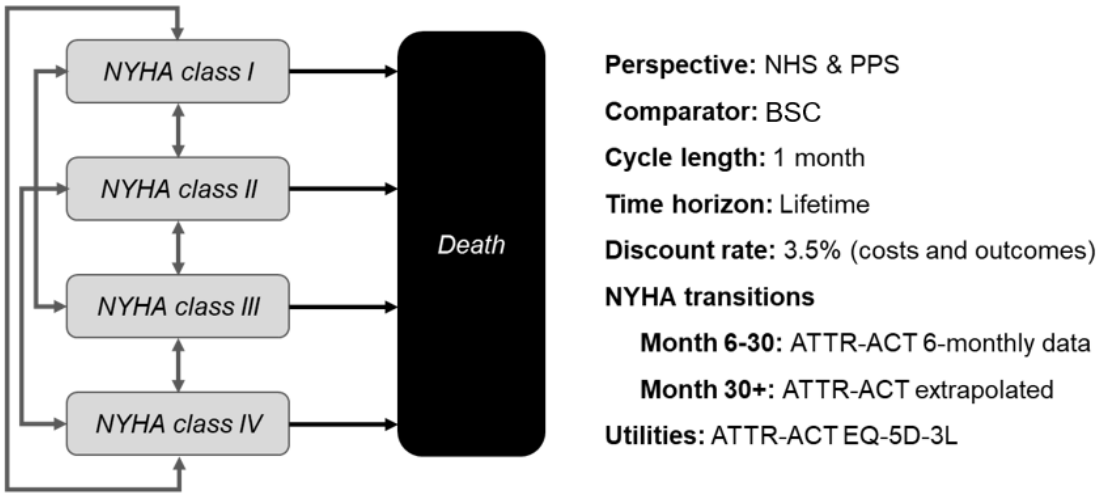
To capture the natural disease progression of ATTR-CM and the patient experience, model health states were based on NYHA functional class (NYHA class I-IV) [68], a widely validated system for staging heart failure (described in Section B.1.3.5). NYHA classification is based on functional limitation and symptom severity and is thus a patient-relevant mechanism that has been observed as a statistically significant predictor of both HRQoL and survival.[63 64,65] As discussed in B.1.3.5, for a staging system to be effective it must also be easily implemented in clinical practice. Clinical experts advised that the NYHA classification is commonly used in heart failure clinics in the UK for ongoing patient assessment. This is because it can be used irrespective of the cause of heart failure, is simple to derive and best reflects patients' symptom burden. The use of NYHA has been used widely in cost-effectiveness models.[104]

Alternative disease staging measures were considered for defining the Markov health states, such as NAC ATTR Disease staging and Mayo Clinic Staging system. However, unlike the NYHA functional class measure, there were no published data to show a relationship between these systems and HRQoL. In addition, clinical advice indicates that these staging systems are not widely used in cardiology clinics. Therefore, the NAC ATTR Disease staging and Mayo Clinic Staging systems were not considered suitable for capturing all aspects of the disease and were not used to define the Markov states. Please refer to Section B.1.3.5 for further information.

All patients enter the model in either the NYHA state I, II or III states and are at risk of transition to alternative NYHA states or death, which is an absorbing state. In each model cycle, patients can accrue costs associated with drug acquisition, general disease-related resource usage, transient hospitalisation events and treatment-related AEs. In addition, for the tafamidis arm, patients can discontinue treatment, which is informed by time-to-event curves estimated from the discontinuation observed in ATTR-ACT (see Section B.3.3.5). An overview of the model structure is presented in Figure 32.

The ATTR-ACT data demonstrates that patients discontinued tafamidis treatment prior to progressing to NYHA IV. This is in line with opinion from clinical experts, who suggested that patients would discontinue treatment prior to progressing to NYHA IV and at least 12 months prior to death, as discussed in Section B.3.3.5.

Figure 32. Schematic diagram of the structure of the economic model



Note: Within each NYHA health state, patients treated with tafamidis were in an ‘active treatment’ or ‘discontinued’ health state.

B.3.2.2.1 Features of the economic analysis

The analysis was constructed from the perspective of the NHS and Personal Social Services (PSS) in England and Wales, consistent with the NICE reference case.[105] Costs were based on 2017/18 prices (which are the latest available publication sources at the time of submission). Consistent with the NICE reference case,[105] a discount rate of 3.5% is applied for both costs and health benefits in the base case analysis.

Employing a monthly cycle length (with half-cycle correction), the model predicts the proportion of the population who experience disease progression (through NYHA classes), a transient event (hospitalisation and/or treatment-related adverse event), treatment discontinuation or death. A cycle length of one month was chosen to adequately capture the occurrence of time to discontinuation and death events. However, in ATTR-ACT, NYHA class and utility evaluations were conducted at six-month intervals. To reflect this, modelled events were evaluated at one of two time-steps:

- **Major time-step:** six-months (six cycles); used for NYHA class-based disease progression
- **Minor time-step:** one month (one cycle); employed for all other modelled events (deaths, discontinuations, treatment-related adverse events, hospitalisations) and the accumulation of costs and health benefits

Reflective of the chronic nature of ATTR-CM, and to fully capture the survival and health benefits associated with tafamidis treatment, evaluations were conducted over a life-time horizon (up to age 101 years).[73]

A summary of the model features is presented in Table 39.

Table 39. Features of the economic analysis

Factor	Current appraisal	
	Chosen values	**Justification**
Model perspective	NHS and PSS	Consistent with the NICE reference case [105].
Comparators	BSC (represented by placebo from ATTR-ACT)	The placebo arm from ATTR-ACT represents BSC without tafamidis, i.e., symptomatic treatment of heart failure as currently used in UK clinical practice.
Cycle length	One month	Provides sufficient granularity to capture the occurrence of discontinuation and death events for time-to-event analyses.
Time horizon	Lifetime (up to 101 years; 26 years in the base case analysis)	Reflects the chronic nature of ATTR-CM and is long enough to reflect all important differences in costs or outcomes between tafamidis and BSC (consistent with the NICE reference case[105]).
Discount rate	3.5%	Consistent with the NICE reference case[105].
Treatment waning effect	Not applicable	Disease progression and survival outcomes following discontinuation of tafamidis are implicitly captured within the overall patient group used to inform model inputs.
Source of utilities	EQ-5D-3L from ATTR-ACT	The trial-based utilities are based on the actual experience of ATTR-CM patients being treated with tafamidis/BSC and are aligned with the NICE reference case[105]. The baseline utilities in ATTR-ACT are similar to values reported for ATTR-CM patients in the literature (see Section B.3.4.3)
Source of costs	NHS reference costs[62], MIMS[106] and PSSRU[107]	Consistent with the NICE reference case[105].

Abbreviations: BSC: Best Supprotive Care; MIMS: Monthly Index of Medical Specialties; PSSRU: Personal Social Services Research Unit

B.3.2.3 Intervention technology and comparators

The intervention, tafamidis, was modelled as per its expected marketing authorisation, and according to the recommended dosing regimen, i.e. 61mg/day (see Section B.1.2). As detailed in Section B.1.1, BSC was considered the relevant comparator, which consists of symptomatic treatment of heart failure and is represented by the placebo arm of ATTR-ACT. Medication use was taken from ATTR-ACT. As patients in both the placebo and tafamidis arms received symptomatic management, it was counted as a concomitant medication and applied to both treatment arms (see Section B.3.5.2.2). This approach has been validated by clinical experts as appropriate and relevant to UK clinical practice.

Further details around BSC in UK clinical practice are detailed in Section B.1.3.3.

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the economic model

Individual patient-level data from ATTR-ACT was used to inform comparative efficacy, given that ATTR-ACT was a Phase III RCT providing direct evidence for tafamidis versus BSC, it was considered the best available evidence.

The ATTR-ACT extension study provided additional follow-up data. However, there was potential for a minor selection bias (discussed in Section B.2.3.3.1) and so has, not been used to inform the base case analysis. Instead, the extension study was used to provide validation of extrapolated outcomes.

Within the economic model, treatment efficacy was captured via the estimation of health state occupancy (Section B.3.3.3), survival (Section B.3.3.4), discontinuation (Section B.3.3.5) and CV-related hospitalisation (Section B.3.3.6).

B.3.3.2 Patient parameters

Baseline patient parameters in the cost-effectiveness model (Table 40) were informed by the baseline characteristics of NYHA I/II patients across both the tafamidis and placebo arms of ATTR-ACT. Thus, these values were not treatment arm-specific. The trial population is considered to be generalisable to the patient population with ATTR-CM in the UK, as described in a recent publication from the NAC by Gilmore et al.[23], discussed in Section B.2.13.4. When comparing the two cohorts, it is important to note that survival in ATTR-ACT was time from trial randomisation, whereas the NAC study reported survival from diagnosis. This difference in the starting point of reporting survival results in a lead-time bias, which should be considered when comparing time-to-event outcomes.

Table 40. Baseline patient parameters in ATTR-ACT

Parameter	Mean	SE	Source
Baseline characteristics			
Age (years)	74.34	0.33	ATTR-ACT
Proportion female	0.10	0.01	
Baseline NYHA class distribution – Tafamidis and BSC			
Proportion NYHA I	0.08	NA[a]	ATTR-ACT
Proportion NYHA II	0.60		
Proportion NYHA III	0.32		

Abbreviations: BSC: Best Supportive Care; NYHA class: New York Heart Association Classification; SE: standard error;
[a]PSA informed by Dirichlet distribution using counts from study data.

B.3.3.3 Health state occupancy

Patients were initiated in the model in the NYHA I, II or III health states, with the initial cohort distribution determined by the baseline distribution in ATTR-ACT.

Patients' NYHA class status may improve, worsen or remain constant, represented by transitions through the respective health states. The rate at which patients transition between health states is determined by treatment- and time-specific transition matrices.

There were two transition matrices, the within-trial phase (Month 0 to 30) and extrapolation phase (Month 30+).

In the within-trial phase, treatment- and population-specific transition matrices for each six-month interval were derived from transitions observed in the individual patient data. Data from ATTR-ACT describe patients as being in one of the following health states at each assessment point: NYHA I, NYHA II, NYHA III, NYHA IV, unmeasured, transplantation/cardiac mechanical assist device (CMAD) or dead. Details of the assumptions adopted to calculate the transitions between NYHA health states at each time point are detailed in Table 41.

Table 41. Assumptions for calculating health state-transition rates

Assumption	Justification
Unmeasured observations were censored	It is not appropriate to model 'unmeasured' NYHA class as a separate health state as this would lack face validity and would not represent clinical practice. Therefore, several options were considered to address 'unmeasured' NYHA observations: • Assume LOCF and assume that patients with 'unmeasured' observations remain in the previous NYHA class until new data is available. However, this may be too optimistic, as those with worsening condition are more likely to be 'unmeasured'. • Assume that patients with 'unmeasured' observations have progressed to NYHA IV health state, reflecting the likelihood that patients who are less fit will be more likely to be 'unmeasured'. However, this would

	be too pessimistic and not reflect all clinical eventualities. • Censor 'unmeasured' observations. Given the limitations associated with these options, censoring these observations is the most accurate approach to addressing this issue.
Transitions from or to the 'transplantation/ CMAD' state were censored	Clinical experts indicated that transplantation and implantation of cardiac devices were unlikely to be used in UK clinical practice, so there were no health states in the model to capture these outcomes. However, these procedures may have significant impact on prognosis. Therefore, these observations were censored, to ensure that future transition rates reflect UK clinical practice rather than any impact of transplants or cardiac devices.
Transitions to the 'dead' state were included as a transition to the patient's existing NYHA health state	These transitions are inherently captured, via the application of NYHA class health state specific survival profiles (Section B.3.3.4.7).

Abbreviations: CMAD, cardiac mechanical assist device; LOCF, last observation carried forward

Consistent with the within-trial phase assessment interval, disease progression was evaluated every six-months during the extrapolation phase. However, during the extrapolation phase, transitions were fixed and were derived by fitting a smoothed multinomial distribution1 to all transition counts observed during the within-trial phase. The transition matrices for the pooled tafamidis and placebo arms are presented in Table 42 to Table 45. Figure 33 and

Figure 34 show that transitions between NYHA classes appear relatively stable, particularly during the latter part of the ATTR-ACT study period, indicating that extrapolation based on this method is appropriate.

1 For each NYHA class prior to transition, NYHA class occupancy post transition was assumed to have a multinomial distribution. WinBUGS was used to determine the characteristics of these distributions via Bayesian inference, with the prior assumed distribution being uniform across all post-transition NYHA classes. The mean Monte-Carlo sampled transition rates from this WinBUGS model were normalised across the possible transitions from each pre-transition class and used as the long-term extrapolating transition rates. Multiplication of this transition matrix by the pooled pre-transition NYHA class distribution yielded the total number of patients assumed to make each transition as used for PSA sampling.

Figure 33. Rates of transition into NYHA classes observed in ATTR-ACT, tafamidis arm

Month 0 6 12 18 24 30

Figure 34. Rates of transition into NYHA classes observed in ATTR-ACT, placebo arm

Month 0 6 12 18 24 30

Table 42. NYHA transition matrix – within-trial phase: Tafamidis

		To NYHA class health state			
		NYHA I	NYHA II	NYHA III	NYHA IV
From NYHA class health state	Month 6				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NYHA class: New York Heart Association Classification.

Table 43. NYHA transition matrix – extrapolation phase: Tafamidis (Month 36+)

		To NYHA class health state			
		NYHA I	NYHA II	NYHA III	NYHA IV
From NYHA class health state	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NYHA class: New York Heart Association Classification.

Table 44. NYHA transition matrix – within-trial phase: Placebo

		To NYHA class health state			
		NYHA I	NYHA II	NYHA III	NYHA IV
From NYHA class health state	Month 6				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30				
	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NYHA class: New York Heart Association Classification.

Table 45. NYHA transition matrix – extrapolation phase: Placebo (Month 36+)

		To NYHA class health state			
		NYHA I	NYHA II	NYHA III	NYHA IV
From NYHA class health state	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NYHA class: New York Heart Association Classification.

B.3.3.4 Overall survival

B.3.3.4.1 Rationale for survival approach in the economic model

Within a population of ATTR-CM patients, observed deaths may be related to ATTR-CM or background mortality expected in the general population. Appropriate modelling of the ATTR-CM population requires disease-related mortality to be reflected accurately in addition to the increasing hazard observed in older people in the general population.

Most overall survival (OS) events observed during ATTR-ACT are likely to be related to ATTR-CM. However, given that ATTR-ACT was only 30 months in duration and the background hazard of death increases significantly for persons aged 80 years and above, trial data are unlikely to capture the increasing disease-unrelated hazard expected over the remainder of a patient's life-time. Furthermore, disease-unrelated hazards differ across countries. As such, several approaches were considered for implementing survival in the economic model:

- Trial-based OS from ATTR-ACT with no adjustment of background mortality observed during the trial period.
- CV mortality from ATTR-ACT with non-CV-related background mortality from the Office for National Statistics (ONS).
- Disease-related excess mortality from ATTR-ACT combined with mortality from Office of National Statistics (ONS) life tables.[108]

Given the potential approaches, an assessment was undertaken to identify differences in background mortality between countries participating in ATTR-ACT and the UK based on an age-matched population (see Appendix L.2 for further details). UK life table hazards (equivalent for age and sex) were applied to ATTR-ACT patients demonstrating higher life expectancies of 2.6 and 3.6 months for tafamidis and BSC, respectively. (Table 46) compared to nationality-specific life tables. Thus, it was concluded that there were material differences in background mortality, and these would have an impact on the modelled outcomes, so that use of trial-based OS alone may not be appropriate.

Table 46. Mean expected survival of a matched general population

Population	Age at randomisation (years)		Female	Mean expected survival (months)		
	Median (min, max)	Mean (SD)		Nationality-specific life tables	UK life tables	Difference
All patients	75.3 (47.0, 89.9)	74.98 (6.99)	9.8%	[redacted]	[redacted]	[redacted]
Overall population						

Pooled tafamidis	75.7 (47.0, 88.3)	75.17 (7.19)	8.7%	[redacted]	[redacted]	[redacted]
Placebo	74.9 (51.4, 89.9)	74.68 (6.68)	11.3%	[redacted]	[redacted]	[redacted]

Abbreviations: SD: standard deviations.

Following this, an assessment of ATTR-ACT non-CV-related mortality was undertaken. Within ATTR-ACT, death events were characterised as CV-related or non-CV-related; [redacted] of the [redacted] death events in the 264 patients [redacted]%) of the tafamidis arm and [redacted] of the [redacted] death events in the 177 patients ([redacted]%) of the placebo arm were characterised as non-CV-related, indicating that treatment may impact non-CV mortality in ATTR-ACT. Further, the ATTR-ACT data demonstrate that ATTR-ACT patients experience additional deaths due to diseases such as pneumonia, which can be expected in this patient population but would not be reflected in CV mortality estimates. To capture any increased risk in non-CV mortality among these patients, relative to the general population, models of all-cause mortality were required.

Table 47 presents an overview of methods for implementation of survival in the economic model, as well as implicit and explicit assumptions required for implementation of these methods and if they are met.

In summary, use of disease-related excess mortality from ATTR-ACT combined with mortality from ONS life tables should be considered the most appropriate method of implementing ATTR-ACT survival data in the economic model.

Table 47. Methods for implementing survival in the economic model

Survival method	Assumptions	Comment
Trial-based OS from ATTR-ACT with no adjustment of background mortality.	Background mortality is not different between countries participating in the trial and the UK	Assumption not met: small material differences will impact cost-effectiveness modelling
	Background mortality captured in the trial period is also reflected over the extrapolated period	Assumption not met: ONS life tables clearly indicate a significant increase in mortality over the time horizon which is not accurately reflected in extrapolation with no adjustment applied
CV mortality from ATTR-ACT with non-CV-related background mortality from the ONS life tables.	CV-mortality was accurately assigned in ATTR-ACT	Assumption met
	No difference in non-CV mortality between patients with ATTR-CM and the UK general population	Assumption not met: ATTR-ACT patients non-CV related hazard is different to general population due to diseases such as pneumonia
	Background mortality has an impact over the modelled period	Assumption met: small material differences will impact cost-effectiveness modelling
	CV related mortality can be accurately attributed within ONS lifetables	Assumption not met: No method to undertaken accurately
	Non-CV mortality is not influenced by treatment	Unclear: differences were observed in non-CV mortality between tafamidis and placebo however, these may be due to random chance
Disease-related excess mortality from ATTR-ACT combined with mortality from ONS life tables.	There are material differences in background mortality between ATTR-CM study centres and the UK general population	Assumption met: small material differences observed
	Background mortality has a material impact over the modelled period	Assumption met: ONS life tables clear indicate a significant increase in mortality over the time horizon
	Removal of disease-related hazard would have negligible impact on life tables	Assumption met: prevalence of ATTR-CM low; proportion of total deaths at any age amongst matched lifetable population due to disease sufficiently low as to assume lifetable hazards represent hazard of mortality due to causes other than specific disease.

Abbreviations: CV, cardiovascular; ONS, Office of National Statistics; OS: Overall survival; UK, United Kingdom

B.3.3.4.2 Application of survival approach in the economic model

The disease-related excess mortality was calculated based on ATTR-ACT data; an overview of the approach is described in Figure 35.

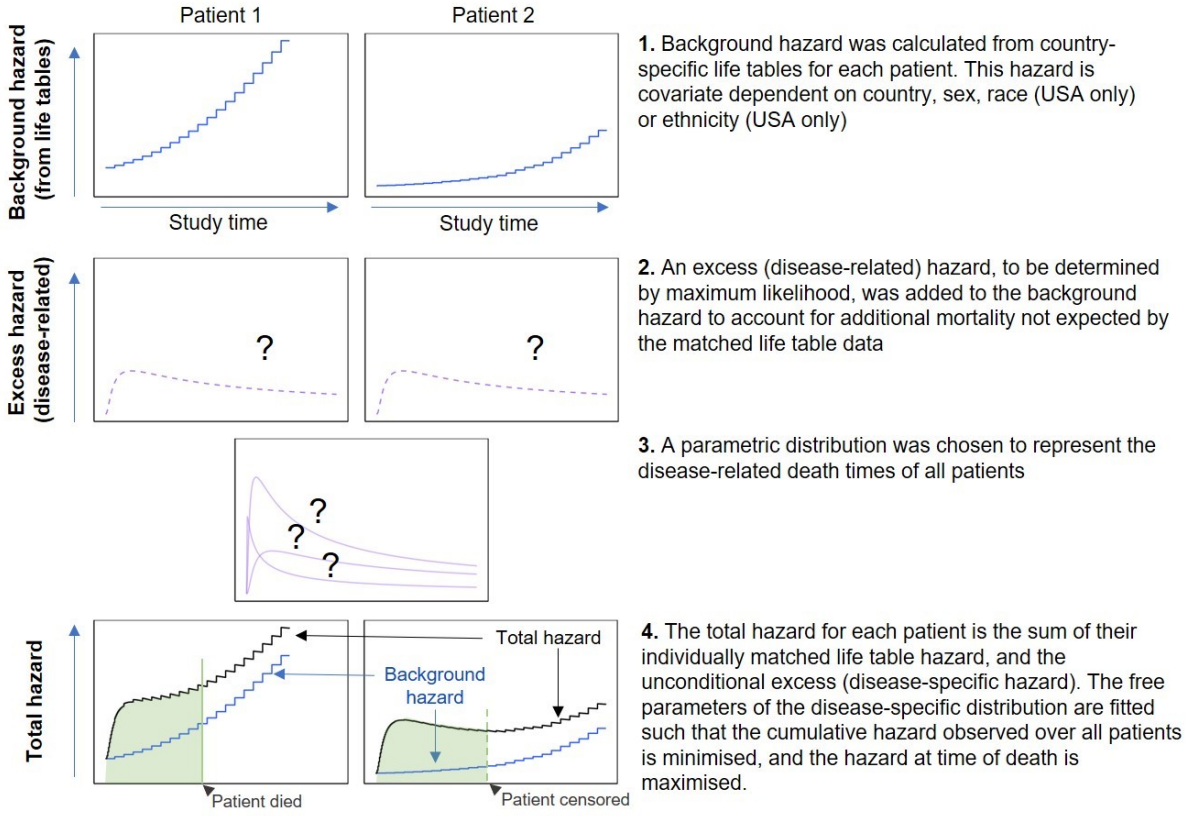
To compensate for the impact of age-, sex- and country-specific background mortality, a relative survival (excess mortality) parametric model structure was used (Appendix L.3). The concept of relative survival was first defined by Ederer et al[109], who defined several non-parametric estimators of this measure in order to compare survival in oncology, controlling for mortality by other means without relying on potentially unreliable cause attribution. The concept is applicable to parametric models, where the excess hazard of mortality above that

of the general population is represented by a parametric hazard function, as in Andersson et al.[110] The method of Andersson et al.[110] (which represents mortality in the general population by a further flexible parametric model) cannot easily include the general population hazards of matched patients from multiple national and sex-specific strata, and so a method is used that allows direct pass-through of look-up values from lifetables into the model fitting routine, as in the non-parametric Pohar-Perme estimation (*R* package *relsurv)*.[111]

As a method of model simplification, it has been assumed that excess hazard and background mortality are independent risks.

In order to supplement this excess hazard (i.e. ATTR-CM-specific mortality), 2015-17 England and Wales life tables are applied in the model to provide an estimate of the rate of UK-specific background mortality.[108] This provides an accurate estimation of mortality in the UK ATTR-CM population and avoids double counting of background mortality events.

Figure 35. Overall survival approach



To note, the following considerations were made:

- Each patient has a time of death after trial index day, which we may or may not observe
- Each patient has an administrative censoring time, which, if lower than the time of death, is observed
- Each patient has an age at study entry, a sex, a country in which the participating clinic is located, a race code and an ethnicity code. Missing or withheld race and ethnicity values are assumed “White” and “Not Hispanic or Latino” respectively; this only has impact in countries reporting differential survival per race and ethnicity (i.e. USA only)

- Patients are assumed to be at hazard from dying by two independent mechanisms:
    - The force of mortality among the general population adjusted for age, sex, country of residence, race and ethnicity (per life tables)
    - An unknown additional force of mortality, primarily attributed to the disease under investigation
- The hazard of death via the first mechanism was determined by looking up the appropriate hazards in national life tables. Appropriate life tables are chosen based upon the country of the investigating clinic, except for Brazil, which does not freely publish life tables. The one patient in a Brazilian clinic was assumed to be impacted by hazards reflected in USA life tables. Hazard and cumulative hazard were characterised from the age of the patient at study index time through to the end of support of the life tables which varied per country. Beyond this point, a very high hazard was introduced
- A distribution for the additional force of mortality was postulated with suitable initial values. For each patient, the hazard due to this distribution was added to the hazard due to life tables, and a resulting cumulative distribution and density of death times was defined
- The value of the inverse cumulative distribution for each patient was taken at their last observation time as part of their contribution to the likelihood. As this represented their probability of surviving over their follow-up, this tends to force the distribution to accumulate slowly (have low hazard)
- For patients observed to die, the density at the time of death was taken as an additional component to the individual likelihood. As this represents the probability of observing a death at that time, this tends to force the density distribution higher (have locally high hazard)
- The sum of the log of these components is then taken (equivalent to taking the log of the product of all these likelihood components, a function that increases monotonically with the likelihood but less likely to suffer from numerical issues during computation)
- The above steps were repeated with alternative values of the parameters, at first to establish the gradient of the likelihood function with respect to each of the parameters, and then to attempt to follow the gradient to the set of parameters that produce maximum likelihood
- These maximum likelihood parameters are used within a parametric model of the same structure within the cost-effectiveness model, allowing us to represent the additional force of mortality above any general force of mortality

B.3.3.4.3 Assessment of proportional hazards

In line with the NICE Decision Support Unit DSU [112] (Figure 1, Appendix L.1), the proportional hazards assumption was assessed to establish if the treatment effect was proportional over time. Log cumulative hazard plots presented in Figure 2, Appendix L.4) demonstrated clear violation of the proportional hazards assumption and therefore, individual parametric models were fitted for each treatment.

B.3.3.4.4 Parametric extrapolation of overall survival: methodology

Overall survival in the model was estimated based on fully parametric survival curves fitted to the ATTR-ACT trial disease related survival with excess non-disease related survival hazard from the ONS applied. This was based on guidance from the NICE DSU and Bagust and Beale (2014) (See Appendix L.1).[113]

Six parametric distributions were considered following guidance from the NICE Decision Support Unit (DSU): Exponential, Weibull, Log-logistic, Lognormal, Gompertz and Generalised-Gamma. All analyses were conducted using the *survival* and *flexsurv packages* in R. 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.[112] 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 KM and parametric survival curves were plotted to assess the fit during the trial period
- Consultation with clinical experts to assess the plausibility of the extrapolations
- Comparison of fitted curves to external data where appropriate

B.3.3.4.5 Tafamidis OS extrapolation

The AIC/BIC (Figure 36) 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 36) with slight overestimations of the observed data for approximately the first 20 months.

On comparison with the ATTR-ACT extension study extension, despite censoring and lower patient numbers at risk, there are approximately [redacted]% of patient alive at [redacted] months, which suggest all the distributions except for the exponential are slightly underestimating survival at around 50 months. Despite low patient numbers, the focus on NYHA I/II and the high proportion of wild-type (89%) patients, the Phase II extension study (Section B.2.6.4.2) provides another valuable source of validation for the long-term prognosis for tafamidis patients. After approximately 5.5 years, 80% of patients are alive which suggests all distributions could potentially be an underestimate after around [redacted] months and those with long tails may be more appropriate.

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.

Figure 36. Overall survival parameterisations – Overall population – tafamidis

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.

B.3.3.4.6 BSC OS extrapolation

All distributions provided similar statistical (AIC/BIC) and visual fits to the observed KM data (Figure 37), with the exception of the exponential which substantially underestimated the observed data for approximately the first 30 months. Beyond the end of the observed data the exponential produced a much higher tail than the other distributions.

Given the progressive nature of ATTR-CM and that placebo has no active mechanism, it is reasonable to assume that the risk of disease related hazard would increase over time, suggesting the Weibull or gompertz with monotonically increasing hazard would be the most appropriate distributions. This was aligned with discussions with clinicians, who suggested that patients would be relatively stable initially followed by a period of rapid progression.

The only available UK external data was the ATTR-CM cohort from the NAC presented by Lane et al.[19] As discussed in Section B.2.13.4, the baseline characteristics of the ATTR-ACT and NAC cohorts are relatively balanced. However, it was not appropriate to compare the survival between the cohorts given that the mean time from ATTR-CM diagnosis to study entry in the ATTR-ACT placebo arm was [redacted] years[73], in comparison to the NAC cohort where survival was measured from diagnosis, introducing the potential for significant lead time bias.

Although all patients in the placebo arm of the extension study crossed over to tafamidis and there is uncertainty in the impact of tafamidis, it would be expected that tafamidis would not have a negative impact on outcomes. Therefore, the placebo/tafamidis arm from the extension study provides a reasonable upper bound up for survival. For the overall population approximately [redacted] are alive at [redacted] months. This suggests the log-logistic and log-normal are overly optimistic with predicted survival rates of [redacted] and [redacted] respectively and the Weibull, generalised gamma or gompertz are more appropriate with survival estimates of [redacted], [redacted] and [redacted], respectively.

Consequently, the 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. Furthermore, the Weibull was close to the placebo/tafamidis extension study arm, which was considered an upper bound of placebo survival outcomes, therefore the Weibull can be considered an optimistic estimate. The generalised gamma was applied in scenario analysis.

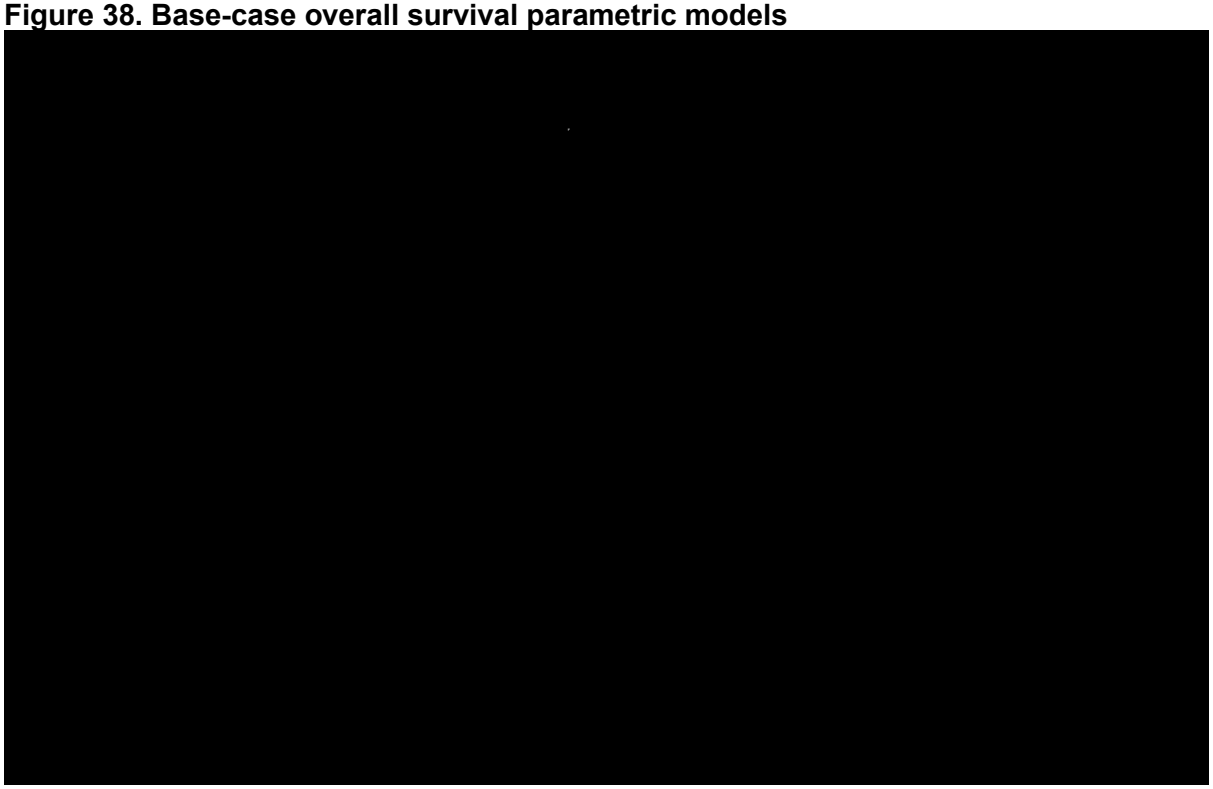
Figure 37. Overall survival parameterisations – Overall population – placebo

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.

B.3.3.4.7 Base-case overall survival

The base-case overall survival curves applied in the model are presented in Figure 38.

Figure 38. Base-case overall survival parametric models



Excess hazard - ONS life tables for average modelled patient applied.

B.3.3.4.8 Relative risk of death per NYHA class

Clinicians advised that patients can expect to have a higher risk of death in latter NYHA stages. Therefore, a different proportion of patients within each NYHA class move to the death state depending on an estimated relative risk.

A survival model derived from all patients unconditional upon NYHA class was preferred over a NYHA-specific survival model, as it requires estimation of fewer direct parameters (for the NYHA-specific risk of mortality) and indirect parameters (for NYHA state transition) that would affect the precision of the overall survival estimate. Disaggregation of this more precise total survival time was then achieved by use of observed NYHA state transition rates and relative risks of mortality derived using a Cox proportional hazards model of overall survival conditional upon time-varying NYHA status.

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.

Table 48. Cox proportional hazard model on OS by last observed NYHA class (LOCF)

NYHA class	Coefficient	Hazard ratio[a]	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]

[a]Applied in the economic model
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.

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.

B.3.3.5 Treatment discontinuation

For the tafamidis arm, discontinuation rates applied in the economic model were informed by fully parametric survival curves fitted to treatment discontinuation observed in ATTR-ACT (Figure 39). The time-to-event analysis was a competing risks analysis of death, to avoid double counting of death events as discontinuation events when implemented in the model.

ATTR-ACT data demonstrates that patients discontinue tafamidis prior to death. This was expected given that ATTR-CM is associated with an elderly population with higher rates of comorbidities and discussions with clinical experts suggested that patient may discontinue when their disease is no longer stabilised in latter NYHA stages and would discontinue treatment at least 12 months prior to death. To reflect real-world clinical practice, it was assumed that all patients would discontinue treatment prior to entering NYHA IV. Therefore, in addition to the censoring applied to OS (censoring for heart transplant, fitting of a CMAD, death and loss of follow-up), to avoid double counting of discontinuation in patients progressing to NYHA IV, ATTR-ACT data were censored for patients on date of progression to NYHA IV.

Discontinuation profiles for the tafamidis arm are presented in Figure 40. Determination of the most appropriate survival function was undertaken, through an evaluation of goodness-of-fit

and the appropriateness of the parametric extrapolation by visual inspection over the observed period.

In summary, Kaplan-Meier plots describing discontinuation in the tafamidis arm of ATTR-ACT suggested that the hazard of discontinuation remains constant over time. In line with the hazard profile, discontinuation in the tafamidis arm was best represented by the exponential model based on BIC. This was aligned with the observed discontinuation rate in the 30-month follow-up of ATTR-ACT. Given the similarities in the statistical fits of the remaining distributions, the log-normal was included in a scenario analysis as a longer alternative.

Figure 39. Kaplan-Meier of time on treatment and overall survival

Figure 40. Tafamidis- censored for NYHA IV. Treatment discontinuation parameterisations with death as a competing risk

Abbreviations; AIC: Akaike information criterion; BIC: Bayesian information criterion; NYHA: New York Heart Association Classification.

B.3.3.6 Hospitalisation events

Aligned with the co-primary endpoints in ATTR-ACT, CV-related hospitalisations were included in the model. CV-related hospitalisation events were evaluated on a cyclical basis. Event rates were determined by the application of both NYHA-specific and treatment-specific probabilities, derived from ATTR-ACT. Monthly probabilities were calculated by scaling and converting the mean of the observed 6-monthly rates. Observations for patients with an unknown NYHA classification were excluded from the derivation.

Applied estimates for the proportion of patients experiencing CV-related hospitalisation in each NYHA class health state are presented in Table 49 for the tafamidis and placebo arms.

Table 49. Monthly rates of CV-related hospitalisation events

Parameter	NYHA I	NYHA II	NYHA III	NYHA IV
Tafamidis				
Proportion hospitalised (per month)	[redacted]	[redacted]	[redacted]	[redacted]
BSC				
Proportion hospitalised (per month)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: Best Supportive Care; NYHA class: New York Heart Association Classification.
Note, value applied in the model on log scale, see Appendix N for standard errors.

B.3.4 Measurement and valuation of health effects

EuroQoL five-dimension 3-level (EQ-5D-3L) data were available directly from the ATTR-ACT trial. To identify further estimates relevant to this submission, a systematic literature review was conducted. This review, described in section B.3.4.3 and Appendix H, yielded several additional studies [redacted].

B.3.4.1 Health-related quality of life data from clinical trials

In ATTR-ACT, EQ-5D-3L data were collected at baseline and at 6-monthly review up to final review at Month 30.

Of the 441 patients in the ATTR-ACT ITT population, the percentage of patients completing the EQ-5D, from baseline to Month 30 ranged from [redacted] in the tafamidis, and from [redacted] in the BSC arm. (Missing data is summarised in Appendix M.1).

The EQ-5D index scores and VAS scores at baseline in ATTR-ACT were comparable between the two arms, [redacted] and [redacted] in the tafamidis and placebo arms, respectively.

Responses to each of the EQ-5D-3L dimension questionnaires for pooled tafamidis and placebo patients at the Month 0 and Month 30 timepoints are summarised in Appendix M.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.

[redacted]

Despite its limitations [redacted]

(Appendix M.3).

EQ-5D-3L index values were derived using the Dolan specific coefficients (preference weights)[114], with treatment and NYHA specific utility values generated using the mean utility experienced by patients occupying each NYHA class, independently for each arm. Autocorrelation between repeated observations of a single patient was accounted for using the Prais-Winsten estimator[115]. This estimate of auto-correlation assumes that correlation between subsequent measurements of a patient within the same NYHA class was constant. The generated utilities are presented in Table 50.

Table 50. ATTR-ACT utility data

Health state	Mean (SE)	Patients/ Observations	95% CI
Tafamidis			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
BSC			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: Best Supportive Care; CI: confidential interval; NYHA class: New York Heart Association Classification; SE: Standard error.

B.3.4.2 Mapping

No mapping was conducted, as EQ-5D-3L data were collected from ATTR-ACT.

B.3.4.3 Health-related quality of life studies

An SLR was conducted to identify relevant HRQoL studies. Details of the search strategy, inclusion criteria and individual study results are described in Appendix H.

Table 51 summarises EQ-5D from the identified studies in patients with ATTR-CM; full data are provided in Appendix H. Besides ATTR-ACT, only two studies (Grogan 2017[20] and Stewart 2018[22]) reported EQ-5D utility values relevant to the ATTR-CM population.

- The Stewart et al. study population[22] consisted of ATTR patients in the US, recruited via advocacy groups and online. Only 6 patients in the study reported having ATTR-CM alone (a further 11 reported having both ATTR-CM and ATTR-PN). In the ATTR-CM-only patients, the mean (SD) EQ-5D utility index score (calculated using US-specific weights) was 0.83 (0.2), and the overall health status rating from the EQ-5D VAS was 63.2 (12.7).
- The Grogan et al. study[20] was published as a conference abstract only. EQ-5D scores were reported by NYHA class and genotype (hereditary [n=213] versus wild-type [n=72]) for 285 patients with ATTR-CM from an international observational study (THAOS); countries of origin and weighting system used were not reported. Mean (SD) EQ-5D index score for the overall population (all NYHA classes) was 0.81 (0.15) for wild-type and 0.79 (0.19) for hereditary ATTR-CM. There was a trend for patients with wild-type ATTR to have higher (better) EQ-5D Index scores than those with hereditary ATTR-CM. Index scores decreased with higher NYHA class. The overall health status rating from the EQ-5D VAS was: 65.2 (18.8) for wild-type and 68.1 (21.7) for hereditary ATTR-CM.
- The EQ-5D index and VAS scores in the two studies are very similar. [redacted] to the EQ-5D index scores at baseline in ATTR-ACT, which were [redacted] in the tafamidis and placebo arms, respectively; and the ATTR-ACT baseline VAS scores, which were [redacted] in the respective arms.

Table 51. HRQoL values identified in the SLR

Author (year)	Instruments used	Population	Sample size	HRQoL outcomes, mean (SD)
Grogan (2017)[20]	EuroQoL-5D and EuroQoL-VAS	Wild-type ATTR-CM Hereditary ATTR-CM (Val122Ile, Thr60Ala, L111M, I688L)	Total: 285 Wild-type: 213 Hereditary: 72	ED-5D Index Score: All ATTR-CM: Wild-type: 0.81 (0.15) Hereditary: 0.79 (0.19) NYHA I Wild-type: 0.91 (0.10) Hereditary: 0.81 (0.23) NYHA II Wild-type: 0.84 (0.12) Hereditary: 0.81 (0.17) NYHA III Wild-type: 0.71 (0.17) Hereditary: 0.69 (0.21) EQ-VAS: All ATTR-CM: Wild-type: 65.2 (18.8) Hereditary: 68.1 (21.7) NYHA I Wild-type: 71.3 (26.3) Hereditary: 70.0 (21.2)

				NYHA II Wild-type: 64.6 (19.5) Hereditary: 69.2 (20.1) NYHA III Wild-type: 57.8 (17.6) Hereditary: 53.0 (20.4)
Stewart (2018)[22]	SF-12 HADS Pain EQ-5D-3L KCCQ	ATTR-CM	6	SF-12 PCS: 32 (9.5) MCS: 54.2 (8.6) HADS Depression: 6 (3.5) Anxiety: 4.2 (4.1) Pain Now:0.8 (2) Average last week: 0.8 (1.6) Worst last week: 1.2 (1.8) EQ-5D-3L Mobility: 1.7 (0.5) Self-care: 1 (NA) Usual activities: 1.7 (0.8) Pain/discomfort: 1.3 (0.5) Anxiety/depression:1.2 (0.4) Utility index score: 0.83 (0.2) Overall health status rating: 63.2 (12.7) KCCQ Physical limitation: 31.1 (25.9) Symptom Stability: 45.5 (10.1) Symptom Frequency: 37.9 (21.6) Symptom burden: 41.7 (20.1) Total symptom: 39.8 (19.3) Self-efficacy: 77.3 (22.2) Quality of life: 46.2 (15.1) Social limitation: 24.6 (21.4) Overall summary: 35.4 (16.5)

Abbreviations: HADS: Hospital Anxiety and Depression Scale; KCCQ: Kansas City Cardiomyopathy Questionnaire; KCCQ-OS: KCCQ Overall Summary; MCS: Mental Health Composite Score; NA: not applicable; NYHA: New York Heart Association Functional Class; PCS: Physical Composite Score; QoL: quality of life; SLR: systematic literature review; standard deviation; SF-12: Short form-12; SF-36: Short form-36; VAS: visual analogue scale.

B.3.4.4 Adverse reactions

An overview of common AEs is provided in Section B.2.10.1, which demonstrates that most common AEs are more frequent in the placebo arm than the tafamidis arm. The EQ-5D data used to inform the NYHA-specific utility values implicitly capture patients who were suffering an AE, so that additional application of AE-related disutility could result in double counting. Thus, the model assumes that utility decrements due to AEs were captured using trial-based EQ-5D-3L data to derive the NYHA class-based utilities. Consequently, no additional utility decrements for adverse events are applied.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Utility data from ATTR-ACT were considered the most appropriate for use in the economic model given that it aligned with the NICE reference case (EQ-5D; derived directly from patients; valued using UK algorithm) and aligned with values identified in the external literature (although potentially low in comparison for NYHA II and III). In addition, 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 (no CV-related hospitalisation utility data was identified in the SLR).

Base case utility values applied in the model are summarised in Table 52.

Table 52. Health state utility by NYHA class and treatment arm

Health state	Mean	SE	95% CI	Source	Justification
Tafamidis					
NYHA I	[redacted]	[redacted]	[redacted]	ATTR-ACT	Direct evidence of HRQoL in patients receiving tafamidis, stratified by the most relevant modifier of quality of life (NYHA status). Values based on direct EQ-5D data elicited from patients in line with NICE reference case.
NYHA II	[redacted]	[redacted]	[redacted]		
NYHA III	[redacted]	[redacted]	[redacted]		
NYHA IV	[redacted]	[redacted]	[redacted]		
BSC					
NYHA I	[redacted]	[redacted]	[redacted]	ATTR-ACT	Direct evidence of HRQoL in patients receiving established clinical management, stratified by the most relevant modifier of quality of life (NYHA status). Values based on direct EQ-5D data elicited from patients in line with NICE reference case.
NYHA II	[redacted]	[redacted]	[redacted]		
NYHA III	[redacted]	[redacted]	[redacted]		
NYHA IV	[redacted]	[redacted]	[redacted]		

Abbreviations: BSC: Best Supportive Care; NYHA class: New York Heart Association Classification; SE: Standard error.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Costs considered in the model are stratified across the following components:

- Treatment-related costs;
- Background health state costs;
- Hospitalisation costs;
- Treatment-related adverse event costs; and
- End of life care costs.

Unless otherwise stated, all specified costs represent monthly values, in line with the model's cycle length. End of life costs were inflated to 2017-2018 values using the PSSRU hospital & community health services (HCHS) inflation index.[107]

B.3.5.1 Published cost and healthcare resource identification, measurement and valuation studies

In line with the NICE guide to the methods of technology appraisal 2013[105], an SLR was conducted to identify published literature reporting the costs and healthcare resource use for patients with ATTR-CM. Full details of the process and methods of the SLR are provided in Appendix I. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) were conducted in September 2018 and subsequently updated in May 2019. The search was extended to include studies describing cardiomyopathy due to the low number of expected studies for ATTR-CM.

The SLR identified 18 studies for cardiomyopathy; there were no published studies identified specifically for ATTR-CM. Of the 18 studies, none were conducted in a UK setting.

B.3.5.2 Intervention and comparators' costs and resource use

While on-treatment, patients are subject to intervention-specific treatment-related costs, comprised of targeted treatment and concomitant medication costs.

Tafamidis and placebo-related costs are summarised in Table 53. An overview of the derivation of each component is provided in Sections B.3.5.2.1 and B.3.5.2.2.

Table 53. Summary of monthly treatment-related costs

Intervention	Cost component	Mean	SE	Dosing info	Source
Tafamidis*	Drug acquisition	£10,685.00	NA	Table 54	
	Concomitant medication	£18.18	£3.64	Table 55; Table 56	MIMS[106]
Placebo	Concomitant medication	£18.92	£3.78	Table 55; Table 56	MIMS[106]

* Tafamidis is an oral therapy and so is assumed to accrue no administration cost.
Calculation of concomitant medication cost provided in Section B.3.5.2.2.
¥SE assumed to be 20% of mean.
Abbreviations: NA: not applicable; SE: standard error.

B.3.5.2.1 Tafamidis costs

For the tafamidis arm, all patients are initiated in the active treatment health states and are assumed to remain on-treatment until discontinuation. Monthly tafamidis treatment costs applied in the model were based on the required dosing schedule, as presented in the SmPC.[9]

Table 54. Tafamidis dosing and unit costs

Intervention	Dosing schedule	Pack size	Unit cost	Cost per monthly cycle
Tafamidis	61 mg per day	30 soft capsules	£10,685.00	£10,840.82

Abbreviations: mg: milligrams

In line with expected clinical management, following discontinuation of tafamidis, patients will cease to accrue any costs associated with tafamidis and are assumed to accrue no further treatment-related costs, but continued to incur health state-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.

Patients who have not yet formally discontinued tafamidis treatment may experience treatment breaks, in which they are not dispensed treatment for a short period of time. To account for this, the applied tafamidis drug acquisition costs (Table 53) were adjusted based on the percentage of patients ([redacted]%) that had dosing adherence <80% ([redacted]% of patient treatment cost*80%)

B.3.5.2.2 Concomitant medications

Concomitant medications considered in the model reflect those commonly used as background therapy for patients with ATTR-CM to manage heart failure symptoms. The list of

relevant therapies was sourced from publications related to ATTR-ACT.[11,31] For each therapy, monthly costs (Table 55) were derived based on unit costs and recommended dosing levels reported by the Monthly Index of Medical Specialities (MIMS).[106] Derived monthly values were subsequently weighted by usage levels, as observed for each arm in ATTR-ACT (Table 56), to provide treatment arm-specific mean monthly per patient concomitant medication costs (shown in Table 53).

Table 55. Monthly concomitant medication unit costs

Medication type	Monthly cost	Dosing	Source
Loop diuretics	£15.81	Furosemide (Frusol); 40mg once daily	MIMS[106]
Anticoagulants	£1.02	Warfarin (Marevan); 10mg daily	
Aspirin	£7.61	Bisoprolol/Aspirin; 5mg/100mg tab once daily	
Statins	£0.84	Simvastatin (Simvador); 40mg once daily	
ACEi	£10.92	Ramipril (Tritace); 5mg once daily	
Aldosterone antagonists	£46.44	Eplerenone (Inspra); 50mg once daily	
Antithrombotic agents	£9.47	Warfarin (Marevan); 10mg daily; Bisoprolol/Aspirin; 5mg/100mg tab once daily; Simvastatin (Simvador); 40mg once daily	
Beta blockers	£3.74	Propranolol; 40mg twice daily	
RAASi	£10.92	Ramipril (Tritace); 5mg once daily	

Abbreviations: angiotensin-converting-enzyme inhibitor; RAASi: renin angiotensin-aldosterone system inhibitor.

Table 56. Concomitant medication usage levels

Medication type	Percentage administered treatment			
	Overall	Pooled tafamidis	Placebo	Source
Loop diuretics	90.30%	66.29%	69.49%	Maurer et al. 2017;[11] Maurer et al. 2018[31]
Anticoagulants	71.00%	NR	NR	
Aspirin	61.30%	NR	NR	
Statins	51.60%	NR	NR	
ACEi	48.40%	NR	NR	
Aldosterone antagonists	29.00%	NR	NR	
Antithrombotic agents[a]	NR	39.77%	40.68%	
Beta blockers	NR	28.79%	29.94%	
RAASi	NR	26.14%	27.12%	

[a]Patients treated with a combination of anticoagulants, aspirin and statins, with costs derived as the sum of the respective components.
Abbreviations: ACEi: angiotensin-converting-enzyme inhibitor; RAASi: renin angiotensin-aldosterone system inhibitor; NR, not relevant (values assumed to be zero for cost derivation purposes).

B.3.5.2.3 Drug administration costs

Tafamidis is self-administered orally by the patient, and hence was not associated with any administration costs. Consistent with this, no administration cost was applied for placebo.

B.3.5.3 Health state unit costs and resource use

No specific routine resource usage for ATTR-CM was identified in the literature. Therefore, a study was commissioned to establish routine resource usage from chart reviews of [redacted] patients' post-diagnosis of ATTR-CM at Guy's and St Thomas' NHS Foundation Trust, between 2010 and 2018. Patient were allocated to the respective NYHA state through chart review at diagnosis. Data was extracted on all available patients and was considered to include all relevant routine resource usage for these patients when validated with a clinician. As expected resource use among those diagnosed in NYHA II to IV ([redacted] of follow-up) was very similar. In contrast, NYHA I resource use was substantially lower ([redacted] of follow-up), related in part, to patients' lack of symptoms which do not require regular follow-up. Therefore, NYHA I resource usage was assumed to differ, which was aligned with a previous analysis[116]. The resource usage identified is outlined in Table 57, with the respective unit costs and total cost per month presented by NYHA state.

Table 57. Health state unit costs and resource usage (NYHA I-IV per month)

Resource		Definition/Source	Units per month

	Unit cost (£)		NYHA I	NYHA II-IV
Echocardiogram	£188.67	EY50Z Complex echocardiogram, Outpatient procedure; Service code 320 Cardiology[62]	[redacted]	[redacted]
Outpatient (new)	£163.36	WF01B Cardiology Consultant Led; Non-Admitted Face-to-Face Attendance, First, Service code 320[62]	[redacted]	[redacted]
Outpatient (follow-up)	£128.05	WF01A Cardiology Consultant Led; Non-Admitted Face-to-Face Attendance, Follow-up, Service code 320[62]	[redacted]	[redacted]
Community nurse	£24.70	Community Nurse - Band 6 £74 per hour of patient-related work; assumed 20 minute appointment [107]	[redacted]	[redacted]
Total cost per month			[redacted]	[redacted]

Abbreviations: ACEi: angiotensin; NYHA: New York Heart Association Classification

B.3.5.4 Hospitalisation costs

CV-related hospitalisation event rates in the model are determined by events observed in ATTR-ACT (see Section B.3.3.6 for derivation). Hospitalisation events are associated with a treatment-independent one-off event cost, applied on event incidence.

Event costs were obtained from 2017/18 NHS reference costs[62], with CV-related hospitalisation costs derived as a weighted average of all non-elective long hospital stays for heart failure or shock and arrhythmia or conduction disorders. Applied event costs are presented in Table 58.

Table 58. CV-related hospitalisation costs

Parameter	Mean	SE	Source
Cost per event	£2,536.88	£507.38¥	NHS ref costs 2017/18[62] Heart Failure or Shock, with CC Score 0-14+ [HRG codes: EB03A; EB03B; EB03C; EB03D; EB03E] Arrhythmia or Conduction Disorders, with CC Score 0-13+ [HRG codes: EB07A; EB07B; EB07C; EB07D; EB07E]

¥SE assumed to be 20% of mean
Abbreviations: SE: Standard error

B.3.5.5 Adverse reaction unit costs and resource use

During ATTR-ACT, tafamidis treatment was safe and well tolerated, with a similar safety profile to placebo. Given the low rate of severe treatment related AEs, the cost of treatment related AEs of any severity were incorporated via the application of treatment-specific probabilities as outlined in Table 59.

Table 59. Incidence of adverse events as applied in the model

	Pooled tafamidis		BSC	
	Frequency (n)	Frequency (%)	Frequency (n)	Frequency (%)
n	264		177	
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: Best Supportive Care

Costs associated with the management of AEs were incorporated via the application of a one-off cost in the first model cycle. Specified event costs were derived from a previous NICE appraisal for cardiovascular disease[117] and NHS reference costs (Table 60). These unit costs were applied in conjunction with the proportion of patients expected to experience each AE (Table 59) to derive the overall mean per patient AE cost presented in Table 61.

Table 60. Adverse event unit costs

Event	Mean	SE[a]	Source
Diarrhoea	£245.44	£49.09	TA197[117], Gastrointestinal AE cost of £217 Inflated from 2009 to 2018 costs using PSSRU HCHS inflation index[107]
Nausea	£245.44	£49.09	TA197[117], Gastrointestinal AE cost of £217 Inflated from 2009 to 2018 costs using PSSRU HCHS inflation index[107]
Urinary tract infection	£250.08	£50.02	NHS ref costs 2017/18[62] Kidney or Urinary Tract Infections, without Interventions, with CC Score 0-13+ [HRG codes: LA04S; LA04R; LA04Q; LA04P; LA04N]

[a]Assumed based on 20% of mean value.
Abbreviations: AE: adverse event; GP: general practitioner; SE: standard error.

Table 61. Total cost of adverse events

Treatment	Total cost (£)
Tafamidis	[redacted]
BSC	[redacted]

B.3.5.6 End of life costs

End of life care costs capture the additional resource use burden incurred by patients in the final months of life. Costs are incurred on the incidence of death. The default value applied in the model (shown in Table 62), is based on a UK primary care database study by Hollingworth et al. that sought to estimate the costs of medications and healthcare in patients who had died from heart failure.[118] The cost applied was estimated as the sum of resource use levels in the

three months prior to death as reported by Hollingworth et al., with cost inflated to 2017/18 values using the PSSRU HCHS inflation index.[107]

Table 62. End of life costs

Parameter	Mean	SE	Source
End of life care cost	£9287.86	£1857.57¥	Hollingworth et al.[118] PSSRU HCHS inflation index[107]

¥ SE assumed to be 20% of mean.
Abbreviations: SE: standard error.

B.3.5.7 Miscellaneous unit costs and resource use

No additional costs or resource use were incorporated.

B.3.6 Summary of base case analysis inputs and assumptions

All model inputs applied in the base-case and sensitivity analyses are summarised in Table 1 (Appendix M).

B.3.6.1 Assumptions

A summary of the assumptions used in the model, together with justifications, is provided in Table 63.

Table 63. List of assumptions used in the model, with justifications

Assumption/decision	Submission Section	Rationale/justification and source
Model structure/techniques		
Treatment discontinuation: Patient will discontinue treatment prior to progression to NYHA IV.	B.3.2.2 and B.3.3.5	ATTR-ACT data demonstrates that many patients discontinue tafamidis prior to progressing to death. This was expected given that ATTR-CM is associated with an elderly population with higher rates of comorbidities and discussions with clinical experts, suggested that patient may discontinue when their disease is no longer stabilised in latter NYHA stages and would discontinue treatment at least 12 months prior to death. To reflect clinical practice, it was assumed that all patients would discontinue treatment prior to entering NYHA IV. Furthermore, there is no clinical evidence for the efficacy of tafamidis in NYHA IV.
Event time resolution: Disease progression (NYHA class transitions) is evaluated at each major	B.3.2.2	Within ATTR-ACT, NYHA classification evaluations were performed at 6-month intervals i.e., discrete timepoints. In contrast, the occurrence of other clinical events was

time-step (six-months/cycles), while the incidence of all other clinical events is evaluated at each minor time-step (one month/cycle).		observed in continuous time and, hence, a higher time resolution is necessary to adequately capture event incidence.
NYHA transition probabilities: A singular transition matrix is employed for the entirety of the extrapolation phase.	B.3.3.3	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.
Clinical efficacy data		
Comparative efficacy data population alignment: Comparative efficacy data employed in the model is based on the Pooled (20 mg and 80 mg dosing groups) population, while the anticipated EMA-recommended dose is 61 mg tafamidis free acid once daily, which is bioequivalent to 80 mg tafamidis meglumine.	B.3.3.1	ATTR-ACT was powered to show a statistically significant difference between the Pooled (20 mg and 80 mg dosing groups) and placebo populations; a total of 300 participants were required to yield a power of greater than 90% for the primary comparison and, hence, this population provides the most appropriate evidence
Efficacy data source: Extension study only employed for validation purposes.	B.3.3.1	The ATTR-ACT extension study provided additional follow-up data. However, there is potential for a minor selection bias and has therefore not been used to inform the base case analysis. Instead, the extension study was used to provide validation of extrapolated outcomes.
Utility		
Health state utilities: Applied health state utility profiles are assumed to be treatment-specific.	B.3.4.5	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.
Adverse event utility decrements: Adverse event utility decrements not explicitly modelled.	B.3.4.4	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.

Costs and resource use		
Treatment-related costs on discontinuation: On discontinuation of tafamidis, patients are assumed to incur no further treatment-related costs.	B.3.5.2	Data on treatments received post-discontinuation of tafamidis are not available from ATTR-ACT 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.
Treatment discontinuation: Patients treated with BSC (placebo arm) are assumed to remain on-treatment until death or the model horizon has elapsed.	B.3.3.5	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
Cost of adverse events: The cost of adverse events are applied as a one-off cost at the start of treatment	B.3.5.5	Most adverse events will occur within the first year of treatment and any adverse events occurred beyond the first year will only have a minimal difference due to discounting.

Abbreviations: BSC: Best Supportive Care; HRQoL: health related quality of life; NYHA: New York Heart Association

B.3.7 Base-case results

Results of the base-case incremental cost-effectiveness analyses with tafamidis at list price are presented in Table 64. Disaggregated results are presented in Appendix J.

Table 64. Base case results (list price)

	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].

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The joint influence of all model parameters was evaluated via the conduct of a 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 (3,000), 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 65.

Table 65. Probabilistic base-case results (list price)

	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

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 41). The cost-effectiveness acceptability curve (Figure 42) indicated that there is an approximately [redacted] chance of tafamidis being cost-effective compared to BSC at the £30,000 per QALY threshold at list price.

Figure 41. Cost-effectiveness scatter plot

Figure 42. Cost-effectiveness acceptability curve

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted for all key variables in the model. The mean values and ranges applied are detailed in Appendix M.

A tornado plot showing the impact on the ICER of the various deterministic sensitivity analyses is presented in Figure 43.

Table 66 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 B.3.8.3, to assess the impact of the uncertainty in the analysis, with relatively little impact on cost-effectiveness outcomes.

Figure 43. Deterministic sensitivity analysis: impact on ICER

Table 66. Deterministic sensitivity analysis: Summary output for the most influential parameters

Scenario	Parameter variation	Incremental			ICER
		Costs	QALY	LYG	
Time horizon (years)	Lower	[redacted]	[redacted]	[redacted]	[redacted]
	Upper	[redacted]	[redacted]	[redacted]	[redacted]
Discount, benefits (%)	Lower	[redacted]	[redacted]	[redacted]	[redacted]
	Upper	[redacted]	[redacted]	[redacted]	[redacted]
Discount, costs (%)	Lower	[redacted]	[redacted]	[redacted]	[redacted]
	Upper	[redacted]	[redacted]	[redacted]	[redacted]
NYHA 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]
Age (years)	Lower	[redacted]	[redacted]	[redacted]	[redacted]
	Upper	[redacted]	[redacted]	[redacted]	[redacted]

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

B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess the sensitivity of the model to various assumptions. Details of each scenario are provided in Table 67 with results presented in Table 68.

Table 67. Scenario analysis results: additional scenarios

No.	Scenario	Base-case	Scenario description	Reference section in submission
1	Tafamidis survival projection	Log-normal	Exponential	B.3.3.4.5
2			Log-logistic	
3	BSC survival projections	Weibull	Generalised gamma	B.3.3.4.6
4	Tafamidis treatment discontinuation	Exponential	Log-normal	B.3.3.5
5	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 whom would have been mis/undiagnosed.	-
6	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.	B.1.3.4.3
7	Adoption of EAMS	Not included	Expanding number of specialised centres has removed the requirement for lengthy assessments and annual follow-up appointments for most patients at the NAC. Estimated to be a minimum saving of £128.05 per patient per year[2]	B.1.3.4.3
8	Alternative extrapolation of transition rates	Smoothed multinomial distribution fitted to all transition counts observed during the within-trial phase	Final within-trial transition matrix assumed	B.3.3.3
9	Treatment NYHA IV	No	Yes	B.3.3.5
10	Health state utilities	Treatment specific	Non-treatment specific NYHA I: [redacted]; NYHA II: [redacted]; NYHA III: [redacted]; NYHA IV: [redacted]	B.3.4.5
11	CV-related hospitalisation	Included	Excluded	B.3.5.4
12	AE costs	Included	Excluded	B.3.5.5
13	End-of-life cost	Included	Excluded	B.3.5.6

[1]Weighted average time to diagnosis 34.7 months (wild-type 39 months, hereditary 25 months). One third of patient were diagnosed in under 6 months, therefore optimal diagnosis assumed 6 months[19].

[2]Assumed a single cardiologist follow-up (WF01A Cardiology Consultant Led; Non-Admitted Face-to-Face Attendance, Follow-up, Service code 320[62]), does not account for any scans undertaken during visit and cost of travel for patient
Abbreviations: AE: adverse events; BSC: Best Supportive Care; NYHA: New York Heart Association

Table 68 details numeric output for the scenarios. As expected, employing alternative OS extrapolations for both treatment arms had the most significant impact, however these are only applied as indicative and are not the most plausible extrapolations. Furthermore, increasing time on treatment increased the accrual of acquisition costs in the tafamidis arm, causing the ICER to increase. Pathway redesign scenarios where conservative estimates have been applied, provide an indication of the direction of potential QALY and cost impacts that are not captured in the analysis. Other scenarios had a limited impact on the ICER.

Table 68. Scenario analysis results: additional scenarios

Scenario	Incremental		ICER	% change
	Costs	QALY		
Base case	[redacted]	[redacted]	[redacted]	-
1	[redacted]	[redacted]	[redacted]	-2%
2	[redacted]	[redacted]	[redacted]	12%
3	[redacted]	[redacted]	[redacted]	-9%
4	[redacted]	[redacted]	[redacted]	9%
5	[redacted]	[redacted]	[redacted]	-7%
6	[redacted]	[redacted]	[redacted]	-4%
7	[redacted]	[redacted]	[redacted]	0%
8	[redacted]	[redacted]	[redacted]	5%
9	[redacted]	[redacted]	[redacted]	10%
10	[redacted]	[redacted]	[redacted]	5%
11	[redacted]	[redacted]	[redacted]	-1%
12	[redacted]	[redacted]	[redacted]	0%
13	[redacted]	[redacted]	[redacted]	0%

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

B.3.8.4 Summary of sensitivity analyses results

Many sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. The most influential factors are those impacting long-term survival and accrual of costs associated with tafamidis acquisition, as can be expected given the degree of benefit for ATTR-CM patients receiving tafamidis.

B.3.9 Subgroup analysis

As per the final scope, NYHA I/II subgroup analysis was conducted (details of NYHA I/II specific inputs are provided in Appendix E). The results of the subgroup analysis are provided in Table 69.

Incremental survival for the overall population is observed to be lower than that estimated for the NYHA I/II analysis ([redacted] years versus [redacted] years). Although, as expected it resulted in increased treatment duration and thus a higher incremental cost (£[redacted] versus £[redacted]). These factors have an impact on the ICER, which reduced from £[redacted] in the base case population to £[redacted] in the NYHA I/II population.

Table 69. Cost-effectiveness analysis results: subgroup analysis

Subgroup analysis	Incremental			ICER
	Costs	QALY	LYG	
Base case	[redacted]	[redacted]	[redacted]	[redacted]
NYHA I/II	[redacted]	[redacted]	[redacted]	[redacted]

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

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

A technical review of the cost-effectiveness model was conducted by an independent consultant and amendments were made to address areas of concern. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

Further, the relevance of the model structure and assumptions were validated at an Advisory Board held on 6th November 2018, attended by a panel of experienced health economists and clinical experts. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results.

B.3.10.2 Comparison of clinical trial inputs and modelled outputs

A comparison of clinical trial inputs versus modelled outputs is provided in Appendix J. 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.

B.3.11 Interpretation and conclusion of economic evidence

B.3.11.1 Summary of the results

In the base case analysis 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].

B.3.11.2 Generalisability

As discussed in Section B.2.13.4, the ATTR-ACT population is generalisable to the patient population with ATTR-CM in the UK.

B.3.11.3 Strengths of the economic evaluation

The economic analysis has several key strengths:

- The structure was relatively simple whilst utilising the available data from the pivotal trial and capturing the key outcomes of interest in ATTR-CM.
- 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.

B.3.11.4 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. Despite this, by extrapolating based on the observed data in ATTR-ACT (which had complete follow-up up to 30 months), along with use of the extension data where appropriate to validate, the best available evidence has been considered.

In addition, all-cause mortality from the trial 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.

B.3.11.5 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 (HR 0.70 [0.51, 0.95]), CV-related hospitalisations (RR 0.67 [0.56, 0.81]), physical functioning (6MWT) and quality of life (KCCQ-OS, EQ-5D). Evidence from the extension study demonstrated a [redacted] occurring in the 12 months of additional follow-up 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 (and [redacted] in NYHA I/II subgroup analysis).

The availability of a disease-modifying treatment, in conjunction with widespread adoption of the non-invasive diagnostic pathway,[4] will 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). In addition, significant cost savings would be realised (potentially in excess of £20,000 per patient).

ATTR-CM is a rare disease with debilitating morbidity and premature mortality. Tafamidis is the first and only disease-modifying treatment for ATTR-CM, addressing 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 treating transthyretin amyloid cardiomyopathy [ID1531]

Clarification questions

October 2019

File name	Version	Contains confidential information	Date
ID1531_Tafamidis_ Clarification_Response_24OCT19(ACIC)	Final	Yes	24 October 2019

Dear Jasdeep,

Pfizer would like to thank ScHARR 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). The associated cost effectiveness analysis is conservative and in all likelihood underestimates the system impact afforded by the introduction of this new treatment.

Several of the questions raised by the ERG were focused on providing further clarification of the system benefit associated with this new medicine: one suggestion hypothesised that the introduction of scintigraphy is contributing to the reductions in total costs, with improved outcomes already being realised in the system for the ATTR-CM population. We would advise that the method of diagnosis alone would not be expected to influence diagnosis rates or time to diagnosis. Indeed, despite the introduction of scintigraphy at the NAC 7 years ago, the average delay to diagnosis remains at 3 years, by which time some patients have experienced irreversible organ damage. The system benefits afforded by improving overall diagnosis rates and in making earlier diagnoses will be influenced by a greater index of suspicion for the disease in heart failure clinics across the country and regional access to confirmatory diagnostic tests. The introduction of a new medicine, such as tafamidis, would not only provide the first therapy for ATTR-CM patients but would also help to raise the profile and clinical suspicion of the disease. As a direct consequence you would see an increase in the diagnosis rate and critically an acceleration in the time to diagnosis. In the diagnostic pathway alone we have conservatively estimated a saving of £20,000 per patient. This exclude the benefit patients experience following a diagnosis, where the direct benefits of tafamidis arise from arresting progression of the disease leading to improved outcomes and a reduction in hospitalisations.

Pfizer would like to take the opportunity to highlight a few key elements of the ATTR-ACT study design that may not initially be evident when evaluating the submission

- Firstly, the study was designed to have complete follow-up for the first 30 months. Therefore, any discontinuation is accounted for within the base-case cost-effectiveness estimates and therefore introducing assumptions about discontinued patients being equivalent to BSC should not be considered appropriate.
- Secondly, given that ATTR-CM is a rare disease, the pooling of 20mg and 80mg was required to sufficiently power the study and was agreed a priori with regulators. Any additional benefits of the 80mg over the 20mg dose will lead to the pooled analysis presenting a conservative estimate of the overall efficacy of tafamidis.

[redacted]

Sincerely,

[redacted]

Section A: Clarification on effectiveness data

Literature searching

A1. Company submission Appendix D, Section D1.5, Table 4, page 9. In the inclusion criteria for the clinical systematic literature review (SLR) it is stated that *"reference lists of systematic literature reviews will be reviewed"*; however, the ERG notes that the search strategies contained a clause which excluded records with the publication/item type "Review" (which would thereby prevent the retrieval of records of SLRs which are often categorised as such). Was this an error? If not, what steps were taken to ensure that no relevant SLRs were missed?

The exclusion of publication type “review” from the database search strategies was not an error. To ensure no relevant SLRs were missed, published SLRs identified by the search strategy were to be earmarked for later review, even though they were excluded from the clinical SLR. Further, during the grey literature search, any additional SLRs identified were to be set aside for review of its reference list to ensure no relevant clinical studies were missed within this review.

As expected, there were no SLRs identified that published relevant clinical effectiveness evidence in an ATTR-CM setting, so the approach described above was not relevant in practice.

A2. Company submission Appendix D, Section D.1, page 4. Please cite the sources of the study type filters used in the searches for each SLR (providing citations to published validation studies where available).

The study type filters for “randomised controlled trial” and “observational study” search terms were adapted from the SIGN search filters.

Reference: Scottish Intercollegiate Guidelines Network. Search filters. 2019; https://www.sign.ac.uk/search-filters.html

Systematic review methods

A3. Appendix D, Section D.1.6, page 11. For the selection process of the systematic review, please confirm the proportion of citations that were independently checked by a second reviewer.

For the selection process of the systematic review, all studies (100%) were independently checked by a second reviewer. The list of citations retrieved by the literature search was duplicated, so each reviewer assessed all titles and abstracts identified by the search strategy independently.

A4. Appendix D, Section D.1.7, page 12. For the data abstraction process of the systematic review, please confirm the proportion of the data extraction that was checked by a second reviewer.

For the data abstraction process of the systematic review, all studies (100%) from which data were extracted were checked by a second reviewer.

A5. Appendix D, Section D.2.3, pages 25 to 36. Please elaborate the explanation for full text exclusion of the eight studies excluded for the reason of “other” in Table 12.

The reason for exclusion of studies categorised as “other” are provided below:

Table 12. Studies excluded after screening full-text articles

Reference	Reason for
Duca F, Aschauer S, Zotter-Tufaro C, Binder C, Kammerlander AA, Boerries B, et al. 2018. Riociguat in transthyretin cardiac amyloidosis-data from a named patient use program in austria. European Heart Journal.39:1050-1.	Study was identified in the SLR update but was included in the initial SLR
EU Clinical Trials Register. 2015. A study to look at the efficacy and safety of ALN TTRSC in patients with an inherited condition that causes certain protein molecules to deposit in the heart. Http://wwwwhoint/trialsearch/trial2aspx? Trialid=euctr2014-003835-20-es.	Study was terminated
EU Clinical Trials Register. 2014. A double-blind, randomized study looking at the efficacy, safety and tolerability of tafamidis meglumine (PF-06291826) 20 mg or 80 mg compared to placebo when taken daily by oral administration mouth in subjects diagnosed with transthyretin cardiomyopathy (TTR-CM). Http://wwwwhoint/trialsearch/trial2aspx? Trialid=euctr2012-002465-35-se.	Study publication (ATTR-ACT; Maurer 2018) identified in SLR update which was included in the initial SLR

Fox JC, Heitner S, Falk R, Grogan M, Jacoby D, Judge D, et al. 2019. Ag10 Consistently Stabilizes Transthyretin To A High Level In Both Wild Type And Mutant Amyloid Cardiomyopathy: Responder Analyses From A Phase 2 Clinical Trial. Journal of the American College of Cardiology.73(9):660.	Abstract for Judge (2019) which was included in the SLR
Kreusser MM, Kristen AV, Blum P, Tschierschke R, Schoenland SO, Hegenbart U, et al. 2016. Optimizing outcomes after heart transplantation in patients with cardiac amyloidosis - a single center analysis of 43 patients in 2 eras. European Journal of Heart Failure Abstracts Supplement (Supplement 1) 18:350	Abstract for Kristen (2018) which was included in the SLR
Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. 2018. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. New England journal of medicine.379(11):1007-16.	Study was included in original SLR
ClinicalTrials.gov. 2014. ENDEAVOUR: phase 3 Multicenter Study of Revusiran (ALN-TTRSC) in Patients With Transthyretin (TTR) Mediated Familial Amyloidotic Cardiomyopathy (FAC). Https://clinicaltrials.gov/show/nct02319005	No study publication
ClinicalTrials.gov. 2016. Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy. Https://clinicaltrialsgov/show/nct02791230.	No study publication
ClinicalTrials.gov. 2018. A Study of Doxycycline and Tauroursodeoxycholic Acid (Doxy/TUDCA) Plus Standard Supportive Therapy Versus Standard Supportive Therapy Alone in Cardiac Amyloidosis Caused by Transthyretin. Https://clinicaltrialsgov/show/nct03481972.	No study publication
Rosenbaum AN, Ezzeddine A, Omar F, Grogan M, Dispenzieri A, Kushwaha S, Clavell A, Daly R, Edwards B. 2018. Outcomes after cardiac transplant for wild type transthyretin amyloidosis. Transplantation April 19, 2018 Volume Online-First-Issue.	Pre-publication of Rosenbaum (2018) (included in SLR)
Sultan M, Gundapaneni B, Schumacher J, Schwartz J. 2016. Treatment with tafamidis slows disease progression in early stage transthyretin cardiomyopathy. Journal of cardiac failure Conference: 20th Annual Scientific Meeting of the Heart Failure Society of America. United States. Conference Start: 20160917. Conference End: 20160920. 22:[S66 p.].	Abstract for Sultan (2017)
Sultan MB, Gundapaneni B, Schumacher J, Schwartz JH. 2017. Treatment With Tafamidis Slows Disease Progression in Early-Stage Transthyretin Cardiomyopathy. Clinical Medicine Insights Cardiology.11:1179546817730322.	Data taken from Maurer (2015) – included in SLR
Whelan C, Drachman B, Heitner S, Maurer M, Damy T, Judge D et al. 2018. Inotersen improves the quality of life, polyneuropathy, and cardiomyopathy in patients with hereditary transthyretin amyloidosis: results of the phase 3 study NEURO-TTR. European Journal of Heart Failure (Suppl. S1) 20: 361	Population and outcomes

A6. Company submission, Section B.2.2, page 34. The reference provided for trial NCT00935012 (the extension study for tafamidis 20mg) is the clinical trial record which describes this Phase III trial as having recruited 31/35 patients since 2009. As no study results are posted on the clinical trial record and a further source cited is "Pfizer. B3461026: Phase 3, open-label extension study (of Study B3461025) in

patients with ATTR-CM. Data on file. 2018", please provide the safety and efficacy results from the most recent cut-off for this trial.

As of the latest data cut available (01 August 2018), no new deaths were reported in B3461026 beyond the [redacted] reported in Document B.2.6.4.3.

Based on information obtained as of the data cut-off date for this assessment, the safety profile of tafamidis as derived from Study B3461026 is consistent with that previously reported.

Pooling of data

A7. Priority question. Company submission, Section B.2.6.2, pages 58-68. The analysis of ATTR-ACT pools the data from the 20mg and 80mg tafamidis arms.

- **Company submission, Section B.2.4.1. Please justify why it was considered appropriate to pool the data for both arms.**

Common to all rare disease studies where there are small patient populations, the sample size in ATTR-ACT carefully considered the balance between feasibility of recruitment and power to allow clear conclusions about the effectiveness of tafamidis in treating ATTR-CM. Following agreement with regulatory bodies on the design of the study, ATTR-ACT was powered to assess the efficacy, safety, and tolerability of the pooled tafamidis meglumine 20 mg or 80 mg groups in comparison to placebo.[1] Subjects were randomly assigned to 80 mg, 20 mg or placebo in 2:1:2 fashion. Pooling the data across the two doses therefore reduces uncertainty in the primary outcome. While ATTR-ACT was not powered for dose response, a consistent treatment benefit for both doses compared to placebo was observed across all endpoints.[2]

- **Company submission, Section B.2.7.2, page 84. B.2.3.1.5, page 42: Please confirm that the 20mg and 80mg doses are considered as clinically equivalent with respect to the primary outcome. If so, why is the company seeking a marketing authorisation for a dose which is bioequivalent to the higher 80mg dose? If not clinically equivalent, then**

please comment on the appropriate interpretation of the estimated treatment effects based on the pooled data.

The efficacy of the two doses was clinically equivalent for the primary outcome measure and its component endpoints (Table 1).[2]

Table 1. ATTR-ACT: Comparison of Efficacy (primary endpoint and components) in Tafamidis 20 mg and 80 mg subgroups

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)
Primary Outcome		
Finkelstein Schoenfeld method (p-value)	0.0048	0.0030
Win Ratio method (95% CI)	[redacted]	[redacted]
All-cause Mortality		
Hazard Ratio versus placebo (95% CI)	[redacted]	[redacted]
Log-rank test p-value vs placebo	[redacted]	[redacted]
CV-related hospitalisations		
Frequency of CV-related hospitalisations (95% CI)	[redacted]	[redacted]
Relative risk ratio vs placebo (95% CI)	[redacted]	[redacted]
p-value	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CV: cardio vascular

In ATTR-CM, a disease that progressively disrupts functioning of the heart resulting in debilitating morbidity and mortality, consideration of all data is necessary to inform the choice of the recommended dose. Beyond the primary outcome, the totality of evidence to support the higher dose is outlined below:

- A greater degree of TTR tetramer stabilisation for tafamidis meglumine 80 mg compared with 20 mg;
- Clear differentiation favouring 80 mg using data from analysis of NT-proBNP, which is an accepted prognostic indicator for mortality in ATTR-CM;
- [redacted];

- A consistent safety profile between the two dose groups.

Based on the clinical differentiation discussed above the company is seeking a marketing authorisation for a dose which is bioequivalent to the higher 80mg dose. In addition, the clinical differentiation demonstrates that the use of pooled data not only reduces uncertainty but is likely to represent a conservative estimate of the clinical efficacy of tafamidis 80 mg.

[1] All-cause mortality by dose demonstrated a HR in the tafamidis 20mg/ tafamidis 20mg (ATTR-ACT/ATTR-ACT extension) group of [redacted] indicating a [redacted]% reduction in risk of death relative to the placebo/tafamidis group (p=[redacted]) and in the tafamidis 80 mg/ tafamidis 80 mg group, a HR of [redacted] indicating a [redacted]% reduction in risk of death relative to the placebo / tafamidis group (p=[redacted]). In a post hoc direct comparison of the tafamidis 20 mg/ tafamidis 20mg and tafamidis 80 mg/ tafamidis 80mg doses, the HR was [redacted], indicating a [redacted]% reduction in risk of death in patients receiving 80 mg relative to patients receiving 20 mg (p=[redacted]).

- **Company submission, Section B.2.7.2, page 84. The text states *"Following CHMP Opinion, any further information to support the submission will be provided."* Please clarify what additional information will be provided and when will it be provided.**

Following CHMP Opinion, we will share any additional information contained within the CHMP documents and label with respect to dose to support the submission.

Analyses of treatment effects

A8. Priority question. Company submission, Section B.2.6.2.4, page 65. Please clarify how transthyretin stabilisation was defined in ATTR-ACT.

One whole blood sample was collected at Baseline and Months 1, 6, 12, 18, 24, and 30 (or early study discontinuation) to test for stabilisation of TTR. These samples were analysed using validated analytical methods at LabCorp (Los Angeles, California, US).[2]

TTR tetramer stability was determined by comparing TTR tetramer concentration before and after urea denaturation.[3] The ratio of tetramer level post-denaturation to tetramer level pre-denaturation was termed the fraction of initial (FOI). Percent stabilisation was determined by comparing the FOI at each on-drug time point to the FOI at baseline (determined by measuring the FOI in plasma samples prior to the initiation of treatment) using the following formula:

Percent (%) stabilisation = 100 x (FOIdosed – FOIbaseline) / FOIbaseline.

Individuals with a percent stabilisation of >32% were considered stabilised.[4,5] This cut-off point was determined based on data from placebo-treated healthy volunteers in the phase 1, placebo-controlled single and multiple ascending dose study of tafamidis.[4] Means and 95% confidence intervals (CI) of percent stabilisation were calculated and any values above the 95% CI for the placebo-treated healthy volunteers (in this case, 32%) were classified as stabilised.[4]

A9. Priority question. Company submission, Section B.2.4, page 50. Please confirm that all statistical analyses of the primary and secondary endpoints include the stratification factors? If the analyses are not adjusted for stratification factors, please provide analyses which include these.

The stratification factors were accounted for in analyses conducted for this trial when applicable. Details are provided below.

The Finkelstein-Schoenfeld test applied in this study for the primary analysis used a hierarchical comparison of all-cause mortality and the frequency of CV-related hospitalisations and took the stratification factors into account. The Finkelstein-Schoenfeld analysis was applied by strata (based on TTR genotype and NYHA baseline classification) and combined to produce the overall test statistic. Thus the stratification factors were taken into account in the primary analysis.

Time to event (TTE) endpoints were analysed using Cox proportional hazards model (using Proc PHREG in SAS) with treatment, TTR genotype (variant and wild-type), and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors. For the TTE analyses by NYHA baseline classification, the Cox proportional hazard model included treatment and TTR genotype. For the analyses by TTR genotype, the model included treatment and NYHA baseline classification.

Endpoints evaluated at multiple time points were analysed using a mixed model repeated measures ANCOVA (MMRM) with an unstructured covariance matrix (or as appropriate); centre and subject-within-centre as random effects; treatment, visit, TTR genotype (variant and wildtype), and visit-by-treatment interaction, as fixed effects and Baseline score as covariate. While the NYHA baseline classification served as an indicator of baseline severity, for the endpoints that were evaluated at

baseline and at multiple points post-baseline, the respective baseline scores were used as the appropriate covariate for the MMRM analyses. For the MMRM analyses by TTR genotype, the same model specified above was used, with the addition of terms for TTR genotype-by-treatment interaction and TTR genotype-by-treatment-by-visit 3–way interaction. Similarly for dose, the same model specified above was used with replacement of “dose” for “treatment”. The subgroup analysis by NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) was done using ANCOVA (MMRM) with an unstructured covariance matrix (or as appropriate); centre and subject-within-centre as random effects; treatment, visit, TTR genotype (variant and wildtype), NYHA baseline classification, visit-by-treatment interaction, NYHA baseline classification-by-treatment interaction, NYHA baseline classification-by-treatment-by-visit 3–way interaction as fixed effects and baseline score as covariate.

Frequency of cardiovascular-related hospitalisation was analysed using Poisson regression analysis with treatment, TTR genotype (variant and wild-type), NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors adjusted for treatment duration. For the subgroup analyses by NYHA classification (NYHA Classes I and II combined and NYHA Class III), the Poisson regression analysis included treatment, TTR genotype (variant and wild-type), and treatment-by-TTR genotype interaction terms as factors adjusted for treatment duration. For the subgroup analyses by TTR genotype, the Poisson regression analysis had treatment, NYHA baseline classification, and treatment-by-NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors adjusted for treatment duration.

A Cochran-Mantel-Haenszel (CMH) was used as a test of proportions. For the overall, and analyses by dose, a Cochran-Mantel-Haenszel test for proportions stratified by TTR genotype and NYHA baseline severity (NYHA Classes I and II combined and NYHA Class III) was used. For subgroup analysis by TTR genotype, a CMH test for proportions stratified by NYHA baseline severity was used. The analysis was also performed separately by Baseline severity using a CMH test for proportions stratified by TTR genotypes (variant and wild-type).

A10. Company submission, Section B.2.6.2 (multiple instances throughout the submission). Analyses of change from baseline are inefficient unless they include the baseline response as a covariate in an analysis of covariance. Please clarify whether analyses of change from baseline also include baseline as a covariate. If not, please present the impact of including this on the results.

Please see detailed description of analyses above in response to A9. Baseline values were included as covariates for the ANCOVA (MMRM) analyses.

A11. Company submission, Section B.2.7.1.1, pages 75-78. Please confirm that the results presented in Figure 21 simultaneously adjust for New York Heart Association (NYHA) baseline classification, transthyretin (TTR) genotype and their interactions with treatment, whereas those in Tables 26 and 27 are only by NYHA classification and TTR genotype, respectively.

Yes, that is correct.

A12. Company submission, Section B.2.4.1.2, Table 15, page 54. The table mentions that no imputation was applied for the primary analysis. Please clarify how missing data were handled.

As specified in the protocol, vital status (alive/dead) was collected at Month 30 on all 441 subjects enrolled in ATTR-ACT. Thus, there were no missing data for the mortality outcome; data were available for all subjects studied. For the primary analysis, no imputation was done for cardiovascular-related hospitalisation.

A sensitivity analysis of the primary analysis using multiple imputation for CV-related hospitalisation was conducted. For this analysis, the Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of cardiovascular-related hospitalizations with multiple imputations was performed for the ITT analysis set. As observed in the primary analysis without imputation, the sensitivity analysis with multiple imputations demonstrated a significant treatment effect favouring tafamidis ([redacted]).

A13. Priority question. Company submission, Section B.2.4.1.2, Table 15, page 54. Please clarify why receiving a cardiac mechanical assist device (CMAD) or transplant was counted as a death event.

These two interventions have an unknown effect on outcomes in end stage disease and were therefore counted as death events in the primary analysis.

Given this approach assumes the worst outcome and the low frequency of these events (only [redacted] and [redacted] patients received heart transplants in the tafamidis and placebo groups, respectively, and [redacted] cardiac mechanical assist device implantations were performed in the tafamidis group), it can be considered a conservative approach.

A sensitivity analysis for the primary analysis, in which heart transplants and cardiac mechanical assist devices were not assumed as death, found the hazard ratio for all-cause mortality improved ([redacted] [95% CI 0.[redacted]]), indicating a [redacted]% reduction in the risk of death in the tafamidis group relative to the placebo group (p=[redacted]).

A14. Priority question. Company submission, Section B.2.6.2.2, Figures 13 and 14, pages 60 and 61. The titles of both of these figures refer to cardiovascular (CV)-related mortality. Is this an error? Should Figure 13 instead refer to all-cause mortality?

Yes that is correct, Figure 13 should refer to all-cause mortality.

A15. Company submission, Section B.2.6.2.1, Table 18, page 59. Please confirm that the limits of the 95% confidence interval and *p*-value for CV-related mortality are correct.

The correct 95% CIs are [redacted] with a p-value of [redacted].

A16. Company submission, Section B.2.6.2, Table 18, page 59 and page 61 (and elsewhere in the submission). Please confirm that the treatment effect for CV-related hospitalisations is a rate reduction and not a relative risk ratio.

The table presents the relative risk ratio, which is based on the frequency of CV-related hospitalisations.

A17. Company submission, Section B.2.6.2.2, page 60. Please provide results for the effect of treatment on TTR genotype and NYHA class at baseline from the Cox regression analysis of all-cause mortality.

The results of these analyses are reported in Section B.2.7.1.2, pages 76 and 77.

A18. Company submission, Section B.2.6.2.3, Figure 15 and Table 19, page 62. Please clarify the relationship between the results presented in Figure 15 and Table 19, and why they do not correspond at Month 30. Please also explain why the least squares (LS) mean difference is not the same as the difference in LS means.

Please see updated Table 19 below, the previous values reported means and not LS means.

Table 19. ATTR-ACT: Change from baseline to Month 30 in the distance walked during the 6MWT baseline classification (ITT population)

	Pooled Tafamidis	Placebo (N=177)
Distance walked at baseline in metres, mean (SD)	350.6 (121.3)	353.3 (126.0)
LS Mean Change from baseline to Month 30 in metres	[redacted]	[redacted]
LS[a] mean (SE) difference (versus placebo)	75.7 (9.2)	
p-value	<0.0001	

Least squares mean is from an ANCOVA (MMRM) model with an unstructured covariance matrix.
Abbreviations: 6MWT: 6-minute walk test; LS: least squares; N: total number of patients; n: number of patients; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).

A19. Company submission, Section B.2.6.2.3, page 63. Please comment on what inference can be made about the effect of tafamidis from the results in Figure 16.

In Figure 16 of the Company submission, green cells indicate the proportion of patients that improved or remained in their respective NYHA classification at Month 30. Blue cells indicate the proportion of patients that worsened in their NYHA classification at Month 30. Overall, a greater percentage of patients in the tafamidis group ([redacted]) improved upon or remained in their respective NYHA baseline classifications compared with those in the placebo group ([redacted]) at Month 30.[2]

NYHA classification is a validated measure of functional status[6] and a marker of disease severity used to classify patients with heart failure.[7,8] It is based on patients' reported symptoms with levels of activity and therefore aligns closely with patient symptoms and functional capacity. By reducing progression through NYHA stages relative to placebo,[2] tafamidis has been shown to preserve functional capacity in patients with ATTR-CM. Preventing or delaying progression through NYHA classes to late-stage heart failure means patients with ATTR-CM are able to carry out ordinary activities for longer. Late-stage heart failure is highly symptomatic and has a comparable symptom burden to advanced cancer.[9-11]

A20. Priority question: Company submission, page 63. Please comment on why baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) is not included as a covariate in the primary analysis when the submission states that it has *"been shown to independently predict mortality in ATTR-CM."*

At the time the ATTR-ACT study was being designed circa 2011-2012, the available literature indicated that NT-proBNP was a clinically meaningful endpoint to assess. However, it was not understood to be predictive of survival in ATTR-CM until more recent publications such as those of Grogan[12] and Gilmore[13] were available. Thus, NT-proBNP was not included as a covariate in the primary analysis as part of the study design.

Subgroup Analyses

A21. Company submission, Section B.2.7.1.1, page 75. Please confirm the statement

"[redacted]" is correct; the results in Table 26 suggest a rate ratio of [redacted] against tafamidis in NYHA class III patients.

The rate ratio of [redacted] we assume is derived from the frequency of CV-related hospitalisation rates. However, the Finkelstein-Schoenfeld analysis utilised as the primary endpoint is a hierarchical comparison of mortality and frequency of CV-related hospitalisations. A directionally favourable treatment effect was observed in all-cause mortality at Month 30 compared to the placebo group in patients with NYHA III baseline classification ([redacted] vs. [redacted], (HR, [redacted]; 95% CI, [redacted]; [redacted].[14]

A22. Company submission, Section B.2.7.1.3, page 79 and page 80. Please clarify the statistical model that has been used to generate the results in Figures 22 and 23.

Per the response to A9 above, the subgroup analysis by NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) was done using ANCOVA (MMRM) with an unstructured covariance matrix (or as appropriate); centre and subject-within-centre as random effects; treatment, visit, TTR genotype (variant and wildtype), NYHA baseline classification, visit-by-treatment interaction, NYHA baseline classification-by-treatment interaction, NYHA baseline classification-by-treatment-by-visit 3-way interaction as fixed effects and baseline score as covariate.

A23. Company submission, Table 28, page 82. Please confirm that the LS mean differences and the mean changes from baseline are correct, and that both are adjusted for baseline response.

Please see updated Table 19 below, the previous values reported means and not LS means. Both are adjusted for baseline response.

Table 28. ATTR-ACT: Change from baseline to Month 30 in the KCCQ-OS stratified by NYHA baseline classification

	NYHA class I/II (N=300)		NYHA class III (N=141)	
	Pooled tafamidis (N=186)	Placebo (N=114)	Pooled tafamidis (N=78)	Placebo (N=63)
KCCQ-OS at baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline to Month 30 in KCCQ-OS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS[b] mean (SE) difference (versus placebo)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

[a]Overall score is calculated as the mean of physical limitation, symptom frequency, symptom burden, quality of life, and social limitation scores.
Least squares means are from an ANCOVA (MMRM) model with an unstructured covariance matrix.
Abbreviations: KCCQ-OS: Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS: least squares; N: total number of participants; n: number of participants; SD: standard deviation; SE: standard error.
Source: Clinical Study Report (B3461028).

Section B: Clarification on cost-effectiveness

Model structure

B1. Company submission, Section B.1.3.5, page 26. Please clarify whether ATTR-ACT included the measurement of estimated glomerular filtration rate (eGFR), NTproBNP and/or tropotonin T levels at each clinic visit at which the NYHA was measured. If so, would it have been possible to characterise the model health states using the Mayo or National Amyloidosis Centre (NAC) classification systems rather than NYHA?

NT-proBNP and troponin I were only measured at baseline, Month 12 and discontinuation, therefore neither Mayo or NAC classification systems could be used to characterise model health states.

Transition probabilities

B2. Company submission, Section B.3.3.3, Table 41, page 114. With respect to unmeasured observations for NYHA class and transplantation/CMAD, the

submission states that these were “censored.” In this context, does this mean “excluded”?

Correct. In this case censored should be amended to “excluded”, the table refers to a complete-case analysis.

B3. Priority question: Company submission, Section B.3.3.3, page 114. The ERG understands that during the extrapolation period, a single time-independent matrix of probabilities is used and that this is based on a “smoothed multinomial distribution”

- **Please clarify how these Month 36+ matrices have been constructed. Are these based on summing counts of transitions or weighted probabilities for each transition at each timepoint?**

The Month 36 matrices were constructed as the sum of transition counts observed over the 30 months of the trial.

- **Please explain why this approach was adopted for the base case analysis and clarify its underlying assumptions.**

Use of these pooled transition counts was necessary to maximise the data availability for transitions with low counts, such as the transition to NYHA class IV, which would otherwise be dominated by the uninformative prior used in the Bayesian analysis.

- **Please explain the purpose of the “smoothed multinomial distributions”.**

Smoothing of the empirical multinomial distribution was desirable due to the low data availability for some transitions.

- **Please clarify the priors assumed for the smoothed multinomial distributions and provide the accompanying WinBUGs code used to generate the transition probabilities.**

The priors used were uniform Dirichlet distributions with a single count per transition. The Winbugs code used is shown below.

```
model{
        for (i in 1:4){
```

```
                r[i,1:4] ~ dmulti(pi[i,1:4],n[i])
                pi[i,1:4] ~ ddirch(prior[i,1:4])
        }
        for (i in 1:4){
                for (j in 1:4){
                        rhat[i,j]<-pi[i,j]*n[i]
                        dev[i,j]<-
                        2*r[i,j]*log(r[i,j]/rhat[i,j])
                }
                resdev[i]<-sum(dev[i,1:4])
        }
        resdevtot<-sum(resdev[1:4])
}
```

Where pi is the posterior matrix of transition probabilities and r are the observed transition counts.

These posterior transition probabilities were then normalised across each row to ensure that the transition matrix would conserve the model population; only numerical inefficiencies (at or above the 4th significant figure) were affected by this step.

- **Do the values shown in Tables 43 and 45 represent the mean or the median estimates from the posterior distribution?**

The means of the modelled posterior distribution were used in this case; the mean did not differ materially from the median for most transitions; for example, the largest deviation seen in the analysis on the tafamidis arm was a 1.7% change in risk for a transition between NYHA IV to NYHA I; no transitions from any class other than NYHA IV showed a mean to median deviation of greater than 0.3% absolute risk.

B4. Company submission, Table 63, Page 144. The text states that *"there is no clinical evidence for the efficacy of tafamidis in NYHA IV."* However, Tables 42 to 45 show transitions of patients from NYHA IV to other states in both treatment groups. Please comment further.

The text should state 'there is no clinical evidence for the efficacy of tafamidis for patients with NYHA IV at baseline as these patients were excluded from ATTR-ACT'.

Survival analysis and NYHA-related excess mortality

B5. Priority question. Company submission, Section B.3.3.4.8, page 128 and company's model. The base case analysis assumes that mortality risk is dependent on NYHA class.

- **The submission states that the Cox models were fitted to death from any cause, yet the model applies the hazard ratios (HRs) to excess mortality only. Please clarify if the Cox models were fitted to data on all-cause mortality or to excess mortality only. Please clarify the assumptions underlying this approach.**

Cox models were fitted to death from any cause, as deaths from all causes due to an excess hazard mechanism in a relative survival analysis cannot be distinguished from deaths due to the baseline hazard. Whilst technically possible to scale the relative hazards to remove the effect of the baseline hazard, the company is unaware of this being undertaken and is also unaware of development of the statistical theory necessary to adjust the parameter uncertainty to compensate for this.

This approach implies that any deaths during the trial period that would be expected without the excess hazard mechanism result in a reduction in the observed hazard ratio between the classes versus the true hazard ratio of excess mortality. However, it was necessary to make the background rate of mortality unconditional upon NYHA class within the cost effectiveness model. This is because it was believed that there would be a changing ratio of excess mortality to general population mortality deaths in extrapolation. Given that the excess mortality mechanism was dominant during the trial, and in the absence of established methods for adjusting the cox hazard ratios to compensate for the all-class baseline hazard, this is an appropriate assumption.

- **Please comment on the appropriateness of using a Cox proportional hazard model when analysing overall survival (OS) data by NYHA class with respect to the limitations of using this approach in the context of a**

cost-effectiveness analysis (See Discussion of Guyot *et al*, *Value in Health* 2011, 14: 640-646).

The discussion of Guyot et al makes good points when determining a fully integrated conditional model of survival. In this case, however, as the marginal model of overall survival was seen to perform well, this method was preferred for extrapolation. A fully conditional model, in this case to preserve the survival conditional NYHA distribution, would be dependent upon the time-varying NYHA classes of the patients, and the preferred form of the parametric distribution used for the excess hazard mechanism prevents this having validity as an extrapolative model.

In addition to this, a fully integrated conditional model was seen to accumulate errors in the estimation of the NYHA class transitions that would impact the estimation of the marginal survival, which was considered to be of primary importance to maintain. The measurement of NYHA class on an interval basis versus overall survival on a continuous basis also required a two-step system of solution to the multistate differential equation, which severely complicated the final time in state aggregation and did not improve accuracy. As a result, an unconditional model of overall survival that was then disaggregated to determine relative contribution from each NYHA class was determined to provide the most accurate estimation of overall survival whilst maintaining good characteristics for time in NYHA class.

- **Please comment on why it was considered necessary to apply HRs as if they were relative risks.**

Direct use of hazard ratios to provide a population conserving disaggregation of risk would require the solution of the following equation, assuming piecewise constant hazard per NYHA class:

$$N_D = \sum_{i=1}^{4} N_i(1 - e^{-hr_i\lambda_0 t})$$

Where N_D is the number of deaths expected in the cycle, i is the NYHA class indicator, N_i is the number of patients dwelling in class i at t=0, hr_i is the hazard ratio of class i, λ_0 is the baseline constant hazard to be calculated, and t is the length of the model cycle. This equation does not have an analytical solution, and as it would require numeric solution for every model cycle, we made the asymptotically

correct (with decreasing model timestep) simplification of assuming that the hazard ratios corresponded to relative risks in order to balance the computational demand of the simulation with the uncertainty of the system overall.

B6. Priority question: Company submission, Section B.3.3.4.1 and Table 47. Please clarify why ATTR-ACT could not be used to estimate relative treatment effects in a mixture model allowing for effects on CV-related and non-CV related events that could be applied to a UK-specific baseline response.

Two major considerations determined the use of a relative survival model over a model considering cause-specific deaths. The first was that cause-specific deaths are not characterised well in the general population, and therefore determining a baseline risk in the general population for use in long term extrapolation was considered unfeasible. Secondly, characterisation of cause of death was considered an unnecessary source of uncertainty when compared to a relative survival model. Within the trial, cause of death was captured more accurately than in the general population. However, there is still potential for misclassification where there were multiple causes of death and were adjudicated in the knowledge that CV deaths were under scrutiny for this population. In order to correctly determine treatment effect on cause-specific survival outcomes, accuracy of the cause of death specification is necessary; any inaccuracy in application or inconsistency in definition would result in invalid extrapolation when scaled from a baseline rate. The relative survival approach does not introduce this source of uncertainty due to classification.

In relation to the estimation of relative treatment effects, due to the marked difference in profile of the marginal OS hazards of the two curves and by consideration of the mechanism of action of tafamidis, a simple scaling rule for treatment effect was considered inappropriate for this outcome and may similarly have been inappropriate for the CV-related mortality. Patients in the placebo arm experienced a consistently increasing hazard of mortality, as expected in a progressive disease. In the tafamidis arm, this hazard was not observed to consistently increase, which was expected for a treatment that arrests the progress

of the disease. As such, a proportionality of hazard would not be expected between the two arms.

B7. Priority question. Company submission, Section B.3.3.4.2, page 121. Please provide information in support of the statistical properties of the method used to model overall survival.

The method used combines the method of Andersson et al.[15] with the standard parametric distributions advised in TSD 14[16]. The likelihood function is maximised in a conventional manner, via finite difference approximations of the partial derivatives, and the resultant hessian matrix is used to inform the uncertainty in the parameters via the delta method as is standard for the parametric fitting procedure *flexsurvreg* in R.

The adjustment to the methodology utilised in Andersson et al. was applied given the extrapolative properties of splines used in this work are considered to be arbitrary as they are based upon continuation of a gradient reached at an arbitrary time and that is itself dependent on the arbitrary position of intermediate knots. In contrast, the extrapolation of a conventional parametric distribution can be guaranteed as a proper time to event distribution and will be consistent with the observed data, provided that the distribution specified does represent the underlying statistical process determining time of event.

B8. Priority question. Company submission, Section B.3.3.4.4. Please describe the likelihood function that is used to model overall survival from ATTR-ACT allowing for excess non-disease related survival and provide estimates of the proportion of patients dying of non-CV related events with 95% confidence intervals.

The likelihood function to be maximised for overall survival is composed of multiple components. Firstly, the "expected" hazard and cumulative hazard functions of mortality per lifetable are defined:

$$h_E(t|age_0, stratum) = h_{E0}(t + age_0|stratum)$$

$$H_E(t|age_0, stratum) = H_{E0}(t + age_0|stratum) - H_{E0}(age_0|stratum)$$

Where stratum indicates the sex, nationality, and any other stratifying variables used to determine the life table from which to obtain the hazard and cumulative hazard, age_0 is the age of the patient at baseline, t is the time from baseline, and $h_{E0}()$ and $H_{E0}()$ are the hazard and cumulative hazard functions respectively of mortality from birth.

The gross survival models are then specified by addition of a parametric hazard to this life table derived hazard, e.g. for a distribution prm with scale conditional upon covariates $\boldsymbol{z}$ of $\mu(\boldsymbol{z})$ and shape σ:

$$h_{add}(t|\mu(\boldsymbol{z}),\sigma,age_0,stratum) = h_{prm}(t|\,\mu(z),\sigma) + h_E(t|age_0,stratum)$$

$$H_{add}(t|\mu(\boldsymbol{z}),\sigma,age_0,stratum) = H_{prm}(t|\,\mu(z),\sigma) + H_E(t|age_0,stratum)$$

Corresponding probability and density distributions are created within the call to *flexsurvreg*:

$$p_{add}(t|\mu(\boldsymbol{z}),\sigma,age_0,stratum) = \exp\left(-H_{add}(t|\,\mu(z),\sigma,age_0,stratum\right)$$

$$d_{add}(t|\mu(\boldsymbol{z}),\sigma,age_0,stratum) = h_{add}(t|\mu(\boldsymbol{z}),\sigma,age_0,stratum)(1-p_{add}(t|\mu(\boldsymbol{z}),\sigma,age_0,stratum))$$

These are then used to directly evaluate the log-likelihood function within *flexsurvreg*. For the purely right-censored data present, this likelihood function is given by equation (2) in Jackson[17]; using notation defined thus far and where $\boldsymbol{c}$ is a vector of censoring indicators with value 1 if the corresponding $\boldsymbol{t}$ is an observed event and 0 otherwise:

$$l_{add}(\mu(\boldsymbol{z}),\sigma,age_0,stratum|\boldsymbol{t},\boldsymbol{c}) = \{\prod_{i:c_i=1} d_i(t_i) \prod_{i:c_i=0} (1-p_i(t_i))\}$$

It is not possible to provide estimates of the proportion of patients dying of non-CV-related events or non-disease-related events. As can be seen, this model is only able to determine uncertainty in the fitted parameters, which relate to the excess mortality above that expected due to life tables. It does not make any consideration of causality, and therefore would be unable to inform estimates of proportion of deaths due to any causality. As it is only able to express the uncertainty in the

survival due to the excess hazard mechanism, it is also unable to express the true uncertainty in the ratio between expected and excess events, as uncertainty in life tables would have to be externally incorporated.

It should be noted that *flexsurvreg* includes an argument "bhazard" for specifying the hazard offset for relative survival models, which behaves in the same manner, excepting that it only affects the likelihood function contribution for observed events and is used by Nelson et at (2007, Statistics in Medicine, "Flexible parametric models for relative survival, with application in coronary heart disease"); as this does not take into consideration the accumulated hazard of those without observed event, this was considered to be inadequate.

B9. Priority question. Company submission, Section B.3.3.4.5 and B.3.3.4.6, pages 124-128. Please provide plots of the empirical hazard functions as part of the justification for OS.

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.

We observed a marked disparity between the hazard forms; the BSC arm shows the clinically expected monotonically increasing absolute and relative hazards of death that could be considered almost linear over this time horizon; a Weibull excess hazard model is thus appropriate. The hazard of mortality on the tafamidis arm, by contrast, is not clearly monotonic as a relative hazard (it may converge with the hazards of the matched lifetable population) and is not clearly monotonic as an absolute hazard (there is a period of negative rate of change of absolute hazard in both smoothed models after 20 months). The sharp second derivative of hazard seen in the tafamidis arms (the "knee") can be well represented by a lognormal excess hazard model.

Figure 1: Smoothed hazard estimates for overall survival censoring for transplant and CMAD implantation for the pooled tafamidis arms. The dotted period exceeds maximum survival follow-up in study.

Figure 2: Smoothed hazard estimates for overall survival censoring for transplant and CMAD implantation for the BSC arm. The dotted period exceeds maximum survival follow-up in study.

B10. Priority question. Company submission, Section B.3.3.4.5. Please comment on why the Weibull model is not believed to be appropriate for OS in the tafamidis group.

All fitted models underestimated survival at approximately [redacted] months when compared to the extension study[18] data except for that estimated by the exponential. Moreover we observed that all statistical models significantly underestimated survival at approximately [redacted] months when compared with the Phase II data.[19] Therefore, given that the Weibull predicts the second lowest survival estimates at these timepoints it was not considered appropriate.

In addition, the monotonically increasing hazard of the Weibull is not aligned with the smoothed hazard estimates observed in the tafamidis arm of ATTR-ACT presented in response to B9 (Figure 1).

Discontinuation

B11. Priority question. Company submission, Section B.3.3.5, page 129. Discontinuation is applied in the model using two separate mechanisms: (i) all patients are assumed to discontinue treatment when their disease reaches NYHA IV, and (ii) for disease in less severe states (NYHA I-III) a fixed proportion of patients are assumed to discontinue in each cycle.

- **Please clarify whether in the ATTR-ACT trial, patients discontinued on progression to NYHA IV i.e. was there a stopping rule applied on progression to NYHA IV?**

ATTR-ACT did not include a treatment stopping rule and patients with NYHA IV at baseline were excluded from the study.

- **Does the EMA regulatory submission for tafamidis include a stopping rule relating to progression to NYHA IV?**

[redacted]

- **The text on page 129 refers to a "competing risks" analysis. Did this only involve re-analysing the data such that the event not of interest was censored, or did it involve generating cause-specific hazards and cumulative incidence functions (i.e. a formal competing risks analysis)?**

In this case, as the hazards are unconditional, both methods are equivalent. The likelihood function for discontinuation was maximised under the assumption that censors of all forms were not informative of the hazard of discontinuation.

- **Please justify the assumption that the benefits of tafamidis (reflected in the transition matrices, survival functions and health-related quality of life [HRQoL] parameters) will all continue to apply after a patient has discontinued tafamidis.**

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.

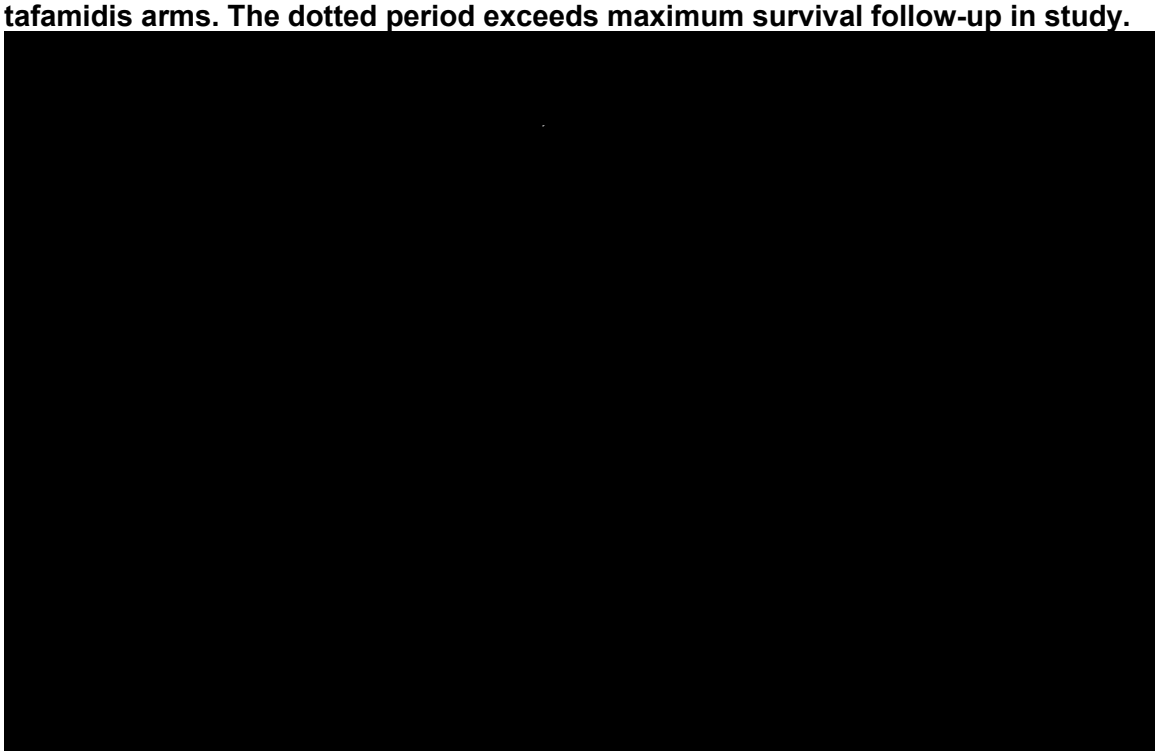
B12. Company submission, Figure 39, page 130. Please provide a plot of the empirical hazard function for time to treatment discontinuation.

As for OS, the empirical hazard functions for time to treatment discontinuation were estimated using a kernel-smoothing function the default bandwidth setting algorithm and default kernel shape, as well as a spline smoothers. In integrating the central values from the kernel-smoothed estimate, the estimation overestimates survival in the tail, and given the variability in the rate of change of patients remaining on treatment in the period between 10 and 30 months, the smoothing is sensitive to the

bandwidth of the smoothing kernel. The spline model asymptotically approaches a constant hazard.

Figure 3: Smoothed hazard estimates for discontinuation censoring for death, transplant, CMAD implantation and progression to NYHA class IV for the pooled tafamidis arms. The dotted period exceeds maximum survival follow-up in study.

Figure 4: Integration of hazard estimates for discontinuation censoring for death, transplant, CMAD implantation and progression to NYHA class IV for the pooled tafamidis arms. The dotted period exceeds maximum survival follow-up in study.



Hospitalisation

B13. Priority question. Company submission, Section B.3.3.6, page 131. With respect to the data on hospitalisations provided in the table:

- **Please provide further information to explain how these values were calculated.**

Hospitalisations recorded were restricted to the on treatment and within trial period, i.e. admission occurred after study day 0 prior to individual discontinuation/last follow up. This resulted in the exclusion of [redacted] records, one of which was after day 913 (30 months) and was therefore excluded to prevent observation bias among patients who would otherwise not have received follow-up. The remaining [redacted] records among [redacted] patients were all within 35 days of discontinuation and could not be assumed unrelated to their reasons for discontinuation and so were reinstated without modification of the exposure period for that patient.

Hospitalisations were then further subset to those adjudicated to be CV-related.

Patient exposure in each NYHA class was calculated by using the baseline and 6-month interval NYHA observations. Provided that survival follow-up did not end prior to the target end day of the NYHA observation interval, this class was assumed to contribute 6 months of exposure; otherwise the difference between the target NYHA measurement day at the start of the interval and the final survival follow-up consistent with the cost effectiveness model. Intervals without NYHA measurement were excluded.

Hospitalisations were assigned to patient/NYHA class per the rules defining exposure; they were assigned to the nearest NYHA class measurement with a target day less than the day of hospitalisation unless the time difference was greater than 6 months, in which case they were excluded.

A simple Poisson intercept model for hospitalisation count was then regressed for each NYHA class, using the log of the above defined exposure times as the offset term.

- **Please clarify whether the estimates of hospitalisation rates relate to the patients' current NYHA class or their baseline NYHA class.**

As described above, hospitalisations are dependent upon the 6-month interval observations of NYHA class, as modelled in the CEM, and not upon the baseline NYHA class.

- **Please confirm that the data presented in Table 49 are rates of hospitalisations per patient per month and not "proportion hospitalised".**

The numbers presented in Table 49 are the expected proportion of patients experiencing an event per month; the table heading is misleading in this case.

Health-related quality of life

B14. Priority question. Company submission, Section B.3.4.1, page 132. Please provide justification for the use of treatment group-specific health utilities. Given that the submission states that patients generally discontinued treatment prior to reaching NYHA IV, please comment on the noticeable difference in utilities for this state between the treatment groups.

Treatment specific utilities were applied given tafamidis was well-tolerated and has the potential to impact quality-of-life beyond stabilising disease, namely reduced hospitalisation and giving patients hope as their disease is controlled (blinded to treatment in the study). However, it was acknowledged that given the 6 months between measurement these impacts may have not been captured sufficiently.

Given the significantly poorer prognosis of patients after entering NYHA IV, there are a very low number of EQ-5D observations within NYHA IV (n=[redacted] tafamidis; n=[redacted] placebo), which may have contributed to the difference observed between treatment arms.

B15. Company submission, Section B.3.4.1, page 132. In ATTR-ACT, did EQ-5D-3L assessments cease at the point at which patients discontinued tafamidis, or were data collected subsequent to this timepoint?

Collection of EQ-5D ceased at the point of discontinuation in ATTR-ACT.

Costs

B16. Company submission, Section B.1.2, page 14. [redacted]. Please clarify when this will happen.

[redacted]

B17. Company submission, Section B.3.5.2, Table 53, page 138. Please clarify what the standard error around concomitant medication is intended to reflect. Is this variability in resource use or in unit cost?

The standard error is intended to reflect the variability around resource use.

B18. Company submission, Section B.3.5.2.1, page 139. The model includes cost reductions for patients who had a dosing adherence level <80%. Please clarify whether dosing adherence resulted in fewer packs of tafamidis being prescribed in ATTR-ACT. Please also comment on how tafamidis would be prescribed in usual practice i.e. would it be prescribed as needed (when the patient has run out) or according to a fixed prescribing schedule. If it is the latter, please clarify how frequently tafamidis would be prescribed in practice.

In ATTR-ACT, participants were instructed to bring study medication and packaging back to the study site at each scheduled visit so that the total amount of drug taken could be determined.[2] Unused medication was collected by site personnel and destroyed at the site.[2] This process enabled the applicant to maintain adequate records documenting the receipt, use, loss or other disposition of the drug supplies in a monitoring plan in the context of a Phase III randomised controlled trial.

In the clinical setting in England, it is anticipated that initiation of tafamidis would be preceded by completion of an initiation form on the NHS Bluetec system. This form would contain the criteria for reimbursement and would be separate from the prescription process. Following NHSE approval through Bluetec, a tafamidis prescription would be fulfilled by a hospital pharmacy. Subsequent prescriptions at the hospital pharmacy would be expected to be adjusted according to usage of medication

(adherence), such that the prescription would only be filled when drug supplies were running low.

In summary, while a fixed prescribing schedule was employed in the setting of the clinical trial, in clinical practice tafamidis would be prescribed as needed. The proposed input was applied as a conservative estimate. Therefore, to fully account for the impact of adherence levels on the anticipated costs to the NHS, the overall relative dose intensity from ATTR-ACT of [redacted] (actual number of capsules taken/expected numbers of capsules) should be applied to 100% of patients. This update has been applied in the model.

B19. Company submission, Section B.3.5.2.2, Table 56, page 140. Please clarify why some of the drug usage levels are available by treatment group, whilst others are not. Please clarify how the monthly costs of concomitant medications used in the model (£18.92 for BSC and £18.18 and tafamidis) have been calculated using the information presented in Tables 55 and 56.

The drug usage levels had been derived from baseline concomitant medication reported in the primary ATTR-ACT publication which may not fully reflect concomitant medication usage whilst on treatment. Therefore, please see updated Table 56 below which reports the usage of the clinically relevant medication groups reported in the tafamidis and placebo arms in ATTR-ACT. The proportion of patients receiving each medication group was calculated by dividing the total number of patients receiving each class of medication by the total number of patients in each arm. This assumes that patients receive treatment throughout the period where they are alive, therefore these costs could be considered overestimates. The dosing and unit costs of the most frequent/relevant treatment in each category have also been updated in Table 55 to reflect these changes using eMIT[20]. The updated concomitant medication costs for tafamidis and BSC are £3.38 and £3.57, respectively. These have been updated in the model.

Table 56. Concomitant medication usage levels

Medication type	Percentage administered treatment		
	Pooled tafamidis	Placebo	Source
Diuretics	[redacted]	[redacted]	ATTR-ACT, data on file
Anticoagulants	[redacted]	[redacted]	

Antiplatelet agents	[redacted]	[redacted]	
Lipid lowering therapy	[redacted]	[redacted]	
ACEi/RAASi	[redacted]	[redacted]	
Beta blockers	[redacted]	[redacted]	

Note usage may be >100% as some patients received more than one type of drug within the class

Table 55. Monthly concomitant medication unit costs

Medication type	Monthly cost	Dosing	Source
Diuretics	£0.67	Furosemide; 40mg daily	eMIT[20]
Anticoagulants	£0.83	Warfarin; 10mg daily	
Antiplatelet agents	£0.08	Aspirin; 75mg daily	
Lipid lowering therapy	£0.23	Simvastatin; 20mg daily	
ACEi/RAASi	£0.41	Ramipril; 5mg daily	
Beta blockers	£0.21	Bisoprolol; 5mg daily	

Abbreviations: ACEi: angiotensin-converting-enzyme inhibitor; RAASi: renin angiotensin-aldosterone system inhibitor.

B20. Company submission, Section B.3.5.2.3, page 141. Please explain why costs of pharmacy preparation and dispensing for tafamidis have not been included in the model.

Tafamidis is an oral therapy and does not require any special preparation by a pharmacist. Therefore, no cost was included in the model. This is aligned with the most recent published NICE submission for an oral therapy (TA598), where no administration cost was included.

B21. Company submission, Section B.3.5.4. Please clarify whether any information on the duration of CV-related hospitalisations was collected within ATTR-ACT.

Information on the duration of CV-related hospitalisations was collected within ATTR-ACT. However, these were not used within the cost-effectiveness model for several reasons. Firstly, there were low numbers of observations for each hospitalisation, resulting in unreliable estimates of mean stay. Secondly, because most participants

in ATTR-ACT were cared for outside the UK, meaningful differences in length of stay were expected relative to management in the UK setting by the NHS.

B22. Company submission, Section B.3.5.5, Table 59, page 142. Please clarify why only three types of adverse event have been included in the economic analysis.

As discussed in B.3.5.5, tafamidis treatment was safe and well tolerated, with a similar safety profile to placebo. Therefore, given the low rate of severe treatment related AEs, for simplicity the cost of treatment related AEs of any severity with ≥5% incidence were included.

B23. Company submission, Section B.3.5.5, Table 60, page 142. Please explain why adverse event costs from 2009 have been uplifted. Why were more up-to-date values from NHS Reference Costs or literature not used?

These costs were applied from a previous heart condition submission (TA197), however we acknowledge these are now outdated. Please see updated unit costs below, source from 2017/18 NHS reference costs utilising HRG codes related to the previous descriptions. These have been included in the updated model.

Table 60. Adverse event unit costs

Event	Mean	SE[a]	Source
Diarrhoea	£284.50	£28.45	NHS ref costs 2017/18[21] Gastrointestinal Infections without Interventions, with CC Score 0-8+ [HRG codes: FD01F, FD01G, FD01H, FD01J]
Nausea	£284.50	£28.45	NHS ref costs 2017/18[21] Gastrointestinal Infections without Interventions, with CC Score 0-8+ [HRG codes: FD01F, FD01G, FD01H, FD01J]

[a]Assumed based on 20% of mean value.
Abbreviations: AE: adverse event; GP: general practitioner; SE: standard error.

Model calculations and formulae

B24. Company submission, Section B.3.2.2.1, page 111. Please explain why the model uses two different time cycles (one cycle length for transitions between states and another cycle length for all other events). Was adjusting the NYHA transition matrices to reflect a shorter interval considered or attempted (e.g. using eigenmatrix

decomposition such as the methods described by Chhatwal *et al*, Medical Decision Making, 2016)?

The method of Chhatwal et al is a useful description of a well-understood problem, but in this case it would require building a redundant model, as the utilities and mortality risks are conditional upon last observed NYHA class and were developed as such. Particularly, survival was disaggregated by last observed NYHA class but was a continuous outcome; therefore, for consistency, the model would have to be run holding a pseudo-state for patients of this class at last observation. Further disaggregation of mortality would then have to make some assumption about the conditional risk of mortality in the unobserved but modelled short time cycle NYHA class that would be consistent with relative risk of mortality of the last observed class.

As the data were collected based upon these 6-month transitions, and to inform either model the utility measurements must be assumed to be random cross-sections of class-specific utility. The model was built to provide consistency with the trial analysis first, and any modelling benefit to further disaggregation would require making further assumptions about the utility-conditional rates of transition between states and so this does not add useful information.

B25. Priority question. Company submission, Section B.3.8.3, Scenario 6 – Early diagnosis impact. Please confirm that this analysis is comparing the use of tafamidis with cost savings attributable to early diagnosis versus best supportive care (BSC) without any cost savings associated with early diagnosis. Given that non-invasive nuclear scintigraphy has already been developed, please clarify why the cost savings are not also included in the BSC comparator group within this analysis.

Yes, that is the correct interpretation that we have compared the use of tafamadis with cost savings attributable to early diagnosis versus BSC without any cost savings associated with BSC.

Nuclear scintigraphy was routinely introduced into the diagnostic algorithm for ATTR-CM at the National Amyloidosis Centre in 2012.[22] The current >3 year delay to diagnosis represents the current BSC paradigm 7 years following the universal use of nuclear scintigraphy at the NAC. Despite the use of nuclear scintigraphy at the NAC,

early diagnosis has not been achieved in most patients with ATTR-CM, 40% currently experience delays >4 years from onset of cardiac symptoms to diagnosis.[22] Around one third of patients are diagnosed within 6 months of the onset of symptoms, making this threshold a reasonable ambition following the introduction of tafamidis.

The introduction of scintigraphy alone at the NAC is not sufficient to realise the full benefits of early diagnosis. The availability of tafamidis is likely to bring about two significant changes in practice that will contribute to a reduction in the current 3-year delay to diagnosis explored in the scenario analysis:

1. Greater index of suspicion for the disease: improved awareness of ATTR-CM and its red-flags among cardiologists interacting with undiagnosed patients in heart failure and cardiomyopathy services. Previously an academic diagnosis, availability of the 1st treatment for ATTR-CM means the diagnosis is actionable.

2. Regional access to confirmatory diagnostic tests: local availability of nuclear scintigraphy imaging embedded in specialist heart failure and cardiomyopathy services (including 16 English centres participating in the tafamidis Early Access to Medicines Scheme). Once a diagnosis of ATTR-CM is suspected, timely access to confirmatory tests will be geographically equitable in England.

Innovation

B26. Company submission, Section B.2.12, page 99. The text states “This paradigm shift in the treatment of the disease will reduce some of the substantial burden of ATTR-CM on patients, caregivers and healthcare systems in an area of significant unmet need.” Is there any evidence to support this statement e.g. is there evidence that caregiver burden would be reduced as a consequence of the availability of tafamidis?

The ATTR-ACT study did not measure endpoints related to caregiver burden, therefore direct evidence to support a reduction in caregiver burden with tafamidis treatment is lacking. Observational data in patients with heart failure in general do support a reduced caregiver burden with improvements in some of the secondary endpoints assessed in ATTR-ACT. A longitudinal study conducted in patients with heart failure and their caregivers in Edinburgh found that severity of heart failure

measured by NYHA classification was associated with poor QoL in carers.[23] In ATTR-ACT, a greater percentage of patients in the tafamidis group improved upon or remained in their respective NYHA baseline classifications compared with those in the placebo group.[2] A further observational study conducted in the Netherlands was in agreement that physical health status of HF patients is significantly associated with markers of poor caregiver QoL, specifically the disruption of daily schedule and loss of physical strength among caregivers.[24]

In addition, the Edinburgh study found that QoL of carers also correlates with QoL of patients with HF (measured by EQ-5D).[23] In ATTR-ACT, significant treatment effects favouring tafamidis were observed in 2 measures of QoL, the KCCQ-OS and the EQ-5D-3L index/ VAS scores.[2]

B27. Company submission, Section B.2.12, page 99. The text states "With expanded use of non-invasive nuclear scintigraphy,[4] the availability of tafamidis (subject to NICE recommendation) is likely to promote the identification of ATTR-CM before advanced cardiac damage has occurred. At an earlier stage, patients may derive the optimal benefit from tafamidis: longer survival, fewer hospitalisations and improved quality of life." Table 7 states that the diagnostic criteria for ATTR-ACT included biopsy or nuclear scintigraphy.

- Please comment on whether some of the claimed benefits of earlier diagnosis might already be captured through the use of nuclear scintigraphy within the design of ATTR-ACT.

- Please provide details regarding the proportion of patients in ATTR-ACT diagnosed through nuclear scintigraphy.

The method of diagnosis alone would not be expected to influence the efficacy of tafamidis. The availability of tafamidis is likely to bring about two significant changes in practice that will contribute to a reduction in the current 3-year delay to diagnosis which have been described in response to B25.

A total of [redacted] ATTR-ACT subjects were diagnosed using scintigraphy. Scintigraphy was not common practice when the ATTR-ACT study was being designed in 2012. A

protocol amendment was done in 2014 to allow sites where it was being done to allow it as part of diagnostic procedures.

B28. Company submission, Section B.2.12, page 99. The submission compares the modelled quality-adjusted life year (QALY) gains (based on the ATTR-ACT ATTR-CM population) against QALY gains reported in the appraisals of sacubitril valsartan and ivabradine (patients with heart failure with reduced ejection fraction (HFrEF). Given that these appraisals relate to different populations, please clarify the relevance of the comparisons of these QALY gains to the current appraisal of tafamidis.

ATTR-CM manifests clinically with heart failure, a heterogenous clinical syndrome.[25] One method of categorising heart failure patients is by ejection fraction, the percentage of blood in the left ventricle that pumps out with each contraction, which can be preserved/ normal (≥ 50%) or reduced (<40%).[8] Most patients with ATTR-CM typically have heart failure with preserved ejection fraction (HFpEF) until late in the disease process,[26] although some will have an ejection fraction below 50%. In a contemporary series of UK patients with ATTR-CM, the median (IQR) ejection fraction at diagnosis in wild-type ATTR-CM was 58% (45-71) and in hereditary ATTR-CM was 49% (39-62).[22]

Several drugs and devices have been shown to improve outcomes in HFrEF, whereas clinical trials of pharmacological agents in HFpEF have been universally disappointing with no treatments that have improved outcomes in this group of patients.[27,28] This section of the Innovation Section (B.2.12) aimed to contextualised the transformative QALY gains from the ATTR-ACT population with those seen in previous appraisals in heart failure. In the absence of any approved therapies in HFpEF, previous appraisals of HFrEF represent the most valid comparison, indeed some patients with ATTR-CM have an ejection fraction <50%.[22]

Section C: Additional data/analysis requests

C1. Priority request. The ERG has plotted the observed all-cause OS Kaplan-Meier functions from the ATTR-ACT trial publication against the company's OS model predictions (see Figure 1). As shown in the figure, there is a significant

discrepancy between these. Please investigate the reasons for this and update the health economic model accordingly.

Figure 1: Observed versus predicted OS from ATTR-ACT and company's model

The company would first like to note that the incorrect endpoint has been digitised by the ERG – the endpoint used for model fitting was overall survival censored for transplantation and implantation of CMAD, whereas the above plot is a digitised version of the endpoint that used transplantation and implantation of CMAD as death, which was considered appropriate for assessment of clinical effectiveness, but not for informing cost effectiveness.

The deviation is caused by two primary mechanisms, both related to the rate of mortality expected from life tables. Both of these mechanisms cause a reduction in the initial rate of hazard due to life tables, which has a greater effect on the tafamidis arm due to the lower ratio of excess hazard versus expected hazard.

Firstly, in evaluating upon a mean patient, there is a reduction in initial marginal hazard, which would be compensated for long-term by a reduction of survival in the tail versus that of the population margin.

Secondly, the expected hazard differs between the modelled English population and the global population upon whom the statistical model was fitted.

The company considers that a mean values approach is consistent with the majority of HTAs of survival-affecting technologies, and that ad-hoc curtailment of survival curves by a mean-values life table approach is appropriate too. In incorporating expected deaths due to life tables in the analytical procedure, the company has made this curtailment less arbitrary and structurally consistent with an extrapolative statistical model.

C2. Priority request. Please provide a comparison of observed NYHA occupancy (from ATTR-ACT) versus model-predicted health state occupancy (using the state transition model trace) for each 6-month cycle. Please explain any apparent deviations.

Note the same population is used for the BSC and tafamidis arms, having the initial NYHA class distribution of the pooled study population from ATTR-ACT. As this baseline distribution does not exactly replicate either arm of the study, neither arm of the study would be expected to have perfect representation in the CEM. The state occupancy predicted by the model is nevertheless very consistent with the observed state occupancy, despite this baseline difference.

Table 2: Observed and predicted state occupancy (Tafamidis arm)

	Proportion of surviving patients in state		
State	Observed	(95% CI by Goodman's formula)	Predicted
Month 0			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 6			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 12			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]

Month 18			
	Class I	[redacted]	[redacted]
	Class II	[redacted]	[redacted]
	Class III	[redacted]	[redacted]
	Class IV	[redacted]	[redacted]
Month 24			
	Class I	[redacted]	[redacted]
	Class II	[redacted]	[redacted]
	Class III	[redacted]	[redacted]
	Class IV	[redacted]	[redacted]
Month 30			
	Class I	[redacted]	[redacted]
	Class II	[redacted]	[redacted]
	Class III	[redacted]	[redacted]
	Class IV	[redacted]	[redacted]

Table 3: Observed and predicted state occupancy (BSC arm)

	Proportion of surviving patients in state		
State	**Observed**	**(95% CI by Goodman's formula)**	**Predicted**
Month 0			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 6			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 12			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 18			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 24			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 30			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]

C3. Priority request. Please provide a comparison of observed time to treatment discontinuation or death versus model-predicted time on treatment (using the state transition model trace).

Please see Figure 5 below. However, note that as the CEM incorporates a rule to cease treatment upon entry to NYHA class IV, the observed time on treatment is not the appropriate comparison to this trace. We have thus also included

Figure 6 comparing the trace to the observed time to treatment cessation or entry to NYHA IV.

Figure 5: Time on treatment. Kaplan-Meier is direct observation of time on treatment from trial without accounting for NYHA IV stopping rule

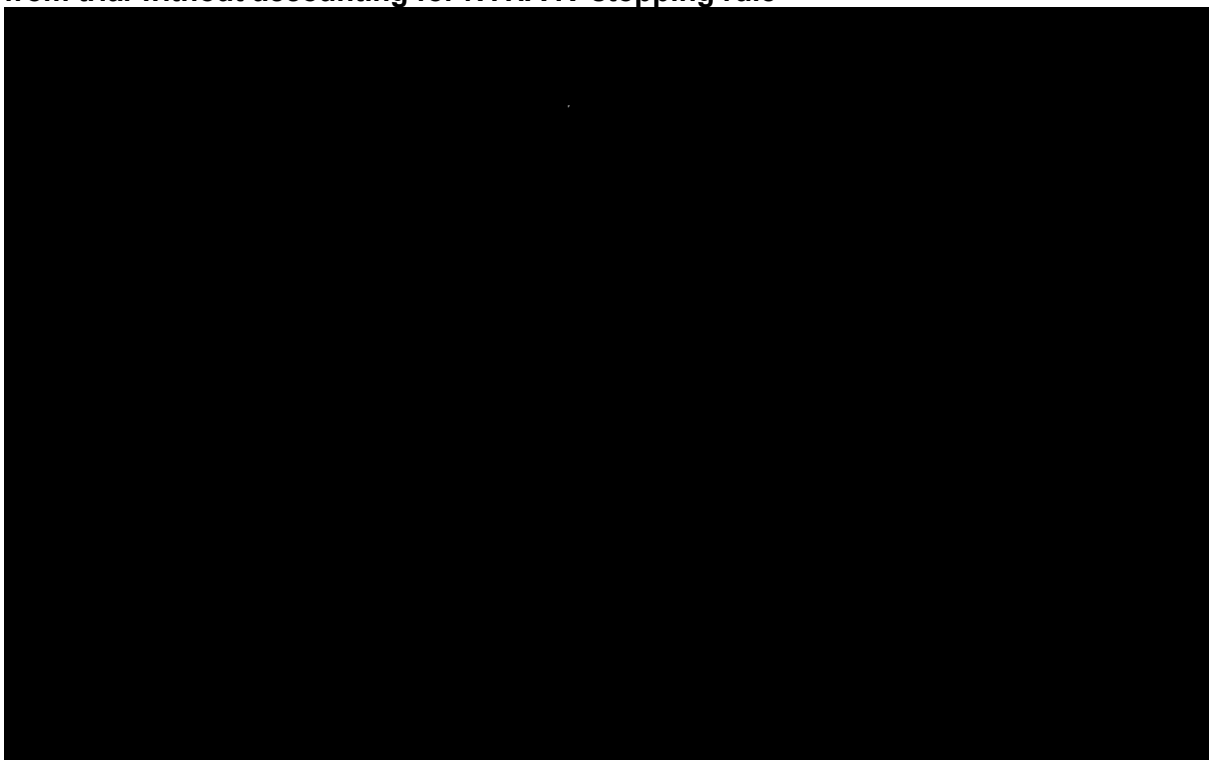


Figure 6: Time on treatment. Kaplan-Meier is direct observation of time until treatment discontinuation or first entry to NYHA class IV.

C4. Priority request. Company submission, Section B.3.3.5, page 129. The submission states ***"to avoid double counting of discontinuation in patients progressing to NYHA IV, ATTR-ACT data were censored for patients on date of***

progression to NYHA IV." **Please clarify how many tafamidis-treated patients were censored under this approach.**

[redacted] patients were censored as entering NYHA class IV prior to any observed or unobserved discontinuation of treatment.

C5. Priority request. 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.

A large number of statistical models were considered for use in representation of the utility data, including various forms of mixed models and generalised estimating equations. The use of repeated-measures mixed models was dismissed as inappropriate for the setting of cost-effectiveness analysis, as these forms of models are capable only of forming patient-level predictions, whereas for the purpose of cost-effectiveness modelling, the mean utility for patients in each NYHA class was required, integrating over the margins of both patient variation and time. Obtaining these estimates from a patient-level model thus additionally requires a model of patient time in NYHA class that is itself dependent upon patient utility.

Generalised estimating equations (GEEs) were preferred as these form predictions upon the margins of the data. However, representation of the data using such a model proved challenging, as the data appeared distributed as a mixture of two beta distributions with an additional threshold "hurdle" of no disutility. Methods for fitting this form of model using GEEs are not developed to the company's knowledge; methods for equivalent mixture models have seen some interest (see e.g. Basu & Manca "Regression estimators for generic health-related quality of life and quality-adjusted life years", Med Decis Making 2012), but such techniques have not yet been implemented in GEEs.

GEEs using gaussian residuals were fitted. First, on an unscaled (Dolan) utility index; secondly, on a utility index scaled to within the unit interval by the formula $\frac{x+0.595}{1.595} - 0.0001$ and fitted with a logit link. Their residual behaviour was unsatisfactory, being highly heteroskedastic and with local non-zero mean. Models were conditional upon (concurrently) observed NYHA class (class II as reference), treatment arm (tafamidis as reference) and genotype (wild-type as reference), with

all first-order interactions included. Observations were assumed regular and to have an AR(1) covariance structure; a “waves” argument was included to indicate the time index of observation and imply any missing observations for the purpose of the covariance estimation. These models and plots of the residuals are presented below. Predictions from these models deviate from the marginal means of the observed data.

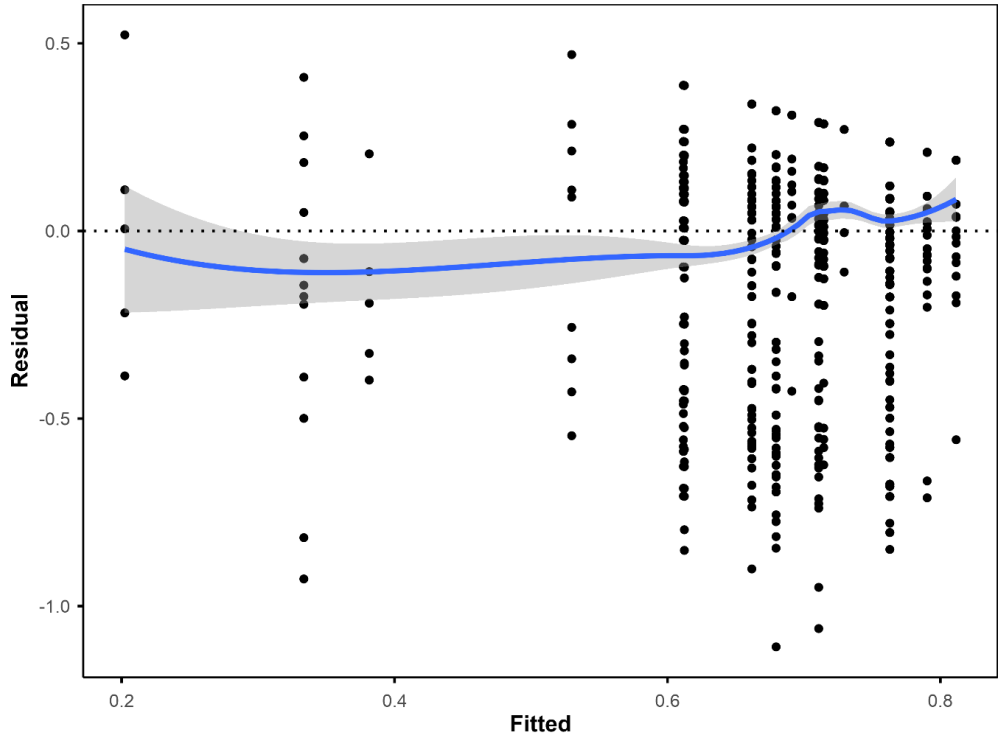
Given the low rates of missingness among the study data and the poor fits of the statistical models, the company considers direct use of the empirical data to be appropriate in estimating marginal mean state utility. The empirical mean makes no assumptions about the distribution of the observations about the mean, and implicitly captures utility-conditional time in NYHA class.

1) Direct fitting to Dolan index, gaussian.

Table 4: Coefficients of linear GEE upon dolan index

Coefficient	Estimate	Std. err	Wald	Pr(>|W|)
Intercept	[redacted]	[redacted]	[redacted]	[redacted] ***
NYHA class I	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III	[redacted]	[redacted]	[redacted]	[redacted] ***
NYHA class IV	[redacted]	[redacted]	[redacted]	[redacted] .
BSC arm	[redacted]	[redacted]	[redacted]	[redacted] *
Variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class I * BSC arm	[redacted]	[redacted]	[redacted]	[redacted] *
NYHA class III * BSC arm	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class IV * BSC arm	[redacted]	[redacted]	[redacted]	[redacted]
BSC arm * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class I * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class IV * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1				

Figure 7: Residuals of linear GEE

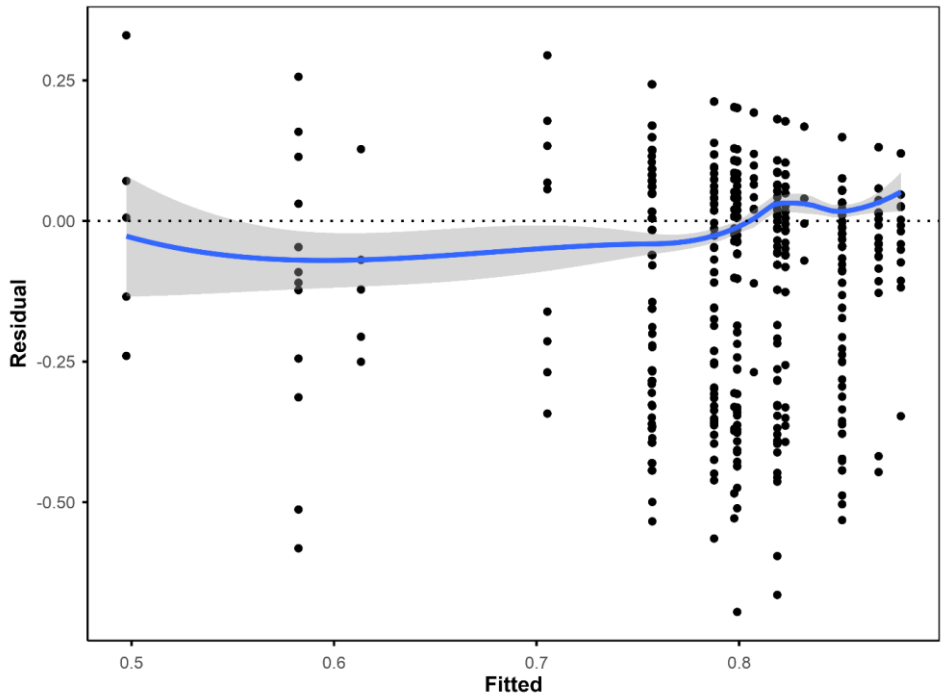


2) Fitting to unit range scaled Dolan index, logit link.

Table 5: Coefficients of logit-link GEE upon unit scaled Dolan index

Coefficient	Estimate	Std. err	Wald	Pr(>|W|)
Intercept	[redacted]	[redacted]	[redacted]	[redacted] ***
NYHA class I	[redacted]	[redacted]	[redacted]	[redacted] .
NYHA class III	[redacted]	[redacted]	[redacted]	[redacted] ***
NYHA class IV	[redacted]	[redacted]	[redacted]	[redacted] *
BSC arm	[redacted]	[redacted]	[redacted]	[redacted] *
Variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class I * BSC arm	[redacted]	[redacted]	[redacted]	[redacted] *
NYHA class III * BSC arm	[redacted]	[redacted]	[redacted]	[redacted] .
NYHA class IV * BSC arm	[redacted]	[redacted]	[redacted]	[redacted]
BSC arm * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class I * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class IV * variant genotype	[redacted]	[redacted]	[redacted]	[redacted]
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1				

Figure 8: Residuals of logit-link GEE upon unit scaled Dolan index



C6. Priority request. Company submission, Section B.3.3.3, page 114. Please provide results of an analysis that allows estimation of tafamadis treatment effects on NYHA class as rate parameters within 6-month time intervals over the duration of ATTR-ACT. Please also provide a justification for assuming that the baseline rate parameters and the tafamadis treatment effects are constant during the extrapolation phase.

Two analyses were run to demonstrate treatment effects on NYHA transitions. In the first, an ordinal logistic regression was run for each source NYHA class over each transition interval, with an offset term included for treatment. Given the large number of coefficients this necessarily produces, a simpler supportive analysis was also undertaken. A binomial logistic regression was undertaken over each transition interval upon patients in NYHA I to III at interval start and surviving, observed, at interval end for the outcome of "worsening", defined as transition to a NYHA class greater than their class at the start of the interval. The log odds of worsening were conditional upon treatment arm and source class.

A clear treatment effect was observed, with tafamidis providing improved outcomes across almost all time points and NYHA classes. However, this treatment effect shows no clear trend in terms of increasing or decreasing odds as the study progressed. It should be noted that the data lacks statistical power for these outcomes and small sample sizes result in a large degree of uncertainty about the scale of the treatment effect.

For the effect of "worsening", the odds ratio is consistently in favour of the tafamidis arm with the exception of the first interval which may be subject to treatment initiation effects / delayed response, the results show acceptable consistency among their confidence intervals.

As there is no evidence to suggest that there is a trend for treatment effect on NYHA state transition for tafamidis versus placebo on NYHA state transition over time, it is appropriate to take the mean rates of transition established over the trial to inform the extrapolative period.

In terms of justification for baseline rate parameters and constant tafamadis treatment effects, there is no evidence to suggest that the alternative is true, so in the absence of evidence this would be the most appropriate approach.

Table 6: Results of ordinal logistic regression; state transition conditional upon treatment arm

Source class	Log odds of transitioning to higher NYHA class (Tafamidis - BSC)	Standard error	95% Confidence interval
Month 0 to 6			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]		
Month 6 to 12			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 12 to 18			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]		
Month 18 to 24			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]
Month 24 to 30			
Class I	[redacted]	[redacted]	[redacted]
Class II	[redacted]	[redacted]	[redacted]
Class III	[redacted]	[redacted]	[redacted]
Class IV	[redacted]	[redacted]	[redacted]

Table 7 Results of logistic regression; worsening of NYHA state transition conditional upon treatment arm for patients surviving and observed at interval end

Transition	Log odds of NYHA class worsening (Tafamidis - BSC)	Standard error	95% Confidence interval
Month 0 to 6	[redacted]	[redacted]	[redacted]

Month 6 to 12	[redacted]	[redacted]	[redacted]
Month 12 to 18	[redacted]	[redacted]	[redacted]
Month 18 to 24	[redacted]	[redacted]	[redacted]
Month 24 to 30	[redacted]	[redacted]	[redacted]

C7: Please provide Appendix F, if available.

All adverse events data relevant to the decision problem were included in section B.2.10, therefore we have not provided Appendix F.

Section D: Model amendments requested

D1. Model. Please provide a version of the model which includes comprehensive annotation of the VBA underpinning the model (including all user-defined functions)

Please see model with additional annotation and debugging code provided 14th October 2019.

D2. Priority request. Model. Please consider age-adjusting health utilities (e.g. using Ara and Brazier, Value in Health, 2010).

Baseline age for the base-case analysis is 74 years, derived from the baseline characteristics from ATTR-ACT, where utility data was collected for up to 30 months (2.5 years). Hence, the ATTR-ACT utility data already represents a significant proportion of the lifespan of an average patient currently treated in clinical practice. As the ATTR-ACT data reflects the decline of patients due to age, additional adjustment due to age may represent double counting.

D3. Priority request. Model. Please provide an amended model which allows the user to evaluate the following scenarios:

- **People discontinuing tafamidis are subsequently assumed to follow transition probabilities and have survival probabilities for the BSC group**
- **People discontinuing tafamidis are subsequently assigned health state utilities associated with the BSC group**
- **People discontinuing tafamidis are assumed to incur costs associated with BSC**
- **People discontinuing tafamidis subsequently incur cardiovascular hospitalisation event rates associated with BSC**

As discussed in response to B11, 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.

D4. Model. Please add functionality to allow the model user to record sampled values for all uncertain parameters for each sample in the PSA.

Functionality enabling the user to select whether or not parameter samples are output for all uncertain parameters for each PSA iteration has been incorporated.

D5. Priority request. Company submission, Section B.3.4.5, page 136. The submission states that *"the HRQoL benefits of tafamidis through reduced hospitalisations and improved safety profile are not fully captured."* Please attempt to include this in the model.

The company is not aware of any suitable evidence that would appropriately capture the added benefit of reduced hospitalisation on HRQoL within the model. There is limited published data to describe disutility associated with CV hospitalisations, while

HRQoL assessments were not frequent enough during ATTR-ACT to adequately reflect the beneficial impact on hospitalisations.

As can be seen from ATTR-ACT data, tafamidis decreases the rate of hospitalisations, through delaying the progression of ATTR-CM. Avoiding hospitalisations has a positive impact on patient lives, enabling them to spend more time at home with their families. Further, reduced hospitalisations impacts carers, which can include family members or nursing homes due to the advanced age of ATTR-CM patients. However, it is not possible to adequately reflect this improvement in HRQoL within the economic model.

Tafamidis is a well-tolerated medicine. Any reduction in adverse events would have a positive impact on patient lives. However, given the similar safety profiles between tafamidis and placebo observed in ATTR-ACT, the incorporation of disutilties would have a minimal impact on the utility estimates and has therefore not been incorporated.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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.

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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	UK ATTR Amyloidosis Patients' Association (UKATPA) (Charity no. 1183624)
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: 1. To inform, support and advocate for people living with ATTR amyloidosis: patients, relatives and caregivers. 2. To work closely with all stakeholders to facilitate the availability of effective treatments for ATTR amyloidosis. 3. To raise awareness of ATTR amyloidosis in order to promote and facilitate early diagnosis. 4. To support research programmes which will be of benefit to those living with ATTR amyloidosis. The UKATPA has a membership of approximately 70 patients, family members and caregivers, and is governed by four Trustees who are all patients with ATTR amyloidosis. We expect the membership to at least double in the next year. We interact with the UK ATTR amyloidosis community by means of email updates and organised 'Info Days'. We have a website, and are planning a quarterly newsletter starting in 2020. As a relatively newly formed organisation, the UKATPA does not have a regular and formalised funding stream at present. However, fundraising plans for the period 2020 to 2021 are being developed. We are also in receipt of two grants from the pharmaceutical industry, one to support patient and caregiver education, and one to support administration and set up of the organisation.
4b. 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 have gathered information about the experiences of patients and caregivers in the following ways: 1. By speaking to our members about their experience of cardiac ATTR amyloidosis 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. 3. By reading websites, articles and publications on the disease 4. Over the last few years the Trustees have attended and participated in a number of conferences and seminars that have been aimed at both patients and healthcare professionals, or just patients and families, providing additional knowledge on this complex disease.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Cardiac ATTR amyloidosis is a debilitating disease. It causes progressive loss of mobility and independence, leading to a poor quality of life for sufferers and their carers. Below is a list of disabling effects of the disease as expressed by **patients**: 1. <u>Severely reduced ability to walk uphill or upstairs</u> Many patients struggle to walk up the stairs in their homes. One patient said he has to rest after climbing every 2 to 3 steps, so it can take a long time to get there. He sometimes has to use his hands and 'crawl' up the stairs. Many people have to simply avoid walking up even small inclines and this can affect every aspect of life from shopping, to visiting family and friends, to holidays. 2. <u>Fatigue</u> Other patients struggle to walk even short distances on the flat due to fatigue. One patient told us 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 is a very common symptom reported by patients, and many are forced to retire early due to fatigue. It is also something which has a substantial impact on every aspect of life, including social life and family life. 3. Breathlessness Breathlessness is another symptom which contributes to reduced mobility, and can be very distressing. Almost all patients with cardiac ATTR amyloidosis, even those thought to have milder forms of the disease, find that the breathlessness is extremely limiting in usual daily activities, and is worrying. *'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 4. Dizziness, falling and fainting Many patients have unstable blood pressure so that 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. '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 shoe laces or whatever and I find I get a little bit lightheaded'.* - Patient 5. Abnormal heart rhythms One of the effects of cardiac amyloidosis is that the heart develops abnormal beats – beating too slow or two 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. To keep the heart beating regularly people need to have pacemakers or other devices inserted. Sometimes even that does not work and the heart can stop beating suddenly. 6. Pain

	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. 7. Loss of independence Being less mobile and breathless after even minor tasks means that patients have to depend on their caregivers (who are usually their spouses, sometimes their children) 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 help out with household tasks. 8. Financial burden Having to retire earlier than expected can place financial strain on patients and their families. Caregivers often also have to retire or reduce working hours due to the burden of care. Travelling to many hospital appointments can pose a financial pressure. Furthermore, purchasing mobility aids (e.g. wheelchair, mobility scooter) and modifying the home to aid mobility can lead to further expense. With NHS social care services under strain, many families have to foot the bill for care. 9. Psychological burden One form of cardiac ATTR amyloidosis is hereditary. We know from the community of patients and their families, as well as some of our Trustees that hereditary ATTR amyloidosis 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 also for their children and grandchildren who may inherit the disease. Many patients suffer from low mood or even depression. The burden on **caregivers** is significant too. Most caregivers are partners or spouses, sometimes children. Caregivers also complain of 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 may also suffer isolation as they are either afraid or unable to leave their spouses alone. Caregivers also suffer from low mood and depression as a result of the impact of the disease on them and their families.

Current treatment of the condition in the NHS	
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 ATTR amyloidosis are those which support heart function, such as water tablets or tablets to control the heart rhythm or thin the blood. There are no medicines available to stop the amyloid from building up in the heart (also known as disease modifying medicines).
8. Is there an unmet need for patients with this condition?	Yes. There are disease modifying medicines available to patients who have ATTR amyloidosis affecting the nervous system (neuropathy) but no treatments for those who have ATTR amyloidosis mainly affecting the heart. 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	
9. What do patients or carers think are the advantages of the technology?	1. The treatment may be able 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. 2. Some patients may have the 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. 3. Many patients end up with pacemakers sometimes in an emergency situation after attending A+E .The treatment for some may remove this requirement. 4. It is an advantage that the medicine is in tablet form.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	It is not known whether people with more severe disease will have a benefit from this treatment.
Patient population	
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.	We have learnt from educational seminars and information on patient forums that the drug may not be of benefit to people with more severe disease, but those with milder disease may benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	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.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Our organisation is aware of the published results of clinical trials involving this treatment. There have been separate trials involving patients with neuropathy and cardiomyopathy, and the results indicate that the treatment may benefit those with earlier stage disease than those with later stage disease. The treatment is innovative in that it is the first of its type (TTR stabiliser) to be approved by the medicine regulators for the treatment of ATTR-CM. However, there are other medicines in the same class, but they have not reached the same stage of development as yet and have not been directly compared to this treatment. Therefore it is not known whether or not they would be more effective in halting or slowing the disease and better in terms of fewer side effects.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Cardiac ATTR amyloidosis significantly shortens the life of patients.
- There is an unmet need as there are no medical treatments for this type of amyloidosis which can stop or stop the amyloid from building up (disease modifying medicines)
- The burden of the disease on patients is significant, affecting all aspects of life, giving them a poor quality of life.
- The burden of the disease on caregivers and families is also significant, including possible financial burden and psychological and mental health effects.
- There should be equal access to the medicine to patients all over the UK.

Thank you for your time.

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Clinical expert statement

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Marianna Fontana**
2. Name of organisation	**University College London**

3. Job title or position	**Associate Professor, Honorary Consultant Cardiologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it x I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. 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 aim of the treatment is to reduce all-cause mortality, to reduce cardiovascular related hospitalizations and prevent progression. The drug does not lead to a clinical improvement but only reduction in disease progression.
8. 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.)	No markers of treatment response have been identified. It is therefore not possible to identify, at an individual level, responders and non-responders.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a clear unmet need, as there is not disease modifying treatment at present for patients with cardiac ATTR amyloidosis.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Only supportive care.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Experts recommendations have currently been published or are in press. The recommendations focus on diagnosis and management (supportive care).
• 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 diagnosis is performed for the vast majority of patients (probably >95%) at the National Amyloidosis Center. A combination of imaging tests is performed that can be used in the majority of patients to reach a diagnosis non-invasively. Gene testing is performed in all patients. In patients where a non-biopsy diagnosis cannot be reached, cardiac or non-cardiac biopsy is performed and analysed with Congo red, immunohistochemistry and mass spect.
• What impact would the technology have on the current pathway of care?	A network of centers (8-10) is currently being created by the National Amyloidosis Center.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be the first modifying treatment available.

• How does healthcare resource use differ between the technology and current care?	The drug will be In addition to the supportive treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be used within the network that the NAC is now creating with selected centers in the country. The condition is a rare disease that can be challenging to diagnose. It is vital that the use of the drug is only in highly specialized centers not only to avoid misdiagnosis but also to try to find markers of treatment response.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The costs related to the creation of a network of treatment centers.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The phase 3 clinical trial published in the NEJM shows improvements in mortality, reduction in the numbers of cardiovascular related hospitalizations and reduction in the decline in functional capacity and quality of life as compared to placebo. There is no evidence of improvement. Furthermore it is not possible to assess if the patients are responding at an individual level, as no biomarkers of treatment response have been identified.
• Do you expect the technology to increase length of life more than current care?	In the trial there is an improvement in mortality at 18 months. However, we have seen a significant increase in the number of patients diagnosed in the last few years and the phenotype has shifted significantly. It is possible that the results may not be entirely applicable to the patients that will be treated prospectively.

• Do you expect the technology to increase health-related quality of life more than current care?	The drug is associated with reduction in the decline in functional capacity and quality of life as compared to placebo. However, it will not be possible to assess the at an individual level, as the disease course is extremely variable, and there was no improvement in quality of life, but only reduction in the decline.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is not clear.
The use of the technology	
14. 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	It will be very easy to use. The disease is felt to be much more common than previously thought. From rare disease, it is now starting to be considered a common disease (up to 20% of patients with AS undergoing TAVI). There will be therefore a significant need for investment in the drugs and NHS infrastructure.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No markers of treatment response have been identified, so that we do not understand whether there are differences in the efficacy of tafamidis therapy between individual patients. Whilst it is likely that stabilization of the TTR protein by tafamidis differs between individuals depending upon the disease stage, comorbidities and different disease genotypes, the identification of responders and non-responders is currently impossible. There is therefore a clear need for a novel tool to measure ATTR-CM burden and to monitor treatment responses. This will lead to individualised patient management decision and a precision medicine approach that will reduce costs for health systems. To implement this protocolized prospective follow up of patients on treatment at the National Amyloidosis Centre will be needed at highly specialized centers.
16. 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 is difficult to know.

17. 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?	It will have an impact on prognosis and reduction in disease progression. There are other treatments that are probably more promising.
• Is the technology a 'step-change' in the management of the condition?	Yes, as there are no disease modifying treatment at present.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as there are no disease modifying treatment at present
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The drug is very well tolerated

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	It is difficult to fully determine. We have seen a significant increase in the number of patients diagnosed in the last few years and the phenotype has shifted significantly. It is possible that the results may not be entirely applicable to the patients that will be treated prospectively.
• If not, how could the results be extrapolated to the UK setting?	We will ned to assess this in the pateints that will be treated in the UK, with a prospective protocolized follow up. This should be a mandatory requirement for the prescription of the drug.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The end points used are very robust: reduction in all cause mortality, hospitalizations and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance HST10?	Not sure.
22. How do data on real-world experience compare with the trial data?	No real world data are available as yet.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Are either patisiran or inotersen used to treat transthyretin amyloid cardiomyopathy in clinical practice?	Yes, these drugs are currently used to treat patients with amyloid related peripheral neuropathy. Some of these patients will also have cardiac amyloidosis. The effect of patisiran on patients with cardiac amyloidosis were recently published (Circulation 2019). Patisiran, as opposed to tafamidis that is associated with only reduction in the disease progression, was associated with improvement in cardiac biomarkers (reduction in left ventricular wall thickness, reduction in global longitudinal strain, reduction in NT-proBNP and reduction in adverse cardiac outcomes compared to placebo at 18 months).
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • The trial used hard endpoints, including mortality and number of cardiovascular hospital admissions and is well tolerated • However, no evidence of improvement was proven only reduction in disease progression • ATTR amyloidosis, previously considered a rare disease, now is considered a common disease • The phenotype of ATTR amyloidosis patients is rapidly changing • Identifying markers of treatment response to individualize treatment will be the next crucial clinical challenge.	

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Prof PN Hawkins**
2. Name of organisation	**National Amyloidosis Centre UCL and Royal Free Hospital**

3. Job title or position	**Professor of Medicine**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. 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 modestly improve prognosis and modestly reduce rate of reduction in quality of life. There is no suggestion that the treatment leads to any clinical improvement however.
8. 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.)	It is absolutely impossible to determine any kind of response to treatment, since the natural history of the disease is of progression which is rather variable. There are no known biomarkers or clinical measurements that can determine whether an individual is benefiting (or otherwise) from this treatment.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, it is a progressive and quite rapidly fatal disease.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	By management of symptoms of heart failure with supportive drugs, medical devices and lifestyle advice.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines are in press.
• 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.)	Diagnosis at the National Amyloidosis Centre has been revolutionised using cardiac MRI and repurposed bone scan technology, which is gradually being adopted throughout the country. Currently all patients suspected or proven to have cardiac ATTR amyloidosis are eligible to be assessed at the National Amyloidosis Centre. About 300 cases diagnosed past year, but very probably the tip of the iceberg.
• What impact would the technology have on the current pathway of care?	The National Amyloidosis Centre is currently developing an English network of 6-12 centres interested in managing patients with this disease
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology represents the only disease modifying treatment for the disease, and there will be a strong push for it to be prescribed locally in many hospitals.

• How does healthcare resource use differ between the technology and current care?	The technology will be in addition to all current care.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care with tertiary review and evaluation at the National Amyloidosis Centre.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Very little other than the cost the new treatment.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It will never be possible to establish the benefit or detrimental effects within individual patients since there are no known biomarkers of response. The trial has shown a modest reduction in mortality at 2 years, slightly fewer hospitalizations and slower loss of quality of life. However, the natural history varies massively across the spectrum of patients, and so it will never be clear how much or indeed whether individual patients may be benefiting.
• Do you expect the technology to increase length of life more than current care?	Slightly, if the results of the small 441 patient trial are representative of the current large UK population, which has been diagnosed using the new non-biopsy imaging method. It is not at all clear that the current UK population of diagnosed patients is comparable with the patients reported in the one multinational trial. The latter patients were diagnosed using biopsies and their characteristics may be different.

• Do you expect the technology to increase health-related quality of life more than current care?	Again, not possible to determine in the real World clinical setting, but hopefully less rapid deterioration of quality of life – NOT IMPROVED however.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not known. Note that the disease is now diagnosed using imaging, whereas the cohort of patients in the one trial were diagnosed using biopsies and histology. At the National Amyloidosis Centre we have observed that our patients with the disease in question more closely align with the tafamidis-treated patients in the trial than the placebo group. This raises important questions as to the apparent efficacy of the technology and / or whether patients currently being diagnosed in the UK by imaging may differ from those in the trial.
The use of the technology	
14. 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	It is additional and is a simple once per day oral preparation. Since there seems no way to determine response, it would seem additional resources will not be used. However, availability of this technology will undoubtedly lead to a huge increase in interest in the disease, and massive upscaling of the diagnostic tests to confirm / exclude the diagnosis. Recent research at the National Amyloidosis Centre indicated that more than 1 in 10 older individuals have cardiac ATTR amyloid, and so our expectation is that a lot more resources will be required one way or the other.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Since response cannot be ascertained, there will be a push for all patients with cardiac ATTR amyloid to be treated, and without any possible stopping criteria other than poor tolerability or adverse effects.
16. 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?	This will be impossible to determine.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	It is innovative although the efficacy appears modest, and there are many other perhaps more promising technologies already in clinical trial.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	It is the *only* change in management, and hopefully one that does delay clinical worsening.
• Does the use of the technology address any particular unmet need of the patient population?	It may benefit amyloid neuropathy in patients who have the hereditary form of cardiac ATTR amyloidosis, but the recently approved RNA inhibitors patisiran and inotersen are probably far more efficacious in this regard.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimal.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Not necessarily. It is not at all clear that the current UK population of patients diagnosed by medical imaging is comparable with the patients reported in the one multinational trial. The latter patients were diagnosed using biopsies and their characteristics may be different.
• If not, how could the results be extrapolated to the UK setting?	Another trial would be very commendable. The disease was thought to be very rare when the single 441 patient RCT was conducted, but it is now abundantly clear that the disease is common. As such, the trial design would be reasonable for a very rare disease, but not a common one – a much larger population should be studied, and one using current new diagnostic methods.
• What, in your view, are the most important outcomes, and were they measured in the trials?	This single RCT study used admirably robust endpoints of death, hospitalization and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogate measures were used that can guide benefit in individual patients.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance HST10?	Not sure what this is
22. How do data on real-world experience compare with the trial data?	We have no real world experience of tafamidis at the NAC.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Are either patisiran or inotersen used to treat transthyretin amyloid cardiomyopathy in clinical practice?	Yes. These two drugs are approved by EMA and NICE for hereditary ATTR amyloidosis, in which amyloid cardiomyopathy is almost always present in the UK. Patisiran in particular was shown in a sub-study of cardiac patients in the pivotal Apollo amyloid neuropathy trial to be associated with improvement of cardiac biomarkers, suggesting that RNA inhibitors may be able to reverse the cardiac disease as opposed to merely modestly reducing its progression.
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Cardiac ATTR amyloidosis is now recognised to be a common and easily diagnosed disorder. • The tafamidis RCT was designed 10 years ago when the disease was thought to be very rare – it is a rare-disease type of trial • Patients now diagnosed through non-biopsy imaging methods may have different disease characteristics to those who participated in the trial and had been diagnosed through biopsies. • The trial suggests that disease progression may be modestly reduced, but not reversed. • There will, in individual patients, be no possible way to determine the degree of benefit, or indeed any benefit, from this technology.	

Thank you for your time.

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Patient expert statement

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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About you	
1.Your name	**David Gregory**
2. Are you (please tick all that apply):	☐ **X** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	UK ATTR Amyloidosis Patients Association (UKATPA)
4. Did your nominating organisation submit a submission?	☐ **X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **X** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I have been diagnosed with Cardiac ATTR amyloid associated with T60A ATTR variant. This was diagnosed 6 years ago , before that I had two years of heart issues which could not be explained, despite having extensive tests . It was my sister who was 10 years older who had many more different symptoms who first got diagnosed, which turned out to be a hereditary disease. In my family ¾ of the siblings have this disease my older sister Ann ,my older brother Hugh who is more advance than me and finally me who is at an earlier stage. My mother who was the carrier died with another illness and did not know she had the gene. It would appear that in my family the disease has effected the heart first. For me the challenge has been noticeable in my walking ability which is one of my main hobbies. I used to hill walk weekly and I was struggling to do this as I was having tightness in my chest with angina like symptoms ,also breathlessness.

	As time went on this overlapped into my work place which had a element of physical work and it was becoming challenging to maintain this. I did fairly long hours and travelling to work and back had become unacceptable as I was constantly suffering with fatigue and I was aware there was a risk in driving. End of 2018 I retired probably 5 years earlier than I wanted but I was aware that my physical limitations were becoming an issue – very disappointing. This was a big challenge for my family as they could see that there was a slow deterioration in my health and as it had been diagnosed with Cardiac ATTR amyloid they had also become aware that it was life threatening , especially as there is no drugs to slow or cure the disease for heart effected people. At the same time as a family we were watching my sister deteriorate significantly having first cardiac issues then onto peripheral neuropathy and finally effecting automonic areas of the body. At her stage of life there was no drugs only supportive medicine . This amyloid goes around the body and clogs the system up . My sister died January 2018 with the disease . I would also like to point that there are 16 potential relatives from the 3 siblings that could get the disease certainly 8 more likely as it effects 50% of the family . In my family it is not a rare disease it is a epidemic. For the first five years of this disease I have not been prescribed a recognised NICE medicine to slow the cardiac issues that I have had. In the last 3 months I am now having peripheral neuropathy issues so I am on one of the new drugs for these symptoms.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is no NICE recognised drug to stop or slow the onset of this disease that relates to the cardiac aspects so that is an issue. It is fantastic that there are the new gene silencers available for the peripheral neuropathy aspects but not for cardiac. The NHS and NAC care has been fantastic in supporting you with this disease and that continues.

10. Is there an unmet need for patients with this condition?	Yes – as explained there is a gap where the disease continues to spread firstly effecting the heart which is a main organ and does damage which cannot be reversed. If there is a drug that can do this then it should be approved.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Tafamadis I believe is a stabiliser which slows the amyloid getting around the body and has been trialled to achieve this. Currently there is no NICE approved alternative.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The % reduction is not as good as the new gene silencers. So likely to be obsolete in a few years but as a gap fill it would be useful.
Patient population	
13. 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.	Cardiac ATTR amyloid patients will benefit the most. As already explained above.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.
Other issues	
15. Are there any other issues that you would like the committee to consider?	No.
Topic-specific questions	
16. Are either patisiran or inotersen used to treat transthyretin amyloid cardiomyopathy in clinical practice?	I am now on Inotersen for the last three months but in is not diagnosed relating to cardiomyopathy, it has been diagnosed for peripheral neuropathy .

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • No signed off NICE drug is available for Cardiac ATTR amyloid patients. • If there was one it would help slow the disease earlier around the body. • Life for that patient could mean continued work and contribution to society. • Mental well being improved as you would not be waiting for the next symptoms to be happening. • Cardiac patients not being second class to other ATTR symptom suffers who have approved medicines.

Thank you for your time.

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About you	
1.Your name	**Paul Pozzo**
2. Are you (please tick all that apply):	☐ **x** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	UK ATTR Amyloidosis Patients Association
4. Did your nominating organisation submit a submission?	☐**x** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ **x** yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **x** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I get tired and out of breath when doing any exertion eg walking up hills, gardening lifting.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I was diagnosed with ATTR wild type in Jan 2015. I am currently taking part in the AG10drug trial which started in November 2019
10. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	To improve quality of life.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. 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.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Topic-specific questions	
16. Are either patisiran or inotersen used to treat transthyretin amyloid	

cardiomyopathy in clinical practice?	

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • • • • •

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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

- 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 10 pages.

About you	
1. Your name	**Dr Ayesha Ali**
2. Name of organisation	**NHS England**

3. Job title or position	**Medical Advisor, Highly Specialised Services**
4. Are you (please tick all that apply):	**x**☐ commissioning services for a CCG or NHS England in general? **x**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England has not published any clinical commissioning policies for this condition.
6. 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	The National Amyloid Centre (NAC) at the Royal Free Hospital in London is the commissioned national highly specialised service which provides a diagnostic service and management of patients suspected of amyloid-forming conditions. This will include patients with transthyretin amyloid cardiomyopathy. New patients would be seen at the NAC. The pathway for ongoing care and treatment of patients with an established diagnosis is less well defined and although most patients will be under the care of the NAC, some patients may be under the care of local cardiologists or other specialists. An amyloidosis network is being planned to formalise these structures and arrangements.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	The technology, if adopted will have a significant impact on the pathway of care as currently only supportive care is available for this patient cohort.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	There was an EAMS scheme in place The treatment is not currently used in the local health economy.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The main extra resource use will be drug costs, increased outpatient attendance and costs of additional investigations and imaging.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatments for new patients with hereditary, intermediate, complex or multisystem disease should be initiated and monitored by the NAC with arrangements for local shared care where appropriate. Local centres would need the necessary infrastructure (in particular access to genetic testing, scintigraphy, echo and cardiac MRI) and expertise.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Early diagnosis is crucial for optimal clinical outcomes. This will require increased awareness amongst referring clinicians early in the patient journey in secondary care (and in some cases even in primary care) to consider this as a differential diagnosis and start appropriate diagnostic tests or make onward referrals to specialised centres. There may also be a need for increased diagnostic capacity.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	There are currently no starting or stopping rules in place. These would be defined in the future.
10. What is the outcome of any evaluations or audits of the use of the technology?	None to date
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	This tends to be a disease with an onset in later life and more predominant in males. Age and sex are protected characteristics.
11b. Consider whether these issues are different from issues with current care and why.	

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Tafamidis for treating transthyretin amyloid cardiomyopathy: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	20th November 2019

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Lesley Uttley and Paul Tappenden acted as joint project leads. Mark Clowes critiqued the company's search strategy. Lesley Uttley summarised and critiqued the clinical effectiveness evidence reported within the company's submission. John Stevens critiqued the statistical aspects of the clinical effectiveness data and health economic analysis. Paul Tappenden and Kate Ennis critiqued the company's health economic analysis. All authors were involved in drafting and commenting on the final report.

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Abbreviations

6MWT	6-minute walk test
ACE	Angiotensin-converting enzyme
AE	Adverse event
AIC	Akaike Information Criterion
ATTR-CM	Transthyretin amyloid cardiomyopathy
BIC	Bayesian Information Criterion
BNP	Brain natriuretic peptide
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMAD	Cardiac mechanical assist device
CS	Company's submission
CSR	Clinical study report
CV	Cardiovascular
DCO	Data cut-off
DSAs	Deterministic sensitivity analyses
EAMS	Early Access to Medicines Scheme
ECG	Echocardiogram
eGFR	Estimated glomerular filtration rate
eMIT	Electronic Market Information Tool
EQ-5D-3L	EuroQol 5-Dimensions, 3-Level
EQ-VAS	EuroQoL visual analogue scale
ERG	Evidence Review Group
FAD	Final appraisal determination
FDA	Food and Drug Administration
GEE	Generalised estimating equation
GI	Gastrointestinal
HCHS	Hospital and Community Health Services
HF	Heart failure
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LTE	Long-term extension
LV	Left ventricular
LYG	Life year gained
mBMI	Modified body mass index
MIMS	Monthly Index of Medical Specialities
MVN	Multivariate normal
NAC	National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal-pro hormone B-type natriuretic peptide
NYHA	New York Heart Association
OPT	Optimal pharmaceutical therapy
ONS	Office for National Statistics
OS	Overall survival

PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
q.d.	Once daily
QALY	Quality-adjusted life year
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TTD	Time-to-treatment discontinuation
TTR	Transthyretin
TTR-FAP	Transthyretin familial amyloid polyneuropathy
UK	United Kingdom
UTI	Urinary tract infection
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) assesses the clinical effectiveness and cost-effectiveness of tafamidis (Vyndaqel®) for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM). The CS highlights that there are currently no effective disease-modifying therapies for ATTR-CM; hence, the anticipated place of tafamidis is as a first-line treatment for adult patients with ATTR-CM (in combination with best supportive care [BSC]). The population in the CS [redacted] is generally in line with the target population described in the final scope issued by the National Institute for Health and Care Excellence (NICE)[redacted].

1.2 Summary of clinical effectiveness evidence submitted by the company

The main source of clinical evidence included in the CS is a pivotal, multi-centre, Phase III randomised controlled trial (RCT) of tafamidis in ATTR-CM (the ATTR-ACT trial). This trial was powered to detect a significant difference between tafamidis, pooled from two dosage groups (20mg and 80mg) and placebo over 30 months. Supporting efficacy and safety data for tafamidis were also presented from an ongoing long-term extension (LTE) study to the ATTR-ACT trial, and a Phase II study of tafamidis with its corresponding extension study.

In the ATTR-ACT study, the analysis of the primary outcome, which was a combined hierarchical analysis of all-cause mortality and cardiovascular (CV)-related hospitalisations, favoured pooled tafamidis over placebo (p=0.006). These differences remained significant when both all-cause mortality (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.51, 0.95; p=0.0259) and CV-related hospitalisations (relative risk [RR] ratio: 0.67; 95% CI: 0.56, 0.81; p<0.0001) were analysed separately. Pooled tafamidis was also associated with statistically significant benefits for secondary outcomes including: CV-related mortality (HR: 0.69; 95% CI: 0.4, 0.98; p=0.0383); the Six-Minute-Walk-Test (6MWT) (p<0.0001); reduction in N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) ([redacted]); health-related quality of life (HRQoL) using the Kansas City Cardiomyopathy Questionnaire-Overall Survival (KCCQ-OS) score ([redacted]), HRQoL using the EuroQol 5-Dimensions, 3-Level (EQ-5D-3L) index score ([redacted]) and EuroQoL visual analogue scale (EQ-5D VAS) ([redacted]); and transthyretin (TTR) stabilisation ([redacted]). Safety data from the studies included in the CS indicate that tafamidis was generally well tolerated. The most commonly reported treatment-related adverse events (TRAEs) were cardiac failure, dyspnoea, dizziness, fall, diarrhoea, nausea and urinary tract infection. Most adverse events (AEs) were mild to moderate in nature, or were in line with the natural disease course of ATTR-CM.

Pre-planned subgroup analyses of the ATTR-ACT trial highlighted two potentially differential treatment responses to tafamidis according to baseline functional status measured using the NYHA classification system, and also for genotype. The significant treatment benefit of pooled tafamidis over placebo appears to be driven largely by the treatment response in patients with NYHA class I/II, as opposed to NYHA class III and also, by patients with wild-type ATTR-CM, rather than hereditary ATTR-CM.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review presented in the CS appears to be comprehensive, and the Evidence Review Group (ERG) considers that all relevant studies of tafamidis for patients with ATTR-CM were included. The decision problem and outcomes of interest were largely consistent with those specified in the final NICE scope. Whilst the pivotal ATTR-ACT trial was an international, multi-centre trial, the study population is largely comprised of patients from the United States, with only four UK patients in the sample.

The ATTR-ACT trial was powered to detect a significant difference between tafamidis, pooled from two study groups of different dosages (20mg and 80mg) in comparison to placebo. *Post hoc* dose analysis found that the 20mg and 80mg doses were broadly comparable for the primary endpoint and the majority of secondary endpoints with the exception of NT-proBNP and troponin I levels, where tafamidis 80mg was statistically superior to tafamidis 20mg. At one month the TTR stabilisation differed by more than 5%, favouring 80mg tafamidis over 20mg tafamidis.

The intervention considered in the CS is tafamidis free acid at a dose of 61mg q.d which has been subject to a bioequivalence study for tafamidis meglumine 80mg q.d. The ERG notes that the CS does not contain efficacy or safety data relating to the new formulation of tafamidis free acid 61mg.

1.4 Summary of cost effectiveness evidence submitted by the company

The CS presents the methods and results of a *de novo* cohort-level state transition model developed by the company to assess the cost-effectiveness of tafamidis versus BSC for the treatment of ATTR-CM. BSC consists of established symptomatic management of HF. The base case population relates to patients with ATTR-CM with NYHA class I-III. The company's model also includes a subgroup analysis relating to patients with NYHA class I/II at baseline. Incremental health gains, costs and cost-effectiveness are evaluated over a 26.67-year time horizon from the perspective of the National Health Service (NHS) and Personal Social Services (PSS).

The company's model includes five health states based on the NYHA functional classification system (NYHA I-IV) and an additional state for death. Model parameters for each arm were informed by

analysis of time-to-event data (time-to-treatment discontinuation [TTD] and overall survival [OS]) collected in ATTR-ACT. The company's model estimates OS using a relative survival modelling approach which combines general population life table risks and additional excess risks of disease-related mortality. The model includes a discontinuation rule whereby all patients are assumed to discontinue tafamidis upon progression to NYHA class IV; this discontinuation rule did not form part of the design of the ATTR-ACT trial. Health state and treatment-dependent utility values are based on mean EQ-5D-3L data collected in ATTR-ACT. Resource use estimates were derived from ATTR-ACT, standard costing sources, literature and assumptions. After discontinuation of tafamidis, the company's model assumes that patients incur no further treatment-related costs, but implied treatment effects are assumed to continue indefinitely.

The probabilistic version of the company's updated model suggests that tafamidis is expected to generate an additional [redacted] quality-adjusted life years (QALYs) at an additional cost of [redacted] per patient compared with BSC; the corresponding incremental cost-effectiveness ratio (ICER) is [redacted] per QALY gained. The company's updated subgroup analysis for patients with baseline NYHA class I/II produces a deterministic ICER of [redacted] per QALY gained.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG's critical appraisal identified several issues relating to the company's model. However, given the list price of tafamidis, several of these concerns have little impact on the conclusions of the economic analysis. Given the company's current model, the most pertinent of these issues relates to uncertainty surrounding the assumed stopping rule and the impact of non-adherence on subsequent health outcomes. This issue has the propensity to increase the ICER for tafamidis considerably.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The CS provides an accurate overview of relevant clinical evidence for tafamidis in ATTR-CM including identification of all relevant trials and presentation of safety data.
- The main source of clinical evidence, the ATTR-ACT trial, was a high quality RCT of tafamidis versus placebo in a relevant study population for the decision problem.
- With the exception of a minor inconsistency regarding the time horizon, the ERG did not identify any programming errors in the company's model.
- The company's description of the model in the CS was generally clear.

1.6.2 Weaknesses and areas of uncertainty

- The company's main source of clinical evidence relates to pooled data from the 20mg and 80mg tafamidis meglumine arms of ATTR-ACT. The CS does not present any clinical effectiveness evidence relating to tafamidis 61mg free acid.
- The two doses of tafamidis (20mg and 80mg) demonstrated similar efficacy for the primary outcome measure and its component endpoints.
- There is uncertainty in the appropriateness of treatment with tafamidis beyond NYHA baseline class I/II due to a lack of benefit for the primary outcome in patients with NYHA baseline class III.
- There is uncertainty regarding the long-term outcomes for tafamidis, particularly with respect to the relationship between the duration of exposure to tafamidis and the duration over which treatment effects apply.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook six exploratory analyses. These included: (i) applying a treatment discontinuation plateau for survivors after 30 months within the NYHA I-III states; (ii) applying BSC group utilities in NYHA IV for patients in the tafamidis group; (iii) applying BSC CV-related hospitalisation rates for all patients in NYHA IV; (iv) age-adjustment of utilities; (v) the inclusion of BSC costs for patients who discontinue tafamidis, and (vi) the inclusion of drug wastage for tafamidis (0.5 packs per patient). The ERG's preferred base case combines all of these model amendments. The ERG undertook additional subgroup analyses, including an analysis in which patients were only eligible to start and continue treatment with tafamidis in NYHA class I/II. The ERG also undertook additional sensitivity analyses to explore the impact of: (i) the application of BSC outcomes for tafamidis discontinuers; (ii) using treatment-independent utilities; (iii) removal of NYHA-specific mortality risks; (iv) carrying forward the last observed transition matrix during the extrapolation period; and (v) using alternative parametric survival models for the disease-related excess hazard of death.

The ERG's preferred analysis suggests that the deterministic ICER for tafamidis versus BSC is [redacted] per QALY gained. However, applying the BSC outcomes to patients who discontinue tafamidis increases the ICER to [redacted] per QALY gained. The ERG believes that neither of these analyses fully addresses issues relating to the relationship between the level of exposure to tafamidis and the treatment effects resulting from that exposure; as such, the ERG believes that the ICER is likely to lie between these two estimates [redacted] to [redacted] per QALY gained). The ERG's exploratory subgroup analysis suggests that restricting the population eligible for treatment to NYHA I/II may lead to [redacted] (ERG's subgroup analysis including treatment discontinuation plateau and treatment in NYHA I/II only: ICER to [redacted] per QALY gained).

2 BACKGROUND

This report provides a brief review of the evidence submitted by the company (Pfizer) in support of tafamidis for treating adults with transthyretin amyloid cardiomyopathy (ATTR-CM). It includes evidence presented within the company's submission (CS) received on 19th September 2019,[1] and responses to the Evidence Review Group's (ERG) clarification questions provided by the company on 25th October 2019.[2]

2.1 Critique of company's description of the underlying health problem

Section B.1.3 of the CS[1] provides an accurate description of ATTR-CM. As described in the CS, ATTR-CM is a rare, progressive and ultimately fatal disease, characterised by the deposition of amyloid fibrils in the heart muscle (myocardium), leading to heart failure (HF).

ATTR-CM falls into two genotypes. Wild-type ATTR-CM is the more common form, which accounts for approximately 69% of ATTR-CM in the UK and is not inherited but occurs in later life, predominantly affecting the heart.[3] The hereditary form of ATTR-CM, is also known as 'variant' or 'mutant' ATTR-CM, and accounts for approximately 31% of ATTR-CM cases in the UK. Among patients with hereditary ATTR-CM, Val122Ile is the most common mutation in the UK and is causative in 63% of cases.[3] Both wild-type and hereditary TTR genotypes occur more commonly in men and diagnosis of the condition from either genotype typically occurs in the seventh decade of life.[4]

The exact prevalence of ATTR-CM in the UK is unknown; however, the largest UK study of ATTR-CM reported data from 711 patients with wild-type ATTR-CM and 323 patients with hereditary ATTR-CM seen at the National Amyloid Centre (NAC) between 2000 and 2017.[5] Diagnostic data from 2000 to 2008 at the NAC suggests an incidence rate of 0.03 per 100,000 for wild-type ATTR-CM.[6]

Build-up of transthyretin (TTR) in the heart damages the myocardium, resulting in stiff heart muscle walls (restrictive cardiomyopathy). TTR is synthesised primarily in the liver and serves as a secondary carrier to transport Vitamin A (retinol) and a thyroid hormone (thyroxine). Alterations in the structure of the TTR protein, caused by ageing or the inherited mutation, increase its tendency to break down into its constituent monomers, which misfold and aggregate forming insoluble amyloid fibrils which accumulate in tissues and organs. Infiltration of insoluble aggregated monomers in the myocardium ultimately leads to HF and death.

ATTR-CM is thought to be underdiagnosed due to its rarity, and heterogeneous clinical presentation, potentially leading to abnormal formation of amyloid in any organ.[7] The CS highlights that diagnoses of wild-type ATTR-CM have increased at the NAC between 2000 and 2016 due to the introduction of

a non-invasive test for suspected cardiac amyloidosis using isotope scanning.[5] However, prior to this most clinicians outside of the NAC would have seen very few cases in their entire clinical career and therefore recognition and diagnosis of amyloidosis was usually very late in the condition's trajectory, with an estimated 40% of patients with wild-type ATTR-CM waiting over 4 years for a diagnosis.[5] Clinical advice received by the ERG confirms that the diagnostic pathway and clinical staging of disease described in the CS[1] accurately describe clinical practice in the UK for ATTR-CM.

Patients with ATTR-CM have a poor life expectancy with median survival in the UK ranging from 2.3 to 6.1 years, depending on genotype.[3] Patients initially present with pain and symptoms of HF or arrhythmias, but as amyloidosis is a systemic disease, non-cardiac manifestations such as gastrointestinal (GI) symptoms (caused by poor intestinal blood flow, gut wall oedema and hepatic congestion) also frequently co-occur.[8]

The most commonly used staging system for ATTR-CM is the New York Heart Association (NYHA) Functional Classification, which is a self-reported measure to categorise HF (CS,[1] Section B.1.3.5). Clinical advice received by the ERG suggests that other markers including the six-minute walk test (6MWT) and renal function are also used in conjunction with the NYHA to assess patients' disease stage. Other classification systems such as the Mayo Clinic[9] and NAC staging systems[10] which combine biomarker thresholds such as troponin, N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR) are sometimes used.

Poor health-related quality of life (HRQoL) is observed in ATTR-CM, which can be assessed in clinical trials by the Kansas City Cardiomyopathy Questionnaire (KCCQ), a measure of patient's health status in HF. In turn, substantial burden is also noted to affect quality of life of carers and families of people with ATTR-CM.[11] The CS highlights that the economic burden in the UK is compounded by the substantial delay in diagnosis, during which a large number of hospital outpatient appointments or inpatient admissions occur.[5]

2.2 Critique of company's overview of current service provision

The CS[1] (Section B.1.3.6) correctly states that at the time of the submission, that there are currently no disease-modifying pharmacological treatments approved for ATTR-CM by the National Institute for Health and Care Excellence (NICE) for use in the National Health Service (NHS) in England and that symptomatic management of HF is the mainstay of best supportive care (BSC).

Symptom management (BSC) aims to relieve symptoms of congestive HF and prevent arrhythmic/thromboembolic events. This includes loop diuretics, aldosterone antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, beta blockers, calcium channel

blockers, and digoxin.[12] Liver transplantation (to remove the primary source of mutant TTR in hereditary cases) and heart transplantation are a potential option but are rarely used in England. The ERG's clinical advisors agreed with these assertions but stated that diflunisal is sometimes used off-label which, as a non-steroidal anti-inflammatory drug (NSAID), can pose disadvantages to patients related to fluid retention and impaired renal function. Section B.1.3.2 of the CS[1] notes that a very small number of patients (<5% of all cases seen at the NAC) who present with mixed phenotype of ATTR-CM with polyneuropathy would be eligible for treatment with patisiran and inotersen, both of which are approved for the treatment of hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final scope issued by the NICE[13] and addressed in the CS is presented in Table 1.

Table 1: Company's statement of the decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	**Decision problem addressed in the CS**	**Rationale if different from the final NICE scope (abridged)**
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*:* • Established clinical management without tafamidis People with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy (TTR-FAP) and hereditary ATTR-CM): • Patisiran • Inotersen	Best supportive care (established clinical management without tafamidis)	The company agrees that there is a small UK population of hereditary ATTR patients with a mixed phenotype. However, the company does not agree that patisiran and inotersen are relevant to this appraisal. The reasons supporting the company's view are discussed further in Section 3.3.
Outcomes	The outcome measures to be considered are: • Overall survival • Cardiovascular-related mortality • Cardiac function (such as longitudinal strain or brain natriuretic peptide [BNP] level) • Cardiovascular-related hospitalisation • Functional exercise capacity • Signs and symptoms of heart failure (such as breathlessness) • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered are: • All-cause mortality • Cardiovascular-related mortality • Cardiac function (6MWT, NT-proBNP, echocardiographic parameters) • Transthyretin stabilisation • Frequency of cardiovascular-related hospitalisation • NYHA classification • Adverse effects of treatment • Health-related quality of life	Not applicable
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. Costs will be considered from an NHS and Personal Social Services perspective.	As NICE scope	Not applicable

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope (abridged)
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • severity of heart failure (such as by NYHA class)	As NICE scope (NYHA I/II)	Not applicable
Special considerations including issues related to equity or equality	Not specified	Not applicable	Not applicable

6MWT - 6-minute walk test; ATTR-CM - transthyretin amyloid cardiomyopathy; ATTR-PN - hereditary transthyretin amyloid polyneuropathy; HF - heart failure; NA - not applicable; NAC - National Amyloidosis Centre; NYHA - New York Heart Association; QALY - quality-adjusted life year; Val122Ile - valine replaced by isoleucine at position 122

3.1 Population

The patient population in the CS[1] relates to people with ATTR-CM with NYHA I-III, based on the ATTR-ACT trial population.[14] This is narrower than the population defined in the final NICE scope [redacted]. As NYHA IV was listed as an exclusion criterion, there is no evidence for the use of tafamidis in this population.

The ATTR-ACT trial was conducted at 48 sites in 13 countries across the world, including Europe, the US, Asia and South America. Of these, 2 sites were based in the UK. The ERG's clinical advisors suggested that the population recruited into the trial broadly reflects the population who would be eligible for treatment with tafamidis in England.

Tafamidis has not yet received a European/UK marketing authorisation for the treatment of ATTR-CM; hence, it is unclear whether particular medical conditions or patient groups may be contraindicated for treatment.

[redacted]

The CS includes subgroup analyses of the primary endpoint in ATTR-ACT[14] (all-cause mortality and CV-related hospitalisations) by TTR genotype, NYHA stage at baseline and tafamidis dose. The company's economic analysis includes one subgroup analysis relating to patients with NYHA class I-II at baseline; the CS does not include any economic analysis relating to patients with mixed phenotype ATTR-CM and TTR-FAP (see Section 3.3).

3.2 Intervention

The intervention considered in the CS[1] is tafamidis free acid (PF-06291826, Vyndaqel®) at a dose of 61mg q.d. In this indication, tafamidis is delivered as a soft capsule and is taken orally. Tafamidis is a selective stabiliser of transthyretin (TTR). Tafamidis binds to TTR at the thyroxine binding sites, stabilising the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.[15] Tafamidis is manufactured by Pfizer. According to the CS, marketing authorisation for tafamidis in the ATTR-CM indication is expected in [redacted]. The CS notes that tafamidis meglumine holds an existing marketing authorisation for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy. However, the clinical advisors to the ERG noted that tafamidis is not available in England in this indication.

The anticipated list price per pack of 30 x 61mg tafamidis capsules (30 days' supply) is [redacted]. [redacted] The company's health economic analysis is based on the list price for tafamidis.

[redacted] the company's health economic analysis assumes that all patients will discontinue all treatment (both tafamidis and other concomitant therapies) upon progression to NYHA IV. This is discussed in further detail in Section 5.3.3.

3.3 Comparators

The final NICE scope[13] lists three comparators. For patients with ATTR-CM, the scope defines the comparator as established clinical management without tafamidis; within the CS,[1] this comparator is represented by BSC (symptomatic management of HF). For patients with mixed phenotype transthyretin amyloidosis (people with both TTR-FAP and hereditary ATTR-CM), the scope lists patisiran and inotersen as comparators. The CS states that the company agrees that there is a small UK population of hereditary ATTR patients with a mixed phenotype, but disagrees that patisiran and inotersen are relevant comparators to the appraisal. The CS lists five reasons supporting this position:

(1) Neither patisiran nor inotersen have been evaluated in patients with HF and neither medicine has a license for ATTR cardiomyopathy.
(2) The trials of patisiran and inotersen (APOLLO[16] and NEURO-TTR[17]) defined cardiac (mixed phenotype) subgroups based on echocardiogram criteria (left ventricular [LV] wall thickness ≥ 13mm) which does not meet consensus diagnostic criteria for ATTR-CM (and therefore may not reflect the ATTR-CM population).
(3) The Val122Ile mutation is causative in 63% of patients with hereditary ATTR-CM in the UK. APOLLO and NEURO-TTR enrolled very few patients with the Val122Ile mutation (<2%); in contrast, 57.5% of the patients enrolled in ATTR-ACT had a Val122Ile mutation.
(4) Non-Val122Ile ATTR-CM in the UK is caused by a number of ultra-rare mutations. The ERG notes that two low penetrance variants are common in specific populations, TTR Val122Ile is present in 3-4% of patients of African American and Afro Caribbean populations and tends to be associated with a late onset cardiac amyloid type with little in the way of neuropathy. Val60Ala is found in 1% of the population of North Western Ireland and is well recognised in the UK where it classically causes a late onset cardiomyopathy with evidence of neurological involvement. Other variants are extremely rare and are variably associated with mixed,

dominant cardiac or dominant neurological phenotypes. Patients may develop additional symptoms over their lifetime.

(5) APOLLO and NEURO-TTR assessed outcomes relating to polyneuropathy and did not include any clinical cardiac-related endpoints.

The clinical advisors to the ERG agreed that there is a very small group of patients with mixed phenotype ATTR amyloidosis who may be eligible for treatment with both a TTR stabiliser (tafamidis) and a TTR inhibitor (patisiran and inotersen). One of the ERG's clinical advisors stated that if tafamidis was available, they would consider using both tafamidis and patisiran. The second advisor stated that if both patisiran and tafamidis were available, they would use patisiran and tafamidis may not be required. The clinical advisors commented that studies are currently ongoing which are assessing the effectiveness of patisiran and inotersen in the ATTR-CM population (patisiran - NCT03997383; inotersen - NCT03702829). Owing to the incompatibility of the clinical endpoints assessed between the ATTR-ACT trial and the APOLLO and NEURO-TTR trials, the ERG agrees that there is currently insufficient evidence to undertake an indirect comparison between tafamidis and patisiran or inotersen for cardiac-related outcomes.

3.4 Outcomes

Outcomes included in the final NICE scope[13] include:

- Overall survival (OS)
- Cardiovascular (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 (HF, such as breathlessness)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS[1] presents clinical data relating to all of these outcomes. The company's health economic model includes data relating to NYHA class, CV-related hospitalisations, OS, AEs and HRQoL.

3.5 Other relevant factors

The CS[1] does not present any issues of equality which are relevant to this appraisal. The CS does not make a case for the consideration of tafamidis as an end of life treatment.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[1] for tafamidis for treating ATTR-CM. Section 4.1 presents a critique of the company's methods for reviewing the clinical effectiveness evidence. Sections 4.2 to 4.4 summarise the relevant trials, their results and the company's interpretation of the evidence. Section 4.5 presents a discussion of the available clinical evidence.

4.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify relevant studies on the clinical efficacy and safety of tafamidis or BSC for ATTR-CM. The methods of the company's SLR are detailed in CS Appendix D.[18]

4.1.1 Searches

Literature searches conducted to identify evidence relating to the clinical efficacy and safety of tafamidis in the treatment of ATTR-CM are reported in CS Appendix D.[18] Searches conducted in two phases cover an appropriate range of databases, including all those required by NICE, from inception to 9th May 2019. Supplementary searches were conducted of conference websites and health technology assessment (HTA) agencies. The search strategies were reproduced in full and appear to have been conducted to a high standard. Filters adapted from those developed by the Scottish Intercollegiate Guidelines Network (SIGN) have been used to identify study types eligible for inclusion. During clarification, the ERG queried the deliberate exclusion of "reviews" in the searches, given that these were eligible for inclusion as a source of primary studies. However, the company's clarification response[2] (question A1) states that, although excluded by the searches, any SLRs being identified through other means e.g. grey literature, would have been scanned for relevant clinical studies. The ERG also notes that no relevant SLRs were identified.

The ERG is generally satisfied with the company's approach to the identification of evidence for the clinical effectiveness review and believes it is unlikely that the searches have missed any relevant studies.

4.1.2 Inclusion criteria

The company's inclusion criteria for the review of clinical effectiveness are presented in Table 2. The inclusion criteria in the company's SLR broadly reflect the decision problem set out in the final NICE scope.[13] One key difference is that this systematic review did not include patisiran or inotersen as comparators, whilst both of these technologies were listed as potential comparators in the scope. The CS[1] (Section B.1.1, Table 4) states that patisiran and inotersen are not included in the CS as relevant

comparators as these drugs have not been evaluated in HF and that the corresponding trials of these treatments actively excluded patients with significant heart disease.

Table 2: Inclusion criteria for the company's SLR (adapted from CS Appendix D, Table 4)

	Inclusion criteria	Exclusion criteria
Population	Patients with hereditary or wild-type ATTR-CM Adults (≥ 18 years old)	Children and young people (under 18 years) Patients without ATTR-CM (e.g. patients with AL or AA amyloid cardiomyopathy)
Intervention	Any intervention for the management of ATTR-CM	Interventions not aimed at treating ATTR-CM
Comparators	Best supportive care (e.g. symptom management, diuretics, transplantation)	Comparators not aimed at treating ATTR-CM Off-label use (e.g. diflunisal)
Outcomes	All-cause mortality Frequency of all-cause hospitalisation Frequency of CV-related hospitalisation CV-related mortality 6-minute walk test Kansas City Cardiomyopathy Questionnaire EuroQol-5 dimension-3 level Patient global assessment Modified body mass index New York Heart Association functional classification TTR stabilisation, oligomer concentration and concentration N-terminal prohormone of brain natriuretic peptide Troponin I Echocardiograms Electrocardiograms Time on treatment Treatment discontinuation Adverse events (SAEs, TRAEs Burden of illness information	Outcomes of interest not reported
Study design	Randomised controlled trials Non-randomised controlled trials Longitudinal cohort studies Observational studies (retrospective, prospective, cohort studies, case control studies, longitudinal studies)	Pharmacokinetics studies Cost-effectiveness studies Clinical trial registry entry only Narrative reviews, editorials, letters or comments, notes, short surveys, case series or reports Animal or *in vitro* studies
Language	English language only	Non-English language

Two Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] diagrams are presented in CS Appendix D[18] to describe the flow of studies in the study selection process from the initial and update SLRs. In total, twenty studies were subject to data extraction and quality assessment

in the company's SLR presented in CS Appendix D.[18] The SLR presented in CS Appendix D only includes published studies and therefore the ongoing extension studies were not retrieved.

Section B.2.2 of the CS[1] concludes that the only interventional studies of tafamidis are the pivotal Phase III ATTR-ACT[14, 20] and the Phase II study,[21] with their respective extension studies. In addition to the main pivotal trial in the CS (ATTR-ACT),[14, 20] the SLR in CS Appendix D[18] found one other randomised controlled trial (RCT) by Judge *et al* (2019),[22] which was a trial of AG10 (NCT03458130), a novel TTR stabiliser manufactured by Eidos Therapeutics. The CS does not include or refer to the Judge *et al* (2019) study of AG10 and concludes that only the ATTR-ACT trial[14, 20] and the Phase II study (NCT00694161),[21] together with their respective extension studies (NCT02791230) are relevant (CS,[1] Section B.2.2, page 32).

4.1.3 Critique of data extraction

According to Section D.1.7 of Appendix D,[18] data abstraction was performed by one reviewer and checked by a second, with any disagreements resolved by mutual discussion. In response to a request for clarification from the ERG[2] (question A3), the company stated that a second reviewer independently checked all citations.

4.1.4 Critique of quality assessment

Quality assessment was described in Section D.3 of CS Appendix D[18] as being appraised using the Cochrane Risk of Bias tool[23] for RCTs and the Downs and Black (1998)[24] tool for non-RCTs. The CS does not describe how many reviewers were involved in conducting quality assessment and whether any double-checking of decisions for reliability was conducted.

4.1.5 Critique of evidence synthesis

As only one RCT (ATTR-ACT[20]) was identified as being an interventional RCT of tafamidis, the CS does not include any formal evidence synthesis of data between studies.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The CS[1] presents data for three studies that examine the efficacy and safety of tafamidis in patients with ATTR-CM:

i. ATTR-ACT, a Phase III multi-centre RCT of tafamidis 80mg, 20mg or placebo (NCT01994889;[14] Maurer *et al* 2018[20])
ii. An open-label long-term extension (LTE) study to ATTR-ACT of tafamidis 61mg or tafamidis meglumine 80mg (NCT02791230)[25]

iii. An open-label multi-centre, single-arm Phase II study of tafamidis 20mg (NCT00694161; Maurer *et al* 2015;[21] Sultan *et al* 2017[26]).

An open-label LTE study to the Phase II study (NCT00935012) is described (CS,[1] Section B.2.6.4.3); however, full efficacy and safety data are not provided.

Two further non-interventional studies are briefly described in Section B.2.2 of the CS:

i. THAOS (B3461001; Coelho *et al,* 2013)[27]
ii. Transthyretin Amyloidosis Cardiac Study (TRACS; Ruberg *et al*, 2012).[28]

These longitudinal studies were conducted to characterise the natural history, morbidity and mortality of patients with ATTR-CM in the absence of disease-modifying treatment. These studies do not provide information relating to the clinical efficacy or safety of tafamidis for ATTR-CM.

The ATTR-ACT trial: Study design

The ATTR-ACT RCT[20] enrolled 441 patients across 13 countries including the UK, Belgium, Brazil, Canada, Czech Republic, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, and the United States (US). The majority of patients were enrolled from the US (n=279); only four patients enrolled in ATTR-ACT were from the UK. All 441 patients were randomised to either:

i. Tafamidis 20mg (1 x 20mg tafamidis meglumine plus 3 x placebo capsules once daily [q.d.]; n=88 patients)
ii. Tafamidis 80mg (4 x 20mg tafamidis meglumine q.d.; n=176 patients)
iii. Placebo (4 x placebo capsules q.d.; n=177 patients)

Treatment assignment was stratified by TTR genotype (wild-type or hereditary) and by baseline severity (NYHA class I and NYHA class II combined versus NYHA class III). Patients received study treatment in addition to BSC in a blinded fashion for 30 months (910 days).

Inclusion criteria for the ATTR-ACT trial are reported in Table 10 of the CS.[1] Eligible patients: were aged between 18 and 90 years; had confirmed wild-type or hereditary ATTR-CM; had evidence of cardiac involvement (demonstrated by echocardiography, with an end diastolic interventricular septal wall thickness exceeding 12mm); had a medical history of HF with at least one prior hospitalisation for HF or clinical evidence of HF; had an NT-proBNP concentration ≥600pg/mL and a 6MWT >100 metres. Exclusion criteria included: HF that was not due to ATTR-CM; NYHA class IV HF; presence of light chain amyloidosis; prior liver or heart transplantation or implanted cardiac mechanical assist device (CMAD); previous treatment with tafamidis; eGFR of <25 mL/min/1.73m^2; liver transaminase levels exceeding two times the upper limit of the normal range; modified body mass index (mBMI) of

less than 600; receipt of concurrent treatment with NSAIDs (other than those permitted), tauroursodeoxycholate, doxycycline, calcium channel blockers (e.g. verapamil, diltiazem) or digitalis.

All 441 patients received at least one dose of study drug and were defined as the safety analysis set. An intention to-treat (ITT) analysis set was defined as patients who had at least one post-baseline efficacy evaluation (i.e. post-baseline hospitalisation, study visit, or date of death). The ITT population was used for the primary analysis. A per protocol (PP) analysis set was defined as all patients in the ITT population who did not violate inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis. Patients who discontinued for transplantation (i.e. heart transplantation and combined heart and liver transplantation) or for implantation of a CMAD, were handled in the primary analysis in the same manner as death. Adherence was defined as the proportion of patients who took their four capsules of study medication per day on at least 80% of days of study participation. Subjects with less than 80% dosing adherence were excluded from the per-protocol analysis.

The intervention primarily used in the studies is tafamidis meglumine (20mg and 80mg). The intervention in the draft SmPC[15] is tafamidis free acid 61mg, which was subject to a bioequivalence trial (to tafamidis meglumine 4 x 20 mg) in 30 healthy volunteers (NCT03266705) in 2018.[15] A protocol amendment to the ATTR-ACT LTE study on the 20th July 2018 allowed assignment to open-label tafamidis (61mg) from tafamidis meglumine (80mg). However, the data cut for the LTE study of ATTR-ACT (15th February 2018) occurred prior to the protocol amendment to use a new formulation of tafamidis free acid (20th July 2018), therefore no data in the CS relate to the new 61mg formulation of tafamidis.

Outcomes of interest in the ATTR-ACT trial are described in Table 11 of the CS.[1] The primary endpoint was a hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations (defined as the number of times a patient was hospitalised for CV-related morbidity), applying the Finkelstein-Schoenfeld[29] method. The primary analysis pooled the tafamidis (20mg and 80mg) treatment groups and compared this with the placebo group. All-cause mortality and frequency of CV-related hospitalisations were also analysed as separate endpoints. Cause of death and hospitalisations were adjudicated by a committee of external experts to determine if they were CV-related. Secondary endpoints included the 6MWT distance and KCCQ-OS.

Subgroup analyses were pre-planned for TTR genotype (wild-type versus hereditary); NYHA class at baseline (class I/II versus class III); and dose analysis (20mg versus placebo; 80mg versus placebo).

The intention to perform a hierarchical combination of the two endpoints and a pooled analysis of the tafamidis treatment groups was described when the trial was registered on clinicaltrials.gov in March 2013. The intention to use the Finkelstein-Schoenfeld method[29] was reported in a publication by Maurer *et al* (2017)[30] and the clinical trial registration record was updated on the clinicaltrials.gov website (NCT01994889) on March 14th 2019.

The clinical advisors to the ERG noted concerns regarding the appropriateness of a study design that pools a study dose of tafamidis 20mg with a dose which is four times as high (80mg). The ERG sought clarification from the company on the justification for pooling the 20mg and 80 mg treatment arms. The company's clarification response[2] (question A7) stated that due to "*rare disease studies where there are small patient populations…[and]…Following agreement with regulatory bodies on the design of the study …Pooling the data across the two doses therefore reduces uncertainty in the primary outcome.*" The ERG also requested clarification from the company as to whether the two different tafamidis doses are clinically equivalent. The company's response stated that the "*efficacy of the two doses was clinically equivalent for the primary outcome measure and its component endpoints*" and provided data comparing the tafamidis 20mg and 80mg subgroups on the primary endpoint of combined analysis of all-cause mortality and CV-related hospitalisations demonstrating very similar efficacy. Clinical advice to the ERG was that a dose-response relationship would be expected, with the 80mg dose providing better efficacy than the 20mg dose, but that the number of patients between treatment groups may have been too small to demonstrate this.

The ATTR-ACT long-term extension study

The LTE study for ATTR-ACT (NCT02791230)[31] is ongoing, but the CS[1] presents data from a cut-off date of the 15th February 2018. This Phase III multi-centre study is enrolling patients for open-label tafamidis treatment over 60 months. Patients who completed 30 months of the ATTR-ACT trial were invited to receive tafamidis meglumine (20mg or 80mg q.d.) and were labelled as Cohort A. Patients initially randomised to placebo in ATTR-ACT were re-randomised 2:1 to 80mg and 20mg, until a protocol amendment when all patients were switched to the higher dose. A second group of patients diagnosed with ATTR-CM who did not previously participate in ATTR-ACT are being recruited to receive tafamidis free acid 61mg q.d. (or if not available, tafamidis meglumine 80mg) and are labelled as Cohort B.

Patients in the LTE study were not permitted to use any investigational therapy; diflunisal; tauroursodeoxycholate and doxycycline; digitalis and calcium channel blockers (e.g. verapamil, diltiazem).

Outcomes of interest are all-cause mortality and the incidence of treatment-emergent adverse events (TEAEs). Subgroup analyses are planned for TTR genotype (wild-type versus hereditary).

Phase II study and extension study

A single-arm, Phase II study of open-label tafamidis 20mg (NCT00694161)[21] was conducted across six US sites in 35 patients between 2008 and 2012. Patients were aged over 40 years old with documented TTR amyloid cardiomyopathy and NYHA classification of I or II. Outcomes of interest included the percentage of participants with stabilised TTR tetramer at Week 6 and at Months 6 and 12.

Data from the Phase II study are provided in the CS[1] (Section B.2.6.4.1) but are not used in the company's economic model. A *post hoc* analysis of the Phase II study[21] is described using the TRACS[32] (observational) study in CS Section B.2.6.4 in order to provide an informal indirect comparison for OS between untreated patients and the single-arm study of tafamidis (n=35).

Complete efficacy data from the Phase II extension study, other than the number of deaths, are not provided in the CS[1] and are described by the company as *"limited and descriptive"* (CS, page 73). Data on AEs and concomitant medication use are collected at each 6-month clinic visits.

Baseline characteristics

Table 3 presents the baseline characteristics of patients enrolled into the ATTR-ACT trial, modified from the CS.[1] The CS also presents baseline characteristics between the 20mg and 80mg study arms, which were generally comparable. Nevertheless, the ERG notes that stratification and other known prognostic factors that were measured should be included in models irrespective of baseline balance in order to estimate correct standard errors. Furthermore, treatment effects in non-linear models will be biased unless they are adjusted for stratification and other known prognostic factors that were measured.

Table 3: Baseline characteristics of patients in the ATTR-ACT trial (adapted from CS, Table 12)

	ATTR-ACT	
	Pooled tafamidis (N=264)	**Placebo (N=177)**
Mean age (SD), years	74.5 (7.2)	74.1 (6.7)
Sex, n (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
Race, n (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0
NYHA classification, n (%)[a]		
NYHA Class I	24 (9.1)	13 (7.3)
NYHA Class II	162 (61.4)	101 (57.1)
NYHA Class III	78 (29.5)	63 (35.6)
NYHA Class IV	0	0
TTR genotype, n (%)		
Wild-type TTR	201 (76.1)	134 (75.7)
Hereditary TTR	63 (23.9)	43 (24.3)
Val122Ile	[redacted]	[redacted]
Thr60Ala	[redacted]	[redacted]
V30M	[redacted]	[redacted]
Mean mBMI (SD)[b]	1058.8 (173.8)	1066.4 (194.4)
Mean creatinine clearance (SD), mL/min	58.8 (17.9)	56.5 (20.4)
Median NT-proBNP (Q1, Q3), pg/ml	2995.9 (1751.5, 4861.5)	3161.0 (1864.4, 4825.0)
Median troponin I (Q1, Q3), ng/ml	0.14 (0.09, 0.20)	0.14 (0.08, 0.19)
Echocardiographic variables		
Mean left ventricular ejection fraction (SD), %	48.4 (10.3)	48.6 (9.5)
Mean interventricular wall thickness, mean (SD), mm	16.7 (3.8)	16.2 (3.5)
Mean left atrial anterior-posterior diameter size (SD), mm	43.8 (7.0)	43.7 (6.1)
Mean left ventricular stroke volume (SD), ml	45.8 (16.1)	45.1 (16.9)
Mean global longitudinal strain (SD), %	-9.3 (3.5)	-9.4 (3.6)
Baseline medication, n (%)[c]		
Agents acting on RAS	69 (26.1)	48 (27.1)
Beta blockers	76 (28.8)	53 (29.9)
Diuretics	175 (66.3)	123 (69.5)
Antithrombotic agents	105 (39.8)	72 (40.7)
Permanent pacemaker, n (%)	13 (4.9)	12 (6.8)
ICD, n (%)	16 (6.1)	9 (5.1)
6MWT (SD), m	350.6 (121.3)	353.3 (126.0)
Mean KCCQ (SD)	67.3 (21.4)	65.9 (21.7)

a NYHA class: I = without resulting limitations, II = slight limitation, III = marked limitation, IV = inability to carry on any physical activity without discomfort. Given the very low number of enrolled patients in ATTR-ACT with a baseline classification of NYHA Class I, the baseline groupings used for efficacy analyses were changed from 'NYHA Class I and NYHA Classes II and II combined' to NYHA Classes I and II combined and NYHA Class III'.

b The modified BMI (mBMI) is calculated by multiplying the body mass index [weight (kg)/height (meters squared)] by serum albumin concentration (g/L).

c Patients may be taking >1 medication in a class, each medication is only counted once per patient.

6MWT - 6-minute walk test; ICD - implantable cardioverter-defibrillator; KCCQ - Kansas City Cardiomyopathy Questionnaire; mBMI - modified body mass index; NT-proBNP - N-terminal pro-brain natriuretic peptide; NR - not reported; NYHA - New York Heart Association; RAS - renin angiotensin system; SD - standard deviation; TTR - transthyretin

The demographics and baseline characteristics of the patients in ATTR-ACT are consistent with the population of patients with ATTR-CM amyloidosis who are typically seen in clinical practice in England and participants were generally similar across treatment arms at baseline.

Baseline characteristics were also provided in the CS for the Phase II study of tafamidis in comparison to an observational study of untreated patients with ATTR-CM (the TRACS study). A *post hoc* analysis was presented in Section B.2.6.4.2 of the CS which aimed to demonstrate that patients in the single-arm Phase II study of tafamidis had longer OS compared with patients receiving BSC. The baseline characteristics between these two studies are presented in Table 4.

Table 4: Baseline characteristics of patients in Phase II study and TRACS (reproduced from CS, Table 25)

	Phase II study (N=35)		**TRACS (N=29)**	
	Wild-type (n=31)	**Hereditary (Val122Ile) (n=4)**	**Wild-type (n=18)**	**Hereditary (Val122Ile) (n=11)**
Mean age (SD), years	76.9 (4.6)	72.8 (3.4)	75.5 (5.6)	71.1 (5.0)
Mean age at TTR-CM symptom onset (SD), years	73.6 (5.3)	69.3 (2.5)	72.7 (5.4)	69.5 (5.6)
Mean age at TTR-CM diagnosis (SD), years	75.0 (4.9)	71.5 (3.1)	74.8 (5.7)	70.3 (5.6)
Sex, n (%) male	93.5	75.0	100.0	81.8
Race, n (%) African American	0.0	75.0	0.0	100.0
NYHA functional classification ≥III, n (%)	1 (3.2)	1 (25.0)	4 (22.2)	3 (27.3)
Duration of TTR-CM–related symptoms (SD), months	94.8 (97.5)	74.5 (34.2)	35.4 (33.6)	21.6 (17.8)
Mean NT-proBNP (SD), pg/mL	4910 (4465)	5318 (343) n=2	4524 (2958) n=11	4762 (4117) n=10
Mean left ventricular posterior wall thickness (SD), mm	20.3 (3.5) n=30	19.5 (3.1)	19.3 (3.3)	18.0 (2.6)
Left ventricular ejection fraction, n (%)	47.8 (13.9) n=30	39.0 (15.0)	59.0 (11.5)	50.4 (12.3)

Note: Sample sizes are provided where patient data are missing.
NT-proBNP - N-terminal pro b-type natriuretic peptide; NYHA - New York Heart Association; TRACS - Transthyretin Amyloidosis Cardiac Study; TTR-CM - transthyretin cardiomyopathy; Val122Ile - valine to isoleucine substitution at position 122

Participants in the Phase II study of tafamidis had a median age of 76 years and median disease duration of 5 years. Most participants (94%) had a baseline NYHA classification of I or II at enrolment. Patients with wild-type ATTR-CM (n = 31) or hereditary ATTR-CM (Val122Ile; n = 4) were enrolled and treated with 20mg tafamidis q.d. for 6 weeks, then continued taking daily oral tafamidis 20mg for up to 12 months.

Ongoing studies

Three ongoing studies of tafamidis in ATTR-CM were identified by the ERG in clinicaltrials.gov; these are reported in Table 5. The first is a newly registered trial (NCT04108091) by Pfizer in Japan of people with ATTR-CM receiving tafamidis and was not described in the CS.[1] The second (NCT02791230) is the LTE study for ATTR-ACT and the third (NCT00935012) is the open-label LTE study to the Phase II study (Maurer *et al*, 2015). The latter two studies are accounted for in the CS.

Table 5: Ongoing studies of tafamidis in people with ATTR-CM

Trial registration number **Status** **Estimated enrolment**	**Trial name** **Study design**	**Description**
NCT04108091 Not yet recruiting 360 participants	Vyndaqel Capsules Special Investigation (ATTR-CM) Observational	To comprehend information on the long-term safety (e.g., onset status of adverse reactions), etc. of patients who are treated with Vyndaqel for the treatment of transthyretin amyloid cardiomyopathy.
NCT02791230 Recruiting 2000 participants	Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy (ATTR-ACT LTE) Open-label safety study	Global Phase 3, open-label long-term extension safety study to obtain additional safety data for tafamidis meglumine 20mg and 80mg (or tafamidis 61 mg where available),
NCT00935012 Active, not recruiting 31 participants	Safety And Efficacy Evaluation Of Fx-1006a In Patients With V122i Or Wild-Type Transthyretin (TTR) Amyloid Cardiomyopathy	Open-label long-term extension study to the Phase II trial

4.2.2 Details of relevant studies not included in the submission

The outputs of the SLR in Appendix D of the CS[18] and the conclusions of the SLR in the CS[1] are not exactly congruent as the CS fails to describe the twenty studies retrieved and included in the Appendix D SLR. In addition, the SLR in Appendix D does not reach the same conclusion as the SLR in the CS - that only four studies are relevant (ATTR-ACT, ATTR-ACT-LTE, Phase II tafamidis, Phase II tafamidis LTE). The ERG confirms that of the twenty studies retrieved by the SLR in CS Appendix D, only one other RCT, in addition to ATTR-ACT, was identified. The Judge *et al*. (2019) RCT[22] was a Phase II safety, tolerability, pharmacokinetic, pharmacodynamics trial of AG10 for ATTR-CM. This novel TTR stabiliser is currently being assessed for efficacy in a Phase III RCT and is therefore not currently a relevant comparator to tafamidis. The other 18 studies identified by the SLR in CS Appendix D were cohort or observational studies. Therefore, the conclusion of Document B regarding relevant studies for inclusion in the review of clinical effectiveness of tafamidis is largely accurate, despite the lack of congruence with Appendix D. The ERG is satisfied no further relevant studies are likely to have been omitted from the CS.

4.2.3 Summary and critique of the company's quality assessment

The ERG reviewed the company's quality assessment for the ATTR-ACT trial using the Cochrane Risk of Bias tool.[23] The ERG considers the ATTR-ACT trial to be a well-conducted RCT and agrees with the company's judgement that the risk of bias in all quality assessment domains is low.

The company's quality assessment using the Downs & Black (1998)[24] checklist for non-RCT studies found that the Phase II study of tafamidis (Maurer *et al*, 2015[21]) performed reasonably well for study reporting quality, but fared less well on external validity, as included participants were not deemed to be representative of the target population. Internal validity was also limited due to the lack of blinding, randomisation and control group in this open-label, single-arm study.

4.2.4 Summary and critique of results

The ATTR-ACT trial: main results

Primary endpoint in ATTR-ACT

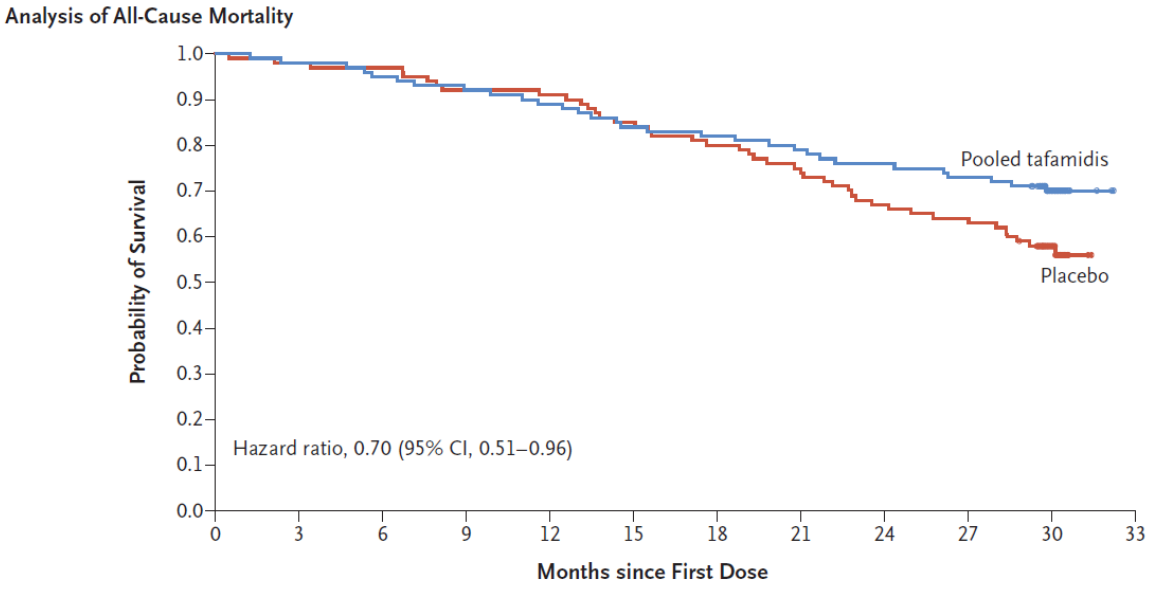
The primary outcome in the ATTR-ACT trial was a combined hierarchical analysis of all-cause mortality and frequency of CV-related hospitalisations using the Finkelstein-Schoenfeld method.[29] A statistically significant treatment effect favouring tafamidis for this primary analysis (p=0.0006) was reported: 186 patients (70.5%) were alive in the pooled tafamidis group compared with 101 patients (57.1%) alive in the placebo group, and the average number of CV-related hospitalisations was 0.297 in the pooled tafamidis group compared with 0.455 in the placebo group (CS, Section B.2.6.2, page 59).

Secondary endpoints in ATTR-ACT

All-cause mortality was analysed separately as a secondary endpoint. All-cause mortality events were observed in 78 (29.5%) and 76 (42.9%) participants for the pooled tafamidis and placebo groups, respectively. The hazard ratio (HR) from the all-cause mortality Cox proportional hazards model for pooled tafamidis was 0.698 (95% confidence interval [CI]: 0.51, 0.96), indicating a 30.2% reduction in the risk of death relative to the placebo group (p=0.0259).

Figure 1 shows the Kaplan-Meier plot for the ITT population in ATTR-ACT for all-cause mortality in patients receiving pooled tafamidis or placebo.

Figure 1: Kaplan-Meier plot of all-cause mortality in patients receiving pooled tafamidis or placebo in the ATTR-ACT trial, ITT population (reproduced from CS, Figure 13)



No. at Risk (cumulative no. of events)

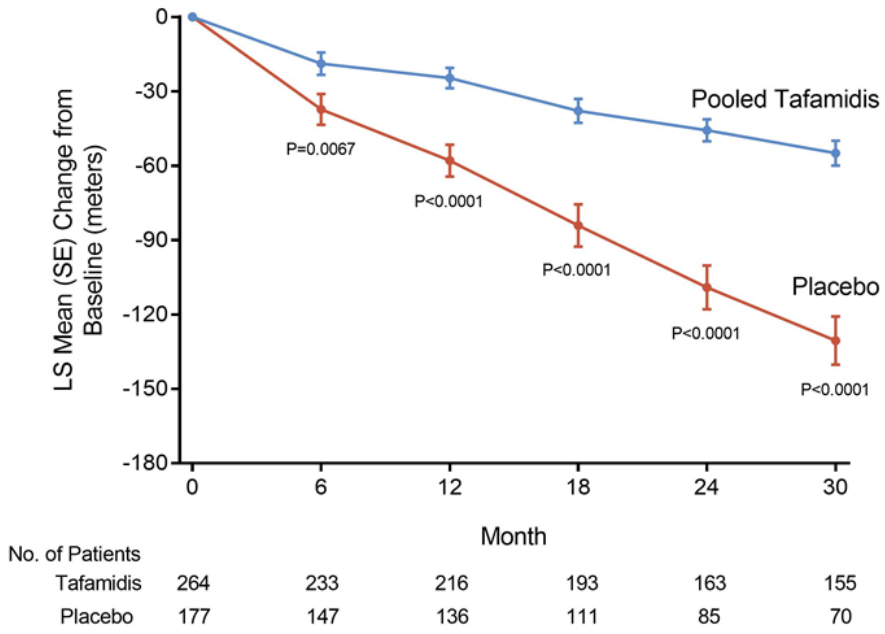
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

CV-related hospitalisations were also analysed separately as a secondary endpoint. The RR ratio between the pooled tafamidis and placebo groups was reported to be 0.676, which the company states indicates a 32.4% reduction in the risk of CV-related hospitalisation in the tafamidis group relative to placebo (p<0.0001) (CS,[1] Section B.2.6.2).

CV-related mortality for pooled tafamidis and placebo groups was observed in [redacted] ([redacted]) and [redacted] ([redacted]) participants, respectively. The HR from the CV-related mortality Cox proportional hazards model was [redacted] (95% CI: [redacted], [redacted]), indicating a [redacted] reduction in the risk of CV-related death in the pooled tafamidis group relative to the placebo group ([redacted]).

The 6MWT was used to assess cardiac functional capacity. Pooled tafamidis reduced the decline in the 6-minute walk test distance compared to placebo (75.7 meters; standard error [SE] =9.2; p<0.0001). A statistically significant difference was first observed at 6 months, and remained statistically significant to Month 30 (see Figure 2).

Figure 2: Change from baseline in distance walked during the 6MWT (ITT population) in the ATTR-ACT trial (reproduced from CS, Figure 15)



Note: The figure shows the least squares (LS) mean (±SE) change from baseline to Month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. I bars indicate standard errors.

Improvement or maintenance of NYHA classification was a secondary endpoint in ATTR-ACT. Section B.2.6.2 of the CS[1] reports that a greater percentage of patients in the tafamidis group improved upon or remained in their respective baseline classifications of NYHA Class I (n=[redacted]), II (n=[redacted])) and III (n=[redacted]), compared with those in the placebo group for NYHA Class I (n=[redacted]), II (n=[redacted]), and III (n=[redacted]) at Month 30. For patients in the pooled tafamidis group with a baseline classification of class II, [redacted] were reported to improve to class I and [redacted] worsened to class III and [redacted] to class IV at Month 30. For patients in the placebo group with a baseline classification of class II, [redacted] patients improved to class I, while [redacted] and [redacted] patients worsened to class III and IV, respectively at Month 30. No tests of statistical significance are reported for this endpoint between pooled tafamidis and the placebo group. The ERG also notes that no adjustment was made to account for differences in baseline NYHA class between the treatment groups.

Concentration of NT-proBNP was used as a secondary endpoint in the ATTR-ACT trial as a potential predictive marker of mortality in ATTR-CM. Patients in the ITT population receiving pooled tafamidis experienced a statistically significant change from baseline difference in NT-proBNP concentration compared to the placebo group (LS mean [redacted] (CS,[1] Section B.2.6.2, Table 20).

Echocardiographic parameters were considered as secondary endpoints for the ITT population in the ATTR-ACT trial. Significant differences between baseline and Month 30 were reported between pooled

tafamidis and placebo for left ventricular stroke volume ([redacted]); circumferential mid global strain [redacted] and radial mid-global strain [redacted]. No significant differences were found between pooled tafamidis and placebo from baseline to Month 30 for the left ventricular end diastolic interventricular septal wall thickness; left ventricular posterior wall thickness; and left ventricular ejection fraction.

TTR stabilisation using pharmacodynamic testing was considered a secondary endpoint in the ATTR-ACT trial using ITT analysis. A statistically significant difference was noted in stabilisation of TTR protein at Month 1 for [redacted] of patients in the pooled tafamidis group and [redacted] of patients in the placebo group [redacted]. Section B.2.6.2.4 of the CS[1] states that this pattern remained consistent through to Month 30 ([redacted]).

HRQoL was measured using the EQ-5D-3L index and VAS scores in the ITT population of the ATTR-ACT trial. The CS[1] (Section B.2.6.2.6) reports that [redacted] in EQ-5D-3L index scores was noted for pooled tafamidis compared with placebo over 30 months. [redacted]

HRQoL was also measured using the KCCQ-OS for the ITT population between baseline and Month 30. Patients in the pooled tafamidis group had a reduced decline at Month 30 compared to placebo (LS mean difference 13.7; SE: 2.1; $p<$[redacted]). Statistically significant results were first observed at Month 6, remaining statistically significant through to Month 30 (CS,[1] Section B.2.6.2.5). [redacted]

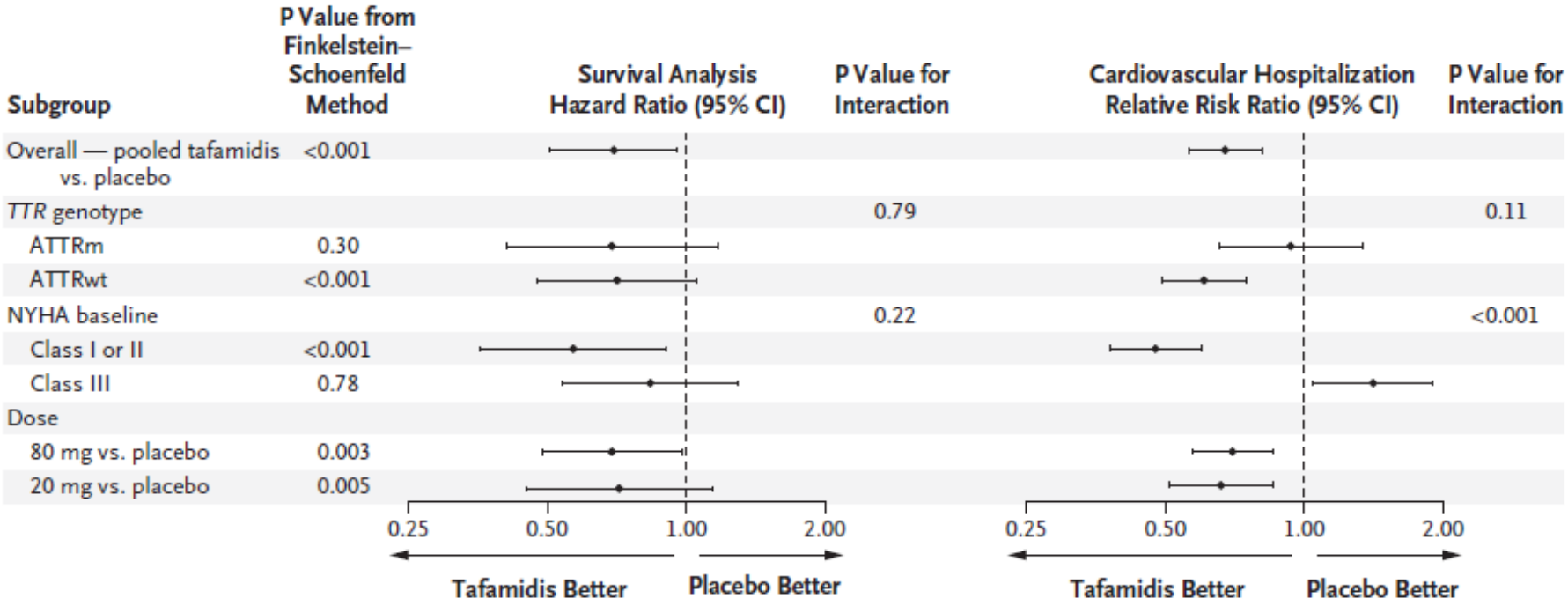
The ATTR-ACT trial: subgroup analyses

Pre-specified subgroup analyses were conducted for the stratification factors of baseline NYHA classification status (I or II versus III) and TTR genotype (wild-type versus hereditary) between pooled tafamidis and placebo. A subgroup analysis was also conducted comparing tafamidis 20mg to placebo and tafamidis 80mg to placebo (CS,[1] Section B.2.7).

Subgroup analysis of baseline NYHA class showed [redacted] for the primary outcome (combined analysis of all-cause mortality and frequency of CV-related hospitalisations). When outcomes were analysed separately, pooled tafamidis was not statistically significantly superior to placebo for all-cause mortality using a Cox proportional hazards model in patients with NYHA III at Month 30 (HR, [redacted]; 95% CI: [redacted]; [redacted]**).** However, the study was not powered to detect a

difference in this subgroup. RR ratios of CV-related hospitalisations analysed with a Poisson regression model were higher in NYHA class III patients for patients receiving tafamidis than those receiving placebo [redacted] (95% CI: [redacted]). Data representing these trends are shown in Figure 3.

Figure 3: Overall and subgroup results: all-cause mortality and CV-related hospitalisations (reproduced from CS, Figure 21)



All-cause mortality was evaluated with the use of a Cox proportional hazards model, with treatment and stratification factors treated as covariates. The survival analysis interaction terms are based on a post hoc analysis. The frequency of cardiovascular-related hospitalisations was assessed with the use of a Poisson regression model.
ATTRm denotes disease that results from an inherited autosomal dominant trait that is caused by pathogenic mutations in TTR (also referred to as hereditary ATTR-CM), ATTRwt disease that results from the deposition of wild-type transthyretin protein (also referred to as wild-type ATTR-CM), and NYHA New York Heart Association.
Source: Maurer et al. 2018.

Subgroup analysis by TTR genotype showed a statistically significant treatment effect favouring pooled tafamidis ([redacted]) over placebo for wild-type ATTR-CM patients (n=335) and a statistically non-significant effect for hereditary ATTR-CM patients (n=106; [redacted]) for the primary outcome (combined analysis of all-cause mortality and frequency of CV-related hospitalisations). When outcomes were analysed separately, the HRs for all-cause mortality in the pooled tafamidis group were not statistically significantly superior to placebo for variant 0.690 (95% CI: 0.41, 1.17) or wild-type TTR genotype (p=0.7256 and p<0.0001, respectively). RRs of CV-related hospitalisations indicated that pooled tafamidis was statistically significantly superior to placebo for wild-type TTR genotype (RR: 0.6073, 95% CI: 0.49, 0.75; p<0.0001) but not for variant TTR genotype (RR: 0.9379, 95% CI 0.66, 1.34; p=0.7256).

Subgroup analyses were performed by NYHA class of cardiac function using the 6MWT outcome (CS,[1] Section B.2.7.1.3). Pooled tafamidis reduced the decline relative to placebo in the 6MWT distance for patients with NYHA class I/II at Month 30 ([redacted] metres; SE: [redacted]; [redacted]), with statistically significant results first observed at Month 6. A statistically significant treatment effect was observed only at Month 24 ([redacted]) for participants with NYHA class III at baseline. Statistically significant treatment effects in the 6MWT were also observed at 6 months among wild-type ATTR-CM patients and at 12 months in those with hereditary ATTR-CM up to Month 30.

Subgroup analysis showed a statistically significantly greater proportion of patients in the pooled tafamidis group with NYHA I/II ([redacted]) and NYHA III ([redacted]) demonstrated TTR stabilisation than was observed in the placebo group ([redacted] and [redacted], respectively [redacted]) (CS,[1] Section B.2.7.1.4, page 81). For subgroup analysis by TTR genotype, data are reported for Month 1, where pooled tafamidis is reported to have demonstrated statistically significantly greater TTR stabilisation over placebo in both wild-type ([redacted] vs [redacted]) and variant ([redacted] vs [redacted]) genotypes ([redacted]).

Subgroup analysis of HRQoL as measured by the KCCQ-OS (CS,[1] Section B.2.7.1.5) reports that a statistically significant treatment effect favouring pooled tafamidis compared with placebo was found for patients with NYHA class I/II which was first observed at Month 6 ([redacted]) and remained statistically significant through to Month 30. A statistically significant treatment effect was also observed for patients with NYHA class III, but only at Month 18 ([redacted]) and Month 30 ([redacted]). Analysis by TTR genotype found statistically significant treatment effects for pooled tafamidis over placebo at Month 12, which remained significant through to Month 30 in both wild-type (p<0.0001) and variant (p=0.0192) genotypes.

The ERG considers the approach taken by the company to assess whether there are differential treatment effects by baseline characteristics to be of limited value. The ERG would prefer a single model including

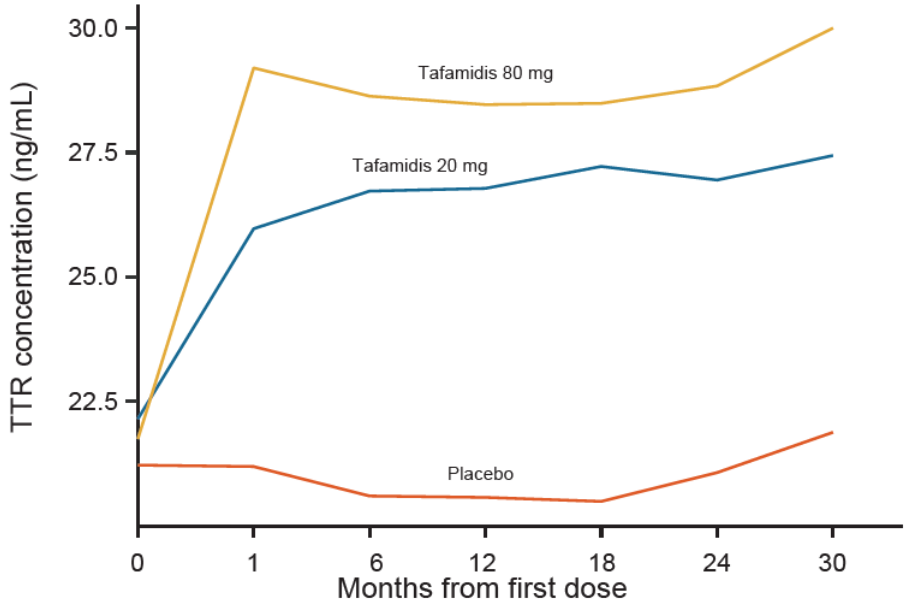
all relevant baseline characteristics and their interactions with treatment. Differential treatment effects should be assessed with respect to the interaction effect. The ERG would also prefer interval estimates of treatment effects presented in addition to *p*-values.

The CS[1] reports that the ATTR-ACT trial was not powered to assess the difference between the two tafamidis dose regimens of 20mg (n=88) and 80mg (n=176) versus placebo (n=177). However, the CS[1] (Section B.2.7.2) reports that the analysis of the primary outcome of combined all-cause mortality and frequency of CV-related hospitalisations demonstrated a statistically significant treatment benefit with tafamidis across both the 20mg ([redacted]) and 80mg ([redacted] doses).

A difference between the two tafamidis dose regimens was noted for the cardiac biomarker NT-proBNP. A statistically significant LS mean difference is reported between baseline and Month 30 for tafamidis 80mg versus placebo (-2587.54pg/mL; $p<0.0001$) but not for tafamidis 20mg versus placebo (-1417.02pg/mL; $p=0.0571$). A similar pattern was also reported for the cardiac biomarker of troponin I levels. A statistically significant LS mean difference was reported between baseline and Month 30 for tafamidis 80mg versus placebo -0.10 ng/mL ($p<0.0001$) but not for tafamidis 20mg versus placebo -0.06 ng/mL ($p=0.2246$).

Section B.2.7.2.5 of the CS[1] highlights that TTR stabilisation rates were greater for tafamidis 80mg compared with tafamidis 20mg, but no statistically significant differences are noted in the CS or the Hanna *et al* (2019) reference cited. Figure 4 displays the mean concentrations between study groups for TTR stabilisation over the course of ATTR-ACT.

Figure 4: Mean TTR concentrations in ATTR-ACT (reproduced from CS, Figure 29)



According to the Clinical Study Report (CSR) for ATTR-ACT, subgroup analyses by dose for TTR stabilisation were only conducted at Month 1. As shown in Figure 5, at Month 1 the TTR stabilisation differed by more than 5%, favouring 80mg over 20mg, the point at which the 20mg and 80mg treatment groups appear to diverge the most on Figure 4 over the 30 months.

Figure 5: TTR stabilisation at Month 1 by dose, ITT analysis set (reproduced from ATTR-ACT CSR, Figure 11)

Figure redacted - AIC

For HRQoL, a statistically significant treatment effect was noted to favour the 80mg tafamidis dose versus placebo earlier (Month 6, [redacted]), whereas a statistically significant treatment effect between the 20mg tafamidis dose and placebo was first observed at Month 12 ([redacted]). Both doses remained statistically significant versus placebo through to Month 30.

ATTR-ACT LTE

Data for this ongoing trial were provided using a data cut-off (DCO) of the 15th February, 2018, which provides a further 12 months of additional follow-up beyond the 30 month ATTR-ACT trial. Patients who received tafamidis in ATTR-ACT and continued to receive tafamidis in the extension study had a [redacted] reduction in risk of death (all-cause mortality) compared with patients who had received placebo in ATTR-ACT and switched to tafamidis 20mg or 80mg in the extension study (placebo/tafamidis group) ([redacted]). Table 6 presents the combined all-cause mortality data for the ATTR-ACT and ATTR-ACT LTE studies.

Figure 6 presents these data as a Kaplan-Meier plot.

Table 6: Combined all-cause mortality of ATTR-ACT and ATTR-ACT extension study (reproduced from CS, Table 24)

Outcome	Pooled tafamidis (N=264)	Placebo (N=177)
Number of all-cause mortality[a]	[redacted]	[redacted]
Number of deaths	[redacted]	[redacted]
Number of heart transplants	[redacted]	[redacted]
Number of CMADs	[redacted]	[redacted]
Number censored	[redacted]	[redacted]
Reason for censoring:		
Alive at time of analysis	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]
Versus placebo		
HR[a]	[redacted]	
95% CI of HR	[redacted]	
Log-rank test *p*-value[c]	[redacted]	

a Hazard ratio from a Cox proportional hazards model with treatment and ATTR-CM genotype (variant and wild type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in a model.
b Reasons related to breach of eligibility criteria, and patient/family decision to discontinue.
c 2 sided maximum likelihood p value from a Cox proportional hazards model with treatment and ATTR genotype (variant and wild type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in a model.
Patients who discontinue for transplantation (i.e. heart or any heart combo transplantation) or for implantation of a CMAD were handled in the same manner as death.

Figure 6: Kaplan-Meier plot of all-cause mortality- combined ATTR-ACT and ATTR-ACT extension study (reproduced from CS, Figure 19)

Phase II study

The CS[1] reports that data from the Phase II study of tafamidis 20mg in ATTR-CM were not used to populate the economic model, but are instead provided for supportive evidence of efficacy and safety.

The primary endpoint was TTR stabilisation. Tafamidis was reported to effectively stabilise TTR in 97.1% of ATTR-CM patients (both wild-type and hereditary) at Week 6, with approximately 88% stabilised throughout the 12 months (CS,[1] Section B.2.6.4, page 71).

Safety and tolerability were secondary endpoints in this single-arm study of tafamidis. In the course of 12 months treatment with tafamidis, in addition to receiving BSC, 2/35 patients (6%) died, 9/35 (26%) experienced at least 1 CV-related hospitalisation, and 9/35 (26%) experienced the composite endpoint of death or a CV-related hospitalisation.

Phase II extension study

Following completion of the Phase II study, 31 patients were enrolled into the respective extension study. Five patients were described as ongoing in this study as of the cut-off date of 15 February 2018. The CS[1] (Section B.2.6.4.3) states that as of "*01 August 2017, [redacted] deaths had occurred in the Phase II extension study.*[31] [redacted]". As part of the clarification process (see clarification response,[2] question A6), the ERG requested the full safety and efficacy data from trial NCT00935012 at the most recent DCO. The company's response stated that *"As of the latest data cut available (01 August 2018), no new deaths were reported in B3461026 beyond the 23 reported in Document B.2.6.4.3*." No further data efficacy data from the Phase II LTE study were provided to the ERG.

Safety and tolerability

Safety data were presented from the four tafamidis studies: ATTR-ACT; the ATTR-ACT LTE study; the Phase II study and the Phase II LTE study (CS, Section B.2.10, pages 90-98).

Adverse events in ATTR-ACT

In ATTR-ACT, tafamidis treatment with either 20mg or 80mg doses was safe and well-tolerated, with a similar safety profile to placebo. The incidence of TEAEs in the tafamidis 20mg, tafamidis 80mg and placebo groups was similar overall. A higher proportion of patients in the placebo arm (50.8%) reported treatment-related TEAEs than patients in the tafamidis 20mg ([redacted]) and tafamidis 80mg arm ([redacted]). The most frequently reported serious TEAEs (≥15%) for tafamidis 20mg were [redacted]. The most frequently reported serious TEAEs (≥15%) for tafamidis 80mg were [redacted]. Within the placebo group, the most frequently reported serious TEAEs (≥15%) were [redacted]

The proportion of patients reporting serious TEAEs was moderately higher in the placebo arm compared to the tafamidis treatment arms. There were no dose reductions due to serious TEAEs in placebo or tafamidis-treated patients. The most commonly reported all-causality TEAEs (≥20%) were cardiac failure, dyspnoea, dizziness, fall, diarrhoea and nausea. The most commonly reported treatment-related TEAEs (≥5%) were diarrhoea, nausea, and urinary tract infection (UTI).

There were 144 deaths reported at the 30-month vital status assessment. The proportion of deaths was [redacted] (n=[redacted] in the tafamidis 20mg treatment group, [redacted] (n=[redacted] in the tafamidis 80mg treatment group and 50.0% (n=72/177) in the placebo group. Of the 144 deaths, [redacted] occurred up to 28 days after last dose. Of the total patients, [redacted], [redacted] and [redacted] in the placebo, tafamidis 20mg and tafamidis 80mg groups, respectively, died up to 28 days after last dose. The majority of deaths in the study were considered to have occurred as a result of underlying disease: [redacted], [redacted], and [redacted] in the placebo, tafamidis 20mg, and tafamidis 80mg groups, respectively. No death was assessed as being related to study treatment.

Adverse events in ATTR-ACT LTE

As of the 15th February 2018 DCO, the mean duration of exposure to tafamidis was [redacted] months for [redacted] patients in the tafamidis 20mg group, and [redacted] months for [redacted] patients in the tafamidis 80mg group. Up to 42 months of exposure has been observed in [redacted] and [redacted] of tafamidis-treated patients in the 20mg and 80mg groups, respectively. Dose interruptions due to AEs in the broad ATTR-CM cohort (ATTR-ACT and ATTR-ACT extension study) occurred at similar rates across the tafamidis 20mg ([redacted]) and 80mg treatment groups ([redacted]). According to the CS,[1] further safety data for the ATTR-ACT extension study are not yet available.

Adverse events in the Phase II study

All 35 patients experienced ≥1 AE during the study. The most frequent AEs included dyspnoea, congestive cardiac failure and dizziness. Of the 35 patients included in the study, 20.0% (7 patients) reported an AE of diarrhoea.

Fifteen patients (42.9%) experienced ≥1 serious adverse events (SAEs). The most common SAEs were cardiac events, such as cardiac failure (10 patients, 28.6%) and atrial fibrillation (3 patients, 8.6%). Four patients experienced SAEs that were assessed as possibly related to tafamidis which included ataxia, falls, HF, a fall induced haemorrhagic stroke and syncope.

Two of the 35 patients died during the study: one patient died of a haemorrhagic stroke after a fall approximately 4 months after study start. The other patient was diagnosed with immunoglobulin light chain (AL) amyloidosis approximately 11 months after starting the study.

Adverse events in the Phase II LTE

In the ongoing Phase II extension study, as of the 1st August 2017, all 31 patients enrolled into this study had experienced at least one TEAE. A total of [redacted] SAEs were reported in 28 patients. The most frequently reported SAEs were congestive cardiac failure ([redacted]), cardiac failure and fall (each reported for [redacted]), cellulitis and disease progression (each reported for [redacted]).

Summary of adverse event data across trials

The available AE data appear to be complete and are generally comparable to patients receiving placebo in the main pivotal trial (ATTR-ACT) which provides data for 30 months of tafamidis treatment. Further supportive data from three other studies indicate that tafamidis was well tolerated and AEs were generally mild to moderate in nature, or were in line with the natural disease course of ATTR-CM.

4.3 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.4 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.5 Conclusions on the clinical effectiveness evidence

4.5.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to tafamidis for ATTR-CM is based primarily on one relevant high-quality RCT (ATTR-ACT), together with supporting evidence from a Phase II single-arm and two corresponding open-label extension studies. The ERG considers that no relevant studies (published or unpublished) of tafamidis for this decision problem were omitted from the CS.[1]

4.5.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is satisfied that the relevant population and intervention have been included in the CS,[1] that is, patients with ATTR-CM treated with tafamidis. The pivotal Phase III RCT (ATTR-ACT) was powered to detect a significant difference between tafamidis, pooled from two dosage groups (20mg and 80mg) in comparison to placebo. The ERG notes that the CS does not contain efficacy or safety data relating to the new formulation of tafamidis 61mg free acid.

In the ATTR-ACT study, the difference in the primary outcome of combined hierarchical analysis of all-cause mortality, and CV-related hospitalisations favoured pooled tafamidis over placebo (p=0.006) and these differences remained statistically significant when both all-cause mortality (HR, 0.70; 95%

CI: 0.51, 0.95; p=0.0259) and CV-related hospitalisation (RR, 0.67 95% CI: 0.56, 0.81; p<0.0001) were analysed separately. Pooled tafamidis was also associated with statistically significant benefits in secondary outcomes including: CV-related mortality (HR 0.69, 95% CI: 0.4, 0.98; p=0.0383); the 6MWT (p<0.0001); NT-proBNP ([redacted]); HRQoL using the KCCQ-OS score ([redacted]), HRQoL using the EQ-5D-3L index score ([redacted]) and EQ-5D VAS ([redacted]); and TTR stabilisation ([redacted]). Patients treated with tafamidis in the LTE study to ATTR-ACT experienced a greater than [redacted] reduction in death compared to those in the placebo arm of ATTR-ACT who switched to tafamidis in the extension study ([redacted]).

Pre-planned subgroup analyses in ATTR-ACT by NYHA baseline classification and TTR genotype highlighted a number of differential treatment responses to tafamidis. Firstly, the significant benefit of pooled tafamidis over placebo was largely driven by the treatment response in patients with NYHA class I/II, and a significant benefit was not noted in patients with NYHA III for both all-cause mortality and CV-related hospitalisations. Indeed, NHYA III patients treated with tafamidis had significantly more CV hospitalisations than patients in the placebo group. Secondly, the significant benefit of pooled tafamidis over placebo was also driven by the treatment response in patients with wild-type ATTR-CM rather than those with the hereditary TTR genotype for both all-cause mortality and CV-hospitalisations. Thirdly, the significant treatment effect in the primary outcome and secondary outcomes is relatively consistent between the two tafamidis dosing regimens (20mg and 80mg) relative to placebo with the exception of biomarker measurements of NT-proBNP and troponin I levels, where the 80mg tafamidis dose appears to be superior to the 20mg tafamidis dose. The company highlights that these biomarkers are accepted prognostic indicators for mortality in ATTR-CM and cites studies reported by Gillmore (2017)[10] and Grogan *et al* (2016)[9] as evidence of this (CS,[1] Section B.2.7.2). However, the clinical advisors to the ERG expressed uncertainty as to whether the difference between 20mg and 80mg using these biomarkers are clinically meaningful.

The safety profile of tafamidis was based on AE data provided from the four included studies which documents the toxicity profile of tafamidis for over 30 months. Safety events from these studies indicate that tafamidis was well tolerated and AEs were generally mild to moderate in nature, or were in line with the natural course of ATTR-CM.

4.5.3 Uncertainties surrounding the reliability of the clinical effectiveness evidence

The ERG would have preferred an assessment of differential treatment effects estimated using interaction terms in a single model. Nevertheless, the differential treatment responses highlighted by the company's subgroup analyses in ATTR-ACT highlight uncertainty in the appropriateness of treatment with tafamidis beyond NYHA baseline class I/II because of an absence of evidence given the lack of statistically significant benefit for the primary outcome in patients with NYHA baseline class

III. Of particular note are the higher rates of CV hospitalisations compared to placebo in the NYHA III subgroup. Clinical advice received by the ERG highlighted that there would be potential difficulties in informing patients that treatment will be terminated when disease progresses to NYHA class III.

Uncertainty regarding the efficacy of treating hereditary ATTR-CM with tafamidis remains because of the lack of evidence of a treatment effect in this subgroup. The CS comments that the subgroups were not powered to assess effect of each subgroup on the study endpoints and, therefore, all analyses undertaken were exploratory and did not control for Type 1 errors.

The ERG notes that the 20mg and 80mg doses are broadly comparable in the *post hoc* dose analysis and were found to be clinically equivalent for the primary endpoint and other endpoints including TTR stabilisation. The only endpoints where tafamidis 80mg demonstrated statistical superiority over tafamidis 20mg was for NT-proBNP and troponin I levels.

5. COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of tafamidis for the treatment of adult patients with ATTR-CM. Section 5.1 presents a critique of the company's review of existing health economic analyses. Section 5.2 summarises the methods and results of the company's model. Sections 5.3 and 5.4 present a detailed critique of the model and additional exploratory analyses undertaken by the ERG, respectively. Section 5.5 presents a discussion of the available economic evidence.

5.1 Summary and critique of the company's search strategy

CS Appendix G[18] reports the searches conducted to identify economic evidence. For this review, due to the expected lack of published evidence on ATTR-CM, the search was expanded to include models of primary cardiomyopathies. As with the other reviews, these searches were well-designed and used appropriate subject headings and free text terms across all the databases required by NICE. Database searches were conducted in two phases and cover the period from database inception to 9th May 2019. Additional searches of HTA agency websites and recent conference proceedings were conducted and reference lists of included studies were checked for missed papers. Based on the information reported in CS Appendix G, the ERG considers it unlikely that this review would have missed any studies meeting the stated inclusion criteria.

CS Appendix H[18] reports the searches conducted to identify studies reporting on HRQoL. As with the other searches, these were well-designed and they cover all of the required sources. The ERG is satisfied that they are likely to have retrieved all the relevant studies.

CS Appendix I[18] reports the searches conducted to retrieve evidence on resource identification, measurement and valuation. As with the cost-effectiveness review, due to the expected lack of published evidence on ATTR-CM, the search was expanded to include models of other primary cardiomyopathies.

These searches are similarly structured to those for the cost-effectiveness review and there is some overlap in the terms used, as might be expected, but the initial searches for each were run on different dates (the update searches for both were on 9th May 2019). All the databases required by NICE were searched, along with searches of HTA websites and conference proceedings, and search strategies are reported in full. Again, the ERG is confident that all relevant evidence is likely to have been identified.

5.1.1 Summary of company's review findings

The company's searches did not identify any economic analyses in patients with ATTR-CM. The searches identified one study which assessed implantable cardioverter defibrillators (ICD) versus

optimal pharmaceutical therapy (OPT) in patients with NYHA II-III HF. The company critically appraised this study using the Drummond checklist[33] and summarised its results in CS Appendix G. However, the company did not consider this study to be relevant to the current decision problem. The ERG agrees with the company's view.

5.2 Description of the company's health economic analysis

5.2.1 Model scope

As part of its submission to NICE,[1] the company submitted a fully executable health economic model programmed in Microsoft Excel.® The majority of the functionality of the model was implemented via user-defined functions coded in Visual Basic for Applications (VBA). The scope of the company's economic analysis is summarised in Table 7. The company's base case analysis assesses the incremental cost-effectiveness of tafamidis versus BSC for treating ATTR-CM from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 26-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Unit costs are valued at 2017/2018 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Table 7: Summary of company's model scope

Population	Adults with ATTR-CM with NYHA class I-III
Time horizon	26.67 years*
Intervention	Tafamidis free acid (61mg q.d., oral administration)
Comparator	Best supportive care (established clinical management of HF)
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2017/2018

ATTR-CM - transthyretin amyloid cardiomyopathy; NYHA – New York Heart Association; QALY – quality-adjusted life year; NHS – National Health Service; PSS – Personal Social Services; q.d. – once daily
** The CS states a time horizon of 26 years is employed, although the results presented in the CS relate to a slightly longer period of 26.67 years*

Population

The target population in the company's base case analysis relates to adult patients with ATTR-CM with NYHA class I-III. This is consistent with the ITT population of the ATTR-ACT trial.[20] [redacted]

Based on data from the ATTR-ACT trial, patients are assumed to have a mean age of 74.34 years at model entry and [redacted] of patients are assumed to be female. The CS[1] also includes the results of a subgroup analysis relating to patients with NYHA class I/II at randomisation in ATTR-ACT; this analysis uses subgroup-specific data from the trial relating to health state transitions, treatment discontinuation, hospitalisation and survival.

Interventions

The intervention evaluated within the model is tafamidis. Within the model, tafamidis is administered orally at a dose of 61mg q.d. [redacted]

The CS[1] states that tafamidis free acid 61mg has been shown to be bioequivalent to 80mg tafamidis meglumine.[15, 34] The effectiveness of the intervention is modelled using pooled outcomes data for the 20mg and 80mg tafamidis meglumine groups evaluated within ATTR-ACT.[14] In addition, patients are also assumed to receive a range of concomitant medications as part of BSC (described in the subsequent section). The company's base case analysis includes a discontinuation rule whereby all patients stop treatment with tafamidis at the point of progression to NYHA IV; these patients are also assumed to simultaneously discontinue all other drug therapies included as part of BSC. Issues relating to the company's proposed discontinuation rule and related assumptions are discussed in Section 5.3.3.

Comparators

The CS[1] (page 28) highlights that there are currently no UK treatment guidelines or approved disease-modifying pharmacological treatments for ATTR-CM. The comparator specified in the final NICE scope[13] within the broader population of patients with ATTR-CM is established clinical management without tafamidis (BSC). For patients with mixed phenotype transthyretin amyloidosis (both hereditary ATTR-CM and TTR-FAP), the final NICE scope lists patisiran and inotersen as comparators.

BSC is assumed to consist of symptomatic management of HF, comprising a range of concomitant medications including: loop diuretics; anticoagulants; antiplatelet agents; lipid lowering therapy; ACE inhibitors / RAAS inhibitors; and beta blockers. These same treatments are also included as concomitant mediations in the tafamidis group. Health outcomes and medication use associated with the BSC comparator within the model were based on data from the placebo arm of ATTR-ACT.[14]

Patisiran and inotersen were not explored as comparators for patients with mixed phenotype transthyretin amyloidosis (TTR-FAP and hereditary ATTR-CM) in the company's model; BSC was the only comparator included and a separate analysis relating to this population was not presented. The CS[1] states that patisiran and inotersen were not included as comparators in the model for the following reasons:

(1) Neither patisiran nor inotersen have been evaluated in patients with HF and neither medicine has a license for ATTR cardiomyopathy.
(2) The pivotal trials of patisiran and inotersen (APOLLO[16] and NEURO-TTR[17]) defined cardiac (mixed phenotype) subgroups based on echocardiogram criteria (LV wall thickness ≥ 13mm) which does not meet consensus diagnostic criteria for ATTR-CM (and therefore may not reflect the ATTR-CM population).

(3) The Val1221Ile mutation is causative in 63% of patients with hereditary ATTR-CM in the UK. APOLLO and NEURO-TTR enrolled very few patients with the Val1221Ile mutation (<2%); in contrast, 57.5% of the patients enrolled in ATTR-ACT had a Val1221Ile mutation.
(4) Non-Val1221Ile ATTR-CM in the UK is caused by a number of ultra-rare mutations, each of which is associated with a predominant phenotype. Patients may develop additional symptoms over their lifetime.
(5) APOLLO and NEURO-TTR assessed outcomes relating to polyneuropathy and did not include any clinical cardiac-related endpoints.

The clinical advisors to the ERG considered that BSC is the main comparator for the vast majority of patients, and agreed that the individual treatments included in the model reflect current treatments given for the management of symptomatic HF. The ERG's clinical advisors further commented that patisiran and inotersen are relevant comparators for patients with mixed phenotype transthyretin amyloidosis (hereditary ATTR-CM and TTR-FAP). However, they noted that the number of these patients in England who would be eligible for treatment with tafamidis, patisiran and inotersen is very small. As discussed in Section 3.3, despite issues surrounding whether it would be possible to identify comparable subgroups of patients with symptomatic HF in NEURO-TTR[17] and APOLLO,[16] the ERG believes that there is insufficient evidence to perform an indirect comparison of tafamidis versus either patisiran or inotersen using HF-related outcomes in patients with ATTR-CM.

5.2.2 Model structure and logic

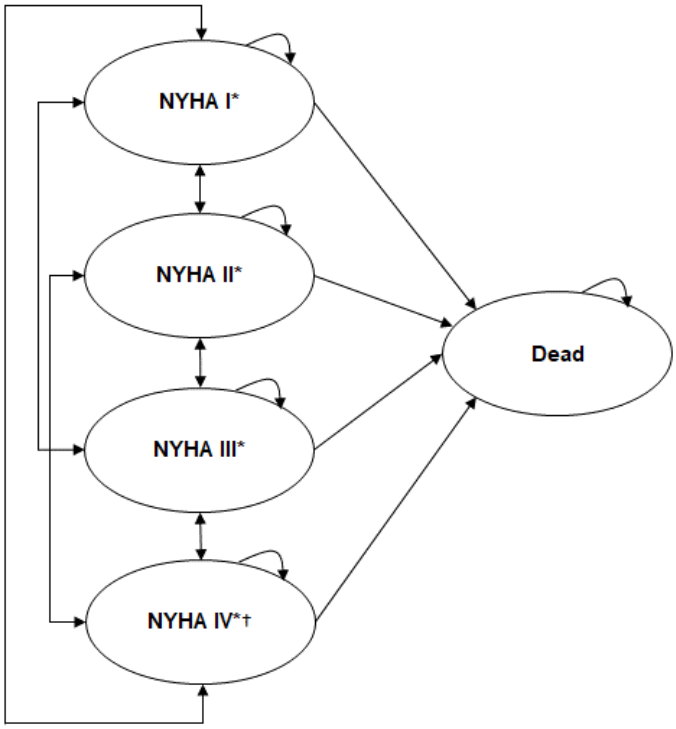
The company's model uses a simple cohort-level state transition approach, comprised of five main health states. The model health states are based on the NYHA functional classification system for HF (NYHA classes I-IV, see Table 8) and an additional health state for death (see Figure 7). The limitations of the NYHA classification system and its use in determining the structure of the model are discussed in Section 5.3.3. Unconventionally, the model uses two different cycle lengths to evaluate the impact of different types of clinical events: (i) 6-monthly cycles are used to model transitions between NYHA states, and (ii) monthly cycles are used to evaluate all other events, including death, discontinuation from tafamidis and the occurrence of CV-related hospitalisations. This issue is discussed in Section 5.3.3.

Table 8: New York Heart Association classification system (reproduced from CS, Table 4)

Class	Patient symptoms
NYHA I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
NYHA II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
NYHA III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
NYHA IV	Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.

NYHA – New York Heart Association

Figure 7: Company's model structure (re-drawn by ERG)



NYHA - New York Heart Association
Notes: Patients enter the model in NYHA states I-III. Patients receiving tafamidis may be on treatment or discontinued within each alive state. Treatment discontinuation is assumed to lead to zero subsequent treatment costs but has no impact on health outcomes (transitions, mortality risk, hospitalisations or HRQoL).
** Health utilities are assumed to decrease with increasing NYHA severity*
† All patients discontinue treatment with tafamidis at the point at which they enter state NYHA IV

Patients enter the model in NYHA states I-III, based on the initial distribution of the ITT population in ATTR-ACT.[14] At each subsequent timepoint, health state occupancy is determined by four separate sets of inputs: (i) 6-monthly transition probabilities between NYHA classes (time-dependent risks up to Month 30, followed by time-independent risks from Month 36 onwards); (ii) monthly general population mortality risks; (iii) monthly disease-related excess mortality risks, and (iv) monthly probabilities of discontinuing tafamidis in NYHA I-III. During each monthly model cycle for the interval between t_j and t_{j+1}, health state occupancy is calculated as follows:

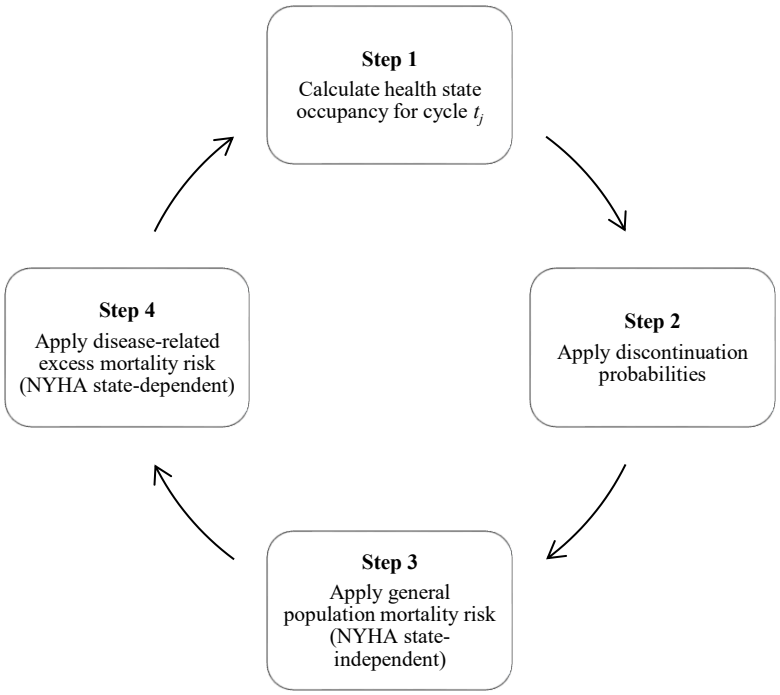
Step 1: The distribution of patients across the four NYHA health states at the end of cycle t_{j-1} is determined (in the first cycle, this is based on the initial distribution of patients in ATTR-ACT[14]). Health state occupancy is calculated using matrix multiplication in every sixth cycle, based on transition probabilities derived from ATTR-ACT.

Step 2: In the tafamidis group, a proportion of patients in NYHA I-III are re-distributed to the "discontinued" NYHA health states, based on a constant monthly probability of discontinuing tafamidis, whilst all patients reaching NYHA IV are assumed to discontinue upon entry into this state. Discontinuation is assumed to have no effect on mortality risks, transition probabilities, CV-related hospitalisation rates or HRQoL - the same outcomes are applied to all tafamidis-treated patients, irrespective of whether they are still receiving treatment. This step is not relevant to the BSC group.

Step 3: The distribution of patients across the NYHA states is adjusted to account for incident deaths attributable to general population mortality risks, based on monthly probabilities derived from life tables. The same general population mortality risk is applied to all surviving patients, irrespective of NYHA state and treatment group.

Step 4: The distribution of surviving patients across the NYHA states and treatment-specific disease-related excess mortality survivor functions are used to calculate the additional risk of death due to disease-related excess mortality in each cycle. This disease-related excess mortality risk is assumed to be independent of general population mortality risk (applied previously in Step 3). Within each treatment group, the same excess mortality risk is applied to all surviving patients in each treatment group, irrespective of their NYHA state, in order to estimate the total absolute excess mortality risk. This absolute NYHA-independent excess mortality risk is then apportioned across the individual health states based on treatment-specific HRs derived from a Cox model in order to estimate NYHA-specific excess mortality risks. The distribution of surviving patients across the NYHA states after applying general population mortality risks is then adjusted to account for the expected excess probability of death in each NYHA state. This vector then forms the health state distribution for Step 1 in the cycle at time t_{j+1}.

Figure 8: Flow diagram of key steps used to determine health state occupancy in the company's model (drawn by the ERG)



NYHA - New York Heart Association

HRQoL is determined by the patient's health state and is assumed to differ between the treatment groups; that is, a patient in a given NYHA class who is receiving tafamidis is assumed to experience a different level of HRQoL compared with a patient in the same state who is receiving BSC alone. Mean utilities for each NYHA class were based on EQ-5D-3L data collected in ATTR-ACT.[14] HRQoL decrements associated with CV-related hospitalisations and AEs were assumed to be already accounted for in the NYHA class utility values. Health utilities were not adjusted by age.

The model includes costs associated with: (i) drug acquisition for tafamidis and BSC; (ii) CV-related hospitalisation events; (iii) disease management (health state costs); (iv) the management of AEs (diarrhoea, nausea and urinary tract infection, any grade), and (v) end of life care costs.

Drug acquisition costs for tafamidis are modelled as a function of dosing adherence and the cost per pack. Concomitant (BSC) medication costs are dependent on treatment group, and are calculated as a function of the proportionate use of each drug, recommended dosing levels and unit costs. The model does not include costs associated with the administration of any treatment. CV-related hospitalisation events are applied in each cycle and are dependent on NYHA class and treatment group. Monthly probabilities of experiencing one or more CV-related hospitalisations (see clarification response,[2] question B13) were derived by scaling and converting six monthly mean log rates obtained from ATTR-ACT.[14] Disease management costs (echocardiograms, cardiologist visits and community nurse visits)

are applied in each model cycle and are assumed to be dependent on the patient's health state, with lower costs applied for the NYHA I state compared with the more severe NYHA states (II-IV). The costs associated with managing AEs are applied as once-only costs during the first model cycle, with AE incidence dependent on treatment. End of life care costs are applied as a once-only cost at the point of death.

The CS[1] states that costs and health outcomes are evaluated over 26 years, although the ERG notes that the company's model actually uses a time horizon of 26.67 years (320 monthly cycles). Half-cycle correction is applied at monthly intervals.

5.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- Patients are permitted from any alive health state to any other alive health state in both treatment groups.
- The modelled regimen of tafamidis free acid 61mg q.d. is assumed to be clinically equivalent to the pooled data for the 20mg and 80mg tafamidis meglumine arm within ATTR-ACT.[14]
- All patients are assumed to discontinue treatment with tafamidis upon progression to NYHA IV. Patients who discontinue tafamidis and subsequently transition to an improved NYHA state on BSC are assumed not to restart treatment with tafamidis.
- No drug-related treatment costs are incurred after patients discontinue tafamidis; the model assumes that patients will not be sufficiently fit to receive any further drug therapy for symptom management.
- BSC-treated patients continue to receive drug treatment for the management of symptomatic HF until death.
- Time to tafamidis discontinuation for patients in NYHA I-III is modelled using an exponential function fitted to time-to-event data of the pooled tafamidis arm of ATTR-ACT (censored for death, heart transplantation, CMAD and progression to NYHA IV).
- After discontinuing treatment with tafamidis, patients are assumed to continue to obtain a level of benefit from tafamidis (disease progression rates, survival rates, CV-related hospitalisation probabilities and HRQoL levels) over the remaining time horizon which reflects the amount of tafamidis received by patients within the ATTR-ACT trial. However, the model assumes that over time an increasing proportion of surviving patients will discontinue treatment with tafamidis, thereby reducing total treatment costs.
- Patients are assumed to transition between the NYHA health states every 6 months. All other clinical events (discontinuation of tafamidis, CV-related hospitalisation and death) are evaluated on a monthly basis.

- During each 6-month interval up to Month 30 (the observed trial period), transitions between the NYHA health states are modelled using observed patient count data from ATTR-ACT. Beyond this timepoint, (all 6-monthly cycles from Month 36 onwards), the model applies a single treatment-specific matrix of time-independent probabilities, calculated based on the sum of all transition counts at all timepoints within the observed trial period.
- Disease-related excess mortality for patients treated with tafamidis is modelled using a log normal survivor function fitted to time-to-event data of the pooled tafamidis arms of ATTR-ACT.
- Disease-related excess mortality for patients receiving BSC is modelled using a Weibull survivor function fitted to time-to-event data of the placebo arm of ATTR-ACT.
- Disease-related excess mortality risk is assumed to be dependent on NYHA state and is modelled using HRs (applied as RRs) estimated using a Cox model fitted to data on all-cause mortality from ATTR-ACT.
- HRQoL is assumed to be dependent on NYHA class and treatment received, but independent of age.
- Additional disutilities associated with AEs and CV-related hospitalisations are not included; these are assumed to be already captured within NYHA state specific utility values.
- Costs associated with managing AEs are applied as a once-only cost in the first model cycle.
- Acquisition costs associated with tafamidis are adjusted to account for the [redacted] of tafamidis-treated patients who had a dosing adherence level <80% within ATTR-ACT. This is intended to reflect treatment breaks.
- As tafamidis is an oral therapy, the model does not include any administration costs. Pharmacy and prescribing costs are not included.

5.2.4 Evidence used to inform the model parameters

Table 9 summarises the evidence sources used to inform the company's model. These are discussed in further detail in the subsequent sections.

Table 9: Evidence sources used to inform the company's model

Parameter / group	Source
Initial patient age	Mean age in ATTR-ACT[14]
Initial distribution by NYHA classes	Based on baseline distribution in ATTR-ACT[14]
Transition probabilities between NYHA classes (observed period – up to Month 30)	Based on observed count data of patients switching between NYHA states during each 6-month interval for each treatment group in ATTR-ACT.[14] Excludes patients with unmeasured observations in each 6-month interval (incomplete pairs) and those undergoing transplantation and implantation of CMAD. Patients who died in the interval were assumed to remain in the same NYHA state.
Transition probabilities between NYHA classes (extrapolation period – from Month 36 onwards)	Based on weighted probabilities of transitions between states across all time points in ATTR-ACT.[14]
General population mortality risk	General population life tables[35]
Excess mortality risk (NYHA-independent, treatment-dependent)	Estimated using data from ATTR-ACT[14] and general population life tables[35] using a relative survival model. Overall mortality risk estimated as general population risk plus a hazard of excess mortality described by a parametric model (log normal model applied in tafamidis group; Weibull model applied in BSC group).
Distribution of excess risk across NYHA classes	Estimated using HRs derived from a Cox model applied to overall mortality risk in ATTR-ACT[14]
Time to treatment discontinuation	Hazard of discontinuing tafamidis calculated using competing risks analysis using data from ATTR-ACT,[14] censoring for deaths, CMAD, heart transplant and progression to NYHA IV). Assumes exponential distribution (constant discontinuation rate in all model cycles).
HRQoL by NYHA class	Observed EQ-5D-3L values collected in ATTR-ACT,[14] conditional on NYHA class.
Probability of CV-related hospitalisation by NYHA class	Based on CV-related hospitalisations in ATTR-ACT.[14]
Acquisition cost – tafamidis	Manufacturer[1]
Acquisition costs – BSC	MIMS[36]
Health state costs (echocardiograms, outpatient appointments and community nursing)	Resource use estimates based on retrospective chart review.[1] Unit costs taken from NHS Reference Costs 2017/18[37] and Curtis and Burns.[38] Higher costs applied to NYHA II-IV compared with NYHA I.
Cost of CV-related hospitalisation	NHS Reference Costs 2017/18[37]
Frequency of AEs (diarrhoea, nausea and UTIs – any severity)	Taken from ATTR-ACT[14]
Costs of managing AEs	NICE TA197[39] (uplifted using HCHS indices[38]) and NHS Reference Costs 2017/18[37]
End of life costs	Hollingworth *et al* 2016 (uplifted using HCHS indices[38])

NYHA - New York Heart Association; ONS - Office for National Statistics; CV - cardiovascular; AE - adverse event; UTI - urinary tract infection; BSC - best supportive care; TA - technology appraisal; CMAD - cardiac mechanical assist device; HCHS - hospital and community health services; MIMS – Monthly Index of Medical Specialities

Initial characteristics

The model assumes a mean patient age of 74.34 years, based on the ITT population of ATTR-ACT.[14] The initial distribution of patients across the NYHA health states was also based on the ITT population in ATTR-ACT (pooled across the 20mg/80mg tafamidis and placebo arms, see Table 10).

Table 10: Initial health state distribution, based on the ATTR-ACT ITT population

Health state	Number of patients	Probability
NYHA I	37	0.08
NYHA II	263	0.60
NYHA III	141	0.32
NYHA IV	0	0.00

NYHA – New York Heart Association

Transition probabilities between NYHA states

The probabilities of transitioning between the NYHA states were based on individual patient count data collected at 6-monthly intervals in ATTR-ACT.[14] The model uses different approaches to estimate these probabilities during the observed trial period (Months 0-30) and the model extrapolation period (from Month 36 onwards).

Observed trial period (Months 0-30, 6-monthly cycles)

During the observed trial period (Months 0 to 30), transition probabilities were calculated using the observed individual patient counts observed within ATTR-ACT.[14] Separate matrices were calculated for each 6-month interval in each treatment group using an arm-based approach. The matrices were generated using the following assumptions:

- Any patient without known NYHA scores at the beginning and the end of each 6-month cycle (i.e. any incomplete pair of observations) was excluded from that matrix
- Patients who underwent transplantation or received a CMAD were excluded from the matrices
- Patients who died during a given cycle were assumed to remain in their current state (as death is handled separately within the model).

Extrapolation period (Months 36 onwards, 6-monthly cycles)

The company's model uses a different approach to estimate transition probabilities during the extrapolation phase. In this period, the probabilities of transitioning between NYHA states were estimated using a smoothed multinomial distribution, fitted using WinBUGS, assuming a uniform prior distribution (n=1 for all state transitions).[2] The underlying data used to inform these distributions was based on the sum of all cell counts for each individual transition in each treatment group during any observed 6-month interval (plus the uniform prior).

The transition probabilities applied in each model 6-month cycle are summarised in Table 11; transitions for which no observations were observed are highlighted in grey. The underlying patient count data from which these transitions are calculated are summarised in Appendix 1, Table 32.

Table 11: Transition probabilities applied in the company's model

Tafamidis					**BSC**				
Months 0-6									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 6-12									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 12-18									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 18-24									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 24-30									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
All subsequent 6-month cycles (from Month 36+ onwards)†									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				

NYHA – New York Heart Association; BSC – best supportive care
** Cells with no observed transitions shaded in grey*
† Values shown represent the mean of the posterior distribution

Survival modelling and NYHA-specific mortality risk

The company modelled OS using a relative survival approach which combines general population life table risks with an additional excess risk of disease-specific mortality associated with ATTR-CM. The company described their approach as a modified version of the relative survival modelling approach described by Andersson *et al*,[40] but with survival functions estimated using standard parametric models rather than flexible parametric models. The company justified the use of a relative survival model on the basis that: (a) sharp increases in background mortality rates for older patients are unlikely to have been observed within the 30-month observed trial period; (b) tafamidis may have an impact on non-CV-related deaths; and (c) background mortality rates differ between countries.[1] The company's modified relative survival model approach is illustrated Figure 9. This involved calculating the country-specific background hazard of death using life tables conditional on covariates (country, sex and race or ethnicity [where available]). An unknown excess mortality hazard, characterised by a parametric model, was then added to the background mortality hazard. Specifically, the all-cause survival, $S(t)$, is:

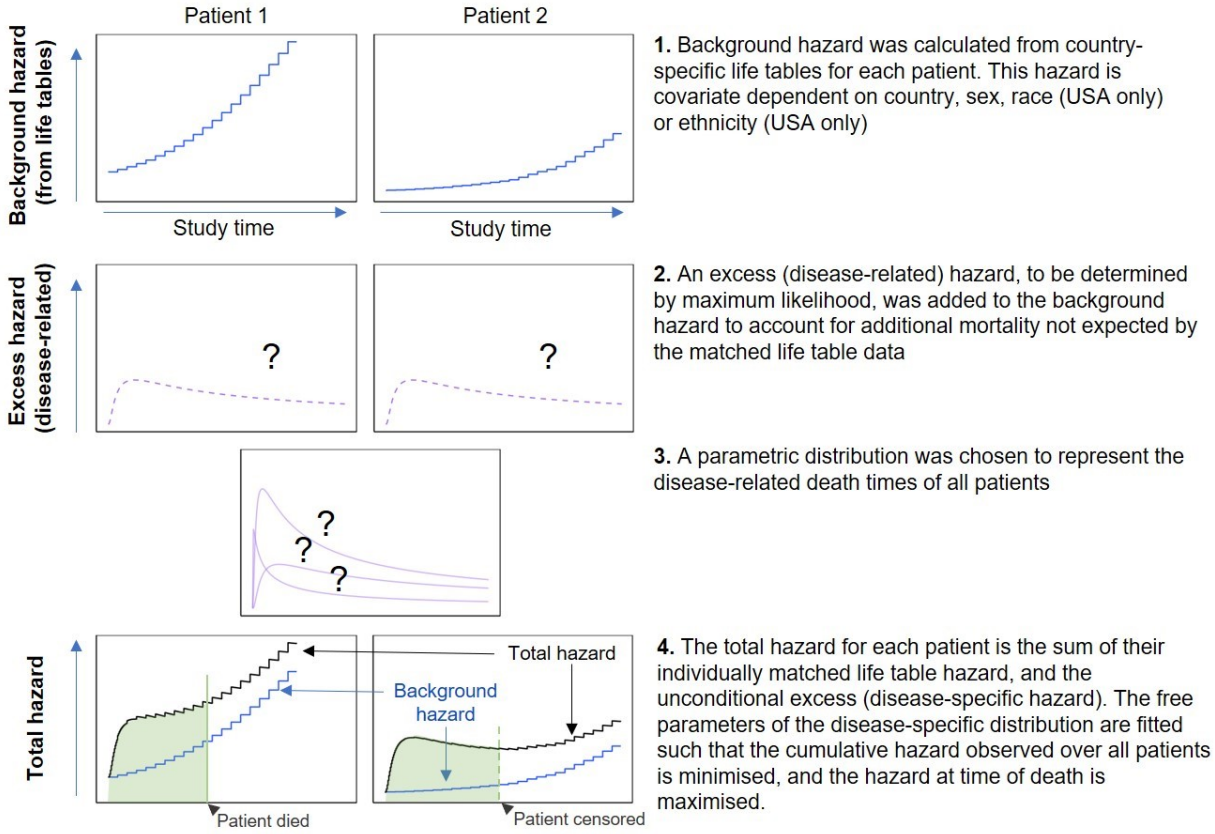
$$S(t) = S_P(t)R(t)$$

where $S_P(t)$ is the expected survival in the general population and $R(t)$ is the relative survival. The all-cause hazard is the sum of the expected hazard in the general population, $h_P(t)$, and the excess hazard associated with the disease, $h_E(t)$:

$$h(t) = h_P(t) + h_E(t).$$

The composite OS model was then fitted to the observed data from ATTR-ACT. The company then re-estimated the background mortality rates for a UK population and applied the model-fitted excess mortality hazard to the UK baseline within their economic model.

Figure 9: Company's approach to statistical modelling of background and disease-specific excess mortality (reproduced from CS, Figure 35)



With respect to the excess disease-related mortality component of the model, the company fitted six standard parametric models: exponential; Weibull; Gompertz; log logistic; log normal and generalised gamma functions. As part of their clarification response[2] (question B7), the company justified the choice of these distributions on the basis that they can "*be guaranteed as a proper time to event distribution and will be consistent with the observed data, provided that the distribution specified does represent the underlying statistical process determining time of event.*" The models were each fitted separately to data for each treatment group. The ERG notes that the sample data are available during the first 30 months and that the models are extrapolated beyond 200 months, giving both structural and parameter uncertainty.

In response to clarification question B8, the company suggested that it is not possible to provide estimates of the proportion of patients dying of non-CV-related events or non-disease-related events because the model does not consider causality, and only deals with uncertainty associated with parameters relating to the excess mortality. Although not explicitly stated by the company, the general form of the log likelihood for a relative survival model is:

$$\log L(\theta) = \delta_i \log\big(h_P(t) + h_E(t)\big) - \int_0^t h_E(u)du - \int_0^t h_P(u)du$$

The ERG notes that it is a common modelling assumption that the expected hazard in the general population is fixed and known so that the last term on the right is a constant and can be dropped from the log-likelihood. The ERG accepts that it is only possible to quantify the proportion of patients dying of disease-related and non-disease-related events, and not because of other causes.

The company selected their preferred model for the excess hazard through consideration of goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]); visual inspection of the predicted survivor functions versus the observed Kaplan-Meier survival functions; consultation with clinical experts to assess the plausibility of the survival functions; and comparisons of the fitted models against external data (from the ATTR-ACT extension study[20]). The company's fitted OS functions for tafamidis and BSC using country-specific background mortality hazards are presented in Figure 10 and Figure 11, respectively (it should be noted that these relate to a population characterised by the ATTR-ACT study and not to the UK general population as applied in the company's economic model). Relative goodness-of-fit statistics for the models are summarised in Table 12.

The company selected the log normal distribution to model the excess hazard for OS for the tafamidis group. This selection was made on the basis that together with the exponential distribution, the log normal distribution was one of the best-fitting models of excess hazards, and because all other models except for the exponential model appeared to underestimate all-cause OS based on a comparison of survival at 50 months in the ATTR-ACT extension study.[41]

The company selected the Weibull distribution to model the excess hazard for OS for the BSC group based on its goodness-of-fit statistics and the nature of the underlying hazard for excess mortality (monotonically increasing). In addition, the company noted that the Weibull model provides a more reasonable all-cause OS projection compared with other models based on a comparison of the model predictions versus all-cause OS for those patients who were randomised to placebo in ATTR-ACT and subsequently switched to tafamidis in the ATTR-ACT extension study.[41]

Figure 10: Overall survival models - general population mortality plus disease-related excess mortality, tafamidis group (reproduced from CS, Figure 36)

Figure redacted - AIC

Note - The figure shows modelled cumulative survival probabilities models based on country-specific background mortality hazards, whilst the economic model uses UK-specific life tables

Figure 11: Overall survival models - general population mortality plus disease-related excess mortality, BSC group (reproduced from CS, Figure 37)

Figure redacted - AIC

Note - The figure shows modelled cumulative survival probabilities models based on country-specific background mortality hazards, whilst the economic model uses UK-specific life tables

Table 12: Relative goodness of fit statistics for company's fitted survival models (all-cause mortality)

Model	Tafamidis		BSC	
	AIC	BIC	AIC	BIC
Exponential	759.85	**819.19**	731.59	786.52
Weibull	758.30	821.21	**718.84**	**776.95**
Gompertz	759.81	822.72	719.47	777.58
Log logistic	758.12	821.03	718.91	777.03
Log normal	**757.75**	820.66	720.13	778.25
Generalised gamma	759.75	826.24	720.95	782.24

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion
Lowest values shown in bold

The company's health economic model assumes that background mortality risk is the same for each NYHA state, but that excess disease-related mortality risk increases with NYHA state. The company used a Cox model conditional on NYHA class at the patient's last 6-monthly assessment point to estimate all-cause HRs for each NYHA class relative to NYHA III in each group (see Table 13). Within their health economic model, the company assumed that these HRs are equivalent to RRs. These RRs (HRs) are combined with the overall NYHA-independent excess mortality risks in order to estimate the distribution of excess mortality deaths across the NYHA states in each cycle (see Section 5.2.2, description of model logic, Step #4).

Table 13: NYHA-specific HRs for all-cause mortality (applied as RRs to disease-related excess mortality)

Health state	Tafamidis		BSC	
	HR	SE of log HR	HR	SE of log HR
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III (reference state)	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]

NYHA – New York Heart Association; HR – hazard ratio; SE – standard error

Time to treatment discontinuation

The model assumes that any tafamidis-treated patient who progresses to NYHA IV will immediately discontinue treatment. The ERG notes that the transition matrices for both treatment groups allow for patients in NYHA IV to transition to improved health states (see Table 11). After discontinuation, the company's model assumes that these patients will not restart treatment with tafamidis. This issue is discussed further in Section 5.3.3.

Within the remaining health states (NYHA I-III), tafamidis-treated patients are assumed to have a time-independent probability of discontinuing treatment in any cycle. Using data from ATTR-ACT,[14] the company undertook a competing risks analysis of time to treatment discontinuation conditional on survival, whereby discontinuations were counted as events, whilst progression to NYHA IV, death,

fitting of a CMAD and heart transplantation were censored. Outcomes for patients who were lost to follow-up or who remained on treatment at the end of the study period were also censored. The company fitted six standard parametric models to the available data: exponential; Weibull; log-logistic; log-normal; Gompertz; and generalised gamma functions. The company selected their preferred parametric function on the basis of goodness-of-fit statistics and visual inspection. Figure 12 presents the company's fitted survivor functions for time to treatment discontinuation. Figure 15 presents the AIC and BIC statistics for each of the fitted parametric models. The company selected the exponential function for use in their base case analysis.

Figure 12: Time to treatment discontinuation, tafamidis, including censoring for progression to NYHA IV, death, fitting of a CMAD and heart transplantation (reproduced from CS, Figure 40)

Figure redacted - AIC

Table 14: Time to treatment discontinuation – AIC and BIC statistics, tafamidis

Model	Tafamidis	
	AIC	BIC
Exponential	506.40	**509.98**
Weibull	506.65	513.80
Gompertz	**505.00**	512.15
Log logistic	506.25	513.40
Log normal	506.26	513.41
Generalised gamma	508.06	518.79

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

Health-related quality of life

Within ATTR-ACT, the EQ-5D-3L questionnaire was administered at the baseline visit and at Months 6, 12, 18, 24, and 30 (or early study discontinuation).[14] Health utilities were valued using the Dolan UK value set.[42] Within the model, health utilities for each NYHA state were estimated using the raw EQ-5D-3L data collected in the trial. Separate estimates were generated for each treatment group. According to the CS,[1] autocorrelation between repeated observations from individual patients was accounted for using the Prais-Winsten estimator (see Table 15). As shown in the table, the mean EQ-5D score decreases with increasing NYHA class, and markedly higher values are assumed for the tafamidis group compared with the BSC group for patients with NYHA IV HF. Health utilities were not age-adjusted.

Table 15: EQ-5D-3L estimates by NYHA class

Health state	Tafamidis		BSC	
	Mean	SE	Mean	SE
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]

NYHA – New York Heart Association; SE – standard error; BSC – best supportive care

Resource use and costs

The model includes resource costs associated with: (i) drug acquisition; (ii) CV-related hospitalisations; (iii) disease management; (iv) management of AEs; and (v) end of life care costs. Table 16 summarises the costs associated with each category within the company's model.

Table 16: Summary of drug, health state and event costs applied in the company's model

Cost parameter	Tafamidis	BSC
Drug acquisition (monthly)	£10,841	N/a
Drug administration (monthly)	N/a	N/a
Concomitant medications (monthly)	£18	£19
Health state- NYHA I, (monthly)	[redacted]	[redacted]
Health state- NYHA II-IV (monthly)	[redacted]	[redacted]
CV-related hospitalisation event (monthly, applied to event probabilities in each NYHA state)	£2,537	£2,537
AEs (once-only, applied in first monthly cycle)	[redacted]	[redacted]
End of life care (once-only)	£9,288	£9,288

NYHA – New York Heart Association; AE – adverse event; BSC – best supportive care; N/a – not applicable

Drug acquisition costs

The list price for tafamidis 61mg free acid is £10,685 per pack of 30 capsules (30 days' supply). [redacted]

[redacted] The model does not include any costs associated with prescriptions or dispensing of drug medications (tafamidis or BSC).

Within the model, the acquisition cost of tafamidis in each monthly cycle is estimated as a function of the probability of being in NYHA I-III, the probability of not having yet discontinued treatment, the probability that a patient is a low-adherer to treatment (<80% dosing adherence) and the unit cost per pack of tafamidis.

The company's model assumes that patients may experience treatment breaks, during which time they are not dispensed further treatment for a short period of time. The model assumes that in any given cycle, [redacted] of patients accrue 80% of the treatment cost; the remaining [redacted] of patients are assumed to accrue the full cost of treatment.

Following discontinuation of tafamidis, the model assumes that patients also discontinue drug treatments included in BSC. According to the CS[1] (page 139), this assumption was made on the basis of clinical opinion, which stated that patients discontinuing tafamidis would not be fit enough to receive additional therapies for symptom management.

Concomitant medication costs

Concomitant medication costs are included in the model to represent BSC and are applied in both arms of the model. Concomitant medications consist of disease management for HF and include: loop diuretics; anticoagulants; antiplatelet agents; lipid lowering therapy, ACE inhibitors / RAAS inhibitors and beta blockers. Resource use is assumed to be dependent on treatment group and is derived from ATTR-ACT.[14] Concomitant medication costs are based on the monthly resource use and unit costs from the Monthly Index of Medical Specialities (MIMS)[36] (see Table 17).

Monthly costs associated with concomitant medications are assumed to apply indefinitely within the BSC group and are assumed to apply only up to the point of tafamidis discontinuation within the tafamidis group.

Table 17: Monthly resource costs associated with BSC applied in the company's model

Medication type	Resource use - tafamidis	Resource use -BSC	Unit cost†	Total cost - tafamidis	Total cost - BSC
Loop diuretics	0.66	0.69	£15.81	£10.48	£10.99
Antithrombotic agents*	0.40	0.41	£9.47	£3.77	£3.85
Beta blockers	0.29	0.30	£3.74	£1.08	£1.12
RAAS inhibitors	0.26	0.27	£10.92	£2.85	£2.96
Total	-	-	-	**£18.18**	**£18.92**

** Combination of anticoagulants, aspirin and statins*
† Based on dosage reported in MIMS

Health state costs

Health state costs include: outpatient echocardiograms; outpatient visit to cardiology (initial and follow-up visits); and community nurse visits. Resource use was based on chart reviews of patients diagnosed with ATTR-CM at Guy's and St Thomas' NHS Foundation Trust. Resource use is assumed to be the same for all patients with NYHA II-IV, with lower resource use assumed for NYHA I, regardless of treatment group. Monthly health state costs are based on the resource use estimates from the chart review and unit costs taken from the NHS Reference Costs 2017/18[37] and the Personal Social Services Research Unit (PSSRU).[38] All health state costs are estimated on a monthly basis and are applied in every monthly cycle. Monthly resource use and costs are summarised in Table 18.

Table 18: Summary of health state resource use and costs (monthly)

Resource type	Frequency – NYHA I (monthly)	Frequency – NYHA II-IV (monthly)	Unit Cost	Total cost – NYHA I	Total cost – NYHA II-IV
Echocardiogram	[redacted]	[redacted]	£188.67	[redacted]	[redacted]
Initial cardiologist visit	[redacted]	[redacted]	£163.36	[redacted]	[redacted]
Follow up cardiologist visit	[redacted]	[redacted]	£128.05	[redacted]	[redacted]
Community nurse visit	[redacted]	[redacted]	£24.70	[redacted]	[redacted]

NYHA - New York Heart Association

Cost of CV-related hospitalisation

Each CV-related hospitalisation was assumed to be associated with a cost of £2,537 per episode, calculated as the weighted mean of all non-elective long stay hospital admissions due to HF/shock and arrhythmia/conduction disorders within the NHS Reference Costs 2017/18.[37] Reliable estimates of length of hospital stay were not available from ATTR-ACT[14] (see company's clarification response,[2] question B21). The probability of CV-related hospitalisation was assumed to vary according to treatment group and NYHA state. Monthly probabilities of experiencing CV-related hospitalisation were calculated using data relating to the proportions of patients who were hospitalised in each NYHA state during the on treatment period in ATTR-ACT[14] (see Table 19). According to the company's clarification response[2] (question B13), a simple Poisson intercept model for hospitalisation count was regressed on each NYHA class using the log of exposure time as the offset term. Within the economic model, these probabilities are applied to all patients who are alive in each state in each monthly cycle. The hospitalisation probabilities for the tafamidis group are applied to all patients, irrespective of whether they are still receiving treatment. Monthly costs of CV-related hospitalisation are calculated by applying the unit cost to the proportions experiencing an event in each state during each cycle.

Table 19: Monthly rate of CV-hospitalisations conditional on current NYHA health state*

Health state	Probability of CV-related hospitalisation - tafamidis (monthly)	Probability of CV-related hospitalisation - BSC (monthly)
NYHA I	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]

NYHA - New York Heart Association; BSC - best supportive care
Further details regarding the methods used to calculate these hospitalisation rates by current NYHA class are presented in the company's clarification response[2] (question B13)

Costs associated with managing AEs

The model includes the costs associated with three types of AEs (any severity): (i) diarrhoea; (ii) nausea; and (iii) urinary tract infections (UTIs). The company's clarification response[2] (question B22) states that these were the only treatment-related AEs of any severity with ≥5% incidence in ATTR-ACT[14] (see Table 20). Unit costs for diarrhoea and nausea were taken from NICE TA197 (dronedarone for non-permanent atrial fibrillation[39]); these costs were uplifted to 2017/18 prices using the PSSRU Hospital and Community Health Services (HCHS) inflation index.[38] Unit costs associated with UTIs were taken from NHS Reference Costs 2017/18.[37] Costs are applied as once-only costs during the first model cycle.

Table 20: Summary of AE frequency and costs (applied in the first model cycle only)

Adverse event	Frequency-tafamidis	Frequency-BSC	Unit cost	Total cost - tafamidis	Total cost-BSC
Diarrhoea	[redacted]	[redacted]	£245.44	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	£245.44	[redacted]	[redacted]
UTI	[redacted]	[redacted]	£250.08	[redacted]	[redacted]
Total	-	-	-	[redacted]	[redacted]

End of life care costs

The costs associated with end of life care were estimated to be £9,288 based on Hollingworth *et al,*[43] uplifted using the HCHS inflation index.[38] This is applied as a once-only cost to all patients at the point of death, irrespective of cause.

5.2.5 Model evaluation methods

The CS[1] presents the incremental cost-effectiveness ratio ([redacted]) for tafamidis versus BSC. Cost-effectiveness results are presented for both the probabilistic and the deterministic versions of the model. The probabilistic ICER was estimated using 3,000 Monte Carlo samples. Table 21 summarises the distributions used to characterise uncertainty around the model parameters within the company's probabilistic sensitivity analysis (PSA). The results of the PSA are presented as a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs).

The CS[1] presents the results of deterministic sensitivity analyses (DSAs) for tafamidis versus BSC using a tornado plot which summarises the ten most influential model parameters. Some of these analyses involve varying parameters according to their 95% CIs where available, or using +/-10% of the expected value where 95% CIs were not available. The ERG notes that some of the analyses presented within the tornado plot reflect scenario analyses rather than DSAs; the reasons for this are unclear.

In addition, the CS[1] also reports the results of 13 scenario analyses undertaken to explore the impact of assumptions around models for excess OS, time to treatment discontinuation models, service redesign due to the availability of tafamidis, extrapolation of transition rates, health state utilities and costs. One subgroup analysis was reported in the CS,[1] which restricts the analysis to those patients with a baseline NYHA class of I or II in ATTR-ACT.[14]

Table 21: Distributions used in the company's PSA

Parameter group	Parameter / parameter group	Distribution	ERG comments
Patient characteristics	Initial age	Normal	-
	Proportion female	Beta	-
	Baseline NYHA class distribution	Dirichlet	-
Efficacy and safety	NYHA transition probabilities, tafamidis	Dirichlet	-
	NYHA transition probabilities, BSC	Dirichlet	-
	CV-related hospitalisation probability, tafamidis	Log normal	Frequencies sampled from log scale and assumed to reflect probabilities
	CV-related hospitalisation probability, BSC	Log normal	Frequencies sampled from log scale and assumed to reflect probabilities
	AE probability, tafamidis	Beta	SE assumed to be 10% of the mean
	AE probability, BSC	Beta	SE assumed to be 10% of the mean
OS	General population mortality	Fixed	No uncertainty included
	OS – excess hazards, tafamidis	MVN	-
	OS – excess hazards, BSC	MVN	-
	Mortality by NYHA class, RRs (HRs), tafamidis	Log normal	-
	Mortality by NYHA class, RRs (HRs), BSC	Log normal	-
Discontinuation	Tafamidis treatment discontinuation	MVN	-
HRQoL	Health state utilities, tafamidis	Beta	-
	Health state utilities, BSC	Beta	-
Resource use and costs	Treatment adherence, tafamidis	Fixed	This parameter is uncertain
	Health state resource use	Gamma	-
	Concomitant medication total costs*	Gamma	The model assumes that the SE is equal to 10% of mean. The CS[1]

Parameter group	Parameter / parameter group	Distribution	ERG comments
	CV-related hospitalisation event cost	Gamma	reports that the SE was assumed to be equal to 20% of mean. The SEs around concomitant medication costs are assumed to reflect uncertainty in resource use
	Costs associated with AEs	Gamma	
	End of life care costs	Gamma	

AE - adverse event; BSC - best supportive care; HRQoL - health-related quality of life; OS - overall survival; QALY - quality-adjusted life year; SE - standard error; MVN - multivariate normal; NYHA- New York Heart Association

5.2.6 Company's model validation and verification

The CS[1] states that the company's model was validated by an independent consultant and cell-by-cell verification was undertaken in order to verify the model calculations. The model predictions were validated through comparisons against observed outcomes in ATTR-ACT[20] in terms of OS, time of treatment and disease progression (CS, Appendix J).[1] In response to a request for clarification from the ERG[2] (question C2), the company provided a further comparison of observed and predicted NYHA health state occupancy during each 6-month interval (see Appendix 2); these indicate that the observed and modelled estimates of health state occupancy are similar within the observed period of the trial. The company also states that the ATTR-ACT extension study[41] was used to validate longer term OS projections. The CS[1] describes various uses of clinical input to inform the assumptions used within the model. The CS also states that the model structure and assumptions were validated by an Advisory Board comprised of health economists and clinical experts.

5.2.7 Company's model results

As part of their clarification response,[2] the company submitted an amended version of their model, which included minor amendments relating to: concomitant medication costs; AE costs; and an updated estimate of relative dose intensity (RDI). This section first summarises the company's results as presented in the CS,[1] and subsequently summarises the impact of these amendments on the company's results.

Central estimates of cost-effectiveness – company's original model

Table 22 presents the central estimates of cost-effectiveness generated using the company's model. The probabilistic version of the model suggests that tafamidis is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared with BSC; the corresponding ICER is [redacted] per QALY gained. The deterministic version of the model produces a slightly lower ICER of [redacted] per QALY gained.

Table 22: Company's base case results - tafamidis versus BSC (generated by the ERG using the company's original model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; BSC- best supportive care
**Undiscounted*

Company's probabilistic sensitivity analysis

Figure 13 presents the CEACs for tafamidis versus BSC generated by the ERG. Assuming willingness-to-pay (WTP) thresholds of £30,000 per QALY gained, the probability that tafamidis produces more net benefit than BSC is approximately [redacted].

Figure 14 presents the company's cost-effectiveness plane for tafamidis versus BSC. As shown in the figure, none of the probabilistic samples suggested an ICER which was below [redacted] WTP threshold.

Figure 13: Company's probabilistic sensitivity analysis results - CEACs for tafamidis and BSC (generated by the ERG using the company's original model)

Figure redacted - CIC

Figure 14: Company's probabilistic sensitivity analysis results, cost-effectiveness plane (generated by the ERG using the company's original model)

Figure redacted – CIC

Company's deterministic sensitivity analysis

The company's tornado plot is shown in Figure 15. The plot indicates that the key drivers of the model are the time horizon, the discount rate and the NYHA-specific health state utilities. The plot also indicates that the ICER for tafamidis versus BSC remains greater than [redacted] per QALY gained in all scenarios evaluated; the ERG notes that this lower ICER relates to a discounting scenario which is not relevant for NICE decision-making.

Figure 15: Company's deterministic sensitivity analysis results - tornado plot for tafamidis versus BSC (reproduced from CS, Figure 43)

Figure redacted - CIC

Table 23 summarises the results of the company's scenario analyses for tafamidis versus BSC. In general, these analyses indicate that none of the scenarios considered lead to a dramatic change in the ICER for tafamidis versus BSC. The most substantial change in the ICER was generated from Scenario 2 (log logistic distribution for tafamidis excess OS), whereby the ICER increased to [redacted] per QALY gained. In addition, treating patients in NYHA IV with tafamidis (i.e. removing the discontinuation rule, Scenario 9) increased the ICER to [redacted] per QALY gained. Scenario 3 produced the lowest ICER (BSC OS modelled using a generalised gamma distribution, ICER=[redacted] per QALY gained). The analyses also show that the exclusion of end of life care and AE costs have virtually no impact on the model results.

Table 23: Company's scenario analysis results - tafamidis versus BSC, deterministic (generated by the ERG using the company's original model)

Scenario	Inc. costs	Inc. QALYs	ICER
Company's base case	[redacted]	[redacted]	[redacted]
Scenario 1: Tafamidis survival projection using exponential distribution for the excess hazard	[redacted]	[redacted]	[redacted]
Scenario 2: Tafamidis survival projection using log logistic distribution for the excess hazard	[redacted]	[redacted]	[redacted]
Scenario 3: BSC survival projection using generalised gamma distribution for the excess hazard	[redacted]	[redacted]	[redacted]
Scenario 4: Tafamidis treatment discontinuation using a log normal distribution	[redacted]	[redacted]	[redacted]
Scenario 5: Model starting age of 71.95 due to reduced time to diagnosis	[redacted]	[redacted]	[redacted]
Scenario 6: Average diagnosis within 6 months. Reduced cost per patient of £20,000	[redacted]	[redacted]	[redacted]
Scenario 7: Adoption of EAMS resulting in a saving of £128.05 per patient per year	[redacted]	[redacted]	[redacted]
Scenario 8: Final within-trial transition matrix used for extrapolation period (36 months onwards)	[redacted]	[redacted]	[redacted]
Scenario 9: Patients in NYHA IV receive treatment with tafamidis	[redacted]	[redacted]	[redacted]
Scenario 10: Non-treatment specific health state utilities applied	[redacted]	[redacted]	[redacted]
Scenario 11: CV-related hospitalisations excluded	[redacted]	[redacted]	[redacted]
Scenario 12: AE costs excluded	[redacted]	[redacted]	[redacted]
Scenario 13: End-of-life cost excluded	[redacted]	[redacted]	[redacted]

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care; EAMS - Early Access to Medicines Scheme; NYHA - New York Heart Association; CV - cardiovascular; AE - adverse event

Company's subgroup analysis

Table 24 presents the results for the company's subgroup analysis for patients with NYHA I/II at baseline. This analysis uses subgroup-specific data from ATTR-ACT[14] for the following model parameters: baseline characteristics; baseline NYHA class; NYHA transition probabilities; treatment discontinuation; excess-related overall survival; HRs for death per NYHA; and hospitalisation event

rates (subgroup data are provided in CS Appendix E[18]). The probabilistic version of the model produces an additional [redacted] QALYs at an additional cost of [redacted] per patient compared with BSC; the corresponding ICER is expected to be [redacted] per QALY gained. This is [redacted] than the ICER for the broader population of patients with NYHA I-III.

Table 24: Results of company's NYHA I/II subgroup analysis (generated by the ERG using the company's model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; BSC - best supportive care
**Undiscounted*

Company's updated model results following clarification

As part of their clarification response,[2] the company provided an updated version of the model which includes three minor amendments:

(i) Unit costs of AEs (diarrhoea and nausea) were updated to use NHS References Costs 2017/2018.[44] The updated total AE costs were [redacted] and [redacted] for tafamidis and BSC, respectively. These are lower than the estimates applied in the original version of the company's model.

(ii) Tafamidis costs were updated to include the overall relative dose intensity (RDI) of [redacted], as observed in ATTR-ACT. The <80% adherence parameter was removed.

(iii) Concomitant medication costs were updated, reflecting changes in expected monthly resource use and updated unit cost from the Electronic Market Information Tool (eMIT).[45] These changes resulted in updated monthly concomitant medication costs of £3.38 and £3.57 for tafamidis and BSC, respectively. Again, these are lower than the estimates applied in the original version of the company's model.

Table 25 summarises the company's base case results using the updated version of the model. The ERG accepts all of the amendments made by the company to the updated model. As shown in the table, the revisions made within the updated model have only a minor impact on the ICER for tafamidis (company's original probabilistic base case ICER = [redacted] per QALY gained; company's revised model ICER = [redacted] per QALY gained). It was not possible to run the PSA for the NYHA I/II subgroup as the model runs repeatedly failed due to a logical #DIV/0! error. However, the model amendments had a minor impact on the deterministic ICER (company's original subgroup analysis = [redacted] per QALY gained; company's updated model subgroup analysis ICER = [redacted]).

Table 25: Company's updated base case results - tafamidis versus BSC (generated by the ERG using the company's model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year
**Undiscounted*

5.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[33, 46]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's 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.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS.[1]
- Examination of sampled parameter values used in the PSA.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.1 Model verification

The ERG rebuilt the deterministic version of the company's original base case model using simple Excel spreadsheet formulae rather than VBA in order to verify its implementation. As shown in Table 26, the ERG's results are virtually identical to those generated using the company's model. The ERG is confident that the company's model is free from significant unintended implementation errors.

Table 26: Comparison of company's base case model and ERG's rebuilt model results, deterministic

	Company's model			ERG's rebuilt model		
Tafamidis versus BSC*						
Model outcome	**Tafamidis**	**BSC**	**Inc.**	**Tafamidis**	**BSC**	**Inc.**
LYGs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-	-	[redacted]	-	-	[redacted]

ERG - Evidence Review Group; ICER - incremental cost-effectiveness ratio; Inc. – incremental; LYG - life year gained; QALY - quality-adjusted life year

5.3.2 Adherence to the NICE Reference Case

The company's economic analysis is generally in line with the NICE Reference Case[47] (see Table 27). The most notable deviation from the scope relates to the comparators included in the company's economic analysis; this is discussed in Section 5.3.3.

Table 27: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	With the exception of the comparators against which tafamidis is compared, the company's health economic analysis is generally in line with the final NICE scope.[13] The economic analyses are largely based on data collected within the ATTR-ACT trial.[14] The ERG's clinical advisors believe that the ATTR-ACT trial broadly represents the patient population seen in clinical practice in the UK.
Comparator(s)	As listed in the scope developed by NICE	The comparators considered within the CS[1] are not consistent with the final NICE scope.[13] The NICE scope defines the following comparators: For people with ATTR-CM: • Established clinical management without tafamidis For people with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy [TTR-FAP] and hereditary ATTR-CM): • Patisiran • Inotersen The only comparator included in the model is BSC. As discussed in Section 3.3, the ERG considers the exclusion of patisiran and inotersen to be reasonable due to a lack of relevant evidence.
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.[14] This was the key study included in the company's systematic review of clinical evidence. The effectiveness of the 61mg free acid formulation of tafamidis is based on the pooled data for the 80mg and 20mg dose arms in the trial.

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health state utility values are based on EQ-5D-3L data collected in ATTR-ACT,[14] valued using the UK tariff.[42]
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
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 2017/18 prices.
Discount rate	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.

5.3.3 Main issues identified within the critical appraisal

The main issues identified during the ERG's critical appraisal are summarised in Box 1. These are discussed in further detail in the subsequent sections. It should be noted that given the list price of tafamidis, most of these issues have little impact on the ICER.

Box 1: Main issues identified within the ERG's critical appraisal

(1) Model implementation issues
(2) Issues relating to the model structure
(3) Uncertainty surrounding the assumed stopping rule and subsequent prognosis
(4) Pooled data used to inform efficacy and safety
(5) Issues regarding transition probabilities used in the extrapolation period
(6) Concerns regarding the company's relative survival modelling approach
(7) Concerns regarding HRQoL assumptions
(8) Issues regarding the application of costs
(9) Concerns regarding claims that early diagnosis benefits are attributable to tafamidis

(1) Model implementation issues

The ERG's double-programming exercise did not reveal any significant programming errors in the company's model. However, the implementation of the company's model is unusual in that it evaluates the risks of different types of events using two different time intervals: the risks of death, CV-related hospitalisation events and treatment discontinuation are evaluated using a monthly cycle, whilst transitions between NYHA states are evaluated using 6-month cycles. Within the model, this means that patients can die, be hospitalised or discontinue treatment with tafamidis during any monthly cycle, but patients can only move to a different NYHA state at month 6 and in every 6th cycle thereafter (hence their underlying NYHA state remains fixed for five of every six cycles). The ERG considers this approach to be unconventional and notes that it leads to problems in the implementation and interpretation of the company's half-cycle correction, as this is applied on a monthly basis. As part of the clarification process, the ERG asked the company whether they had explored methods for matrix decomposition in order to adjust the cycle length (for example, using methods described by Chhatwal *et al*[48] – see clarification response,[2] question B24). In response, the company argued that this would require building a *"redundant model"*, as utilities and mortality risks are conditional on the patient's last observed NYHA class. The ERG agrees that this type of adjustment would have required a number of somewhat arbitrary assumptions, for example, that rates of transitions between NYHA states are constant within, but are time-varying between, each discrete 6-month interval during the observed period. However, the ERG is unclear why a redundant model would be required, as the economic model already applies utilities and CV-related hospitalisation probabilities on a monthly basis, irrespective of

the time interval at which NYHA class was measured in ATTR-ACT.[20] Alternatively, it may have been possible instead to estimate all other outcomes using a 6-monthly cycle duration, in line with the interval between NYHA assessments in ATTR-ACT, although the ERG acknowledges that this would have introduced a degree of "bluntness" due to the use of a longer cycle length. Whilst the ERG considers the company's approach to be unconventional, this issue is unlikely to have a material impact on the ICER for tafamidis.

(2) Issues relating to the model structure

The company's overall model structure is based on NYHA class, as reported by patients in ATTR-ACT at 6-monthly intervals throughout the course of the trial. During the clarification process, the ERG asked whether ATTR-ACT included the measurement of eGFR, NT-proBNP and/or tropotonin T levels over time and whether it would have been possible to characterise the model health states using an alternative classification system (the Mayo or NAC systems; see clarification response,[2] question B1). The company's clarification response states that these endpoints were measured only at baseline, Month 12 and at discontinuation; hence, neither classification system could be used to characterise the model health states. The ERG agrees that these alternative classification systems could not have been used to model the progression of the disease over time.

However, the NYHA classification system is associated with several limitations which have been noted within the literature.[49] In particular, the classification system is self-reported by the patient and requires the evaluation of their ability to undertake physical activities based on subjective interpretations of terms including "slight", "marked" and "less than ordinary". This may lead to problems regarding reproducibility of judgements made across patients and for individual patients at different timepoints. As shown in the observed NYHA transition count data (see Appendix 1), some patients in both the tafamidis and placebo groups transitioned from NYHA IV to NYHA II and NYHA III. It is unclear whether these improvements reflect acute improvements in the patients' health status as a consequence of the treatments received, or whether they may be explained by the lack of reliability in assessments of NYHA class. This issue also has implications for the company's assumed treatment discontinuation rule (discussed in critical appraisal point [3]).

Despite these concerns, the ERG considers that the company's decision to structure the model around NYHA classification is reasonable, but its limitations should be borne in mind.

(3) Uncertainty surrounding the assumed stopping rule and subsequent outcomes

(a) Absence of a discontinuation rule within ATTR-ACT

The company's model assumes that all patients will discontinue treatment with tafamidis upon progression to NYHA IV. According to the CS[1] (page 110), this treatment discontinuation rule is based

on data from ATTR-ACT[14] which shows that patients discontinued treatment prior to progressing to NYHA IV and opinion from clinical experts. However, the company's clarification response[2] (questions B11 and C4) confirms that ATTR-ACT did not include a treatment stopping rule and clarifies that a small number of patients (n=[redacted]) entered NYHA IV prior to any observed or unobserved discontinuation of treatment. [redacted]

Given the lack of effective alternative treatments for the majority of patients who would be eligible for treatment with tafamidis (i.e. those without a mixed phenotype), it is unclear whether the proposed discontinuation rule for tafamidis would be adhered to in usual clinical practice. In addition, the transition probabilities used in the company's model allow for a proportion of patients to transition from NYHA IV to an improved health state (NYHA II or III) within most of the model cycles. The company's model assumes that these patients would have discontinued treatment upon progression to NYHA IV. [redacted]

As shown in the company's scenario analyses (see Table 23), removing the NYHA IV discontinuation rule increases the ICER for tafamidis to [redacted] (original model).

(b) Assumption of lifetime treatment effect and cost reductions due to discontinuation

The company's analysis does not explicitly model relative treatment effects. Instead, the company used an arm-based approach to estimate outcomes separately for the tafamidis and BSC groups using data from ATTR-ACT:[14]

- Within the extrapolation period (Month 36 onwards), the model repeatedly applies a single treatment-specific matrix describing transitions between NYHA states, based on time-averaged transition rates across all 6-month intervals in the trial.
- Treatment-specific OS models were fitted to data from ATTR-ACT to estimate disease-related excess mortality risks. HRs derived from a separate Cox model are applied indefinitely to estimate NYHA-specific mortality risks.
- Treatment-specific utility values were estimated using data which were restricted to the on-treatment period of the trial. These are applied indefinitely throughout the extrapolation period.
- Treatment-specific CV-related hospitalisation rates were estimated using data which were restricted to the on-treatment period of the trial. These are also applied indefinitely throughout the extrapolation period.

Within the tafamidis group, the evidence used to inform all of these aspects of the model reflects the average level of exposure to tafamidis during the observed period of ATTR-ACT.[20]

The model also includes a time to treatment discontinuation function which is conditioned on patients remaining alive (i.e. censoring death events, see Figure 12); this survival function indicates that for any surviving patient in NYHA I-III, the cumulative probability of remaining on treatment decreases at a constant rate over time. This survival function reduces the costs of treatment, but has no impact on health outcomes – patients who discontinue treatment are assigned the same event risks and utilities as those who are still receiving treatment.

As such, the ERG believes that this assumes an indefinite treatment effect, which reflects the average level of exposure to tafamidis by patients within the trial, whilst simultaneously assuming that costs will be reduced because fewer patients will still be receiving tafamidis as time progresses. The ERG considers that these assumptions are unlikely to be reasonable.

As part of the clarification process[2] (question D3), the ERG asked the company to provide an amended version of the model which would allow for an analysis in which tafamidis discontinuers are assigned the transition probabilities, utilities and hospitalisation rates associated with the BSC group. In response, the company stated the following:

"…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." (company's clarification response,[2] question D3).

The company did not provide the model amendment requested by the ERG. 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. As such, the ERG believes that the ICER of tafamidis versus BSC is likely to be underestimated.

(c) Subgroup analysis stopping rule inconsistent

The CS[1] presents a subgroup analysis which is restricted to patients with an initial NYHA class of I or II in ATTR-ACT.[14] Within this subgroup analysis, the model assumes the following treatment pathway for patients treated with tafamidis:

- Patients are eligible to start treatment with tafamidis if they have NYHA I or II

- Patients are eligible to continue treatment with tafamidis if they have NYHA I, II or III
- Patients will discontinue treatment upon progression to NYHA IV.

The ERG is unclear whether it is clinically appropriate to assume that a patient who has NYHA III without prior tafamidis use would not be eligible to receive the drug, but that a patient who is receiving tafamidis and whose disease worsens to NYHA III would remain eligible to continue receiving the drug. One of the ERG's clinical advisors commented that it may be difficult to withdraw treatment from patients, especially if they believe that they are still obtaining some benefit from it. Despite this ambiguity, the ERG notes that the ICER for tafamidis within the NYHA I-II subgroup is [redacted] than that for the broader ITT population (company's updated deterministic base case ICER=[redacted] per QALY gained; company's updated subgroup analysis deterministic ICER=[redacted] per QALY gained).

(d) Assumption of discontinuing BSC

The company's model assumes that upon discontinuation of tafamidis, patients will also discontinue treatment with BSC. According to the CS[1] (page 139), this assumption was made on the basis that patients discontinuing tafamidis would not be sufficiently fit to receive further additional therapies for symptom management, as supported by expert clinical opinion received by the company. However, the clinical advisors to the ERG commented that this assumption is not appropriate and it is unlikely that patients would not receive any treatment for symptom management. In addition, the ERG notes that this assumption is inconsistent with the assumptions applied in the BSC group, whereby patients continue to receive BSC drug therapies indefinitely, irrespective of their NYHA state. Given the low monthly costs of these therapies, the impact of this assumption on the ICER is negligible.

(4) Use of pooled data used to inform efficacy and safety

The CS[1] states that 80mg tafamidis meglumine is bioequivalent to the anticipated dosage of 61mg free acid tafamidis, yet the company's model uses evidence from the pooled data for 20mg and 80mg tafamidis meglumine from ATTR-ACT[14] to inform the model. The CS[1] and the company's clarification response[2] (question A7) state that the 80mg dose showed moderately greater benefits compared to the 20mg dose in terms of all-cause mortality and TTR stabilisation. The company's clarification response states that the decision to pool the data within the trial was agreed with regulatory bodies and notes that pooling the data for the tafamidis 20mg and 80mg arms will result in a conservative estimate of efficacy. The ERG agrees that this may underestimate of the clinical effectiveness and cost-effectiveness of 61mg free acid dose tafamidis.

(5) Issues regarding transition probabilities used in the extrapolation period

The company's model uses time-dependent transition probabilities for the first 30 months of the model, based on the patient count data observed within each 6-month interval. From Month 36 onwards, the model employs time-independent transition probabilities, based on a smoothed multinomial distribution fitted to the sum of transition counts within each 6-month interval in ATTR-ACT.[14] The company's clarification response[2] (question B3) states that the use of pooled transition count data was necessary to maximise data availability for transitions with low counts which would otherwise be dominated by the uninformative prior used in the Bayesian analysis. The company's response to clarification question B3 states that the smoothed multinomial distribution was used due to the low number of patients making certain transitions. However, if prior distributions do not represent reasonable prior beliefs then, in the absence of sufficient sample data, posterior distributions will not represent reasonable posterior beliefs. The ERG is concerned that the combination of prior information and sample data may not reflect reasonable posterior beliefs during the extrapolation phase. Furthermore, the ERG does not believe that Figures 33 and 34 of the CS provide support to the approach used by the company to estimate transition probabilities during the extrapolation phase. Nevertheless, the ERG notes that the transition probabilities derived from the company's smoothed multinomial distribution are similar to the probabilities derived from the sum of the unadjusted count data, and that the use of the latter has a negligible impact on the ICER for tafamidis versus BSC.

The ERG also notes that it may be considered inconsistent to assume that transition rates are time-dependent for some cycles and time-independent for others. In their response to clarification question C6,[2] the company presented additional logistic regression analyses which indicate that there is no evidence to suggest a trend for the treatment effect of tafamidis over time, which may be considered to justify the use of the time-averaged transition probabilities in the company's base case analysis. The ERG notes that an alternative approach would be to carry forward the last observed transition matrix (Months 24-30) for all subsequent cycles during the extrapolation phase. This alternative approach was explored in the company's scenario analyses (see Table 23, Scenario 8). Within this scenario, the company's base case ICER increased from [redacted] to [redacted] per QALY gained (company's original model results). The ERG notes that the last observed matrices for Months 24-30 in ATTR-ACT[14] are subject to low patient transition counts, particularly within the BSC group, and no patients who were in NYHA I and NYHA IV at the beginning of the interval improved or worsened. Given the limitations of the available data, the ERG considers the company's approach to be reasonable and notes that the company's scenario analysis indicates that this is not a key driver of the ICER.

(6) Concerns regarding the company's relative survival modelling approach

(a) Model estimation approach

As with many submissions involving survival analyses, survival functions were estimated using frequentist methods. Frequentist estimates of survival functions and population means are derived using plug-in maximum likelihood estimates of model parameters, and standard errors are estimated using the same plug-in values in asymptotic approximations to the standard errors. Given the amount of extrapolation involved, the ERG would have liked to have seen the same models fitted using a Bayesian approach, which would estimate parameters exactly. Furthermore, a Bayesian estimate of a survival function is the expected value of its posterior distribution as a function of the uncertain model parameters. The difference may be particularly important in the context of a PSA in which parameter uncertainty is approximated using a multivariate normal distribution using a frequentist approach, whereas a Bayesian analysis generates the joint posterior distribution of model parameters and functions of them exactly. However, given the list price for tafamidis, the ERG notes that this would not impact on the conclusions of the analysis.

(b) Issues relating to the selection of the model for the excess hazard

With respect to the company's survival modelling, the ERG notes the following:

- Only six standard parametric models of excess hazards are considered for each treatment, and none may represent the true underlying excess hazards.
- A difference between models in BIC of less than 2 is barely worth a mention. For tafamidis, this means that, based on the fit of each model to the sample data, the exponential, log logistic and log normal distributions provide potentially plausible models, whilst for BSC, the Weibull, Gompertz, log logistic and log normal distributions provide potentially plausible models.
- The best fitting model to sample data does not necessarily represent the best model overall when considering the extrapolation phase.
- It is very difficult to compare models with respect to survival functions but better to do so on the hazard scale.
- As a general point, presenting clinical experts with fitted survival functions and asking them to indicate which, in their opinion, is the most plausible is subject to several limitations: (1) it implies that the clinical expert is able to express their opinion about the true proportion of patients surviving at each time without any uncertainty; (2) it ignores uncertainty associated with each model's parameter estimates, and the consequent uncertainty associated with the survival functions; (3) survival functions derived from distributions with very different underlying hazards may look similar to clinical experts. In practice, the question should be asked using a formal elicitation of experts' beliefs before seeing the data.

(c) Transportability of the relative treatment effect on OS

The economic model assumes that the all-cause survival function estimated for patients treated with BSC in ATTR-ACT applies to the target population both in terms of the hazard in the general population and the excess hazard associated with the disease. The hazard in the general population applies to tafamidis and BSC subject to suitable adjustment for population-specific characteristics. However, the excess hazard for patients treated with BSC may differ between the target population and the population characterised by patients in ATTR-ACT, and only a relative treatment effect may be transportable. In response to clarification question B6, the company stated that the excess hazards for tafamidis and BSC followed different underlying parametric distributions and that proportional hazards "*would not be expected*". In general, the ERG does not advocate assuming proportional hazards and notes that a flexible modelling approach such as that suggested by Andersson *et al*, would have allowed for time-varying HRs without the need to assume a standard parametric distribution. However, the ERG accepts that the extrapolation involved would have required the use of external information in order to estimate parameters in the spline-based model.

(d) Use of Cox models to estimate NYHA-specific mortality risks

In response to clarification question B5, the company stated that, "*Cox models were fitted to death from any cause, as deaths from all causes due to an excess hazard mechanism in a relative survival analysis cannot be distinguished from deaths due to the baseline hazard. Whilst technically possible to scale the relative hazards to remove the effect of the baseline hazard, the company is unaware of this being undertaken and is also unaware of development of the statistical theory necessary to adjust the parameter uncertainty to compensate for this.*" The ERG considers it a limitation to use a semi-parametric model to estimate parameters, and to assume that HRs are constant over time.

In response to clarification question B5, the company stated that it made the asymptotic assumption that "*the hazard ratios corresponded to relative risks in order to balance the computational demand of the simulation with the uncertainty of the system overall*". The ERG notes that RRs and HRs are not interchangeable and is not clear in what sense this is asymptotically correct. Furthermore, estimates of HRs will be correlated, although the ERG assumes that the company has assumed them to be independent.

The ERG also notes that within the economic model, the model multiplies the HRs from the Cox model by the health state occupancy of general population mortality survivors and then normalises this to estimate expected NYHA-specific deaths in each cycle. Given that the HRs are estimated using NYHA III as a reference state, the appropriateness of this method is unclear.

(7) Concerns regarding HRQoL assumptions

The company's model includes estimates of health utility by NYHA state, based on the observed EQ-5D-3L data collected within ATTR-ACT.[14] Different utility estimates are applied between the tafamidis and BSC groups. With respect to these data, the ERG notes the following observations:

- The company's utility estimates suggest a marked difference in HRQoL between the groups for patients in NYHA IV (utility NYHA IV tafamidis = [redacted]; utility NYHA IV BSC = [redacted]). The company's clarification response[2] (question B14) highlights that these estimates are based on small numbers of observations in each group (tafamidis group, n=[redacted] observations; placebo group, n=[redacted] observations).
- Within ATTR-ACT,[14] EQ-5D-3L data collection was restricted to the on-treatment period (see company's clarification response,[2] question B15). The CS[1] (page 110) states that in ATTR-ACT, patients discontinued tafamidis prior to progressing to NYHA IV. The fact that there are EQ-5D-3L estimates for tafamidis-treated patients in the NYHA IV state suggests that this statement is not entirely accurate and indicates that if patients did subsequently discontinue whilst in NYHA IV, the utility estimates for the tafamidis group may be subject to informative censoring.
- The company's assumption of treatment-specific utilities is inconsistent with their assumed NYHA IV stopping rule. It is unclear why a patient with NYHA IV who discontinues tafamidis would have an improved level of HRQoL relative to a patient with NYHA IV who continues to receive BSC, as neither patient is receiving tafamidis.
- In response to a request for clarification by the ERG (see clarification response,[2] question C5), the company fitted a generalised estimating equations (GEE) model to the available EQ-5D data collected within ATTR-ACT. In their response, the company commented that this model suggested unsatisfactory behaviour of the residuals, high levels of heteroscedasticity and local non-zero means. As such, the company expressed a preference for the use of the empirical data without the use of parametric assumptions. The ERG notes that the problems of fitting linear models to EQ-5D response data have been discussed in the literature (for example, Hernandez *et al*[50]). The ERG considers that a mixture model, rather than a linear GEE model, would have been better able to reflect the underlying distribution of the EQ-5D data and may have produced more appropriate estimates of mean utility in each NYHA state. However, in the absence of such a model, the ERG also prefers the use of the empirical data from ATTR-ACT.
- Utilities are not adjusted to account for the impact of increasing age. Figure 16 shows the mean utility in surviving patients in the model versus the expected age- and sex-specific utility in the general population (based on Ara and Brazier[51]). As shown in the figure, the mean utility in the tafamidis group is higher than that for the general population from age 82 years, whilst the mean utility in the BSC group is higher than the general population estimate from age 84 years.

The ERG notes that the unusual fluctuations in mean utility for the modelled BSC group are a consequence of the 6-month cycle length for NYHA transitions, the small patient numbers informing some of the transitions, and the 1-month cycle length for mortality events. As a result, during the modelled extrapolation period patients can transition to improved NYHA states every 6 months, which leads to 'jumps' in mean utility at each 6 month time point followed by a decrease in mean utility caused by the application of monthly mortality risks. The ERG believes that utilities should have been adjusted for age, but notes that this would likely have only a minor impact on the ICER for tafamidis.

- The company's model does not include an additional disutility associated with CV-related hospitalisation. In response to a request for clarification from the ERG[2] (question D5), the company stated that there is a lack of suitable evidence that could be used to quantify the disutility associated with CV hospitalisations and any disutility is already partly captured within the NYHA state utility data collected in the ATTR-ACT trial.[14] The company states that tafamidis reduces hospitalisations through delaying progression and therefore it is conservative approach to not include separate disutility for CV-related hospitalisations. The ERG agrees that the company's approach is conservative, but notes that if additional disutilities were available, these would have virtually no impact on the ICER for tafamidis.

Figure 16: Comparison of mean utility in the company's model versus general population mean utility (generated by the ERG)

Figure redacted - AIC

(8) Issues regarding the application of costs

(a) Adverse event costs

The company included three AEs in the economic model, based on data from ATTR-ACT[14] and the ATTR-ACT extension study.[41] In their clarification response[2] (question B22), the company stated that due to the high tolerability of tafamidis, only those AEs with an incidence of ≥5% were included in the model. The ERG notes that within the original model, the costs of AEs appeared very high and were based on outdated sources. The company's updated model applies lower costs which are likely to be more appropriate. These have little impact on the ICER for tafamidis.

(b) Potential underestimation of NYHA IV health state costs

The company's model assumes the same health state costs for NYHA classes II, III and IV, based on data collected from a chart review (n=[redacted]). The ERG's clinical advisors commented that the health state costs for NYHA IV used in the company's model are likely to underestimate the true costs of managing advanced HF. The ERG's clinical advisors suggested that the burden of disease is significantly higher for these patients, that they often require frequent visits from carers and HF nurses and potentially hospice care, and that health care costs are very high for most of these patients. The ERG therefore believes that the health state costs assigned to the NYHA IV state are underestimated in the model. However, health state costs are not a key driver of the model; applying considerably higher costs in the NYHA IV state has virtually no impact on the ICER.

(c) Unit costs for concomitant medication

One of the clinical advisors to the ERG noted that the unit costs applied to several concomitant medications included in the company's original model were higher than expected (in particular, aspirin, ramipril and eplerenone). The company's updated model includes lower costs associated with concomitant medications, based on eMIT[45] rather than MIMS.[36] The ERG believes that the company's updated costs are more appropriate. The ERG's clinical advisor also stated that the warfarin dose used in the concomitant medication costs is much higher than the majority of patients would be able to tolerate, and that apixaban is more likely to be used in clinical practice. Given the low monthly costs of warfarin and as the concomitant medication costs do not differ significantly between the treatment groups, this has little effect on the ICER for tafamidis.

(d) Drug administration and dosing adherence cost reductions

The original version of the company's model included cost reductions for patients with dosing adherence levels of <80%. In response to a request for clarification from the ERG,[2] (question B18), the company stated that within the ATTR-ACT study, a fixed prescribing schedule was used, with any unused medication being destroyed. The updated version of the company's model amended this assumption and the company's clarification response stated that in clinical practice tafamidis would

only be prescribed when needed by the patient. In the updated model, the <80% adherence cost reduction was replaced with a parameter which reflects the overall relative dose intensity (RDI) of [redacted] for all tafamidis-treated patients. The ERG considers this amended assumption to be reasonable. However, the ERG notes that RDI has been calculated on the basis of the number of capsules taken, rather than packs dispensed, and as such this assumes that tafamidis is associated with no wastage. The ERG believes that this underestimates the true cost of tafamidis and that it would be more reasonable to assume that, on average, each patient who initiates treatment with tafamidis will waste half a pack over their lifetime.

(9) Concerns regarding claims that early diagnosis benefits are attributable to tafamidis

The CS[1] states that there are additional benefits of tafamidis which have not been captured fully within the company's model. The company assumes that the introduction of tafamidis as the first disease-modifying treatment for ATTR-CM, alongside the increased availability of non-invasive diagnostic tests, will improve the rate and time to diagnosis through increased awareness and suspicion of disease. The CS states that this earlier diagnosis will lead to additional cost savings due to reduced hospital attendances and improved outcomes due to delayed disease progression. The CS includes two scenario analyses which attempt to capture these additional benefits (see Table 23, Scenarios 5 and 6). The first scenario analyses applies a lower start age to the model to reflect diagnosis occurring 28.7 months earlier; the second scenario includes a saving of £20,000 per patient receiving tafamidis which is intended to reflect reduced hospital attendances incurred prior to diagnosis. The ERG has concerns regarding the assumptions underpinning these scenario analyses:

- The CS does not present any empirical evidence to support the claims that the introduction of tafamidis will lead to earlier diagnosis.
- One of the ERG's clinical advisors commented that there has been a dramatic increase in the awareness of ATTR-CM in recent years, particularly since the introduction of patisiran and inotersen, and therefore the introduction of tafamidis is unlikely to make a significant difference in terms of earlier diagnosis.
- One of the ERG's clinical advisors also noted that diagnosis rates have already been increasing since the introduction of scintigraphy which is now becoming widely available.

Despite concerns regarding the plausibility of these additional assumptions, the ERG notes that the company's additional scenario analyses to reflect these added benefits do not have a substantial impact on the ICER (reduced model starting age corresponding ICER: [redacted] per QALY gained; reduced costs of £20,000 per patient corresponding ICER: [redacted] per QALY gained, calculated by the ERG using the company's updated model).

5.4 ERG's exploratory analysis

5.4.1 ERG's exploratory analysis – preferred analysis

The ERG's preferred base case analysis is comprised of six sets of amendments to the company's updated model; these are detailed below. All exploratory analyses use a 26-year time horizon as this was the intended time horizon described in the CS.[1]

The implementation of the ERG's exploratory analyses was repeated by a second modeller to ensure that the results are free from errors. All of the individual exploratory analyses which make up the ERG's preferred base case were undertaken using the updated version of the company's model provided following the clarification process. Owing to a lack of flexibility in the company's VBA user-defined functions, the ERG had difficulties in implementing some of the ERG's additional sensitivity analyses using the company's model; instead, these analyses were conducted using the ERG's double-programmed model (see Section 5.3.1). The ERG is confident that the two models generate the same results. Technical details regarding the implementation of these analyses are presented in ERG Appendix 3.

ERG exploratory analysis 1: NYHA I-III discontinuation probability equal to zero in the extrapolation period (after Month 30)

As discussed in Section 5.3.3 (critical appraisal point [3b]), the company's model implicitly assumes a continued lifetime treatment effect based on the level of exposure to tafamidis observed in the trial, whilst also assuming that the average amount of tafamidis received by surviving patients in each cycle will decrease over time. The ERG considers this to be highly optimistic. The ERG believes that the problem relates to non-adherence and the impact of this non-adherence on subsequent treatment effects. Given the company's existing model structure, there are two ways of exploring the impact of this. The first would involve aligning treatment effects with the costs required to achieve those effects. This is applied in ERG exploratory analysis 1 and involves assuming that the time to treatment discontinuation function plateaus at the end of the observed trial period (30 Months). The second approach would involve applying BSC outcomes to all patients from the point at which they discontinue tafamidis. This is applied in ERG additional sensitivity analysis 1. The ERG notes that neither approach is ideal: applying the discontinuation plateau may not be externally valid if in reality the likelihood of remaining on treatment continues to decline in the longer-term, whilst applying BSC outcomes to tafamidis discontinuers would disadvantage the tafamidis group as the treatment effect would be diluted by discontinuations which had already occurred during the trial period. In addition, the latter scenario assumes that upon discontinuation, patients will immediately experience the same event risks and outcomes as BSC patients and that that transitions between NYHA states at each 6 month interval are equivalent to the mixture of patients in the BSC group. The ERG believes that the most appropriate analysis would involve formally adjusting for non-adherence using causal inference methods (e.g. using

g-methods or IPCW). However, this analysis has not been done by the company. Whilst the ERG has selected the assumption of a plateau in discontinuation of tafamidis as a preferred analysis, it is likely that the true ICER will lie somewhere between these two approaches.

Within this exploratory analysis, the cumulative probability of remaining on treatment for survivors in NYHA I-III is assumed to plateau after Month 30 (the end of the observed trial period). The ERG notes that within this scenario, patients may still discontinue tafamidis beyond this timepoint, but only in line with the rates of progression to NYHA IV and death.

ERG exploratory analysis 2: Use of BSC utilities for discontinuers in NYHA IV

As discussed in Section 5.3.3 (critical appraisal point [7]), the ERG does not consider it reasonable to assume that patients in NYHA IV in the tafamidis group experience a different level of HRQoL compared with patients in the BSC group, as neither group is assumed to receive tafamidis once they have progressed to this state. Within this exploratory analysis, patients who discontinue treatment with tafamidis and enter NYHA IV were assumed to have the same utility as patients with NYHA IV in the BSC group.

ERG exploratory analysis 3: Use of BSC CV-related hospitalisation rates for patients in NYHA IV

The issue described above regarding HRQoL also applies to CV-related hospitalisations. Within this exploratory analysis, the CV-related hospitalisation probability for NYHA IV for patients in the tafamidis group was set equal to the probability for the BSC group.

ERG exploratory analysis 4: Use of age-adjusted utilities using Ara and Brazier[51]

The company's model suggests that the average utility in survivors exceeds that of the general population in their ninth decade of life. Within this exploratory analysis, utilities for each NYHA state were adjusted for age using general population norms for England.[51]

ERG exploratory analysis 5: Inclusion of BSC costs for patients who discontinue tafamidis

As discussed in Section 5.3.3 (critical appraisal point [8]), the ERG's clinical advisors disagreed with the company's assumption that tafamidis-treated patients who progress to NYHA IV would also discontinue BSC. In this exploratory analysis, BSC costs were applied to patients after discontinuing tafamidis.

ERG exploratory analysis 6: Inclusion of wastage for tafamidis (0.5 packs)

The company's model excludes wastage (see Section 5.3.3., critical appraisal point [8]). The company's model was modified to assume that each patient initiating treatment with tafamidis would waste half a pack (applied at the point of death).

ERG exploratory analysis 7: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1-6.

ERG's exploratory analysis – NYHA I/II subgroup

The company's model included one subgroup analysis which was restricted to patients with a baseline NYHA class of I or II. As discussed in Section 5.3.3 (critical appraisal point [3c]), the ERG has concerns regarding the plausibility of the treatment pathway assumed in this subgroup analysis. Two exploratory subgroup analyses were conducted: (i) the ERG's preferred assumptions were applied to the company's subgroup analysis assuming that patients in NYHA III remain on tafamidis, and (ii) the same analysis was conducted including an assumption that all patients discontinue treatment on progression to either NYHA III or IV.

5.4.3 ERG's exploratory analysis – additional sensitivity analyses

The following additional sensitivity analyses were undertaken using the ERG's preferred model.

ERG additional sensitivity analysis 1: Use of BSC outcomes for tafamidis discontinuers

Within this sensitivity analysis, the transition probabilities, AE rates, CV-related hospitalisations, survival and utilities for the BSC group were applied to tafamidis discontinuers from the point of discontinuation. Within this analysis, the assumption applied in ERG exploratory analysis 1 (all patients remain on treatment past 30 months) is no longer applied.

ERG additional sensitivity analysis 2: Use of treatment independent utilities

Within this analysis, treatment-independent utilities for each NYHA health state were applied based on the mean utilities for the whole ATTR-ACT trial population.[52]

ERG additional sensitivity analysis 3: Removal of NYHA-specific mortality risks

Within this sensitivity analysis, NYHA-specific mortality risks were removed from the model.

ERG additional sensitivity analysis 4: Use of last matrix carried forward for extrapolation period transition probabilities

Within this sensitivity analysis, the last observed NYHA transition matrix (Months 24-30) was carried forward for all subsequent cycles during the extrapolation period.

ERG additional sensitivity analysis 5: Use of alternative parametric survival models for both tafamidis and BSC

Within this sensitivity analysis, all combinations of alternative parametric OS function for tafamidis and BSC were applied within the company's model (36 different combinations).

5.4.4 ERG exploratory analysis – results

ERG preferred base case analysis

Table 28 presents the results of the ERG's preferred analysis. As shown in the table, assuming that the cumulative probability of discontinuing tafamidis plateaus after 30 months (ERG exploratory analysis 1) increases the ICER from [redacted] to [redacted] per QALY gained. Adjusting utilities for age (ERG exploratory analysis 4) increases the ICER to [redacted]. The ERG's other model amendments have only a minor impact on the ICER. The ERG's preferred analysis, which combines ERG exploratory analyses 1-6 leads to an ICER for tafamidis versus BSC of [redacted] per QALY gained.

Table 28: ERG exploratory analysis results, deterministic, tafamidis versus BSC†

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Company's base case*							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1: NYHA I-III discontinuation probability equal to zero							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2: Use of BSC utility for tafamidis discontinuers in NYHA IV							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 3: Use of BSC CV-hospitalisation rates for tafamidis patients in NYHA IV							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 4: Use of age-adjusted utilities using Ara and Brazier[51]							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 5: Inclusion of BSC costs for discontinuers							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 6: Inclusion of wastage for tafamidis (0.50 packs)							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 7: ERG preferred base case (ERG analyses 1-6 combined)							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

** Using the company's model post clarification, 26-year time horizon*

† With the exception of the ERG's preferred base case, all results reflect individual analyses applied to the company's base case model

Results of ERG's subgroup exploratory analysis

Table 29 presents the results of the ERG's exploratory subgroup analysis. These analyses were performed using the ERG's preferred base case model. As shown in the table, the ICER for the NYHA I/II subgroup is [redacted] than that for the ITT population when the company's NYHA IV

discontinuation rule is applied. However, assuming that patients are only eligible for treatment with tafamidis in NYHA class I or II substantially improves the ICER for tafamidis (ICER= [redacted] per QALY gained). This decrease in the ICER is driven by the reduction in treatment costs for tafamidis, as patients are assumed to discontinue earlier.

Table 29: Results of ERG's exploratory subgroup analysis

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
(i) ERG's exploratory subgroup analysis: Continue treatment in NYHA III							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
(ii) ERG's exploratory subgroup analysis: Discontinue treatment on progression to NYHA III							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Results of additional sensitivity analyses undertaken using the ERG's preferred model

Table 30 and Table 31 present the results of the ERG's additional sensitivity analyses.

Table 30: Results of the ERG's additional sensitivity analyses, deterministic

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
ERG-preferred analysis							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Additional sensitivity analysis 1: Use of BSC outcomes for tafamidis discontinuers*							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Additional sensitivity analysis 2: Use of treatment independent utilities							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Additional sensitivity analysis 3: Removal of NYHA-specific mortality risks							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Additional sensitivity analysis 4: Use of last transition matrix carried forward							
Tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

** In this sensitivity analyses, ERG exploratory analysis 1 (All patients remain on treatment past 30 months) is not applied to the ERG's preferred base case*

Table 31: Results of ERG additional sensitivity analysis 9 - Use of alternative parametric survival models for excess hazards, deterministic

OS - tafamidis	OS - BSC	Inc. QALYs	Inc. Costs	ICER
Log normal	Weibull			
Exponential	Weibull			
Weibull	Weibull			
Log-logistic	Weibull			
Generalised gamma	Weibull			
Gompertz	Weibull			
Log normal	Log normal			
Exponential	Log normal			
Weibull	Log normal			
Log-logistic	Log normal			
Generalised gamma	Log normal			
Gompertz	Log normal			
Log normal	Exponential			
Exponential	Exponential			
Weibull	Exponential			
Log-logistic	Exponential			
Generalised gamma	Exponential			
Gompertz	Exponential			
Log normal	Log-logistic			
Exponential	Log-logistic			
Weibull	Log-logistic			
Log-logistic	Log-logistic			
Generalised gamma	Log-logistic			
Gompertz	Log-logistic			
Log normal	Generalised gamma			
Exponential	Generalised gamma			
Weibull	Generalised gamma			
Log-logistic	Generalised gamma			
Generalised gamma	Generalised gamma			
Gompertz	Generalised gamma			
Log normal	Gompertz			
Exponential	Gompertz			
Weibull	Gompertz			
Log-logistic	Gompertz			
Generalised gamma	Gompertz			
Gompertz	Gompertz			

BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio
** Base case analysis scenario*

As shown in Table 30, applying the outcomes for BSC to tafamidis-treated patients after discontinuation (ERG additional sensitivity analysis 1) has a significant impact upon the ICER for tafamidis (ICER= per QALY gained); this is considerably higher than the ERG's preferred base case ICER. The other analyses relating to treatment-independent utilities, NYHA mortality risk and extrapolation of transition probabilities have only a minor impact on the ICER.

The ERG's additional sensitivity analyses relating to the use of alternative models for excess hazards indicate that the models selected by the company are towards the lower end of the range. Across all of the ERG's additional sensitivity analyses, the lowest ICER for tafamidis versus BSC in the overall ATTR-CM population is in excess of [redacted] per QALY gained.

5.5 Discussion of the cost-effectiveness evidence

The company's systematic review did not identify any existing economic analyses in patients with ATTR-CM.

The CS[1] presents the methods and results of a *de novo* cohort-level state transition model developed by the company to assess the cost-effectiveness of tafamidis versus BSC for the treatment of ATTR-CM. BSC consists of established symptomatic management of HF. The base case population relates to patients with ATTR-CM with NYHA class I-III. The company's model also includes a subgroup analysis relating to patients with NYHA class I/II at baseline. Incremental health gains, costs and cost-effectiveness are evaluated over a 26.67-year time horizon from the perspective of the NHS and PSS.

The company's model includes five health states based on the NYHA functional classification system (NYHA I-IV) and an additional state for death. Model parameters for each arm were informed by analysis of time-to-event data (TTD and OS) collected in ATTR-ACT.[20] The company's model estimates OS using a relative survival modelling approach which combines general population life table risks and additional excess risks of disease-related mortality. The company's model includes a discontinuation rule whereby all patients are assumed to discontinue tafamidis upon progression to NYHA class IV; this discontinuation rule did not form part of the design of the ATTR-ACT trial. Efficacy data were informed by the ATTR-ACT trial. Health state and treatment-dependent utility values are based on mean EQ-5D-3L data collected in ATTR-ACT. Resource use estimates were derived from ATTR-ACT, standard costing sources, literature and assumptions. After discontinuation of tafamidis, the company's model assumes that patients incur no further treatment-related costs, but implied treatment effects are assumed to continue indefinitely.

The probabilistic version of the company's updated model suggests that tafamidis is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared with BSC; the corresponding ICER is [redacted] per QALY gained. The company's updated subgroup analysis for patients with baseline NYHA class I/II produces a deterministic ICER of [redacted] per QALY gained.

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified several issues

relating to the company's model. However, given the list price of tafamidis, several of these concerns have little impact on the conclusions of the economic analysis. Given the current model, the most pertinent of these issues relates to uncertainty surrounding the assumed stopping rule and the impact of non-adherence on subsequent health outcomes.

The ERG undertook six exploratory analyses. These included: (i) applying a treatment discontinuation plateau for survivors after 30 months within the NYHA I-III states; (ii) applying BSC group utilities in NYHA IV for patients in the tafamidis group; (iii) applying BSC CV-related hospitalisation rates for all patients in NYHA IV; (iv) age-adjustment of utilities; (v) the inclusion of BSC costs for patients who discontinue tafamidis, and (vi) the inclusion of drug wastage for tafamidis (0.5 packs per patient). The ERG's preferred base case combines all of these model amendments. The ERG undertook additional subgroup analyses, including an analysis in which patients were only eligible to start and continue treatment with tafamidis in NYHA class I/II. The ERG also undertook additional sensitivity analyses using the ERG's preferred base case to explore the impact of: (i) the application of BSC outcomes for tafamidis discontinuers; (ii) using treatment-independent utilities; (iii) removal of NYHA-specific mortality risks; (iv) carrying forward the last observed transition matrix during the extrapolation period; and (v) using alternative parametric survival models for the disease-related excess hazard of death.

The ERG's preferred analysis suggests that the deterministic ICER for tafamidis versus BSC is [redacted] per QALY gained. However, applying the BSC outcomes to patients who discontinue tafamidis increases the ICER to [redacted] per QALY gained. The ERG believes that neither of these analyses fully addresses issues relating to the relationship between exposure to tafamidis and the treatment effects resulting from that level of exposure; as such, the ERG believes that the ICER is likely to lie between these two estimates [redacted] to [redacted] per QALY gained). The ERG's exploratory subgroup analysis suggests that restricting the population eligible for treatment to NYHA I/II may lead [redacted] (ERG's subgroup analysis including treatment discontinuation plateau and treatment in NYHA I/II only: ICER to [redacted] per QALY gained). However, this treatment approach has not been put forward by the company.

6 OVERALL CONCLUSIONS

6.1 Clinical effectiveness

The study population in the CS are appropriate to the decision problem, that is, patients with ATTR-CM treated with tafamidis. The ERG considers that all relevant studies of tafamidis for this decision problem were presented in the CS. The company's primary source of clinical evidence, the pivotal Phase III ATTR-ACT RCT, demonstrated that pooled tafamidis was superior to placebo and that both the 20mg and 80mg doses were broadly comparable for the primary endpoint and the majority of secondary clinical endpoints. *Post hoc* dose analysis of the two study doses found that the proposed dosage of tafamidis 80mg was statistically superior to tafamidis 20mg for NT-proBNP and troponin I levels only. As highlighted by the company's pre-planned subgroup analyses, the significant treatment benefit of tafamidis over placebo appears largely to be driven by the treatment response in patients with NYHA class I/II, as opposed to NYHA class III and also, by patients with wild-type ATTR-CM, rather than hereditary ATTR-CM. The ERG notes that the evidence comprised in the CS does not contain efficacy or safety data relating to the new formulation of tafamidis 61mg free acid.

6.2 Cost-effectiveness

The company's updated base case probabilistic ICER for tafamidis versus BSC is [redacted] per QALY gained. The ERG believes that this is likely to be optimistic because it assumes an indefinite treatment effect which reflects the average level of exposure to tafamidis for patients within the trial, whilst simultaneously assuming that costs will be reduced because fewer patients will still be receiving tafamidis as time progresses. The ERG considers that these assumptions are unlikely to be reasonable. The ERG's preferred base case ICER is [redacted] per QALY gained (based on an assumption of a plateau in discontinuation at Month 30). The ERG's additional sensitivity analysis in which BSC outcomes are applied to patients discontinuing tafamidis suggests a higher ICER of [redacted] per QALY gained. The ERG believes that the true ICER for tafamidis is likely to lie between these two values.

6.3 Implications for research

The ERG notes that additional data collection in the target population through the ongoing the LTE studies for ATTR-ACT (NCT02791230) and the Phase II study of tafamidis (NCT00935012) offers the opportunity for further validation of long-term outcomes for tafamidis in patients with ATTR-CM. The ATTR-ACT LTE study is currently recruiting and aiming to enrol 2,000 patients, providing long-term survival and AE data for both tafamidis meglumine (20mg or 80mg) and tafamidis free acid (61mg), upon completion, which is estimated to be 2024. Considering that ATTR-CM is a relatively rare disease, collection of further real-world data may add further clarification on the effectiveness and safety in populations eligible for treatment with tafamidis but who are not eligible for clinical trials.

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8 APPENDICES

Appendix 1: Observed NYHA class patient count data from ATTR-ACT

Table 32: Observed NYHA patient count data used to inform company's transition probabilities

Tafamidis					Best supportive care				
Months 0-6									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 6-12									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 12-18									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 18-24									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
Months 24-30									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				
All subsequent 6-month cycles (from Month 36+ onwards)									
From\To	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**	**From\To**	**NHYA I**	**NHYA II**	**NHYA III**	**NHYA IV**
NHYA I					**NHYA I**				
NHYA II					**NHYA II**				
NHYA III					**NHYA III**				
NHYA IV					**NHYA IV**				

NYHA – New York Heart Association
** Cells with no observed transitions shaded in grey*

Appendix 2: Observed versus model-predicted NYHA class at each time interval

Table 33: Observed versus predicted health state occupancy, tafamidis group (adapted from company's clarification response, question C2)

NYHA state	Proportion of surviving patients in state		
	Observed	95% CI by Goodman's formula	Predicted
Month 0			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 6			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 12			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 18			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 24			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 30			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]

NYHA – New York Heart Association; CI – confidence interval

Table 34: Observed versus predicted health state occupancy, BSC group (adapted from company's clarification response, question C2)

NYHA state	Proportion of surviving patients in state		
	Observed	95% CI by Goodman's formula	Predicted
Month 0			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 6			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 12			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 18			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 24			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Month 30			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]

NYHA – New York Heart Association; CI – confidence interval

Appendix 3: Technical appendix – instructions for implementing the ERG's exploratory analyses within the company's model

For all ERG exploratory analyses, set the time horizon in company's model to 26 years. All of the ERG's exploratory analyses (1-7) were undertaken in the company's model and double-programmed in the ERG's rebuilt model for verification of results.

Add a new worksheet called "ERG scenarios." Apply scenario flags called "BSC_utils_flag", "Age_adjust_utils_flag", "Disc_BSC_cost_flag" and "Wastage_flag" to cells D8 to D11, respectively. Flags will need to be set to zero to turn off individual scenarios.

ERG exploratory analysis 1: All patients remain on treatment past 30 months

In worksheet "Trace- Treatment arm", replace cells "L44:L673" with the value in cell L43. This analysis does not work using a flag.

ERG exploratory analysis 2: Use of BSC utilities for discontinuers in NYHA IV

In worksheet "Utilities" replace the value of cell D18 with the following formula: "=IF(BSC_utils_flag=[redacted],dblMeanHsUtilityPboOverall_Nyha4)".

In worksheet "Utilities" replace the value of cell D25 with the following formula: =IF(BSC_utils_flag=0,[redacted],dblMeanHsUtilityPboNyhaI_II_Nyha4)

This amendment is implemented by entering a value of "1" into the new worksheet "ERG scenarios" cell D8 and running the model. Ensure that model calculations are set to automatic before running results.

ERG exploratory analysis 3: Use of BSC CV-related hospitalisation rates for all patients in NYHA IV

In worksheet "Safety", set cell "X9" equal to cell "X29"

ERG exploratory analysis 4: Use of age-adjusted utilities using Ara and Brazier

In VBA module "modEngine", a new variable was added and defined used to switch on age-adjustment of utilities using the following code:

"*Dim Age_adjust_utils_flag As Integer*"

"*Age_adjust_utils_flag = Sheets("ERG scenarios").Range("Age_adjust_utils_flag").Value*"

1. The following code in the company's model:

Dim arrdblHsUtils (0 To 3) As Double
Is replaced with:
"Dim arrdblHsUtilsTafa(0 To 3) As Double"
"Dim arrdblHsUtilsPbo(0 To 3) As Double"

Under *Public Sub initialiseArm(strArm As String, strTraceWs As String)*, the below code:
For lngColIndex = 0 To 3
arrdblHsUtils(lngColIndex) = Sheets("Utilities").Range("dblUsedHsUtility" & strArm & "_Nyha1").Offset(lngColIndex, 0).Value
Next lngColIndex

Is changed to:
For lngColIndex = 0 To 3
arrdblHsUtilsTafa(lngColIndex) = Sheets("Utilities").Range("dblUsedHsUtility" & "Tafa" & "_Nyha1").Offset(lngColIndex, 0).Value
Next lngColIndex
For lngColIndex = 0 To 3
arrdblHsUtilsPbo(lngColIndex) = Sheets("Utilities").Range("dblUsedHsUtility" & "Pbo" & "_Nyha1").Offset(lngColIndex, 0).Value
Next lngColIndex

2. Under "re-initialise input and output arrays" within the 'Public Sub stateTransition(strArm As String, strTraceWs As String)' section of the modEngine, the following code:
   Erase arrdblHsUtils

   Is replaced with the following:
   Erase arrdblHsUtilsTafa
   Erase arrdblHsUtilsPbo

3. Under the 'Public Sub evaluateHealthBenefits(lngRowIndex As Long, strArm As String)' section of modEngine, the below code under 'Case "Tafa"':

   *arrOutQalysNyha(lngRowIndex, lngColIndex) = arrOutLysNyha(lngRowIndex, lngColIndex) * arrdblHsUtils(lngColIndex)*

   Is replaced with the following code in order to adjust utilities by age using Ara & Brazier formula:

If Age_adjust_utils_flag = 0 Then
*arrOutQalysNyha(lngRowIndex, lngColIndex) = arrOutLysNyha(lngRowIndex, lngColIndex) * arrdblHsUtilsTafa(lngColIndex)*
Else
*arrOutQalysNyha(lngRowIndex, lngColIndex) = arrOutLysNyha(lngRowIndex, lngColIndex) * arrdblHsUtilsTafa(lngColIndex) * ((0.9508566 + 0.0212126 * 0.90249 - 0.0002587 * (74.34 + (lngRowIndex / 12)) - 0.0000332 * (74.34 + (lngRowIndex / 12)) ^ 2) / (0.9508566 + 0.0212126 * 0.90249 - 0.0002587 * 74.34 - 0.0000332 * 74.34 ^ 2))*
End If

4. Under the 'Public Sub evaluateHealthBenefits(lngRowIndex As Long, strArm As String)' section of modEngine, the below code under 'Case "Pbo"':

   *arrOutQalysNyha(lngRowIndex, lngColIndex) = arrOutLysNyha(lngRowIndex, lngColIndex) * arrdblHsUtils(lngColIndex)*

   Is replaced with the following code in order to adjust utilities by age using Ara & Brazier formula:
   If Age_adjust_utils_flag = 0 Then
   *arrOutQalysNyha(lngRowIndex, lngColIndex) = arrOutLysNyha(lngRowIndex, lngColIndex) * arrdblHsUtilsPbo(lngColIndex)*
   Else
   *arrOutQalysNyha(lngRowIndex, lngColIndex) = arrOutLysNyha(lngRowIndex, lngColIndex) * arrdblHsUtilsPbo(lngColIndex) * ((0.9508566 + 0.0212126 * 0.90249 - 0.0002587 * (74.34 + (lngRowIndex / 12)) - 0.0000332 * (74.34 + (lngRowIndex / 12)) ^ 2) / (0.9508566 + 0.0212126 * 0.90249 - 0.0002587 * 74.34 - 0.0000332 * 74.34 ^ 2))*
   End If

This amendment is implemented by entering a value of "1" into the new worksheet "ERG scenarios" cell D9 and running the model.

ERG exploratory analysis 5: Inclusion of BSC costs for patients who discontinue tafamidis

1. In VBA module 'modEngine', a new variable was added and defined used to switch on the addition of BSC costs for discontinuers using the following code:
   Dim Disc_BSC_cost_flag As Integer

2. Under 'Public Sub initialiseCommonParams()' in modEngine, the following code was added:

Disc_BSC_cost_flag = Sheets("ERG scenarios").Range("Disc_BSC_cost_flag").Value

3. Under 'Public Sub initialiseArm(strArm As String, strTraceWs As String)', the following code:

```
If strArm = "Tafa" Then
    dblDrugAcqCostsTafa = Sheets("Costs").Range("dblUsedDrugAcqCost_Tafa").Value
    dblAdminCostsTafa = Sheets("Costs").Range("dblUsedAdminCost_Tafa").Value
    dblConcMedCostsTafa =
Sheets("Costs").Range("dblUsedConcMedCost_Tafa").Value
ElseIf strArm = "Pbo" Then
    dblDrugAcqCostsPbo = Sheets("Costs").Range("dblUsedDrugAcqCost_Pbo").Value
    dblAdminCostsPbo = Sheets("Costs").Range("dblUsedAdminCost_Pbo").Value
    dblConcMedCostsPbo = Sheets("Costs").Range("dblUsedConcMedCost_Pbo").Value
End If
```

Is replaced with the following code:

```
If Disc_BSC_cost_flag = 0 Then
If strArm = "Tafa" Then
    dblDrugAcqCostsTafa = Sheets("Costs").Range("dblUsedDrugAcqCost_Tafa").Value
    dblAdminCostsTafa = Sheets("Costs").Range("dblUsedAdminCost_Tafa").Value
    dblConcMedCostsTafa =
Sheets("Costs").Range("dblUsedConcMedCost_Tafa").Value
ElseIf strArm = "Pbo" Then
    dblDrugAcqCostsPbo = Sheets("Costs").Range("dblUsedDrugAcqCost_Pbo").Value
    dblAdminCostsPbo = Sheets("Costs").Range("dblUsedAdminCost_Pbo").Value
    dblConcMedCostsPbo = Sheets("Costs").Range("dblUsedConcMedCost_Pbo").Value
End If
ElseIf Disc_BSC_cost_flag = 1 Then
If strArm = "Tafa" Then
    dblDrugAcqCostsTafa = Sheets("Costs").Range("dblUsedDrugAcqCost_Tafa").Value
    dblAdminCostsTafa = Sheets("Costs").Range("dblUsedAdminCost_Tafa").Value
    dblConcMedCostsTafa =
Sheets("Costs").Range("dblUsedConcMedCost_Tafa").Value
    dblDrugAcqCostsPbo = Sheets("Costs").Range("dblUsedDrugAcqCost_Pbo").Value
    dblAdminCostsPbo = Sheets("Costs").Range("dblUsedAdminCost_Pbo").Value
    dblConcMedCostsPbo = Sheets("Costs").Range("dblUsedConcMedCost_Pbo").Value
ElseIf strArm = "Pbo" Then
```

dblDrugAcqCostsPbo = Sheets("Costs").Range("dblUsedDrugAcqCost_Pbo").Value
dblAdminCostsPbo = Sheets("Costs").Range("dblUsedAdminCost_Pbo").Value
dblConcMedCostsPbo = Sheets("Costs").Range("dblUsedConcMedCost_Pbo").Value
End If
End If

4. Under 'Public Sub evaluateCosts(lngRowIndex As Long, strArm As String)' for 'Case "Tafa"', the following code:

*arrOutDrugAcqCosts(lngRowIndex, 0) = arrOutDrugAcqCosts(lngRowIndex, 0) + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * dblPercentTrtBreaks * (dblDrugAcqCostsTafa * (1 - dblPercentMissedDoses)) + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * (1 - dblPercentTrtBreaks) * dblDrugAcqCostsTafa + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * (dblAdminCostsTafa + dblConcMedCostsTafa)*

Is replaced with the following code:

If Disc_BSC_cost_flag = 0 Then
*arrOutDrugAcqCosts(lngRowIndex, 0) = arrOutDrugAcqCosts(lngRowIndex, 0) + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * dblPercentTrtBreaks * (dblDrugAcqCostsTafa * (1 - dblPercentMissedDoses)) + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * (1 - dblPercentTrtBreaks) * dblDrugAcqCostsTafa + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * (dblAdminCostsTafa + dblConcMedCostsTafa)*
Else
*arrOutDrugAcqCosts(lngRowIndex, 0) = arrOutDrugAcqCosts(lngRowIndex, 0) + (arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * dblPercentTrtBreaks * (dblDrugAcqCostsTafa * (1 - dblPercentMissedDoses)) + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * (1 - dblPercentTrtBreaks) * dblDrugAcqCostsTafa + arrdblOutActiveTrtHc(lngRowIndex, lngColIndex) * (dblAdminCostsTafa + dblConcMedCostsTafa)) + (arrdblOutDiscTrtHc(lngRowIndex, lngColIndex) * (dblDrugAcqCostsPbo + dblAdminCostsPbo + dblConcMedCostsPbo))*
End If

This amendment is implemented by entering a value of "1" into the new worksheet "ERG scenarios" cell D10 and running the model.

ERG exploratory analysis 6: Inclusion of wastage for tafamidis (0.5 packs)

1. In VBA module 'modEngine', a new variable was added and defined to switch on the inclusion of wastage for tafamidis, using the following code:
   Dim Wastage_flag As Integer

2. Under 'Public Sub initialiseCommonParams()' in modEngine, the following code was added:
   Wastage_flag = Sheets("ERG scenarios").Range("Wastage_flag").Value

3. Under 'Public Sub evaluateCosts(lngRowIndex As Long, strArm As String)' for 'Case "Tafa", the following code:

   *arrOutEolCosts(lngRowIndex, 0) = arrdblIncidentDeathCount(lngRowIndex) * dblEolCosts*
   Is changed to the following:
   If Wastage_flag = 0 Then
   *arrOutEolCosts(lngRowIndex, 0) = arrdblIncidentDeathCount(lngRowIndex) * dblEolCosts*
   Else
   *arrOutEolCosts(lngRowIndex, 0) = arrdblIncidentDeathCount(lngRowIndex) * dblEolCosts + (arrdblIncidentDeathCount(lngRowIndex) * (dblDrugAcqCostsTafa * 0.5))*
   End If

This amendment is implemented by entering a value of "1" into the new worksheet "ERG scenarios" cell D11 and running the model.

ERG exploratory analysis 7: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1-6; therefore, apply all the changes listed above.

ERG subgroup exploratory analysis 1: Continue treatment in NYHA III

In worksheet "Model Control" of the company's model with the ERG preferred base case applied, select "NYHA I & II" from the drop down menu in cell E18.

Run the model in order for the NYHA I & II population settings to be applied. Go to worksheet "Trace-Treatment arm", and replace cells "L44:L673" with the value in cell L43. Re-run the model to obtain results.

ERG's subgroup exploratory analysis 2: Discontinue treatment on progression to NYHA III

In worksheet "ERG scenarios add a flag called "Subgroup_disc_flag" to cell D12

1. In VBA module "modEngine", a new variable was added and defined to switch on the ERG's subgroup analysis, using the following code:

   Dim Subgroup_disc_flag As Integer
2. Under 'Public Sub initialiseCommonParams()' in modEngine, the following code was added:
   Subgroup_disc_flag = Sheets("ERG scenarios").Range("Subgroup_disc_flag").Value

3. Under "Public Sub stateTransition(strArm As String, strTraceWs As String)" in modEngine, after the following code:
   If Sheets("Model Control").Range("intDiscOnProg").Value = 1 And lngColIndex = 3 Then
   arrdblDiscProb(lngRowIndex, lngColIndex) = 1#
   End If
   The following code was added:
   If Subgroup_disc_flag = 1 And Sheets("Model Control").Range("intPopIndex").Value = 2 And Sheets("Model Control").Range("intDiscOnProg").Value = 1 And lngColIndex = 2 Then
   arrdblDiscProb(lngRowIndex, lngColIndex) = 1#
   End If

To implement these changes, in worksheet "Model Control" of the company's model with the ERG preferred base case applied, select "NYHA I & II" from the drop down menu in cell E18. Run the model in order for the NYHA I & II population settings to be applied. Go to worksheet "Trace- Treatment arm", and replace cells "L44:L673" with the value in cell L43. In worksheet "ERG scenarios", set the value of cell D17 to 1. Re-run the model to obtain results.

ERG additional sensitivity analysis 1: Use of BSC outcomes for tafamidis discontinuers

Due to the company's use of VBA and user-defined functions to construct the model, this sensitivity analysis is implemented in the ERG's rebuilt model with the ERG's exploratory analyses implemented. ERG exploratory analysis 1 (NYHA I-III discontinuation probability equal to zero, post 30 months) is not implemented for this sensitivity analysis ("discontinue_plateau_flag" on worksheet "Scenario Flags" of the ERG's rebuilt model set to 0).

To implement these changes in the ERG's model, in worksheet "Scenario Flags":

1. Set the value of cell C6 to 0
2. Set the values of cells C7:C11 to 1
3. Set the values of cells C17:C21 to 1

ERG additional sensitivity analysis 2: Use of treatment independent utilities

In the company's model with the ERG's exploratory analysis applied, in worksheet "Utilities", replace the values in cells D15 & D38 with [redacted], values in cells D16 & D39 with [redacted], values in cells D17 and D40 with [redacted] and the values in cells D18 & D41 with [redacted]. Note that this additional sensitivity analysis overrides ERG exploratory analysis 2.

ERG additional sensitivity analysis 3: Removal of NYHA-specific mortality risks

In the company's model with the ERG's exploratory analysis applied, in worksheet "Model Control", select "No" from the dropdown menu in cell J19.

ERG additional sensitivity analysis 4: Use of last transition matrix carried forward

In the company's model with the ERG's exploratory analysis applied, in worksheet "NYHA transitions", copy cells N38:Q41 and paste into cells N45:Q48. Copy cells N84:Q87 and paste into N91:Q94.

ERG additional sensitivity analysis 5: Use of alternative parametric survival models

In the company's model with the ERG's preferred base case applied, go to worksheet "Survival" and use the drop down menus in cells D33 and P33 to select alternative combinations of OS for tafamidis and BSC.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 2 December 2019** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 TTR stabilisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.3, page 4 The ERG report states: "Post hoc dose analysis found that the 20mg and 80mg doses were broadly comparable for the primary endpoint and the majority of secondary endpoints with the exception of NT-proBNP and troponin I levels, where tafamidis 80mg was statistically superior to tafamidis 20mg". Differences observed in TTR stabilisation are not addressed in this summary statement.	The statement should be amended to include: "Exploratory analyses of TTR stabilisation beyond one month demonstrated superiority of 80mg versus 20mg."	At one month the TTR stabilisation differed by more than 5% and that is consistent with Figure 4 (ERG report) which demonstrates clear differentiation of 80mg over 20mg with respect to TTR stabilisation over the 30 month trial period[1].	The text on page 4 has been amended to: "*Post hoc* dose analysis found that the 20mg and 80mg doses were broadly comparable for the primary endpoint and the majority of secondary endpoints with the exception of NT-proBNP and troponin I levels, where tafamidis 80mg was statistically superior to tafamidis 20mg. **At one month the TTR stabilisation differed by more than 5%, favouring 80mg tafamidis over 20mg tafamidis.**"
Section 4.2.4, page 29 The ERG report states: "A statistically significant difference was noted in stabilisation of TTR protein at Month 1 for [redacted] of patients in the pooled tafamidis group and [redacted] of patients in the placebo group (p<[redacted]). Section B.2.6.2.4 of the CS[1] states that this pattern remained consistent through to Month 30 (p<[redacted]). The ERG notes that this is a within group comparison	The following statement should be deleted: "The ERG notes that this is a within group comparison and that only between group comparisons provide meaningful estimates of treatment effects".	Incorrect interpretation of analyses in the CS.	Page 29 amended as suggested

and that only between group comparisons provide meaningful estimates of treatment effects." The comparison of pooled tafamidis and placebo is a between group comparison.			
Section page 4.2.4, page 43 "According to the Clinical Study Report (CSR) for ATTR-ACT, subgroup analyses by dose for TTR stabilisation were only conducted at Month 1. As shown in Figure 5, the proportion of TTR stabilisation between the 20mg and 80mg tafamidis dosages was very similar at Month 1, the point at which the 20mg and 80mg treatment groups appear to diverge the most on Figure 4 over the 30 months." At one month the TTR stabilisation differed by more than 5% and that is consistent with Figure 4 (ERG report) which demonstrates clear differentiation of 80mg over 20mg with respect to TTR stabilisation over the 30 month trial period[1]. In addition, in the CS it was stated that any time point beyond 1 month were conducted as exploratory analyses.	This statement should be deleted.	Incorrect interpretation of analyses in the CS and CSR.	Amended to: "As shown in **Error! Reference source not found.**, **<u>at Month one the TTR stabilisation differed by more than 5%, favouring 80mg over 20mg,</u>** the point at which the 20mg and 80mg treatment groups appear to diverge the most on **Error! Reference source not found.** over the 30 months."

Issue 2 Evidence of benefit in NYHA III Classification

Description of problem	Description of proposed amendment	Justification for amendment	
Section 1.6.2, page 12 & Section 4.5.2, page 40 The ERG report suggests a lack of benefit in patients in NYHA class III, based on the lack of statistical significance in the primary endpoint in this subgroup. Furthermore, reference is made to a significantly higher rate of CV-related hospitalisation in this subgroup. Despite the lack of power for both primary and secondary analyses in this subgroup, the company wish to highlight to the ERG the statistically significant >[redacted]% reduction in overall mortality observed in the tafamidis group. Exclusion of this endpoint from a summary of evidence in NYHA III seems unbalanced, especially given its importance to patients.[2] The ERG report states on page 12: "There is uncertainty in the appropriateness of treatment with tafamidis beyond NYHA baseline class I/II due to a lack of statistically significant benefit for the primary outcome in patients with NYHA baseline class III."	The following sentences (or similar) should be updated: Section 1.6.2, page 12 "There is uncertainty in the appropriateness of treatment with tafamidis beyond NYHA baseline class I/II due to a lack of statistically significant benefit for the primary outcome in patients with NYHA baseline class III; **however, the study wasn't powered to detect a difference in this subgroup.** Section 4.5.2, page 40 "Indeed, NHYA III patients treated with tafamidis had significantly more CV hospitalisations than patients in the placebo group, **although it should also be noted that mortality rates were improved compared to placebo in the NYHA III subgroup. The CS references the pivotal study publication suggesting that higher rates of hospitalisation in the NYHA III subgroup are a result of the mortality benefit, ie, patients living longer in a more advanced health state**." Section 4.5.2, page 40	For a balanced representation of the evidence in patients with NYHA III Classification. The totality of the evidence, including mortality which is the most important endpoint for patients, could be considered when determining appropriateness of treatment in more advanced disease. ATTR-CM is a rare disease, limiting the available patients that can be enrolled into ATTR-ACT. Hence, the study was powered to show a difference between the pooled tafamidis group and the placebo group for the primary endpoint.	Amended Section 1.6.2 to delete mention of statistical significance: "There is uncertainty in the appropriateness of treatment with tafamidis beyond NYHA baseline class I/II due to a lack of benefit for the primary outcome in patients with NYHA baseline class III." Amendment to Section 4.2.4 (page 30): "When outcomes were analysed separately, pooled tafamidis was not statistically significantly superior to placebo for all-cause mortality using a Cox proportional hazards model in patients with NYHA III at Month 30 (HR, [redacted]; 95% CI: [redacted]; [redacted]). **However, the study was not powered to detect a difference in this subgroup.**"

The ERG report states on page 40: "Indeed, NHYA III patients treated with tafamidis had significantly more CV hospitalisations than patients in the placebo group" The ERG report states on page 40: "the differential treatment responses highlighted by the company's subgroup analyses in ATTR-ACT highlight uncertainty in the appropriateness of treatment with tafamidis beyond NYHA baseline class I/II because of an absence of evidence given the lack of statistically significant benefit for the primary outcome in patients with NYHA baseline class III. Of particular note are the higher rates of CV hospitalisations compared to placebo in the NYHA III subgroup."	"Of particular note are the higher rates of CV hospitalisations compared to placebo in the NYHA III subgroup, **although it should be noted that mortality rates were improved compared to placebo in the NYHA III subgroup. The CS references the pivotal study publication suggesting that higher rates of hospitalisation in the NYHA III subgroup are a result of the mortality benefit, ie, patients living longer in a more advanced health state**."		Other suggestions are speculative and no further amendments have been made.

Issue 3 Statements concerning relevance of comparators

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.3 page 15 & Section 5.2.1 page 44 A list of reasons from the CS that explain why patisiran and inotersen were not considered as comparators is stated on page 14 & 44.	The following sentence (or similar) should be included: "Inotersen and patisiran are both licensed for hereditary transthyretin amyloidosis in adult patients with Stage 1 or 2	For a balanced representation of the licensed indication of both patisiran and inotersen.	For the sake of clarity, the ERG has amended bullet point 1 on page 14 and 43 to the following: "Neither patisiran nor inotersen have been evaluated in patients with HF and neither medicine has a

In the CS (Table 1. Decision Problem), an additional point is included that forms the primary rationale for their exclusion- neither medicine is licensed for use in ATTR-CM.	polyneuropathy.[3,4] Neither medicine has a license for ATTR cardiomyopathy."		license for ATTR cardiomyopathy."

Issue 4 Bioequivalence of doses

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.2.1, page 21 & Section 4.5.2, page 40 The ERG correctly on page 33, notes that while similar efficacy was observed across the doses for the primary endpoint and its component endpoints, the 80mg dose was superior in secondary endpoints of cardiac biomarkers that are independently associated with mortality in ATTR-CM (NTpro-BNP and troponin). However, there is some inconsistency in statements regarding the differences in efficacy across the 20 mg and 80 mg doses The ERG report states on page 21: "Clinical advice to the ERG was that a dose-response relationship would be expected, with the 80mg dose providing better efficacy than the	Section 4.2.1, p20 The following sentences (or similar) should be included: "….to demonstrate this. **Although it is noted that significant benefits with the 80mg over the 20mg dose were observed in secondary endpoints including NT-proBNP and troponin biomarkers."** Section 4.5.2, page 40 The following sentence should be deleted: "However, the clinical advisors to the ERG expressed uncertainty as to whether the difference between 20mg and 80mg using these biomarkers are clinically meaningful." This expert opinion should reflect the robust evidence supporting an independent association of NT-proBNP with mortality in ATTR-CM. The prognostic	Expert opinions do not reflect the views of cardiologists or the evidence base for NT-proBNP as important and sensitive marker for prognosis in ATTR-CM.	This is not a factual inaccuracy. This is the opinion of our clinical experts and their interpretation of what is clinically relevant. No amendment has been made.

20mg dose, but that the number of patients between treatment groups may have been too small to demonstrate this." This statement seems misleading given that better efficacy in secondary endpoints was demonstrated. Furthermore, the following is stated on page 40: "However, the clinical advisors to the ERG expressed uncertainty as to whether the difference between 20mg and 80mg using these biomarkers are clinically meaningful." The Company believe that most cardiologists would consider these endpoints to be very clinically relevant, indeed the prognostic score that was proposed by the NAC is based on NTpro-BNP and eGFR alone.[5] The company notes that no cardiology clinical expert opinions are included in the ERG report. The CS (Section B.2.7.2.4) states that "the LS mean difference between the 20 mg and 80 mg doses was 1170.51 pg/mL which was statistically significant (p=0.0468), favouring the 80 mg dose group." Given the NAC prognostic model[5] suggests a >30% mortality difference between patients with NTproBNP <=3000ng/L and >3000ng/L, a	model based on >850 patients diagnosed with ATTR-CM at the NAC suggests that NT-proBNP is a sensitive prognostic marker and that changes >1000 pg/mL are likely to be highly clinically significant.		

difference of 1170.51 pg/mL between doses seems highly clinically significant.			

Issue 5 AIC marking

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.2.4, page 32 AIC highlighting	"a statistically non-significant effect for hereditary ATTR-CM patients (n=106; [redacted]) for the primary outcome (combined analysis of all-cause mortality and frequency of CV-related hospitalisations)."	Update AIC marking to reflect CS	Amended as suggested
Section 4.4.2, page 34	Figure 5 should be marked as AIC	Update AIC marking to reflect CS	Amended as suggested

Issue 6 Issues relating to the selection of the model for excess hazard

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.2.2, page 82 (b) Issues relating to the selection of the model for the excess hazard The section has failed to mention that data from the Phase II and ATTR-ACT LTE have been used to validate the extrapolated phase.	The following sentence (or similar) should be added: "Selection of the best fitting model considered the extrapolations compared to follow-up data from ATTR-ACT and Phase II extension studies."	For a balanced representation of the model selection process.	We did not mention this in the critical appraisal section because we did not have a problem with it. This aspect of the analysis is already mentioned descriptively in Section 5.2.4, page 55.
Section 5.2.2, page 82	It is unclear where this note of the selection of the most appropriate parametric model has come from, as it not mentioned in the model	Inaccurate representation of what was presented in the CS.	We have amended the text to the following:

The ERG report states: "Presenting clinical experts with fitted survival functions and asking them to indicate which, in their opinion, is the most plausible is unlikely to be of much use for the following reasons: (1) it implies that the clinical expert is able to express their opinion about the true proportion of patients surviving at each time without any uncertainty; (2) it ignores uncertainty associated with each model's parameter estimates, and the consequent uncertainty associated with the survival functions; (3) survival functions derived from distributions with very different underlying hazards may look similar to clinical experts. In practice, the question should be asked using a formal elicitation of experts' beliefs before seeing the data."	justification sections in the CS. In the CS, the only mention of clinician discussions with respect to model justification was in CS page 126 where it was '*suggested that patients would be relatively stable initially followed by a period of rapid progression.*' which reinforced the selection of a model with increasing hazard over time for BSC. This section should be deleted.		"As a general point, presenting clinical experts with fitted survival functions and asking them to indicate which, in their opinion, is the most plausible is subject to several limitations: (1) it implies that the clinical expert is able to express their opinion about the true proportion of patients surviving at each time without any uncertainty; (2) it ignores uncertainty associated with each model's parameter estimates, and the consequent uncertainty associated with the survival functions; (3) survival functions derived from distributions with very different underlying hazards may look similar to clinical experts. In practice, the question should be asked using a formal elicitation of experts' beliefs before seeing the data."

Issue 7 Description of ERG additional sensitivity analysis 1

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.2.2, page 89 The ERG report states: "The second approach would involve applying BSC outcomes to all	All assumptions behind this approach should be made explicit. The following sentence (or similar) should be added:	For a balanced representation of the most conservative scenario.	We have amended the text on page 85: "The ERG notes that neither approach is ideal: applying the

patients from the point at which they discontinue tafamidis. This is applied in ERG additional sensitivity analysis 1… The ERG notes that neither approach is ideal:….. whilst applying BSC outcomes to tafamidis discontinuers would disadvantage the tafamidis group as the treatment effect would be diluted by discontinuations which had already occurred during the trial period.”	“Furthermore, this scenario also assumes; i) upon discontinuation, tafamidis patients immediately experience the same events and accrue QALYs in the same way as BSC patients, with no transition period; ii) that the prognosis of each patient upon discontinuation is equivalent to the mixture of patients in BSC (NYHA classification mix) at each respective time of discontinuation; iii) despite the complete follow-up (no censoring) up to 30 months in ATTR-ACT, the impact of the observed discontinuation is not reflected in any capacity in the extrapolation.”		discontinuation plateau may not be externally valid if in reality the likelihood of remaining on treatment continues to decline in the longer-term, whilst applying BSC outcomes to tafamidis discontinuers would disadvantage the tafamidis group as the treatment effect would be diluted by discontinuations which had already occurred during the trial period. In addition, the latter scenario assumes that upon discontinuation, patients will immediately experience the same event risks and outcomes as BSC patients and that that transitions between NYHA states at each 6 month interval are equivalent to the mixture of patients in the BSC group.”

Issue 8 Early diagnosis benefits are attributable to tafamidis

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.3.3, page 88 The ERG report states on page 8: "However, most clinicians outside of the NAC will see no or very few cases in their entire clinical career and therefore recognition and diagnosis of amyloidosis is usually very late in the condition's trajectory and an estimated 40% of patients with wild-type ATTR-CM can wait over 4 years for a diagnosis" This contrasts with the following statements on page 88: "One of the ERG's clinical advisors also noted that diagnosis rates have already been increasing since the introduction of scintigraphy which is now becoming widely available." "One of the ERG's clinical advisors commented that there has been a dramatic increase in the awareness of ATTR-CM in recent years, particularly since the introduction of patisiran and inotersen, and therefore the introduction of tafamidis is unlikely to make a significant difference in terms of earlier diagnosis."	The company suggest including a statement on page 88 to clarify that inotersen and patisiran are not licensed for ATTR-CM therefore their introduction is unlikely to have a meaningful effect on the current delays to diagnosis of ATTR-CM.[3,4] Furthermore, to highlight the current inequity of access to nuclear scintigraphy which is not widely available outside the NAC for the indication of investigating cardiac amyloidosis. Prior to the tafamidis EAMS that commenced in Autumn 2019, only a handful of centres in the UK were using scintigraphy for this indication. The development of a diagnosis and treatment network of centres that is being led by NHS specialised commissioning in response to the availability of the 1st effective therapy for ATTR-CM (tafamidis) is likely to reduce the current delays to diagnosis significantly.	To clarify that patisiran and inotersen are not licensed in ATTR-CM. In the company's opinion it would be unreasonable to conclude that the introduction of these medicines would have any meaningful impact on the diagnosis of a condition for which they are not licensed. To reflect the current changes to clinical practice in response to the availability of tafamidis, which among other aspects, is addressing the inequity of access to scintigraphy for investigating cardiac amyloidosis which is available in just a handful of UK centres.	Amended page 8 to avoid inconsistency to: "However, prior to this most clinicians outside of the NAC would have seen very few cases in their entire clinical career and therefore recognition and diagnosis of amyloidosis was usually very late in the condition's trajectory, with an estimated 40% of patients with wild-type ATTR-CM waiting over 4 years for a diagnosis."

Patisiran and inotersen do not have a license in ATTR-CM therefore their introduction should have little impact on awareness of ATTR-CM among cardiologists who interact with ATTR-CM patients in heart failure services. Outside specialist centres participating in the tafamidis EAMS, awareness of ATTR-CM is very poor among cardiologists.			

1. Hanna M, Thibaud D, García-Pavía P, et al. Efficacy and Safety of Tafamidis Doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). 2019 Heart Failure Society of America (HFSA) 23rd Annual Scientific Meeting, September 13–16, 2019, Philadelphia, Pennsylvania, USA; 2019.
2. S. S. What Do Heart Failure Patients Really Want, and Do Doctors Get it? https://www.medscape.com/viewarticle/904440. Published 2018. Accessed2019.
3. Alynylam. Summary of product characteristics: Onpattro (patisiran). https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf. Published 2018. Accessed 21 June 2019.
4. Therapeutics. A. Summary of product characterstics: Tegsedi (inotersen). https://www.ema.europa.eu/documents/product-information/tegsedi-epar-product-information_en.pdf. Published 2018. Accessed 21 June 2019.
5. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J.* 2017;39(30):2799-2806.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Tafamidis for treating transthyretin amyloid cardiomyopathy

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background

Transthyretin amyloidosis (ATTR) is caused by abnormal transthyretin (TTR) proteins being produced by the liver and accumulating as deposits in the tissues of the body (amyloidosis). Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of transthyretin amyloidosis in which most deposits accumulate in the heart, causing the heart tissue to thicken and stiffen (restrictive cardiomyopathy), which in turn leads to an inability to pump an adequate supply of blood through the circulatory system (heart failure). There are two causes of ATTR-CM:

- Wildtype ATTR-CM is the more common form. It is not inherited, mostly affects older people, and affects more men than women.
- Hereditary ATTR-CM (also known as familial amyloid cardiomyopathy) affects people born with inherited mutations in the TTR gene. These variants are thought to be less stable than the wildtype and so are more likely to form very small amyloid fibres (fibrils).

Symptoms of ATTR-CM can include shortness of breath, palpitations and abnormal heart rhythms, most frequently atrial fibrillation or atrial flutter, ankle swelling, fatigue, fainting and chest pain. ATTR-CM is a progressive disease with symptoms usually starting after the age of 70 years in people with wildtype ATTR-CM or after the age of 60 years in people with hereditary ATTR-CM. Death in most people with ATTR-CM is from sudden death and progressive heart failure.

1.2 Treatment pathway

There are no UK treatment guidelines or approved disease-modifying treatments for ATTR-CM. Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care such as diuretics. A small proportion of people with cardiomyopathy caused by transthyretin amyloidosis also have polyneuropathy (that is, they have a mixed phenotype). Inotersen is recommended as an option for treating stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis (HST9). Patisiran is recommended as an option for treating

hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy (HST10). Liver transplantation, which prevents the formation of additional amyloid deposits by removing the main source of abnormal transthyretin production, or heart transplantation, are options for some people with ATTR-CM and a specific genetic mutation. However, this mutation is uncommon in England, and transplantation can only take place early in the course of the disease, so it is very rarely used in England.

1.3 The technology

Tafamidis (Vyndaqel, Pfizer) binds to transthyretin (TTR) in the blood. This binding stabilises the shape of TTR and prevents the formation of abnormal proteins. In turn, this then stops the formation of amyloids. Tafamidis is taken orally. In December 2019 tafamidis received a positive opinion from the committee for medicinal products for human use (CHMP) to adopt a new indication for "… the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)." It has been studied in a clinical trial for ATTR-CM (wildtype or hereditary) compared with placebo and additional safety data is being collected as part of a long-term extension study. The list price of tafamidis is [redacted] (30 x 20 mg capsules).

1.4 Clinical evidence

The company identified 20 studies for data extraction. Of those identified, 6 main clinical studies were considered, 2 of which were used to inform the company's economic model.

Studies used to inform the economic model

- ATTR-ACT (pivotal): a 30-month, phase III double-blind randomised control trial (RCT) evaluating the efficacy, safety and tolerability of tafamidis compared with placebo in adults with wild-type or hereditary ATTR-CM (n=441).
- ATTR-ACT extension study: an open-label extension of ATTR-ACT including people who completed ATTR-ACT and another cohort of people with ATTR-CM diagnosis who did not participate in ATTR-ACT (ongoing; n not reported).

Other studies in the tafamidis clinical development programme

- Phase II study: a 12-month, an open-label, multicentre, tafamidis safety and efficacy study (n=35).
- Phase II open-label extension: an open-label extension of phase II study, capturing data on the long-term safety and clinical effectiveness of tafamidis in adults with ATTR-CM (n=31).
- THAOS: a global, longitudinal observational study in people with ATTR amyloidosis, which aimed to characterise natural history (no predetermined cohort size).
- TRACS: a 2-year prospective, longitudinal, natural history study to assess the morbidity and mortality of patients with ATTR-CM (n=29).

Other relevant studies identified in the systematic literature review

Author (year)	Country	Study type and design	Population	Cohort (N)
Aus dem Siepen (2015)[2]	Germany	Observational study	Male wild-type ATTR-CM patients	25
Benson (2017)	USA	Observational study	ATTR-CM patients with moderate to severe cardiomyopathy	15
Cappelli (2018)	Not reported	Retrospective study	Patients with wild-type ATTR-CM and hereditary ATTR-CM	65 EGCG: 30 Control: 35
Davis (2015)	USA	Observational study	ATTR amyloidosis patients	10
Duca (2018)	Austria	Cohort study	ATTR-CM patients	13
Duca (2016a)	Austria	Cohort study	Wild-type ATTR-CM patients	6
Duca (2016b)	Austria	Cohort study	Wild-type ATTR-CM patients	6
Judge (2019)	Not reported	Randomised	ATTR-CM with symptomatic chronic heart failure	49 AG10 400 mg:16 AG10 800 mg: 16 Placebo: 17
Karlstedt (2019)	Canada	Retrospective study	ATTR-CM patients	47
Kristen (2012)	Germany	Observational study	ATTR-CM patients	14
Kristen (2018)	Germany	Retrospective study	ATTR-CM patients	16
Mirto (2016)	USA	Controlled trial	ATTR-CM patients	40 Treated: 30 Untreated: 10
Nelson (2013)	Denmark	Retrospective study	Patients with hereditary ATTR-CM who underwent transplant at Righospitalet, Copenhagen, Denmark.	7

Nelson (2015)	Denmark	Retrospective study	Hereditary ATTR-CM patients with L111M mutation	6
Rosenbaum (2018)	USA	Retrospective, observational study	Wild-type ATTR-CM patients	7
Rosenblum (2018)	USA	Retrospective study	Hereditary ATTR-CM and wild-type ATTR-CM patients	120 Treated: 29 Untreated: 91
Swiecicki (2013)	USA	Retrospective study	ATTR-CM patients	8
Wixner (2017)	Sweden	Prospective study	ATTR-CM patients	28

1.5 Key trial results

ATTR-ACT trial outcomes at 30 months

Results presented for pooled tafamidis doses (20 mg and 80 mg) and placebo.

Primary endpoint

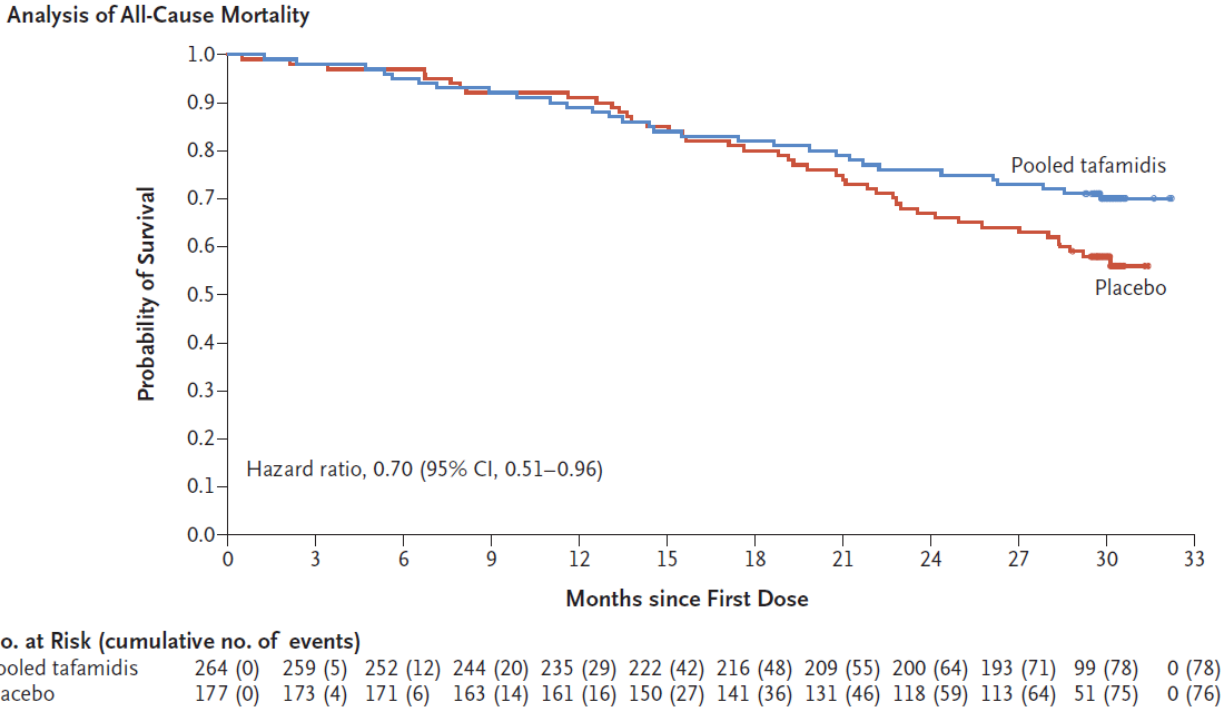
The Finkelstein-Schoenfeld test is a combined hierarchical analysis of mortality and frequency of CV-related hospitalisations. The primary endpoint counts and compares, in one combined measure, differences in all-cause mortality and the frequency of CV related hospitalisations between the tafamidis and placebo treatment groups.

	Pooled Tafamidis (N=264)	Placebo (N=177)
Finkelstein-Schoenfeld analysis		
Number of patients alive, n (%)	186 (70.5)	101 (57.1)
Average frequency of CV-related hospitalisations (per year) among those alive at Month 30	0.297	0.455
p-value	0.0006	-

Abbreviations: CI: confidence interval; CV: cardiovascular; N: total number of patients; n: number of patients; SD: standard deviation.
Source: table 18 company submission

Secondary endpoints:

Kaplan-Meier plot of all-cause mortality (ITT population)



Source: Figure 13 company submission

CV-related mortality, CV-related hospitalisations, 6MWT-6-minute walk test, Kansas City Cardiomyopathy Questionnaire Overall summary (KCCQ-OS)

	Pooled Tafamidis (N=264)	Placebo (N=177)
CV-related mortality		
CV-related events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	-
p-value	[redacted]	-
CV-related hospitalisations		
Total number of patients with CV-related hospitalisation, n (%)	138 (52.3)	107 (60.5)
Frequency of CV-related hospitalisation (95% CI)	0.48 (0.42, 0.54)	0.70 (0.62, 0.80)
Relative risk ratio (95% CI)	0.68 (0.56, 0.81)	-
p-value	<0.0001	-
6MWT		
Change from baseline to Month 30 in metres, mean (SD)	-30.5 (87.9)	-89.7 (105.2)

LS mean (SE) difference (versus placebo)	75.7 (9.2)	
p-value	<0.0001	
KCCQ-OS		
Change from baseline to Month 30 in KCCQ-OS, mean (SD)	-3.9 (19.3)	-14.6 (21.4)
LS mean (SE) difference (versus placebo)	13.65 (2.13)	
p-value	<0.0001	

Abbreviations: CI: confidence interval; CV: cardiovascular; LS: least squares; N: total number of patients; n: number of patients; SD: standard deviation

Source: adapted from tables 18, 19, 22 company submission

ATTR-ACT extension study:

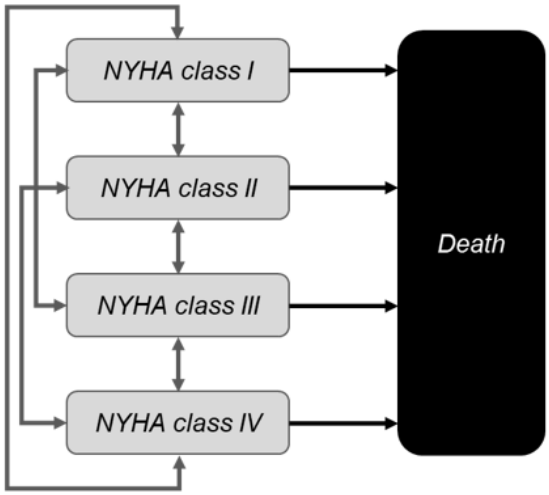
Combined all-cause mortality of ATTR-ACT and ATTR-ACT extension

Figure redacted - AIC

Source: adapted from figure 19 and table 24 company submission

1.6 Model structure

The company's economic model is a cohort-level Markov state-transition model, incorporating 5 health states: 4 based on New York Heart Association (NYHA) functional classification system (classes I-IV; see below) and death. NYHA classification system is used for staging heart failure and is based on functional limitation and symptom severity.



Perspective: NHS & PPS
Comparator: BSC
Cycle length: 1 month
Time horizon: Lifetime
Discount rate: 3.5% (costs and outcomes)
NYHA transitions
Month 6-30: ATTR-ACT 6-monthly data
Month 30+: ATTR-ACT extrapolated
Utilities: ATTR-ACT EQ-5D-3L

Source: figure 32 company submission

Class	Patient symptoms
NYHA I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
NYHA II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea.
NYHA III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
NYHA IV	Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.

People can enter the model in the NYHA health states I-III. The length of time spent in each health state is determined by:

i. 6-monthly transition probabilities

ii. monthly general population mortality risks

iii. monthly disease-related excess mortality risks, and

iv. monthly probabilities of discontinuing tafamidis.

1.7 Key model assumptions

- Patients can move from any alive health state to any other health state. Death is an absorbing state.

- Tafamidis free acid 61 mg (once a day dose) is assumed to be clinically equivalent to the pooled data for the 20 mg and 80 mg tafamidis arm from ATTR-ACT. The company justify this assumption by stating that tafamidis 80 mg is bioequivalent to tafamidis free acid 61 mg, and by through a post-hoc analysis demonstrating the clinical equivalence of 20 mg and 80 mg tafamidis.
- All patients discontinue after progression to NYHA IV. Anyone who subsequently moves to an improved health state from NYHA IV does not restart treatment.
- No drug-related costs are incurred after discontinuing tafamidis. People are assumed to not be fit enough to receive any further treatment for symptom management.
- Best supportive care (BSC) patients receiving BSC continue to receive drug treatment for the management of symptomatic heart failure until death.
- Time to tafamidis discontinuation for patients in NYHA I-III is modelled using an exponential function fitted to time-to-event data of the pooled tafamidis arm of ATTR-ACT.
- Patients are assumed to transition between the NYHA health states every 6 months. All other clinical events (discontinuation of tafamidis, CV-related hospitalisation and death) are evaluated on a monthly basis.
- Transitions to month 30 are modelled using the observed patient count data from ATTR-ACT. Beyond this point, the model applies a single treatment-specific matrix of time-independent probabilities, calculated based on the sum of all transition counts at all timepoints within the observed trial period.
- Disease-related excess mortality for people on tafamidis is modelled using a normal survival function fitted to pooled tafamidis time-to-event data from ATTR-ACT. Excess mortality risk for BSC is modelled by fitting a Weibull survival function to placebo time-to-event data from ATTR-ACT.
- Disease-related excess mortality is dependent on NYHA health state and modelled using hazard ratios (HRs) estimated from a Cox model fitted to all-cause mortality data from ATTR-ACT.
- Health-related quality of life (HRQoL) is not dependent on age.

- Disutilities associated from adverse events and CV-related hospitalisations are assumed to be captured within NYHA health state utility values.
- Adverse event costs are applied once in the first model cycle.
- Tafamidis is only prescribed when needed, therefore costs in the model are updated to reflect the relative dose intensity (RDI) of [redacted] observed in ATTR-ACT.
- No administration costs are included.

1.8 Overview of how quality-adjusted life years accrue in the model

The company's model includes health states which are defined by NYHA class (I-IV) and associated with a specific utility value depending on which treatment is received, tafamidis or BSC. The mean health state utility values were calculated using EQ-5D-3L data collected in ATTR-ACT. Therefore, a person's NYHA classification and the treatment they receive drive the accumulation of QALYs in the economic model.

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Starting and stopping rules
Issue 2 Continued treatment benefit
Issue 3 Health state utility values
Issue 4 Tafamidis effectiveness in hereditary ATTR-CM.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There is limited evidence of the clinical benefit for tafamidis compared with placebo beyond NYHA classes I/II.
- ATTR-ACT was not powered to show the clinical effectiveness of tafamidis in the subgroup of patients with hereditary ATTR-CM
- The clinically effectiveness estimates come from a pooled analysis of 20 mg and 80 mg tafamidis doses administered in ATTR-ACT. This

does not align with the 61 mg tafamidis acid free dose/formulation expected in to be used in clinical practice.

2.3 Taking these aspects into account, and including a proposed commercial arrangement for tafamidis, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) higher than what NICE normally considers an acceptable use of NHS resources (see table 1a).

2.4 The relevant benefits associated with tafamidis are adequately captured in the economic model.

2.5 It was noted that ATTR-CM disproportionally affected people with certain genes which are prevalent in people of African Caribbean family origin and in people from parts of Northern Ireland. However, it was agreed this was not something that can be addressed in the recommendations of a technology appraisal.

3. Key issues for consideration

Issue 1 – Starting and stopping and rules

Questions for engagement	1.In clinical practice, would people continue to receive tafamidis after their disease progresses to NYHA IV? 2.Is it clinically appropriate that people would not be eligible to start tafamidis if their disease is classed as NYHA III, yet they would be allowed to continue treatment if their disease worsens from NYHA II to III? 3.Would people be offered best supportive care after stopping tafamidis because of disease progression?
Background/description of issue	**The company:** In ATTR-ACT most people stopped tafamidis before their disease progressed to NYHA IV. To reflect this, and clinical expert opinion, it was assumed that all people receiving tafamidis in the model would stop treatment (tafamidis and any other therapies they were receiving) after progression to NYHA IV. Anyone who subsequently moved to an improved health state from NYHA IV did not restart treatment. After progressing to NYHA-IV no drug-related costs were incurred after tafamidis was stopped. It was also assumed that people were not fit enough to receive any further treatment for symptom management, therefore no BSC costs were incurred after tafamidis was stopped. In a subgroup analysis the company presented results where it was assumed that: • Patients were eligible to start treatment with tafamidis if they had NYHA I or II • Patients were eligible to continue treatment with tafamidis if they have NYHA I, II or III • Patients would discontinue treatment upon progression to NYHA IV. The effect of only starting tafamidis treatment in those with NYHA classes I-II improved the cost-effectiveness of tafadmis compared with BSC. **The ERG:** At clarification the company confirmed that [redacted] people in ATTR-ACT progressed to NYHA IV before treatment was observed, or not observed, to have stopped. Given the lack of alternative treatments it is unclear whether a tafamidis stopping rule on progression to NYHA-IV would be adhered to in

	clinical practice. Also, the company's model assumed that a proportion of people who have stopped treatment can transition in most model cycles from NYHA IV to improved NYHA classes (II-III). [redacted] it is unclear whether people would stop treatment on progression to NYHA IV or be eligible to restart treatment in clinical practice. It is unclear if allowing treatment with tafamidis to continue after progression to NYHA III, but not allowing treatment to start in NYHA III, is clinically appropriate or not. A clinical expert to the ERG suggested that it may be difficult to withdraw treatment if people are continuing to experience some benefit. The ERG considered it unrealistic that people who discontinue tafamidis would go on to have no treatment costs as clinical advice suggested that people would revert to BSC after tafamidis is stopped. To account for this the ERG applied BSC costs to people who discontinued tafamidis in its exploratory analyses. **Clinical expert input:** • It is presumed that the treatment benefit of tafamidis will be sustained in NYHA IV. • In clinical practice it would be challenging to define exact progression to NYHA IV. • People will be offered BSC after stopping tafamidis because of disease progression.
Why this issue is important	For estimates of cost-effectiveness to be truly reflective of clinical practice, it is essential to know which people would be eligible to receive tafamidis and in which situations it would be stopped. Therefore, clinical validation of starting and stopping rules is required.
Technical team preliminary judgement and rationale	It may be challenging to withdraw treatment with tafamidis from people after progression to NYHA IV. Some people may still be achieving a small treatment benefit and may continue treatment. Also, given that the proposed stopping rule [redacted] it is unclear whether it would be adhered to in clinical practice. Therefore, it may be reasonable to assume that a proportion of people continue receiving tafamidis after progressing to NYHA IV. The technical team would like clinical expert input to confirm that such assumptions are reasonable. It is unrealistic to assume people who discontinue tafamidis will receive no treatment at all, therefore BSC costs should be applied to those who have stopped tafamidis.

Issue 2 –Continued treatment benefit

Questions for engagement	4. 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? 5. Would the proportion of people stopping tafamidis treatment in health states NYHA I-III increase over time (as age increases)? 6. Would people in health state NYHA I-III discontinue treatment with tafamidis for any reason other than progression to NYHA IV or death?
Background/description of issue	**The company:** The company's model included a time to treatment discontinuation function which was conditional on people remaining alive. Discontinuation rates applied in the model were estimated from a survival function fitted to observed treatment discontinuation data from ATTR-ACT. This function showed that, for people still alive in health states NYHA I-III, the cumulative probability of remaining on treatment decreased at a constant rate over time. In response to clarification, the company highlighted that the tafamidis data from ATTR-ACT included people who had stopped treatment with tafamidis and therefore underestimated the treatment effect for those who remain on treatment. Therefore, the clinical effectiveness results extrapolated from ATTR-ACT reflect the combined treatment effect of both people who remained on treatment and those who stopped. Because of this, the company stated that further adjusting trial outcomes for people who have stopped treatment was not appropriate. **The ERG:** The company's treatment stopping function reduced treatment costs but had no impact on health outcomes, meaning people who stopped treatment had the same risk of clinical events and utility values as those who were still receiving treatment. Therefore, the company's model assumed treatment benefit was maintained indefinitely while reducing tafamidis costs over time as more people stopped treatment. The ERG considered these assumptions were unlikely to be reasonable and therefore the ICERs for tafamidis compared with BSC are likely to be underestimated. To address this, the ERG did exploratory analysis in which it was assumed that after month 30 the probability of stopping tafamidis in NYHA I-III was equal to zero. Therefore, people who received tafamidis treatment benefit were still on treatment and continued to incur tafamidis costs. The ERG noted that in this analysis people could still stop treatment beyond month 30, but only in line with

	progression rates to NYHA IV and death. It acknowledged that this analysis may not be externally valid if the probability of remaining on treatment naturally declined over time. As an alternative, the ERG did a sensitivity analysis in which it explored the impact of assigning people who discontinued treatment to the transition probabilities, utility values, and hospitalisations associated with BSC. The ERG acknowledged the company's concerns about this approach, noting that it would disadvantage the tafamidis treatment group as the treatment effect for those on treatment also captured the treatment effect of people who stopped tafamidis in ATTR-ACT. **Clinical expert input:** • It is unreasonable to assume that treatment benefit will be indefinitely maintained after tafamidis is stopped. • ATTR-CM affects an older population often with comorbidities, therefore, symptoms due to cardiac amyloidosis or other common causes will result in a proportion of people discontinuing tafamidis. • Because tafamidis seems to delay disease progression, but does not noticeably improve health, some people may not be committed to remaining on treatment. However, tafamidis is well tolerated and convenient to take (1 daily table) so good compliance is expected.
Why this issue is important	Assuming continued treatment benefit of tafamidis after treatment and associated costs are stopped affects the accrual of QALYs and costs in the model and drives the ICER.
Technical team preliminary judgement and rationale	Assuming continued effectiveness of tafamidid at zero cost is optimistic and underestimates the ICER. It is reasonable to assume that people in NYHA I-III health states remain on treatment until progression to NYHA IV or death.

Issue 3 – Health state utility values

Questions for engagement	7. Would people receiving tafamidis have greater quality of life benefits than those on BSC when their disease has the same NYHA classification? If yes, what clinical events outside of those captured in the NYHA do you expect tafamidis to improve more than BSC? 8. Is it clinically plausible that people who discontinue tafamidis on progression to NYHA IV would achieve greater quality of life benefit than those on BSC?

	9. Is it clinically plausible that people with ATTR-CM, receiving tafamidis or BSC would have greater quality of life than the age equivalent general population?
Background/description of issue	**The company:** EQ-5D-3L index values were estimated from HRQoL data collected in ATTR-ACT for each NYHA class (I-IV) and treatment (tafamidis or BSC) independently. The company noted that these utility data were the most appropriate for the economic analysis because it was aligned to the NICE reference case (EQ-5D-3L) and other values which had been identified in the literature. Health state utility values were not adjusted for age. The company highlighted that the utility values may reflect differences in HRQoL between tafamidis and placebo associated with different rates of hospitalisation and adverse events. However, it suggested that the differential HRQoL effect for people receiving tafamidis or placebo may not have been fully captured as EQ-5D-3L was only measured every 6-months in ATTR-ACT. Figure redacted - AIC Source: created using data from table 50 company submission **The ERG:** The company modelled substantially different on and off treatment utility values in the NYHA IV health state ([redacted] for tafmidis and [redacted] for BSC). The ERG noted that these estimates were based on very few observations (tafamidis group, n=[redacted]; placebo group, n=[redacted]). It also noted that the difference was inconsistent with the assumed stopping rule (issue 1) where everyone who progressed to the NYHA IV health state stopped treatment. Nobody in the NYHA IV health state received tafamidis

	and it was unclear whether people who discontinued tafamidis would retain a relative utility benefit over those who continued to receive BSC. The ERG highlighted that the company suggested that the majority of people discontinued treatment before entering NYHA (issue 1), however EQ-5D-3L data collection in ATTR-ACT was limited to the on-treatment period. Therefore, the utility values for tafamidis may be subject to informative censoring, that is, the measurement of EQ-5D-3L for people who had progressed to NYHA IV and discontinued treatment will not have been captured. The company did not adjust the model health state utility values to account for the effect of increasing age. The mean utility values for tafamidis and BSC were higher than that of the general population from ages 82 and 84 years onwards respectively. The ERG considered that utility values should be adjusted for age. **Clinical expert input:** • People whose disease is within the same NYHA class are not expected to achieve greater quality of life benefits on tafamidis than BSC. • It is not clinically plausible that people who discontinue tafamidis on progression to NYHA IV achieve a greater quality of life benefit than those on BSC. • People with ATTR-CM whose disease has been treated with tafamidis cannot plausibly achieve a greater quality of life than the age equivalent general population.
Why this issue is important	The estimation of treatment dependent health state utility values based on very few observations introduces uncertainty into the estimation of relative HRQoL benefits and therefore has implications on the ICERs. Furthermore, failing to adjust utility values for age can result in implausibly high utility values.
Technical team preliminary judgement and rationale	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.

Issue 4 – Tafamidis effectiveness in hereditary ATTR-CM

Questions for engagement	10. Is tafamidis equivalently effective in people with wild-type or hereditary ATTR-CM? If not, how would the treatment effectiveness of tafamidis differ between people with wild-type and hereditary ATTR-CM.

Background/description of issue	**The company:** Subgroup analyses in ATTR-ACT explored the effectiveness of tafamidis in people with either wild-type or hereditary TTR genotypes. The results of this subgroup analyses found statistically significant improvements in the primary outcome for tafamidis compared with placebo for people with wild-type genotypes. However, tafamidis did not demonstrate a statistically significant improvement for people with hereditary ATTR-CM. The company noted that patient numbers in the hereditary subgroup were too small to be powered to assess treatment effectiveness (tafamidis, n=63; placebo, n=43). **The ERG:** In ATTR-ACT, statistically significant benefits for pooled (20 mg and 80 mg) tafamidis compared with placebo were demonstrated for both CV-hospitalisation and all-cause mortality. This overall effect is driven by tafamidis treatment response in wild-type ATTR-CM, benefits reported in people with hereditary ATTR-CM were not statistically significant. Therefore, there is a lack of evidence supporting the treatment effect of tafamidis in people with hereditary ATTR-CM.
Why this issue is important	In clinical and economic evaluations, the effectiveness of an intervention is often averaged over a population of patients. However, the average clinical or cost-effectiveness can, mask important sources of variation which may be important to reflect in decision making. By 'explaining variation according to patients' characteristics it is possible to identify sub-groups of patients in whom a given intervention is both clinically and cost-effective and in those in whom it is neither. The results from ATTR-ACT suggest that the tafamidis is clinically effective compared with placebo for the whole patient population with ATTR-CM, but that the relative treatment effect was greater in people with wild-type ATTR-CM than in people with hereditary ATTR-CM, Given this, it is plausible that the cost effectiveness of tafamidis may also differ between the whole trial population, people with wild-type ATTR-CM, and people with hereditary ATTR-CM. It is therefore important for the appraisal committee to separately consider the cost effectiveness estimates for these 3 populations. The results from ATTR-ACT for people with hereditary ATTR-CM are associated with uncertainty because patient numbers in the hereditary subgroup were too small to be powered to assess treatment effectiveness. The appraisal committee will therefore need to consider whether the results from the trial for this population have biological or clinical plausibility. The appraisal committee will

	take this into account when considering the subgroup cost effectiveness analyses (see section 5.10.7 of NICE's Guide to methods of technology appraisal).
Technical team preliminary judgement and rationale	Subgroup analyses should be provided reporting ICERs for the wild-type and hereditary ATTR-CM separately. Analyses incorporating genetic testing cost should be presented. It is unclear whether the results from ATTR-ACT for people with hereditary ATTR-CM have biological or clinical plausibility. The technical team would like input from clinical experts to determine this. -

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (all NYHA classes) – including a proposed commercial arrangement for tafamidis

Alteration	Technical team rationale	ICER
Company base case	**–**	**> £30,000**
1. Inclusion of BSC costs for people who discontinue tafamidis	People who stop tafamidis will likely revert to BSC and therefore BSC costs should apply (issue 1)	> £30,000
2. NYHA I-III discontinuation probability equal to zero	The technical team agreed that assuming continued tafamidis treatment benefit at zero cost after stopping treatment was unrealistic. The ERG's analysis removing treatment discontinuation in NYHA I-III addressed this (issue 2).	> £30,000

Alteration	Technical team rationale	ICER
3. Equivalent utility values in NYHA IV	Applying on and off treatment utility values in the NYHA IV health state is inconsistent with the proposed tafamidis stopping rule where people discontinue tafamidis on progression to NYHA IV. People in NYHA IV receive the same treatment, therefore it's reasonable to assume they would achieve BSC utility values (issue 3).	> £30,000
4. Use of age-adjusted utility values	It's implausible that model utility values for people with ATTR-CM are higher than those of the general population (issue 3)	> £30,000
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	> £30,000

Table 1b: Subgroup analysis - including a proposed commercial arrangement for tafamidis

The company presented a subgroup analysis in which treatment is restricted to people who an initial NYHA class of I or II. People who progress to NYHA III can continue treatment with tafamidis, but those with an initial NYHA III are not eligible to initiate tafamidis. On progression to NYHA IV people treated with tafamidis discontinue.

Alteration	Technical team rationale	ICER
Company base case	**–**	**> £30,000**
1. Subgroup analysis • Patients are eligible to start treatment with tafamidis if they have NYHA I or II • Patients are eligible to continue treatment with tafamidis if they have NYHA I, II or III	This subgroup analysis demonstrates the effect of restricting the treatment to population of people whose disease was classed NYHA I/II.	> £30,000

Alteration	Technical team rationale	ICER
• Patients will discontinue treatment upon progression to NYHA IV.		

2. Subgroup analysis
• Subgroup from the above scenario (1)
• Technical team preferred assumptions table 1a
  ○ BSC costs for people who discontinue tafamidis in NYHA IV
  ○ NYHA I-III discontinuation probability equal to zero
  ○ Equivalent utility values in NYHA IV
  ○ Use of age-adjusted utility values
	Exploring the effect of implementing the technical teams preferred assumptions in the subgroup of people who could only initiate tafamidis if their disease was classed as NYHA I or II.	> £30,000

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Clinical effectiveness of tafamidis beyond NYHA classes I/II	There is a lack of evidence of tafamidis treatment benefit over placebo in people whose disease has progressed to NYHA III. Tafamidis benefits in the primary outcome from ATTR-ACT are not statistically significant, and there are higher rates of CV hospitalisations compared to placebo	The impact of this uncertainty on the ICER is unknown.
Clinical equivalence of tafamidis dosing regimens	The effectiveness of tafamidis is modelled using pooled data from the 20 mg and 80 mg dosing from ATTR-CM, whereas the	The clinical and cost-effectiveness results based on pooled data from the tafamidis 20 mg and 80 mg doses are likely to

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	anticipated dose/formulation of tafamidis is tafamidis free acid 61 mg once a day. The clinical and cost-effectiveness estimates produced from the model may not be reflective of the dose expected to be used in clinical practice.	underestimate those of the tafamidis free acid 61 mg dose.

Table 3: Other issues for information

Issue	Comments
Impact of ATTR-CM on families and carers	Hereditary ATTR-CM can affect multiple generations of a single family as the TTR variants are inherited as a single dominant trait.
Ongoing studies	There are a number of ongoing studies in the ATTR-CM population which could improve understanding of the condition and the treatment effectiveness and safety of tafamidis.
Innovation	The company considered that tafamidis is a breakthrough treatment for ATTR-CM. It noted that it represents a step-change in the management of the condition, and it will reduce a burden on patients and carers in any area of substantial unmet need. The technical team acknowledge that there is an unmet need for an effective treatment for ATTR-CM, but considered that the relevant benefits associated with tafamidis are adequately captured in the economic model.
Equality considerations	The most common transthyretin (TTR) variants associated with hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) are Val122I, which is prevalent in people of African Caribbean family origin, and T60A, which is prevalent in white people and endemic to parts of Northern Ireland. The technical team recognised that ATTR-CM disproportionally affected people from certain ethnic backgrounds, but agreed this was not something that can be addressed in the recommendations of a technology appraisal.

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Technical engagement response form

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **14 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement 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.

About you

Your name	**Pfizer Ltd**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Pfizer Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Starting and stopping rules	
1.In clinical practice, would people continue to receive tafamidis after their disease progresses to NYHA IV?	People with NYHA Class IV heart failure are mostly bed bound with symptoms at rest. We heard from the clinical expert on the technical engagement telephone conference that NYHA IV could be used as a stopping criterion given the absence of evidence for treatment benefit, however they also highlighted the discussion with patients regarding cessation of treatment is difficult. We also heard from patients with hereditary ATTR on the call that withdrawing treatment, albeit at end stage disease, would represent a loss of hope and may be devastating for patients. In palliative heart failure in general, medicines optimisation and rationalisation is the 1st step in a suggested treatment algorithm following the exclusion of reversible causes of end-stage heart failure.[1] Ordinarily, medicines rationalisation in palliative care would focus on symptomatic relief and stopping unnecessary medicines that do not contribute to symptomatic improvement. Given that tafamidis is such a treatment, i.e. it offers no short-term symptomatic relief but addresses the underlying disease mechanism in reducing cumulative exposure to transthyretin amyloid over time, it is felt that a stopping rule at NYHA IV could be clinically appropriate. In practice, observations from the ATTR-ACT study (without an explicit stopping rule) confirmed that patients discontinued tafamidis a median of [redacted] days after entering NYHA IV functional classification ([redacted]). This observation suggests that discontinuations in practice mirror an NYHA stopping rule which is therefore feasible in clinical practice.

2.Is it clinically appropriate that people would not be eligible to start tafamidis if their disease is classed as NYHA III, yet they would be allowed to continue treatment if their disease worsens from NYHA II to III?	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. The current average delay to diagnosis experienced by ATTR-CM patient in the UK is greater than 3 years. The introduction of the 1st treatment for ATTR-CM is expected to reduce this through greater awareness among cardiologists in heart failure services and equity of access to confirmatory diagnostic tests across England (as confirmed by the clinician on the technical engagement TC). This is expected to translate into a greater proportion of patients diagnosed at an early stage of disease (NYHA I/II) in England. Therefore, the NYHA I/II subgroup was presented in the manufacturers submission (MS) to demonstrate the additional health gains expected in the overall population once tafamidis becomes available. A trend toward a greater proportion for patient with early stage disease (NYHA I/II) has already been observed in the Early Access to Medicines Scheme (EAMS; see final issue and Appendix C for further details).
3.Would people be offered best supportive care after stopping tafamidis because of disease progression?	Clinical expert opinion discussed in the MS, suggested that patients discontinuing tafamidis would not be fit enough to receive additional therapies for symptom management. However, to reduce uncertainty the company agrees that the cost of BSC can be included following the discontinuation of tafamidis in the base-case analysis.
Issue 2: **Continued treatment benefit**	
4. 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?	ATTR-CM is a progressive disease characterised by amyloid accumulation. Ongoing benefits of tafamidis treatment after stopping would result from a reduced cumulative exposure of the heart to amyloid while receiving tafamidis. Therefore, if patients discontinued for any other reasons than death or transition to NYHA IV, treatment effect would be maintained for an unknown duration. However, the company acknowledges this would not be indefinitely. Those than discontinue in earlier NYHA stages would have disease arrested by tafamidis and would therefore have a better prognosis than patient who have been on BSC. For example, if you

	looked at any time point across the study, the mix of patient in BSC had worse NYHA stage/ prognosis than patients on tafamidis. The company acknowledges that discontinuation in the original base-case analysis may be overestimating discontinuation beyond the observed data. Therefore, the application of the NICE technical team and ERG preferred case where discontinuation is assumed to plateau reduces uncertainty related to assumptions post discontinuation beyond the observed data. New data available from the ATTR-ACT long-term extension (LTE) suggests that the plateau from 30 months is overly conservative. Treatment discontinuation Kaplan-Meier data from ATTR-ACT LTE up to [redacted] months (Appendix B; Figure 1) has been presented compared to updated extrapolation and provides an accurate estimate up to [redacted] months, therefore the plateau has been applied from [redacted] months in the updated scenario (Appendix D; Table 4). However, given that this provides an upper bound for the treatment duration, additional scenarios have also been provided (Appendix D; Table 4) where the log-normal and exponential are applied without a plateau, as these were included as a scenario and the base-case in the MS and predicted a reduction in the rate of discontinuation beyond the observed period. For completeness, updated overall survival Kaplan-Meier and parametric survival models (Appendix A; Figure 2) are also presented and included in the updated model which are aligned with the original base-case parametric model. The generalised gamma has also been presented as a more optimistic scenario (Appendix D; Table 4) and the generalised gamma for placebo has been presented aligned with a scenario included in the MS. In conclusion, the updated scenarios provide an accurate account of the longer-term data observed in ATTR-ACT and makes conservative assumptions in the extrapolated phase thereby helping to minimising uncertainty.
5. Would the proportion of people stopping tafamidis treatment in health states NYHA I-III increase over time (as age increases)?	The company does not believe that there would be a meaningful increase in discontinuation over time due to age. The latter part of the Kaplan-Meier data suggests a reduction in discontinuation in the end on the observed data, which may be more informative of long-term trends. In addition,

	within the LTE periodic observations of NYHA class were not recorded therefore, some of the events observed may have been due to progression to NYHA IV.
6. Would people in health state NYHA I-III discontinue treatment with tafamidis for any reason other than progression to NYHA IV or death?	There are limited additional reasons for patient to discontinue tafamidis such as, organ transplantation/cardiac mechanical assist device neither of which are performed in the UK, patients no longer willing to receive the drug or adverse events. However, given that tafamidis has a similar safety profile to placebo[2], these are infrequent.
Issue 3: Health state utility values	
7. Would people receiving tafamidis have greater quality of life benefits than those on BSC when their disease has the same NYHA classification? If yes, what clinical events outside of those captured in the NYHA do you expect tafamidis to improve more than BSC?	As previously stated, treatment specific utilities were applied given tafamidis was well-tolerated and has the potential to impact quality-of-life through several different mechanisms. The

	application of treatment specific utility values is reinforced by analysis of KCCQ by NYHA stage from ATTR-ACT (Appendix B; Table 1). The disease specific quality-of-life questionnaire the Kansas City Cardiomyopathy Questionnaire (KCCQ) accounts for symptoms, physical function, social limitations and quality of life scores, thereby capturing domains outside of NYHA classification. [redacted] were observed between the EQ-5D and post hoc analysis of KCCQ by NYHA stage and treatment (Appendix B; Table 1). • In NYHA I, [redacted] in KCCQ scores between treatments which [redacted] the EQ-5D. This difference was expected given that these patients will be mostly asymptomatic at this early stage of the disease. • [redacted] was observed in KCCQ between treatments [redacted], which is aligned with the difference observed in [redacted] EQ-5D by treatment and suggests the utility benefit in [redacted] may be underestimated. • Comparable differences were observed in KCCQ scores and EQ-5D values observed in [redacted]. In conclusion, given that in the more sensitive disease specific measure there were [redacted] and other difference observed in KCCQ [redacted] with the EQ-5D, the company agrees that treatment specific utility values are appropriate.
8. Is it clinically plausible that people who discontinue tafamidis on progression to NYHA IV would achieve greater quality of life benefit than those on BSC?	The company agrees with the ERG and NICE technical team recommendation where the BSC utility is applied to both arm in NYHA IV.
9. Is it clinically plausible that people with ATTR-CM, receiving tafamidis or BSC would have	The company accepts the application of age-related utilities. However, utility data in ATTR-ACT were collected for up to 30 months (2.5 years), thus reflecting the decline in age beyond the baseline age. Therefore, the company suggests that age-related utility decrements are only

greater quality of life than the age equivalent general population?	applied from month 30 onwards in the model. Details of this changed in the updated model are provided in Appendix E3.
Issue 4: Tafamidis effectiveness in hereditary ATTR-CM	
10. Is tafamidis equivalently effective in people with wild-type or hereditary ATTR-CM? If not, how would the treatment effectiveness of tafamidis differ between people with wild-type and hereditary ATTR- CM .	The ATTR-ACT study was not powered to assess the effect of subgroups on the study endpoints, therefore these analyses were exploratory and not controlled for Type 1 errors. Event rates in the subgroup of 106 patients with hereditary ATTR-CM (tafamidis n=63; placebo n=43) were insufficient for statistical power and wide confidence intervals reflect the greater uncertainty in subgroup estimates compared to wild-type which was also not powered. With that caveat, and consistent with the results observed among people with wild-type ATTR-CM, treatment effects favouring tafamidis over placebo were observed for people with hereditary ATTR-CM in CV mortality, all-cause mortality and frequency of CV-related hospitalisations. Hazards ratios from the all-cause mortality Cox-proportional hazard model for hereditary and wild-type TTR genotype participants in the pooled tafamidis group had almost equivalent point estimates of 0.690 (95% CI 0.408, 1.167) and 0.706 (95% CI 0.474, 1.052), respectively (p=[redacted] and [redacted], respectively). The treatment difference calculated using Poisson model that considers total CV-hospitalisations and total exposure across all subjects collectively and then calculates the annualised rate, shows numerical benefits in favour of tafamidis [redacted] versus [redacted]. The relative risk ratios for CV-related hospitalisation among variant and wild-type TTR genotype were [redacted] (95% CI [redacted], [redacted]) and [redacted] (95% CI [redacted], [redacted]), respectively (p=[redacted] and [redacted], respectively). Consistent and significant treatment effects favouring tafamidis in both hereditary and wild-type subgroups were also observed in key secondary endpoints such as 6MWT and KCCQ.
Additional issue: Impact of early diagnosis	

Explanation of the expected impact on costs and QALYs with early diagnosis, that will be associated with the introduction of tafamidis	Patients in the UK currently experience an average of >3 years delay from presentation with cardiac symptoms to reaching a diagnosis of ATTR-CM. During this 3-year delay many patients will progress to a more advanced disease state (NYHA class) and have significant NHS resource use including 17 hospital attendances across inpatient admissions, outpatient and emergency department visits.[3] The availability of tafamidis, the 1st treatment for ATTR-CM, will result in earlier detection of the disease through greater awareness among cardiologists in heart failure services and equity of access to confirmatory diagnostic tests across England. During the tafamidis Early Access to Medicine Scheme, 14 hospitals have established new diagnostic services for cardiac amyloidosis. These advances in the UK diagnostic landscape suggest the overall ratio of patients with NYHA I/II : NYHA III will increase over time. Early evidence for this trend has been observed in the tafamidis Early Access to Medicine Scheme where [redacted]% of patients were NYHA I/II at treatment initiation compared to 68% in ATTR-ACT. Although not directly comparable because it recorded NYHA classification at diagnosis (not treatment initiation), 75% of people diagnosed with ATTR-CM prior to the availability of tafamidis in the NAC database were in NYHA class I/II (Appendix C). The impact on the ICER of a shift to earlier diagnosis of patients in a less advanced disease state is demonstrated in the NYHA I/II subgroup analysis presented in Appendix D (for completeness ATTR-ACT LTE Kaplan-Meier data for NYHA I/II is presented in Appendix A, which are aligned with base-case parametric models). In the company submission Pfizer presented conservative estimates for the cost of the 3-year average diagnostic delay of ATTR-CM to the NHS. The NAC reported on resource use during the 3-year period of delay using an analysis of Hospital Episode Statistics (excluded primary care, occupational and physical therapy).[3] During the 3-year delay patients attended secondary care 17 times, including a median of 3 inpatient admissions. Many of these secondary care attendances will be avoidable with an early diagnosis. There are additional costs that are potentially avoidable

	with early detection of ATTR-CM including unnecessary investigations and procedures that would have been avoided with a confirmed diagnosis: • Use of implantable cardiac defibrillators that are generally not recommended in ATTR-CM and occur in [redacted] of patients in the 6 months prior to diagnosis. • Coronary angiography investigation in diagnostic work-up that would be avoided with use of the non-invasive diagnostic pathway in cardiology services. • Repetition of investigations when cycling through secondary care specialist clinics- electrocardiogram, echocardiogram, cardiac MRI and cardiac CT. Overall it is acknowledged that we can't provide hard empirical estimates, particularly for a reduction in hospital, primary care and imaging resource use during the 3-year delay to diagnosis, but the range of scenarios provided (Appendix D) demonstrate the direction and potential impact of early detection on cost effectiveness. The impact of diagnostic delay on patients can be significant. The absence of an explanation for symptoms and waiting for the results of multiple investigations creates anxiety and/ or depression. If the assumption is made that patients would report 'some problems' or 'extreme problems' on the anxiety/depression domain of the EQ-5D-3L, this would represent a 0.071 or 0.236 (up to 0.505 if no other domains are reported at level 3) reduction in utility per year. Therefore, with a reduction in diagnosis of 2.5 years, a disutility of approximately 0.1775 up to 1.2625 could be avoided (the lower of these scenarios has been provided in Appendix D). Although not all patients will experience anxiety, this scenario demonstrates the directional impact of reducing the time to diagnosis on patients' quality-of-life.

References

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Technical engagement response Appendix

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

Appendix A: EQ-5D and KCCQ by NYHA class

Table 1. ATTR-ACT KCCQ by NHYA

Health state	Mean (SE)	No. observations	95% CI
Tafamidis			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
BSC			
NYHA I	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CI: confidence interval; NYHA: New York Heart Association Classification; SE: standard error

Appendix B: ATTR-ACT [redacted] DCO

Figure 1: Treatment discontinuation – Overall population parametric survival models with Kaplan-Meier from [redacted] LTE data

Times are censored at death, heart transplant, implantation of CMAD throughout, and at first progression to NYHA class IV within ATTR-ACT follow-up (30 months). Periodic observations of NYHA class were not recorded in the LTE.

Figure 2: Overall survival parameterisations – Overall population parametric survival models with Kaplan-Meier from [redacted] LTE data

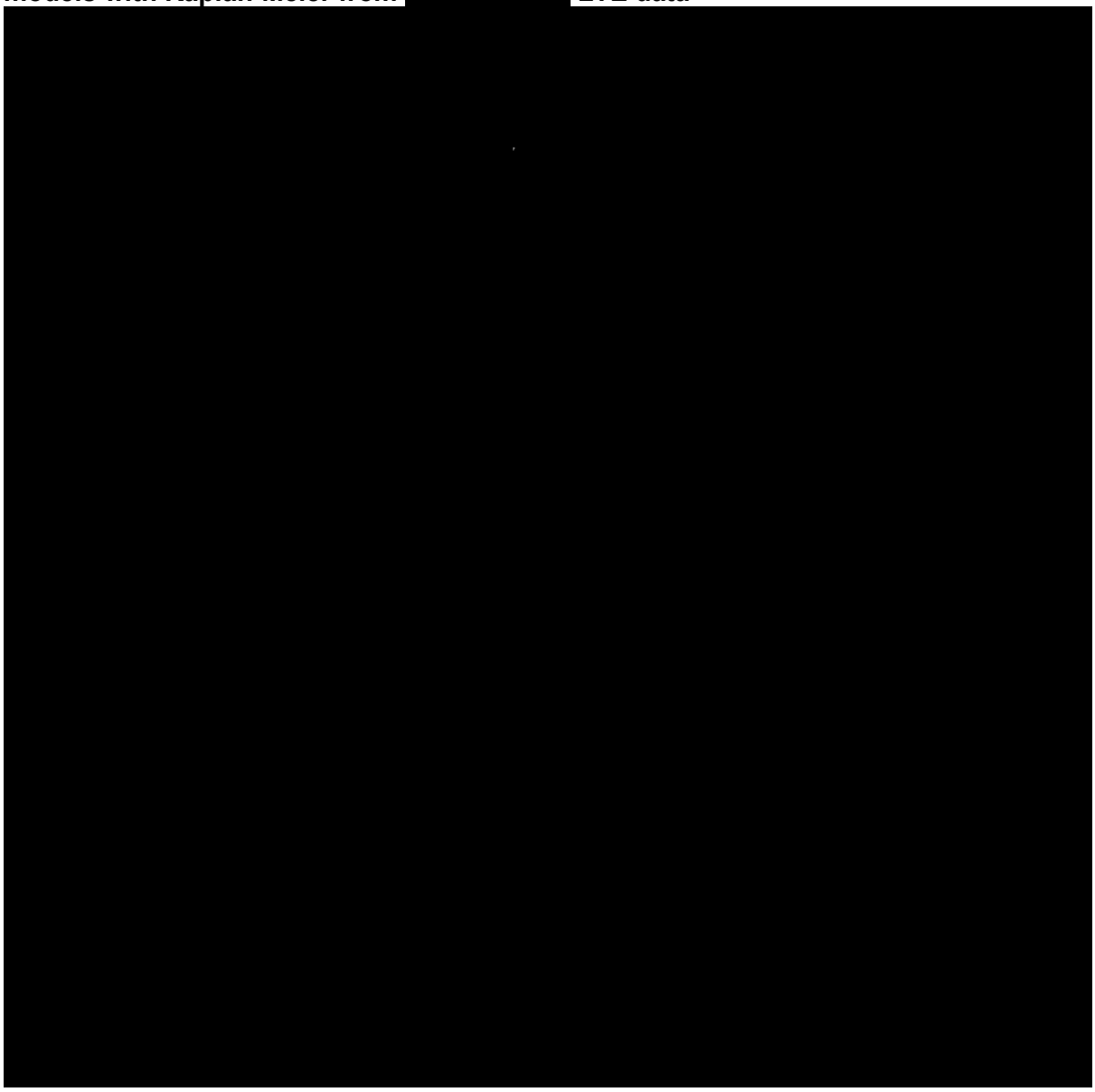
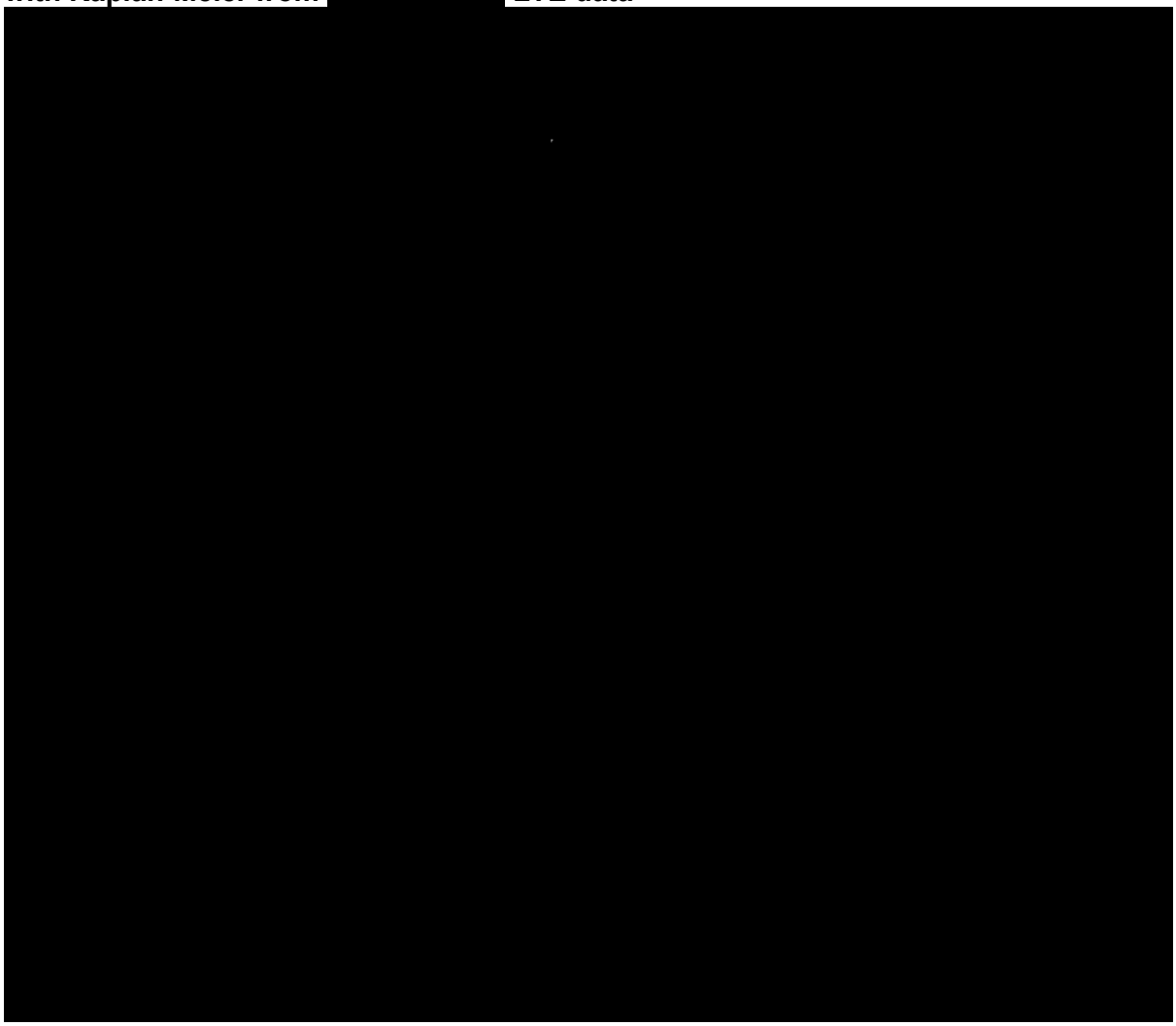


Figure 3: Treatment discontinuation – NYHA I/II parametric survival models with Kaplan-Meier from [redacted] LTE data

Times are censored at death, heart transplant, implantation of CMAD throughout, and at first progression to NYHA class IV within ATTR-ACT follow-up (30 months). Periodic observations of NYHA class were not recorded in the LTE.

Figure 4: Overall survival parameterisations – NYHA I/II parametric survival models with Kaplan-Meier from [redacted] LTE data



Appendix C: Impact of early diagnosis

Table 2. NYHA classification in UK NAC cohort, ATTR-ACT and EAMS*

	NAC cohort at diagnosis of ATTR-CM (n=869) [1]	ATTR-ACT at randomisation (n=441)[2]	EAMS at treatment initiation (n=141)
NYHA I	0	37 (8)	[redacted]
NYHA II	656 (75)	263 (60)	[redacted]
NYHA III	205 (24)	141 (32)	[redacted]
NYHA IV	8 (1)	0	[redacted]

*Given the NAC data reflects disease stage at the point of diagnosis and not treatment, the magnitude of change in earlier detection of ATTR-CM observed in the EAMS population is conservative.

Table 3. Potentially avoidable costs in the diagnostic pathway with the availability of tafamidis and continuation of the diagnostic network established through EAMS

Avoidable investigation/ procedure during 3-year diagnostic delay	Costs
Use of implantable cardiac defibrillators (ICDs) in the 6 months prior to diagnosis of ATTR-CM was observed in [redacted].[3] There is no evidence of a survival benefit or clear indication for ICD use in ATTR-CM, and ICD therapy is generally not advised.[4]	ICD £4,306 weighted average cost EY01A-B, EY02A-B, EY14A-B, EY15A-B[5] Implantation of Cardioverter Defibrillator in [redacted] ([redacted]) of ATTR-CM patients in the 6 months preceding a diagnosis in CPRD = £[redacted]
Reduction in secondary care attendance across inpatient, outpatient and emergency department where 17 attendances are recorded across an average of 3 years delay to diagnosis. Data from the NAC suggest that a third of patients are diagnosed in <6 months.[6] It is therefore feasible to reduce average delays to 6 months through implementation of the non-invasive pathway across a network of centres combined with availability of a disease modifying treatment. Given the diagnostic odyssey of most patients in ATTR-CM, much of this resource use would be avoided with early detection of disease and a corresponding management plan. Because ATTR amyloidosis often represents a unifying diagnosis for a constellation of symptoms, it can avoid patients cycling through multiple specialities.[7] Similar patterns of delayed diagnosis and lack of disease awareness were also described by patients advocates on the NICE technical engagement call.	Applying NHS reference costs[5] to the median 3 inpatient stays (£2,537) and assuming the remaining 14 consist of 12 hospital outpatient appointment (£163 first; £128 subsequent) and 2 emergency room visits (£211), the total cost over the 3 years of these resources leading up to diagnosis is approximately £9,605 per patient. The published NAC resource usage was derived from HES data and therefore excluded primary care and investigations. Therefore, examples of additional unnecessary costs could include repeated GP appointments (£37), occupational and physical therapy (£47)[8] and imaging (such as repeated echocardiograms (£189)

	and ECGs (£120), cardiac MRI (£389 per test).[5]
Independent market research conducted on behalf of Pfizer suggests that patients in the UK are seeing as many as [redacted] in the diagnostic pathway from onset of symptoms with multiple investigations (often unnecessary). [redacted] that would be unnecessary if the non-invasive diagnostic algorithm was followed in local cardiology service.[7]	Coronary angiogram £1,725 weighted average cost EY43-A to EY43-F.[5] Coronary angiogram performed in [redacted] ([redacted]) of ATTR-CM patients in Pfizer sponsored market research = £[redacted]

Appendix D: Updated cost-effectiveness results

Table 4: Updated cost-effectiveness estimates (with PAS)

#	Scenario	Description	Incr. costs	Incr. QALYs	ICER change from original base-case	Deterministic ICER
1	NICE technical team base-case	Company submitted base-case settings with NICE technical team preferred assumptions applied	[redacted]	[redacted]	-	[redacted]
2a	Treatment discontinuation	Updated [redacted] extrapolation (exponential from ERG base-case with plateau applied from [redacted] months)	[redacted]	[redacted]	[redacted]	[redacted]
2b		Updated [redacted] extrapolation (log-normal as discussed in Issue 2)	[redacted]	[redacted]	[redacted]	[redacted]
2c		Updated [redacted] extrapolation (exponential as discussed in Issue 2)	[redacted]	[redacted]	[redacted]	[redacted]
3a	Overall survival (tafamidis)	Updated [redacted] extrapolation (log-normal base-case from MS)	[redacted]	[redacted]	[redacted]	[redacted]
3b		Updated [redacted] extrapolation (generalised gamma as scenario)	[redacted]	[redacted]	[redacted]	[redacted]
4	Age adjusted utility decrements	Age adjusted utility decrements applied after 30 months	[redacted]	[redacted]	[redacted]	[redacted]
5	Overall survival (placebo)	Generalised gamma (included as scenario in MS)	[redacted]	[redacted]	[redacted]	[redacted]
6	NYHA IV stopping rule	Removing NYHA IV stopping rule	[redacted]	[redacted]	[redacted]	[redacted]
7	Early diagnosis QALY impact (reduction in age)	Patients are diagnosed 28.7 months earlier[1], start age 71.95. Does not capture impact of diagnosing with lower disease severity (included as scenario in MS)	[redacted]	[redacted]	[redacted]	[redacted]

8	Early diagnosis QALY impact (utility decrement associated with delayed diagnosis)	If the average patient reported 'some problems' and the average delay to diagnosis reduced by 2.5 years which reduced anxiety to 'no problems'; potentially utility gain of 0.1775	[redacted]	[redacted]	[redacted]	[redacted]
9	Early diagnosis cost impact	£20,000 saving on average per patient	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of updated assumptions on base-case*						
NICE technical team base-case plus updated assumptions (2c, 3b, 4, 5)			[redacted]	[redacted]	[redacted]	[redacted]
Above plus impact of early diagnosis (7, 8, 9)			[redacted]	[redacted]	[redacted]	[redacted]

*Does not capture directionally favourable impact of caregiver burden that was not possible to quantify (discussed in clarification response B26)

Table 5: Updated cost-effectiveness estimates for NYHA I/II subgroup to demonstrate impact of greater proportion of patients being diagnosed in earlier NYHA stages (with PAS)

Scenario	Incr. costs	Incr. QALYs	ICER change from original base-case	Deterministic ICER
NICE technical team base-case with NYHA I/II subgroup	[redacted]	[redacted]	[redacted]	[redacted]
Above plus updated assumptions (2c, 3b, 4, 5)	[redacted]	[redacted]	[redacted]	[redacted]
Above plus impact of early diagnosis (7, 8, 9)	[redacted]	[redacted]	[redacted]	[redacted]

Appendix E: Model amendments

Appendix E1

The following changes were applied in the updated model to adjust the treatment discontinuation plateau to reflect the additional data up to [redacted] months:

- Sheet 'Tafamidis' K36:K317 =IF(discontinue_plateau_flag=0,Params!J97,K35)updated to =IF(AND(discontinue_plateau_flag=1,B36>discontinue_plateau_months),K35, Params!J97) Note: the above example corresponds to cell K36, with equivalent formulae applied in cells K37:K317.

Appendix E2

The following changes were applied in the updated model to adjust the age-related utility decrements to reflect the duration of the observed data from ATTR-ACT:

- Sheet 'Utilities graph' F3:F33 = 1
- Sheet 'Utilities graph' F34 =C34/**$C$33** with equivalent formulae applied to F35:315

Appendix E3

The following change was applied to apply the log-normal curve for discontinuation:

- Sheet 'Params' J67:J726 =EXP(-$J$62*I67),1) updated to =IF(discontinued_logn=0,EXP(-$J$62*I67),(1-LOGNORM.DIST(I67,$J$62,$J$63,TRUE))) Note: the above example corresponds to cell J67, with equivalent formulae applied in cells J68:J726.

Appendix E4

The following changes were applied to remove the NYHA IV stopping rule and update the extrapolations:

- Sheet 'Tafamidis' M6:M665 {=IF(NYHAIV_stop=0,1,L6:L665)}
- Sheet 'Params' J62 =IF(discontinued_logn=0,IF(NYHAIV_stop=0,[redacted]),IF(NYHAIV_stop=0,[redacted]))
- Sheet 'Params' J63 =IF(discontinued_logn=0,"-",IF(NYHAIV_stop=0,[redacted]))

Appendix E5

The following change was applied to apply the tafamidis generalised gamma curve for overall survival:

- Sheet ‘Params’ G67:G726 =IF(survival_geng=0,1-LOGNORM.DIST(F67,$G$62,$G$63,TRUE),GAMMA.DIST(($G$64^(-2))*EXP($G$64*(LN($F67)-$G$62)/$G$63),$G$64^(-2),1,TRUE))

  Note: the above example corresponds to cell G67, with equivalent formulae applied in cells G68:G726.

Appendix E6

The following changes were applied to update the overall survival extrapolations for tafamidis:

- Sheet ‘Params’ G62 =IF(survival_geng=0,[redacted])
- Sheet ‘Params’ G63 =IF(survival_geng=0,[redacted])
- Sheet ‘Params’ G64 =IF(survival_geng=0,"-",[redacted])

Appendix E7

The following change was applied to apply the placebo generalised gamma curve for overall survival:

- Sheet ‘Params’ C67:C726 =IF(survival_geng_plc=0,1-WEIBULL.DIST(B67,$C$62,$C$63,TRUE),1-GAMMA.DIST(($C$64^(-2))*EXP($C$64*(LN($B67)-$C$62)/$C$63),$C$64^(-2),1,TRUE))

  Note: the above example corresponds to cell C67, with equivalent formulae applied in cells C68:C726.

Note: when the generalised gamma is applied negative values occur in the trace due to a lack of bounds checking the resulting risk after applying the risk ratio when distributing deaths between NYHA states. When this was explored, correcting the error resulted in a minimal change in the ICER in favour of tafamidis, therefore the model has not been modified for simplicity

Appendix E8

The following changes were applied to update the overall survival extrapolations for placebo:

- Sheet ‘Params’ C62 =IF(survival_geng_plc=0,[redacted])
- Sheet ‘Params’ C63 =IF(survival_geng_plc=0,[redacted])
- Sheet ‘Params’ C64 =IF(survival_geng_plc=0,"-",[redacted])

Appendix E9

The following changes were applied to include the reduction in age given earlier diagnosis:

- Lifetable survival from original model for ages 74.34 and 71.95 included on ‘Scenario Flags’ sheet
- Sheet ‘Tafamidis’ E5:E665 =IF(age_flag=0,'Scenario Flags'!R4:R664,'Scenario Flags'!S4:S664)
- Sheet ‘Model_BSC’ E5:E665 =IF(age_flag=0,'Scenario Flags'!R4:R664,'Scenario Flags'!S4:S664)
- Sheet ‘Utilties graph” B3:B315 =Tafamidis!D5

  Note: the above example corresponds to cell B3, with equivalent formulae applied in cells B4:B315
- Sheet ‘Tafamidis’ & ‘Model_BSC’ D5 =IF(age_flag=0,74.34,71.95)

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **14 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement 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.

About you

Your name	**Prof Philip Hawkins**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**National Amyloidosis Centre Royal Free Hospital and UCL**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Starting and stopping rules	
1.In clinical practice, would people continue to receive tafamidis after their disease progresses to NYHA IV?	**In practice it will be difficult to withdraw in many patients at any stage, but aim would be to inform patients that the treatment should be discontinued on progressing to NYHA IV (i.e. that the treatment had failed at this point)**
2.Is it clinically appropriate that people would not be eligible to start tafamidis if their disease is classed as NYHA III, yet they would be allowed to continue treatment if their disease worsens from NYHA II to III?	**No. Since the small RCT did not show benefit in NYHA III patients, it does not make sense to continue the treatment in patients who have progressed to this stage.**
3.Would people be offered best supportive care after stopping tafamidis because of disease progression?	**Yes**
Issue 2: Continued treatment benefit	
4. 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?	**No, there are no data to support treatment benefit being maintained indefinitely; the single RCT did not illuminate the mechanism of action, and it is entirely possible that amyloid deposition (if reduced during treatment) could rapidly catch up to the point it would have been without any treatment.**

5. Would the proportion of people stopping tafamidis treatment in health states NYHA I-III increase over time (as age increases)?	**No reason to suppose this would be the case since the treatment is simple and well tolerated.**
6. Would people in health state NYHA I-III discontinue treatment with tafamidis for any reason other than progression to NYHA IV or death?	**A high compliance and continuance of treatment is anticipated since disease progression is expected (i.e. the treatment slows but not halts this), and there will be no way of evaluating individual patients' degree of response or lack of response. There are no biomarkers identified as yet that are associated with or predict the reported clinical benefits.**
Issue 3: Health state utility values	
7. Would people receiving tafamidis have greater quality of life benefits than those on BSC when their disease has the same NYHA classification? If yes, what clinical events outside of those captured in the NYHA do you expect tafamidis to improve more than BSC?	**No. There is no reason why treatment would improve symptoms or QoL other than the reported slowing of disease progression.**
8. Is it clinically plausible that people who discontinue tafamidis on progression to NYHA IV would achieve greater quality of life benefit than those on BSC?	**No. Other than not needing to take the treatment every day / attend clinics to have it prescribed / monitored etc.**
9. Is it clinically plausible that people with ATTR-CM, receiving tafamidis or BSC would have greater quality of life than the age equivalent general population?	**No.**
Issue 4: Tafamidis effectiveness in hereditary ATTR-CM	

10. Is tafamidis equivalently effective in people with wild-type or hereditary ATTR-CM? If not, how would the treatment effectiveness of tafamidis differ between people with wild-type and hereditary ATTR-CM.	**There are insufficient data available to answer this. However, there are alternative (gene silencing) treatments available for patients with hereditary ATTR who have neuropathy. The available data suggest that the alternative gene silencing treatments are more effective than tafamidis, and hence would be preferred by many experts.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **14 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement 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.

About you

Your name	**Dr Thomas Treibel**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**On be half of the Royal College of Physicians**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Starting and stopping rules	
1.In clinical practice, would people continue to receive tafamidis after their disease progresses to NYHA IV?	**Yes, I believe that the majority of patients would continue tafamidis after their disease progresses to NYHA IV. The assumption in the economic model that ALL patients would stop tafamidis when entering NYHA IV is not realistic. I have not seen the data on futility of continuation and on cost effectiveness of continuation to make a judgement to the contrary.** **Although patients in NYHA IV were not included at study recruitment, patients would be expected to have progressed to NYHA IV during the study or its extension study. The extension study has so far shown continued treatment benefit.**
2.Is it clinically appropriate that people would not be eligible to start tafamidis if their disease is classed as NYHA III, yet they would be allowed to continue treatment if their disease worsens from NYHA II to III?	**The ATTR-ACT study (NCT01994889) suggests that patients in earlier stages of the disease (NYHA I and II) yield greater benefit of tafamidis. The higher numbers of cardiovascular hospitalisations in patients in NYHA III on tafamidis were attributed to longer survival on tafamidis. There is no suggestion not to start tafamidis in NYHA III or discontinue it if patients worsen from NYHA II to III.**
3.Would people be offered best supportive care after stopping tafamidis because of disease progression?	**All patients should be on BSC and tafamidis in the first place, and after discontinuation would continue on BSC. But in practice, BSC is very limited (to symptomatic treatment with diuretics and prevent complications of heart rhythm abnormalities).**
Issue 2: Continued treatment benefit	
4. Is it reasonable to assume that treatment	**Tafamidis stabilises, but does not remove the ATTR protein. It therefore slows down**

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?	**progression of the disease, but does not reverse the disease.** **After stopping tafamidis, accumulation of ATTR is expected to continue at its original rate, and disease progression would accelerate again (i.e. at the same rate as on BSC).**
5. Would the proportion of people stopping tafamidis treatment in health states NYHA I-III increase over time (as age increases)?	**Data from the ATTRact extension studies do not suggest this (3% discontinuation).**
6. Would people in health state NYHA I-III discontinue treatment with tafamidis for any reason other than progression to NYHA IV or death?	**Yes – a small number. In ATTRact and its extension study, patients stopped tafamidis due to treatment associated side effects. Interestingly, these side effects were the same (and even worse) in the placebo arm, and are attributable to the systemic complaints due to progressive amyloidosis rather than the drug itself. Overall, the rate of discontinuation was low. Side effects are summarised in the ATTRact study supplementary document Table S6. Furthermore, in the ATTRact extension study, the discontinuation rate was very low at 3%.**
Issue 3: Health state utility values	
7. Would people receiving tafamidis have greater quality of life benefits than those on BSC when their disease has the same NYHA classification? If yes, what clinical events outside of those captured in the NYHA do you expect tafamidis to improve more than BSC?	**Yes. Quality of life deteriorates on BSC and on tafamidis, though tafamidis slow down this decline. NYHA classes are captures are relative wide spectrum of functional capacity, therefore patients in each NYHA class can have differences in quality of life.** **ATTR-act showed that beyond NYHA class, deterioration in 6 minute walking test (functional assessment) and KCCO (quality of life) were slower on tafamidis and occurred from 6 months following first dose. In contrast, the Kaplan Meier diverge at 9 months for hospitalisation and at 18 months for mortality.**
8. Is it clinically plausible that people who discontinue tafamidis on progression to NYHA	**Patients on BSC will reach NYHA IV earlier than tafamidis patients. But once patients on tafamidis reach NYHA IV and then discontinue tafamidis, they would be expected to**

IV would achieve greater quality of life benefit than those on BSC?	**deteriorate at a similar pace as patients on BSC and likely have similar QoL (put as said before, at a later time).**
9. Is it clinically plausible that people with ATTR-CM, receiving tafamidis or BSC would have greater quality of life than the age equivalent general population?	**No. These patients have a multi-system disease that causes a wide range of symptoms and functional impairment. They will therefore have a significantly worse QoL than their peers in the general population.**
Issue 4: Tafamidis effectiveness in hereditary ATTR-CM	
10. Is tafamidis equivalently effective in people with wild-type or hereditary ATTR-CM? If not, how would the treatment effectiveness of tafamidis differ between people with wild-type and hereditary ATTR-CM.	**Tafamidis appears to be more effective in patients with wtATTR with greater effect on reduction of hospitalisation rate. Nevertheless there was a significant treatment effect in patients with hATTR with regards to symptomatic status.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531]

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- Do not use abbreviations.
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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	**DR AYESHA ALI**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS ENGLAND**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Starting and stopping rules	
1.In clinical practice, would people continue to receive tafamidis after their disease progresses to NYHA IV?	The ATTRACT trial specifically excluded patients with Type IV heart failure. Therefore even if a licence were granted to include this patient group there would be a poor quality evidence base for continued treatment.
2.Is it clinically appropriate that people would not be eligible to start tafamidis if their disease is classed as NYHA III, yet they would be allowed to continue treatment if their disease worsens from NYHA II to III?	ATTRACT's data did not show definitive clinical benefit in Class III patients and Class IV patients were excluded (as above). Given this relatively clear delineation between the NYHA I & II group and the III & IV cohorts it may be worth NICE considering evaluating the clinical and cost effectiveness of the two cohorts separately (I&II) (III&IV) as well as the entire patient group (I,II, III and IV). Tafamadis has demonstrated an impact in reducing all-cause mortality, cardiovascular related hospitalisations, reduction in decline in functional capacity, reduction in decline in quality of life etc in Class I and II patients. Therefore if a sub-group analysis were possible it may be of benefit to this group of patients. There is considerable patient interest in tafamadis as there have not been treatment options apart from best supportive care for many years. Patient groups are interested in maximising access to the treatment.
3.Would people be offered best supportive care after stopping tafamidis because of disease progression?	Yes

Issue 2: Continued treatment benefit	
4. 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?	
5. Would the proportion of people stopping tafamidis treatment in health states NYHA I-III increase over time (as age increases)?	
6. Would people in health state NYHA I-III discontinue treatment with tafamidis for any reason other than progression to NYHA IV or death?	
Issue 3: Health state utility values	
7. Would people receiving tafamidis have greater quality of life benefits than those on BSC when their disease has the same NYHA classification? If yes, what clinical events outside of those captured in the NYHA do you expect tafamidis to improve more than BSC?	
8. Is it clinically plausible that people who discontinue tafamidis on progression to NYHA	

IV would achieve greater quality of life benefit than those on BSC?	
9. Is it clinically plausible that people with ATTR-CM, receiving tafamidis or BSC would have greater quality of life than the age equivalent general population?	
Issue 4: Tafamidis effectiveness in hereditary ATTR-CM	
10. Is tafamidis equivalently effective in people with wild-type or hereditary ATTR-CM? If not, how would the treatment effectiveness of tafamidis differ between people with wild-type and hereditary ATTR-CM.	

Additional statement on the importance of early diagnosis in the treatment of transthyretin amyloid cardiomyopathy

Heart failure is a common clinical presentation that increases in prevalence with age and for which treatment options are limited. It is likely that a proportion of heart failure cases are caused by accumulation of amyloid fibrils. These accumulations can also cause other cardiovascular pathology such as rhythm and conduction abnormalities. However, cases of amyloid cardiomyopathy are often misdiagnosed. Given the relatively high mortality of the disease early diagnosis and treatment are essential to improve survival.

As clinical knowledge and understanding of the disease and the drug becomes more widespread rates of diagnosis are likely to improve. This could be augmented by awareness raising or clinical education campaigns by patient groups, specialist clinicians or the drug company. In the future there may also be clinical digital tools that use patient data to highlight those individuals that require further investigation.

From a commissioning perspective the responsibility for earlier diagnosis will lie with services that may not be directly commissioned by NHSE as it will take clinicians early in the patient journey in secondary care (and in some cases even in primary care) to consider this as a differential diagnosis and start appropriate diagnostic tests or make onward referrals to specialised centres.

Dr Ayesha Ali
Medical Advisor
Highly Specialised Services
NHS England

Tafamidis for treating transthyretin amyloid cardiomyopathy: A Single Technology Appraisal

Addendum: ERG comments on company's response to the draft NICE technical report

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Kate Ennis, Research Associate in Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Lesley Uttley, Senior Research Fellow in Systematic Reviewing, ScHARR, University of Sheffield, Sheffield, UK John W Stevens, Reader in Decision Science, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	2nd March 2020

1. Introduction

This addendum presents a brief commentary on the company's technical engagement response and presents the results of additional exploratory analyses undertaken by the ERG.

The company's technical engagement response is comprised of the following:

- A completed technical engagement response form which details the company's responses to issues raised during the technical engagement process[1]
- An additional document[2] which includes 5 appendices:
    - Appendix A: Comparisons of EQ-5D-3L and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores by New York Heart Association (NYHA) class and treatment group in ATTR-ACT.
    - Appendix B: Comparisons of Kaplan-Meier plots and parametric survival model predictions for time-to-treatment discontinuation (TTD) and overall survival (OS) in the tafamidis arm of ATTR-ACT[3] and the LTE study[4] (up to [redacted] months; data cut-off [redacted])
    - Appendix C: Comparison of NYHA classification in the UK National Amyloid Centre (NAC) cohort, ATTR-ACT and the Early Access to Medicine Scheme (EAMS), together with estimates of potentially avoidable costs in the diagnostic pathway.
    - Appendix D: Updated cost-effectiveness results
    - Appendix E: Technical details relating to the implementation of the company's new economic analyses.
- An amended version of the ERG-rebuilt model which includes functionality to implement all of the company's new analyses.

As part of their technical engagement response, the company has proposed a Patient Access Scheme (PAS). This PAS takes the form of a simple price discount of [redacted]; this discount is included in all updated analyses presented within the company's technical engagement response.

2. Summary of company's technical engagement response and ERG comments

Table 1 presents a summary of the key issues discussed in the company's technical engagement response,[1] together with brief comments from the ERG.

Table 1: Summary of company's technical engagement response (abridged) and ERG comments

Issue / question	Summary of company's response	ERG comments
Issue 1: Starting and stopping rules		
1. In clinical practice, would people continue to receive tafamidis after their disease progresses to NYHA IV?	Withdrawing treatment even at a late stage would represent a loss of hope and may be devastating for patients. A stopping rule at NYHA IV could be clinically appropriate. Discontinuations in ATTR-ACT mirror an NYHA IV stopping rule and are therefore feasible in usual practice.	One of the ERG's clinical advisors commented that it would be difficult to withdraw treatment from patients, especially if patients believe that they are still obtaining some benefit from it. Additionally, the implementation of an NYHA IV discontinuation rule will to some degree depend on the wording of the anticipated marketing authorisation for tafamidis. [redacted] Given this and the anticipated difficulties raised by clinical advisors, such a rule may be difficult for clinicians to implement, particularly as the NYHA classification is a self-reported measure.
2. Is it clinically appropriate that people would not be eligible to start tafamidis if their disease is classed as NYHA III, yet they would be allowed to continue treatment if their disease worsens from NYHA II to III?	The company agrees it would be clinically inappropriate for patients in NYHA III to be considered ineligible to start treatment, but for patients in NYHA I/II to remain on treatment upon progression to NYHA III. The introduction of tafamidis is expected to reduce delays to diagnosis, leading to a greater proportion of patients diagnosed with NYHA I/II disease.	The ERG has concerns regarding the clinical relevance of the treatment pathway implied by the NYHA I/II subgroup analysis. The ERG's concerns regarding whether a positive recommendation will reduce diagnostic delays is discussed in the final row of this table.
3. Would people be offered best supportive care (BSC) after stopping tafamidis because of disease progression?	Clinical advisors to the company suggested that patients would not be fit enough to continue additional therapies for symptom management. To reduce uncertainty, the company agrees the cost of BSC can be included following discontinuation of tafamidis.	Clinical advisors to the ERG suggested that patients would continue to receive BSC after discontinuation. The inclusion of these costs has [redacted].

Issue / question	Summary of company's response	ERG comments
Issue 2: Continued treatment benefit		
4. 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?	The company believes that post-discontinuation, the treatment effect of tafamidis would be maintained for some period of time, but acknowledges that this would not be indefinitely. The application of the NICE technical team and ERG's preferred base case, where discontinuation is assumed to plateau, reduces uncertainty related to assumptions post-discontinuation beyond the observed data. Longer-term data from the ATTR-ACT LTE (combined with ATTR-ACT) suggest a plateau in time to treatment discontinuation (TTD) at [redacted] months. One of the company's new scenario analyses includes a plateau in the risk of discontinuation from this timepoint. Additional economic analyses are also presented in which TTD is modelled using a log-normal distribution and an exponential distribution (both excluding a plateau). A generalised gamma OS model has been presented as a more optimistic scenario. The company states that the updated scenarios provide an accurate account of the longer-term data observed in ATTR-ACT and make conservative assumptions in the extrapolated phase, thereby helping to minimise uncertainty.	A key issue in this appraisal relates to the long-term tafamidis discontinuation rate and the impact of discontinuation on the treatment effects of tafamidis. The company's original model[5] assumed indefinite treatment effects (survival, cardiovascular [CV] events, transitions and health-related quality of life [HRQoL]) together with an assumption that the hazard of discontinuation will remain at a constant rate beyond the observed duration of the trial (30 months). Therefore, patients who discontinue tafamidis are assumed to continue to accrue the benefits of treatment, based on the average level of exposure to tafamidis observed in ATTR-ACT, whilst incurring no additional treatment costs. The ERG report[6] presents two scenarios (using the list price for tafamidis), both of which assume that treatment effects persist only whilst the patient remains on treatment: • ERG-preferred scenario - assumes TTD plateaus at 30 months, treatment effects apply indefinitely (ICER=[redacted] per QALY gained). • Alternative ERG sensitivity analysis 1 - assumes the discontinuation rate continues beyond the trial period, outcomes for the tafamidis arm are applied to patients remaining on treatment, outcomes for the BSC arm are applied to tafamidis discontinuers (ICER=[redacted] per QALY gained). As discussed in the ERG report,[6] the ERG-preferred scenario may not be externally valid if, in usual practice, patients have an ongoing risk of discontinuing treatment after 30 months. The ERG's alternative sensitivity analysis is limited in that it assumes that the treatment effect is immediately lost at the time at which patients discontinue tafamidis, and because it does not account for discontinuation which occurred within the observed period of the trial. Hence, neither of these scenarios is ideal.

Issue / question	Summary of company's response	ERG comments
		The ERG believes that the most appropriate analysis would involve formally adjusting for non-adherence using causal inference methods (e.g. using g-methods or IPCW). The ERG considers that the inclusion of data from the LTE study, including the revised plateau at month [redacted], may be reasonable, but notes that this introduces an inconsistency as all health outcomes except for OS in the tafamidis group are modelled using 30-month data from the trial - it is unclear whether the same treatment effects would apply despite the greater cumulative level of discontinuation observed in the LTE study. The ERG notes that the several of the company's new analyses, including their updated base case, make the same assumptions as the company's original base case, i.e. the application of indefinite treatments effect and no further treatment costs for patients after they discontinue tafamidis. The ERG believes that these analyses should be disregarded.
5. Would the proportion of people stopping tafamidis treatment in health states NYHA I-III increase over time (as age increases)?	The company does not believe that there would be a meaningful increase in discontinuation due to age. The company notes that the reduction in the rate of discontinuation in the tail of the TTD function may be informative of long-term trends.	The ERG considers it reasonable to include longer-term data from the LTE study. As noted above, several of the company's new analyses retain the company's original assumption of continued treatment effects and no further treatment costs for tafamidis discontinuers. The company's updated base case model applies an exponential distribution with no plateau; this is inconsistent with the company's statement that the rate of discontinuation is reduced at later timepoints in the LTE study.
6. Would people in health state NYHA I-III discontinue treatment with tafamidis for any reason other than progression to NYHA IV or death?	The company believes there are limited additional reasons for discontinuation. Organ transplantation and cardiac mechanical assist devices are not performed in the UK. Tafamidis has a similar safety profile to placebo.	The ERG believes that, in principle, this may support the notion of a plateau in terms of TTD (excluding those patients who progress to NYHA IV or die). There is however no evidence to inform longer-term discontinuation rates. As noted above, the key uncertainty relates to health outcomes for patients who discontinue tafamidis.

Issue / question	Summary of company's response	ERG comments
Issue 3: Health state utility values		
7. Would people receiving tafamidis have greater quality of life benefits than those on BSC when their disease has the same NYHA classification? If yes, what clinical events outside of those captured in the NYHA do you expect tafamidis to improve more than BSC?	The company presents comparisons of KCCQ scores and EQ-5D scores by NYHA stage and treatment group using data from ATTR-ACT.[3] The company believes that these support the use of treatment-specific utility values in the model.	With the exception of NYHA IV, the ERG believes it may be reasonable to apply different HRQoL estimates by NYHA class and treatment group. This is generally supported by the company's analysis of the KCCQ and EQ-5D. The ERG notes that EQ-5D data collection in ATTR-ACT ceased at the point of discontinuation of the study drug (see company's clarification response,[7] question B15), hence the estimated utilities for tafamidis reflect only those patients who had not yet discontinued. It is possible that this may exaggerate differences in HRQoL between the treatment groups within the model.
8. Is it clinically plausible that people who discontinue tafamidis on progression to NYHA IV would achieve greater quality of life benefit than those on BSC?	The company agrees that the BSC utility should be applied to both treatment groups.	The ERG believes that the utility estimate for tafamidis in NYHA IV is likely to be subject to informative censoring, as EQ-5D data collection in ATTR-ACT ceased at the point of discontinuation of the study drug. In line with the ERG's preferred analyses, the company's updated model applies the BSC utility to both treatment groups.
9. Is it clinically plausible that people with ATTR-CM, receiving tafamidis or BSC would have greater quality of life than the age equivalent general population?	The company accepts the application of age-related utilities and suggests that these should be applied after month 30.	The ERG believes that the company's approach to including age adjusted utilities after month 30 is reasonable. The decision to begin adjusting utilities by age before/at month 30 [redacted].
Issue 4: Tafamidis effectiveness in hereditary ATTR-CM		
10. Is tafamidis equivalently effective in people with wild-type or hereditary ATTR-CM? If not, how would the treatment effectiveness of tafamidis differ between people with wild-type and hereditary ATTR- CM	ATTR-ACT was not powered to assess the effect of subgroups on the study endpoints and such analyses may be subject to Type I errors. Treatment effects favouring tafamidis over placebo were observed for people with hereditary ATTR-CM in CV mortality, all-cause mortality and frequency of CV-related hospitalisations.	Whilst ATTR-ACT was not powered to assess the effect of subgroups by TTR genotype, this was a stratification factor in randomisation between subgroups and the subgroup analyses of TTR genotype were pre-specified. Subgroup analysis by TTR genotype found that the treatment effect favouring pooled tafamidis over placebo was mainly driven the significant treatment effect found in wild-type ATTR-CM patients (n=335; [redacted]) which was not found in

Issue / question	Summary of company's response	ERG comments
	HRs for the all-cause mortality Cox proportional hazards model for hereditary and wild-type TTR genotype participants in the pooled tafamidis group had very similar point estimates. Consistent and significant treatment effects favouring tafamidis in both subgroups were also observed for key secondary endpoints such as 6MWT and KCCQ.	hereditary ATTR-CM patients (n=106; [redacted]) for the primary outcome. Moreover, when outcomes were analysed separately, it was seen that this effect was driven by a significant treatment effect for CV hospitalisations in wild-type patients, but not for all-cause mortality. Given that only 24% of the ATTR-ACT population had hereditary ATTR-CM, any economic subgroup analysis would be subject to small patient numbers and may be over-reliant on non-informative priors.
Additional issue: Impact of early diagnosis		
Explanation of the expected impact on costs and QALYs with early diagnosis, that will be associated with the introduction of tafamidis	Patients with ATTR-CM currently experience an average delay from presentation with cardiac symptoms to diagnosis of >3 years. This results in a more advanced disease state at diagnosis. The availability of tafamidis will result in earlier detection through greater awareness among cardiologists in heart failure services. Data on the stage distribution of patients in the EAMS, compared with stage distributions from entry into ATTR-ACT and time of diagnosis in the NAC database suggest a shift towards earlier diagnosis. Exploratory analyses are presented using the updated model to explore the impact of: (a) cost-savings associated with achieving a diagnosis 2.5 years earlier (£20,000 per patient), (b) avoiding QALY losses associated with anxiety/depression by achieving a diagnosis 2.5 years earlier, and; (c) assuming an earlier age at diagnosis of 71.95 years.	The company's analysis relating to cost-savings are the same as those presented in the original submission (see CS,[5] Table 67, Scenario Analyses 5 and 6). As discussed in the ERG report,[6] the ERG has three concerns with these analyses: 1) The CS does not present any empirical evidence to demonstrate the claims that the introduction of tafamidis will lead to earlier diagnosis. 2) One of the ERG's clinical advisors commented that there has been a dramatic increase in the awareness of ATTR-CM in recent years, particularly since the introduction of patisiran and inotersen, and therefore the introduction of tafamidis is unlikely to make a significant difference in terms of earlier diagnosis. 3) One of the ERG's clinical advisors also noted that diagnosis rates have already been increasing since the introduction of scintigraphy which is now becoming widely available. The company's technical engagement response notes that a greater proportion of patients in the EAMS had NYHA I/II compared with ATTR-ACT ([redacted] versus 68%). However, it is unclear whether this difference is entirely a consequence of tafamidis being available through the EAMS, or whether other

Issue / question	Summary of company's response	ERG comments
		factors may have contributed to the apparent shift in stage at diagnosis, e.g. increased awareness of ATTR-CM and/or wider availability of nuclear scintigraphy. In addition, the company's subgroup analysis assumes that 100% of patients have NYHA I or II; [redacted] (this is shown later in the ERG's additional analyses, see Table 5 and Table 6). The company's technical engagement response does not provide any evidence relating to a reduction in time to diagnosis. The source of the estimate 28.7 month reduction in age at diagnosis is unclear: the CS reports the source as the Summary of Product Characteristics for patisiran,[8] whilst the technical engagement response cites Gillmore *et al*.[9] The ERG was unable to locate this value in either source. The ERG notes that the company's analysis of anxiety-/depression-related QALY losses assumes that: (a) in the absence of a positive recommendation for tafamidis, all patients with undiagnosed ATTR-CM have "some problems" in anxiety/depression, and; (b) if tafamidis received a positive recommendation, all patients with an earlier diagnosis of ATTR-CM would have "no problems" in anxiety/depression for 2.5 years following diagnosis. This assumption is not supported by evidence. The derivation of the estimated cost saving of £20,000 per patient is not clear from the company's response.

2. Company's updated economic analyses

2.1 Summary of company's model amendments

The company's technical engagement response[1] presents a number of additional analyses based on the NICE technical team's preferred assumptions,[10] which in turn were based on the ERG's preferred analysis.[6] The scenarios explored by the company are summarised in Table 2. All of the company's updated analyses include a simple PAS discount of [redacted].

Table 2: Summary of company's model amendments and updated base case analysis

Model feature	Scenarios explored by company	Company's updated base case assumption(s)
TTD	(2a) Exponential distribution applied to RCT and LTE dataset with plateau from month [redacted] (2b) Log-normal distribution applied to RCT and LTE dataset with no plateau (2c) Exponential distribution applied to RCT and LTE dataset with no plateau	Exponential distribution applied to RCT and LTE dataset with no plateau (Scenario 2c) included in updated base case
OS	(3a) Log-normal distribution fitted to OS data from RCT and LTE dataset for tafamidis group (3b) Generalised gamma distribution fitted to OS data from RCT and LTE dataset for tafamidis group (5) Generalised gamma distribution fitted to OS data from RCT dataset for BSC group	Generalised gamma OS model applied to both treatment groups (Scenarios 3b and 5 combined) included in updated base case.
Health state utilities*	(4) Age-adjusted utilities applied after 30 months	Age-adjustment from month 30 included
Stopping rule†	(6) No NYHA IV stopping rule	Not included
Early diagnosis	(7) Population start age reduced to 71.95 years (8) Avoidable health losses of 0.18 QALYs applied per patient (9) Cost-savings of £20,000 per patient	All cost-savings and avoidable health losses (Scenarios 7, 8 and 9) included in updated base case

** The utility for BSC is already applied to both groups in the NICE technical team's preferred model*
† Costs associated with BSC following discontinuation of tafamidis are already included in the NICE technical team's preferred model

2.3 Results of company's new analyses

The results of the company's new analyses using the updated version of the model for the overall population (NYHA I-III) are summarised in Table 3. The equivalent results for the NYHA I/II subgroup are presented in Table 4.

Table 3: Results of company's updated scenario analyses for the overall population, includes proposed PAS for tafamidis (adapted from company's technical engagement response, Appendix D, Table 4)

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
1. NICE technical team base-case			
2a. TTD exponential (plateau from [redacted] months)*			
2b. TTD log-normal (updated [redacted] RCT+LTE TTD dataset, no plateau)			
2c. TTD exponential (updated [redacted] RCT+LTE TTD dataset , no plateau)			
3a. Tafamidis OS log-normal (updated [redacted] RCT+LTE OS dataset)			
3b. Tafamidis OS generalised gamma (updated [redacted] RCT+LTE OS dataset)			
4. Age-adjusted utility decrements applied after 30 months			
5. BSC OS generalised gamma			
6. No NYHA IV stopping rule			
7. Early diagnosis impact: start age=71.95 years			
8. Early diagnosis impact: QALY loss=0.18			
9. Early diagnosis impact: cost-saving= £20,000 per patient			
Cumulative impact on NICE technical team base-case			
10. TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), updated tafamidis OS ([redacted] RCT+LTE OS dataset) and BSC OS generalised gamma, age-adjusted utilities from 30 months			
11. Scenario 10 plus: start age=71.95 years, QALY loss=0.18, cost-saving=£20,000 per patient			

TTD - time to discontinuation; OS - overall survival; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** The ERG was unable to replicate the company's ICER for this scenario. The values presented in the table have been generated by the ERG*

Table 4: Results of company's updated scenario analyses for the NYHA I/II subgroup, includes proposed PAS for tafamidis (adapted from company's technical engagement response, Appendix D, Table 5)

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
1. NICE technical team base-case in NYHA I/II subgroup			
Cumulative impact on NICE technical team base-case			

10. TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), updated tafamidis OS ([redacted] RCT+LTE OS dataset) and BSC OS generalised gamma, age-adjusted utilities from 30 months	[redacted]	[redacted]	[redacted]
11. Scenario 10 plus: start age=71.95 years, QALY loss=0.18, cost-saving=£20,000 per patient	[redacted]	[redacted]	[redacted]

2.4 ERG comments on company's new economic analyses

The ERG makes the following observations regarding the company's new economic analyses:

- The ERG was able to replicate all of the company's updated analyses except for Scenario 2a. The results shown in Table 3 reflect the ERG's analysis rather than the company's.
- The ERG believes that the use of updated data for TTD and OS (tafamidis only) which includes the LTE data, and the decision to age-adjust utilities after 30 months, are reasonable.
- As noted in Table 1, the company's technical engagement response acknowledges that treatment effects will not persist indefinitely after discontinuation, and the company's technical engagement response states that the new LTE data indicate a plateau in TTD at around [redacted] months. However, the company's updated base case excludes this plateau and instead assumes that the hazard of discontinuation is constant at all timepoints. The ERG considers that the results for the company's updated base case (and Scenarios 2b and 2c) should be disregarded.
- Scenario 3b (tafamidis OS modelled using generalised gamma) has been included in the company's updated base case and subgroup analyses. The company's technical engagement response describes this addition as an "optimistic scenario" – it is unclear why the company has applied this survival distribution as part of their updated base case and the company has not presented any justification to support its inclusion.
- As noted in Table 1 (Response to Additional Issue), the company has not presented any reliable evidence to inform the potential cost-savings or avoidable health losses associated with the earlier diagnosis of ATTR-CM resulting from a positive recommendation for tafamidis. The results of scenarios which include these aspects of value should be interpreted with caution.
- The costs associated with wastage were not included in the NICE draft technical report[10] and have not been included in any of the company's new analyses. The ERG believes that the costs of wastage should be included in the analyses.

3. Additional analyses undertaken by the ERG

3.1 Description of ERG's additional analyses

In light of the ERG's concerns regarding the company's new economic analyses, the ERG undertook three sets of additional analyses: each analysis is applied in the ITT population (Table 5) and the NYHA I/II subgroup (Table 6). All of these additional analyses include the PAS for tafamidis:

- Scenario ERG1: NICE technical team's preferred scenario plus:
    - Updated TTD (exponential with plateau at [redacted] months)
    - Updated OS for tafamidis (log-normal)
    - Age-adjusted utilities from month 30
    - Inclusion of drug wastage

- Scenario ERG2: ERG additional sensitivity analysis 1, i.e. outcomes (OS, transition probabilities, CV events and utilities) for tafamidis discontinuers assumed to be equal to those for the BSC group plus:
    - Updated OS for tafamidis (log-normal)
    - TTD modelled using updated exponential distribution (with no plateau)
    - Age-adjusted utilities from month 30
    - Inclusion of drug wastage
- Scenario ERG3: Same as Scenario ERG1 plus:
    - Inclusion of early diagnosis cost-savings of £20,000 per patient
    - Inclusion of QALY losses avoided
    - Start age set equal to 71.95 years.

3.2 Results of ERG's additional analyses

Table 5 presents the results of the ERG's additional analyses for the overall population. The ERG's preferred base-case with wastage included (Scenario ERG1) produces an ICER for tafamidis versus BSC of [redacted] per QALY gained. Applying BSC outcomes from the point of discontinuation and assuming no plateau in discontinuation (Scenario ERG2) [redacted] per QALY gained. The inclusion of potential cost-savings and avoidable health losses within the ERG's preferred base case analysis (Scenario ERG3) leads to an ICER of [redacted] per QALY gained. As shown in Table 6, the ICERs for the NYHA I/II subgroup [redacted]; [redacted] (Scenario ERG3) is estimated to be [redacted] per QALY gained.

Table 5: Results of ERG's additional analyses for the overall population, includes PAS for tafamidis

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
ERG1 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, plateau at [redacted] months), wastage included	[redacted]	[redacted]	[redacted]
ERG2 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), BSC outcomes upon discontinuation, wastage included	[redacted]	[redacted]	[redacted]
ERG3 – Scenario ERG1 plus early diagnosis cost-savings, health losses avoided and start age 71.95 years	[redacted]	[redacted]	[redacted]

Note – all analyses include the PAS for tafamidis, updated [redacted] extrapolation for discontinuation and overall survival, age-adjusted utilities from 30 months, BSC costs after discontinuation, BSC utilities in NYHA IV, and the NYHA stopping rule

Table 6: Results of ERG additional analyses for the NYHA I/II subgroup, includes PAS for tafamidis

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
ERG1 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, plateau at [redacted] months), wastage included	[redacted]	[redacted]	[redacted]
ERG2 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), BSC outcomes upon discontinuation, wastage included	[redacted]	[redacted]	[redacted]
ERG3 – Scenario ERG1 plus early diagnosis cost-savings, health losses avoided and start age of 71.95 years	[redacted]	[redacted]	[redacted]

Note – all analyses include the PAS for tafamidis, updated [redacted] extrapolation for discontinuation and overall survival, age-adjusted utilities from 30 months, BSC costs after discontinuation, BSC utilities in NYHA IV, and the NYHA stopping rule

4. References

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Appendix 1: Company's updated scenario analyses based on the list price for tafamidis

Table 7: Results of company's updated scenario analyses for the overall population, excludes PAS for tafamidis (generated by the ERG)

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
2. NICE technical team base-case*			
2a. TTD exponential (plateau from [redacted] months)			
2b. TTD log-normal (updated [redacted] RCT+LTE TTD dataset, no plateau)			
2c. TTD exponential (updated [redacted] RCT+LTE TTD dataset , no plateau)			
3a. Tafamidis OS log-normal (updated [redacted] RCT+LTE OS dataset)			
3b. Tafamidis OS generalised gamma (updated [redacted] RCT+LTE OS dataset)			
4. Age-adjusted utility decrements applied after 30 months			
5. BSC OS generalised gamma			
6. No NYHA IV stopping rule			
7. Early diagnosis impact: Start age=71.95 years			
8. Early diagnosis impact: QALY loss=0.18			
9. Early diagnosis impact: saving= £20,000 per patient			
Cumulative impact on NICE technical team base-case			
10. TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), updated tafamidis OS ([redacted] RCT+LTE OS dataset) and BSC OS generalised gamma, age-adjusted utilities from 30 months			
11. Scenario 10 plus: start age 71.95 years, QALY loss=0.18, saving=£20,000 per patient			

Table 8: Results of company's updated scenario analyses for the NYHA I/II subgroup, excludes PAS for tafamidis (generated by the ERG)

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
1. NICE Technical Team base-case in NYHA I/II subgroup			
Cumulative impact on NICE technical team base-case			
10. TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), updated tafamidis OS ([redacted] RCT+LTE OS dataset) and BSC OS generalised gamma, age-adjusted utilities from 30 months			

11. Scenario 10 plus: start age 71.95 years, QALY loss=0.18, saving=£20,000 per patient	[redacted]	[redacted]	[redacted]

Appendix 2: ERG additional analyses based on the list price for tafamidis

Table 9: Results of ERG's additional analyses for the overall population, excludes PAS for tafamidis

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
ERG1 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, plateau at [redacted] months), wastage included,	[redacted]	[redacted]	[redacted]
ERG2 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), BSC outcomes upon discontinuation, wastage included,	[redacted]	[redacted]	[redacted]
ERG3 – Scenario ERG1 plus early diagnosis cost-savings, health losses avoided and start age of 71.95 years	[redacted]	[redacted]	[redacted]

Note – all analyses include updated [redacted] extrapolation for discontinuation and overall survival, age-adjusted utilities from 30 months, BSC costs after discontinuation, BSC utilities in NYHA IV, and the NYHA stopping rule

Table 10: Results of ERG additional analyses for the NYHA I/II subgroup, excludes PAS for tafamidis

Scenario	Inc. QALYs	Inc. costs	Deterministic ICER
ERG1 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, plateau at [redacted] months), wastage included	[redacted]	[redacted]	[redacted]
ERG2 - TTD exponential (updated [redacted] RCT+LTE TTD dataset, no plateau), BSC outcomes upon discontinuation, wastage included	[redacted]	[redacted]	[redacted]
ERG3 – Scenario ERG1 plus early diagnosis cost-savings, health losses avoided and start age of 71.95 years	[redacted]	[redacted]	[redacted]

Note – all analyses include updated [redacted] extrapolation for discontinuation and overall survival, age-adjusted utilities from 30 months, BSC costs after discontinuation, BSC utilities in NYHA IV, and the NYHA stopping rule

Impact of tafamidis on early diagnosis of ATTR-CM

Patients in the UK currently experience >3 years average delay from presentation with cardiac symptoms to a diagnosis of ATTR-CM. This delay is occurring despite the introduction of routine nuclear scintigraphy at the NAC in 2012.

During this 3-year delay, patients have significant NHS resource use including 17 hospital attendances (inpatient admissions, outpatient and emergency department), and many will progress to an advanced disease state (NYHA class III/IV).[1] During these attendances, patients will undergo unnecessary investigations (eg, coronary angiograms) and procedures (implantation of cardiac defibrillators) that would be avoided with a diagnosis of ATTR-CM.

Phase I: The impact of tafamidis on early diagnosis of ATTR-CM in EAMS

The availability of tafamidis in EAMS meant that ATTR-CM was no longer an academic diagnosis. For the first time, cardiologists at 17 UK EAMS centres were actively looking for patients with suspected ATTR-CM and confirming the diagnosis locally. Evidence from the NHS suggests a significant shift to earlier diagnosis of patients in a less advanced disease state during EAMS (Table 1). Furthermore, we observed very short delays to diagnosis of some patients in EAMS (Figure 1). Delays are clearly differentiated between those with heart failure diagnosed pre-EAMS (long delays), and those newly presenting with heart failure during EAMS, where an ATTR-CM diagnosis was made quickly. The former group with longer delays would be expected to diminish over time.

Table 1. Comparison of disease states in UK practice, the ATTR-ACT study and EAMS

	NAC patients at diagnosis (n=869) [2]	**ATTR-ACT at randomisation (n=441)[3]**	[redacted]
NYHA I & II (early)	75%	68%	[redacted]
NYHA III (advanced)	24%	32%	[redacted]

Figure 1: redacted - AIC

Phase 2: Early diagnosis will be accelerated further post EAMS

[redacted]

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