For Public – CON information redacted

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

Technology appraisal committee C [06 Feb 2024]

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Technical team: Emma Bajela, Lizzie Walker, Linda Landells

Company: Pfizer

Tafamidis for treating transthyretin amyloid cardiomyopathy

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Appraisal history

- **TA696, published May 2021:**
  - **Tafamidis is not recommended, within its marketing authorisation, for treating wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults.**
  - Cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources
  - Not enough evidence that recommending tafamidis would reduce diagnosis delays and uncertainty about how long the treatment works after it is stopped
- **Pfizer initiated a review and submitted:**
  - Updated data from their long-term extension study (ATTR-ACT LTE)
  - Revised PAS
  - Stated that would accept committee's assumptions from TA696

Abbreviations: PAS, Patient access scheme

Background on transthyretin amyloidosis with cardiomyopathy (ATTR-CM)

Causes

- Abnormal transthyretin protein produced in the liver → accumulates as amyloid deposits in the heart tissue → tissue thickens and stiffens → unable to pump blood efficiently

Epidemiology

- ~800 people with ATTR-CM in UK. Underdiagnosis means true prevalence is unknown

Diagnosis and classification

- **Wild type** – TTR protein becomes unstable with age-related breakdown in homeostatic mechanisms. Onset usually after 70 years
- **Hereditary** – Inherited mutations in *TTR* gene. Most common are Val122Ile and T60A. Val122Ile variant mostly associated with isolated cardiomyopathy without polyneuropathy. Onset usually after 60 years

Symptoms and prognosis

- Shortness of breath, palpitations and arrythmias, ankle swelling, fatigue and chest pain. Median survival is around 2 to 4 years (differs by type)

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy

Equality considerations

From scoping consultation and patient and professional group submissions:

- ATTR-CM disproportionally affects people with certain variants (such as Val122Ile) which are prevalent in people of African Caribbean and Hispanic family origin
    - Population often diagnosed later and has worse outcomes than other ATTR-CM patients
- Val122Ile is not associated with polyneuropathy so people with this variant do not have access to disease-modifying therapy
- Prescribing tafamidis might be restricted to specialist centres. Need to develop an integrated clinical care network that provides acceptable local access so patients can choose where they are offered treatment. Particularly important as people diagnosed with wtATTR are often over 80 years.

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy

Patient perspectives

People with ATTR-CM experience substantial physical, psychological and financial burden

Submission from UK ATTR Amyloidosis Patients Association (UKATPA), Cardiomyopathy UK and 1 patient expert:

- Progressive, debilitating, and fatal condition that significantly shortens the life of patients
- Burden of the disease on patients is substantial. It includes severely reduced exercise capacity, fatigue, breathlessness, pain and loss of independent leading to increasing reliance on caregivers
- Tafamidis would be first treatment available for ATTR-CM in the UK. Positive recommendation is likely to increase the recognition of the condition among the clinical community and lead to increased diagnosis
- Since NICE's last review of tafamidis, NHS has implemented significant improvements in the infrastructure, processes, training and understanding needed to identify ATTR-CM

"I would say that the grinding daily fatigue is the hardest of all the symptoms to cope with as it takes away much of the enjoyment of life"
Cardiomyopathy UK 2022 survey

"I'm existing, not living I've lost much of my mobility and have to rely on a walking stick, can't walk more than about 3 feet without having to stop due to the pain and breathlessness and sheer exhaustion, … I barely leave the house anymore except for appointments mainly. I want a life back."
Cardiomyopathy UK 2022 survey

NICE Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy

Clinical perspectives

Currently no disease-modifying treatments for most people with ATTR-CM

Submissions from British Society for Heart Failure, British Cardiovascular Society, Royal College of Physicians and 2 clinical experts:

- ATTR-CM is a progressive condition associated with a very poor quality of life, and recurrent hospital admissions for heart failure
- Many ATTR-CM patients are now diagnosed at an earlier stage and would not have been in tafamidis trial, but likely that progression of their disease could be similarly delayed
- NHS England does not offer disease modifying therapy. Around 89% of people with ATTR-CM do not have a polyneuropathy so are not eligible for vutrisiran, patisiran or inotersen
- Tafamidis trial results and real-world evidence indicate a marked slowing of deterioration in quality of life for patients and reduces cardiovascular admissions in ATTR-CM
- Tafamidis is an oral medication with no major side effects and has excellent patient acceptability

ATTR-CM is associated with a relentlessly progressive fall in quality of life – with a higher rate of reduction than other forms of heart failure. Tafamidis resulted in a significantly slower decline in quality of life for treated patients in the ATTRACT trial

British Society for Heart Failure submission

Reduction in mortality in elderly patients with advanced disease is remarkable, but the slowing of disease progression is even more impressive and likely to be of most relevance to patients and families

Clinical expert

NICE

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy

Technology (Vyndaquel, Pfizer)

Marketing authorisation	• Tafamidis is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). • GB marketing authorisation granted in January 2021
Mechanism of action	• Tafamidis is a transthyretin stabiliser which inhibits amyloid formation, thereby delaying the development of nerve and cardiac muscle damage caused by transthyretin amyloidosis.
Administration	• Tafamidis is administered orally. The dose is 61 mg once a day.
Price	• The list price per pack is £10,685 • The list price for 12 months of treatment is £128,220 • Confidential simple discount patient access scheme available

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy, BSC; best supportive care

Key issues for discussion

Overview of EAG's key issues

Issue	Resolved?	ICER impact
Extrapolation of tafamidis OS data	No – for discussion	Large
Utility values in some health states higher than the UK general population age-matched average	No – for discussion	Large
Continuation of the tafamidis treatment effect in patients who discontinued treatment	No – for discussion	Large
Unclear if decision problem should include people with mixed phenotype ATTR-CM	No – for discussion	Unknown

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy, OS; Overall survival, NYHA; New York heart association

Other issues for consideration

Overview of EAG's key issues

Issue	Resolved?	ICER impact
Not using treatment-independent utility values for the NYHA 4 health state.	No – for discussion	Small 
No comparative clinical effectiveness data in the company submission	No – in back-up slides	Unknown 
No updated SLR for economic evaluations, resources/costs, or utilities	No – in EAG report	Unknown 
Appropriateness of diflunisal as a comparator	No – in back-up slides	Unknown 

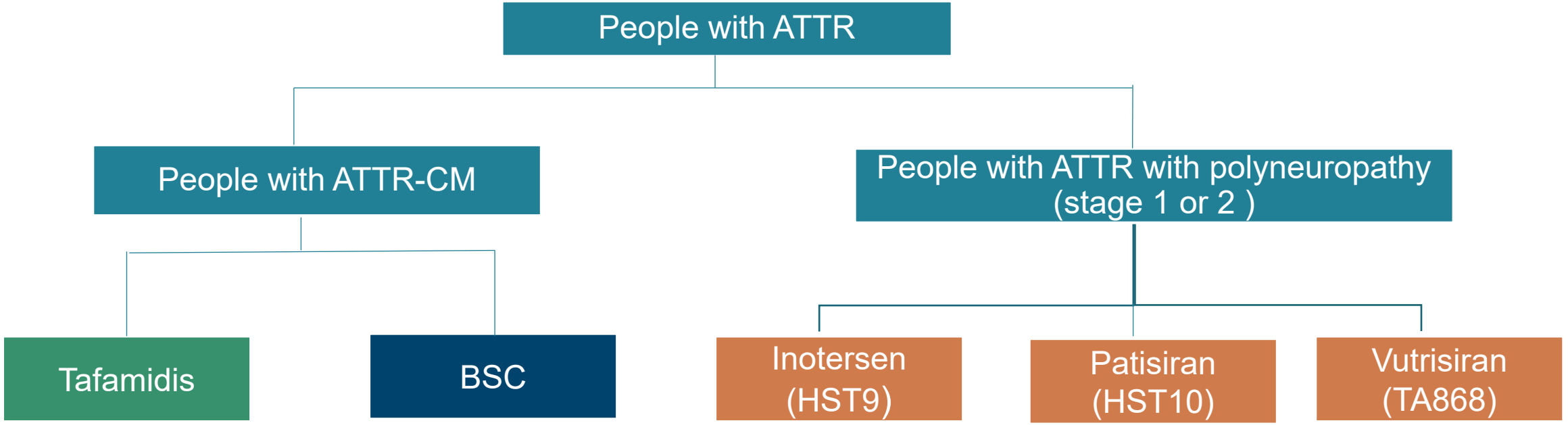
Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy, OS; Overall survival, NYHA; New York heart association

Treatment pathway

Currently no disease-modifying treatments for ATTR-CM

- No UK treatment guidelines or approved disease-modifying treatments for ATTR-CM
- Company positioning tafamidis as an alternative to best supportive care (established clinical management without tafamidis)
  - Current treatment options mainly focus on symptom management such as diuretics
- Some people with hereditary ATTR-CM also have polyneuropathy (mixed phenotype)

Figure: Treatment options for people with ATTR-CM



Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy, BSC; best supportive care

Key issue: Population and relevant comparators

Company excluded patisiran, inotersen and vutrisiran as comparators

Background

- Patisiran, inotersen and vutrisiran in scope as treatment options for mixed phenotype ATTR, but company did not present comparisons for these.
- In TA696, not considered comparators

Company

- Lack of evidence for patisiran, inotersen and vutrisiran and not licensed for ATTR-CM
- UK clinicians indicate that mixed phenotype patients subdivided by "predominant" symptoms
  - If polyneuropathy predominant, would be treated with ATTR-PN drugs (e.g. patisiran, inotersen, vutrisiran)
  - If cardiomyopathy predominant, would be treated with tafamidis
- List prices for patisiran, inotersen and vutrisiran higher than tafamidis

EAG comments

- Feasible that the excluded comparators are currently used in clinical practice for patients in this mixed phenotype subgroup, who might be eligible for tafamidis
- Proposed that decision problem could be limited to only include people without mixed phenotype ATTR-CM

Are patisiran, inotersen and vutrisiran relevant comparators for those with mixed polyneuropathy and cardiomyopathy? Should decision problem exclude people with mixed phenotype ATTR-CM?

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy, RCT; randomised controlled trial

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy

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Key clinical trials

Summary of key trial characteristics

	ATTR-ACT (30 months)	ATTR-ACT LTE (60 months)
Design	Phase III, multicentre, international, double-blind, randomised placebo-controlled trial	Phase III, multicentre, long-term extension study of ATTR-ACT
Population	Adults aged 18 and 90 years of age with ATTR-CM (wild-type or hereditary)	ATTR-ACT participants who completed 30 months; adults diagnosed with ATTR-CM who did not participate in ATTR-ACT
Intervention	Tafamidis	Tafamidis
Comparator(s)	Placebo	N/A
Duration	30 months	60 months
Primary outcome	All-cause mortality, CV related hospitalisation	All-cause mortality, TEAEs
Key secondary outcomes	All-cause mortality, CV mortality, AEs, HRQoL, NYHA classification	All-cause mortality
Locations	Conducted at 48 sites worldwide (including 2 UK sites)	ATTR-ACT sites and additional sites worldwide.
Used in model?	Yes	Yes

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Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy, CV; Cardiovascular, TEAE; treatment emergent adverse event, AE; adverse event, HRQoL; health related quality of life

Key new clinical effectiveness evidence

Company presented longer-term data from ATTR-ACT LTE for tafamidis (84 months follow-up), but no new comparative data is available

Company presented longer-term data from ATTR-ACT LTE (84 months follow-up) for:

- Overall survival with tafamidis (**Figure 1**)
- Time to treatment discontinuation with tafamidis (**Figure 2**)
- Treatment benefit in NYHA class I to III
- AEs
- No new SLRs

Fig.1: Kaplan-Meier plot of OS – tafamidis

Fig. 2: Proportion not discontinued – tafamidis

80mg tafamidis meglumine in ATTR-ACT to tafamidis free acid 61mg in ATTR-ACT LTE (August 2021 data cut)

AE, adverse event; NYHA, New York heart association classification; OS, overall survival; SLR, systematic literature review

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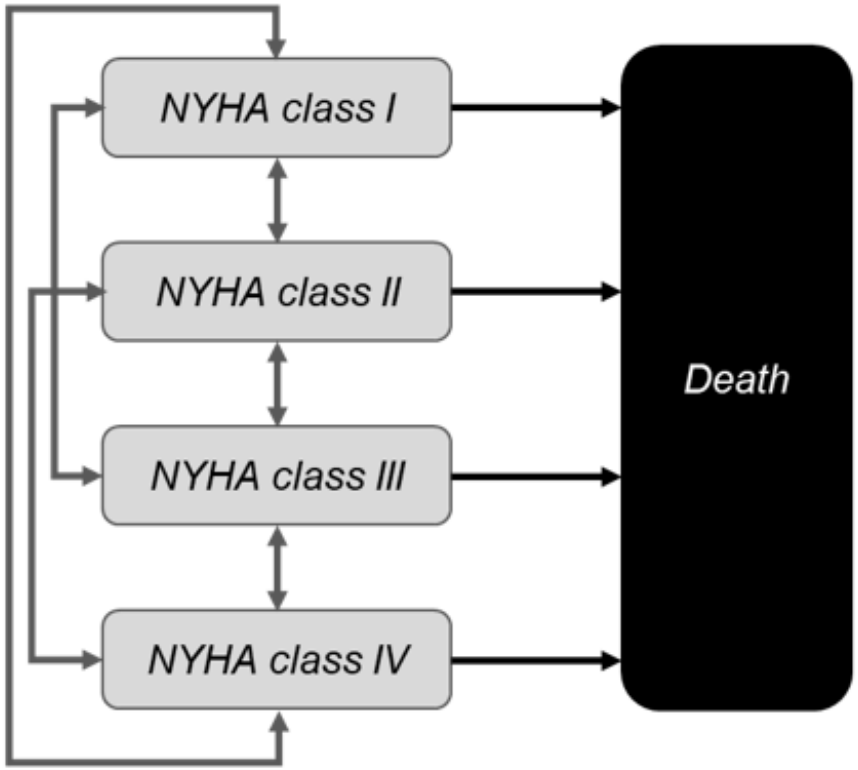
Company's model overview

Recap on model structure and committee's preferred assumptions from TA696

Figure: Model structure



Model diagram: Markov state-transition model was developed. Model health states were based on NYHA functional class

Technology affects costs by:

- Higher treatment costs for tafamidis

Technology affects QALYs by:

- Reduction of limitations in physical activity for tafamidis
- Increased OS for tafamidis

Assumptions with greatest ICER effect:

- Discount rates of costs and QALYs
- NYHA class health state utilities
- Cardiovascular (CV)-related hospitalisation event rates.

Preferred assumptions from TA696:

- Continuation of treatment in NYHA 4
- Treatment independent utilities in NYHA 4
- Age-adjusted utility decrements after month 30
- Included drug wastage costs
- Removal of early diagnosis assumptions
- Log-normal curve to model tafamidis OS

Abbreviations: QALY; Quality adjusted life year ICER; Incremental cost effectiveness ratio, OS; Overall survival, NYHA; New York heart association classification, CV; cardiovascular

Key issue: Extrapolation of tafamidis overall survival

Company used generalised gamma curve to extrapolate tafamidis OS

Background

- In TA696, committee preferred log-normal curve for extrapolation of tafamidis OS
- Company used the generalised gamma curve for extrapolation of tafamidis OS

Company

- Incorporated updated ATTR-ACT LTE data with 84-month follow-up. Generalised gamma selected as:
  - Showed most rapid reduction in excess hazard, matches the gradient of the observed hazard during the 3rd year
  - Lowest AIC of candidate parametric models
  - Agrees with non-parametric hazard profile (see **all-cause hazard predictions** figure)

EAG comments

- Unable to validate the extrapolated tafamidis OS beyond the observed trial data, as no long-term external data was provided by the company
- Generalised gamma curved gives highest tafamidis OS estimates of candidate parametric survival curves
- Not sufficient argument from company to support use of generalised gamma
- Using log-normal for the modelling of tafamidis OS resulted in an increased ICER

The company says use generalised gamma, EAG says use lognormal – which extrapolation is more plausible?

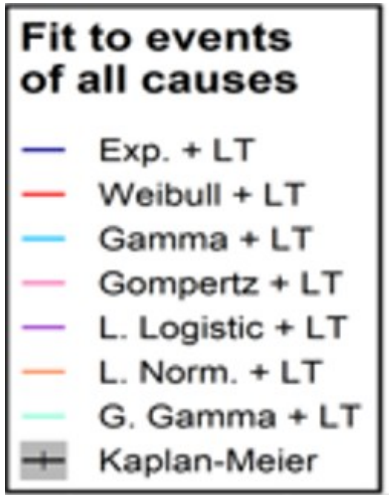
Abbreviations: ICER, incremental cost effectiveness ratio; OS, overall survival

Key issue: Extrapolation of tafamidis overall survival (2/3)

Company used generalised gamma curve to extrapolate tafamidis OS, EAG preferred log normal

Figure: Possible parametric survival models of OS for tafamidis

[redacted]



EAG, Evidence assessment group; CMAD, Cardiac mechanical assist device; HT, Heart transplant; LT, Life table; OS, Overall survival

Key issue: Extrapolation of tafamidis overall survival (3/3)

Log-logistic, lognormal or generalised gamma predict a local peak hazard

Figure: All-cause hazard predictions for parametric survival models of OS for tafamidis

Company

- Non-parametric hazard profiles show peak at ~2 years, followed by absolute decline towards a rising general population hazard
- Only log-logistic, lognormal or gen. gamma predict a local peak hazard

EAG, Evidence assessment group; CMAD, Cardiac mechanical assist device; HT, Heart transplant; LT, Life table; OS, Overall survival

Key issue: Higher utility values than UK general population

Company utility values for NYHA 1 and tafamidis arm of NYHA2 are higher than UK general population age-matched average

Table: Utility values for tafamidis and BSC arms for each NYHA health state

NYHA class	Utility value	
	Tafamidis	BSC
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]

UK general population age-matched average = (0.779)
Baseline age in model= 74.34 years

Company

- People in NHYA 1 are typically asymptomatic and have no limitation of physical activity. Patients in NYHA 2 only suffer from slight limitations of physical activity
- General population in this age group may have other multi-morbidities

EAG comments

- Lacks face validity as highlighted by clinical experts in TA696 technical engagement and seems to overestimate the effect of both treatment and comparator
- The EAG base-case included a cap for all the values higher than the utility value from the UK general population age-matched average

Is the company assumption of higher utility values than age-matched general population plausible for: people with NYHA 1? people with NYHA 2 receiving tafamidis?

Abbreviations: ICER; Incremental cost effectiveness ratio BSC; best supportive care, NYHA; New York heart association classification, HRQoL; health related quality of life

Key issue: Treatment effect in treatment discontinuers

Company assumed continued tafamidis treatment effect in patients who discontinued

Background

- In TA696, committee concluded that assuming continued treatment benefits without a cost was overly optimistic and EAG's analyses are suitable for consideration

	Observed trial period	Extrapolated period
Company and EAG base case	Treatment discontinuation from trial	• Exponential used to extrapolate tafamidis TTD curve • **Treatment effect:** ATTRACT-LTE data assumed to include discontinuers • **Treatment costs:** applied to those on treatment only
EAG scenario 1	Treatment discontinuation from trial	• No further treatment discontinuation • **Treatment effect and costs:** applied across extrapolated period
EAG scenario 2	Treatment discontinuation from trial	• Exponential used to extrapolate tafamidis TTD curve • **Treatment effect:** BSC outcomes applied to discontinuers • **Treatment costs:** applied to those on treatment only

Is the assumption of sustained treatment benefit after discontinuation reasonable? Has any new evidence been provided to change committee's preference from ACM1?

BSC; best supportive care, ICER, incremental cost effectiveness ratio; NYHA, New York heart association classification

Key issue: Treatment independent utility values for NYHA 4 health state

Company used treatment dependent utilities for NYHA 4 despite committee preference in TA696

Background

- In TA696, committee concluded that BSC utility values should be applied for NYHA 4 health state because:
  - Substantial difference in utility values between arms in NYHA 4, while utility values for tafamidis and BSC in the other NYHA classes were similar.
  - NYHA 4 utility values were also based on a low number of observations

Company

- Applied treatment-specific utility data from ATTR-ACT for NYHA 4 as considered plausible that those in NYHA 4 would have higher utility than those on BSC

EAG comments

- Preferred using BSC utility values for the tafamidis arm (both in treatment and after treatment discontinuation) in the NYHA 4 health state.
- Applying treatment independent utility values in NYHA class 4 increased the ICER.

Company says use treatment independent utilities for NYHA 4, EAG prefers BSC utility values - which approach is more plausible?

Abbreviations: ICER; Incremental cost effectiveness ratio BSC; best supportive care, NYHA; New York heart association classification, HRQoL; health related quality of life

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
OS extrapolation for tafamidis	Uses generalised gamma	Uses log-normal
Health state utilities	Utility values higher than the general population age-matched average for NYHA class 1 and tafamidis arm of NYHA 2	Uses capped utility values for above general population utility values
Treatment discontinuation	Assumes indefinite tafamidis treatment effect after discontinuation	Assumes indefinite tafamidis treatment effect after discontinuation Includes 2 modelled scenario analyses 1) no discontinuation after observed trial period and treatment effect and costs are indefinitely applied 2) BSC outcomes after discontinuation
Treatment-effect on health state utilities	Assumed to be treatment specific for all NYHA health states	Assumed BSC utility values both in treatment and after treatment discontinuation) in the NYHA 4 health state.

Abbreviations: OS; Overall survival NYHA; New York Hear Association Classification

Company base case results

Company's probabilistic base-case ICER is slightly above the range normally considered cost effective

Deterministic incremental base case results

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

Probabilistic incremental base case results

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

Abbreviations: QALY; Quality adjusted life year ICER; Incremental cost effectiveness ratio BSC; best supportive care

EAG base case results

EAG's probabilistic and deterministic base-case ICERs are above the range normally considered cost effective

Deterministic incremental base case results

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

Probabilistic incremental base case results

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

Abbreviations: QALY; Quality adjusted life year ICER; Incremental cost effectiveness ratio BSC; best supportive care, NHB; net health benefit, PSA; probabilistic sensitivity analysis

EAG deterministic scenario analyses applied to company base case

No.	Scenario (applied to company base case)	Incremental costs (£) versus Tafamidis	Incremental QALYs versus Tafamidis	ICER (£/QALY) versus Tafamidis
1	**Company base case**	[redacted]	[redacted]	[redacted]
2	Log normal tafamidis OS extrapolation	[redacted]	[redacted]	[redacted]
3	Treatment independent utility values in NYHA 4	[redacted]	[redacted]	[redacted]
4	Cap on utility values above the general population age-matched average	[redacted]	[redacted]	[redacted]
5	**EAG base case**	[redacted]	[redacted]	[redacted]

Rows 2, 3 and 4 show the impact of the individual changes applied separately. Row 5 shows the EAG base case where the changes are applied simultaneously

Abbreviations: QALY; Quality adjusted life year ICER; Incremental cost effectiveness ratio BSC; best supportive care, OS; Overall survival, TTD; Time to treatment discontinuation, NYHA; New York heart association classification, CV; cardiovascular, AE; adverse event

EAG deterministic scenario analysis

EAG scenario analyses (deterministic)

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus Tafamidis	Incremental QALYs versus Tafamidis	ICER (£/QALY) versus Tafamidis
1	**EAG base case**	[redacted]	[redacted]	[redacted]
2	discontinuation plateau with indefinite treatment effect	[redacted]	[redacted]	[redacted]
3	BSC outcomes for tafamidis discontinuers	[redacted]	[redacted]	[redacted]

Abbreviations: QALY; Quality adjusted life year ICER; Incremental cost effectiveness ratio BSC; best supportive care, OS; Overall survival, TTD; Time to treatment discontinuation, NYHA; New York heart association classification, CV; cardiovascular, AE; adverse event

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Key issues for discussion

Overview of EAG's key issues

Issue	Resolved?	ICER impact
Extrapolation of tafamidis OS data	No – for discussion	Large
Utility values in some health states higher than the UK general population age-matched average	No – for discussion	Large
Continuation of the tafamidis treatment effect in patients who discontinued treatment	No – for discussion	Large
Unclear if decision problem should include people with mixed phenotype ATTR-CM	No – for discussion	Unknown

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy, OS; Overall survival, NYHA; New York heart association

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Thank you.

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6131]

Supplementary appendix

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Key trial results – ATTR-ACT (30 month) from TA696

Primary endpoint (Finkelstein-Schoenfeld)

The primary endpoint counts and compares, in one combined measure, differences in all-cause mortality and the frequency of CV related hospitalisations between tafamidis and placebo

	Tafamidis* (N=264)	Placebo (N=177)
Number of patients alive, n (%)	186 (70.5)	101 (57.1)
Average frequency of CV-related hospitalisations (per year) among those alive	0.297	0.455
p-value	0.0006	-

Abbreviations: CV: cardiovascular; N: total number of patients; n: number of patients.

Source: table 18 company submission

Notes: * Results for pooled tafamidis 20 mg and 80 mg doses

Key trial results (from TA696)
ATTR-ACT and ATTR-ACT extension

Secondary endpoints

	Pooled Tafamidis (N=264)	Placebo (N=177)
CV-related mortality		
CV-related events, n (%)	64 (24.2)	63 (35.6)
Hazard ratio (95% CI)	0.69 (0.40, 1.14)	-
p-value	0.038	-
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	-
6-minute walk test (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	

Source: tables 18 and 19 CS (TA696). Note: results for other secondary outcomes included in CS and TR.

Abbreviations: CI: confidence interval; CV: cardiovascular; N: total number of patients; n: number of patients; SD: standard deviation; SE: standard error; LS: least-squares

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Key issue: Appropriate comparators

Company excluded diflunisal as comparator, despite inclusion in NICE scope

Background

- NICE scope included 'Established clinical management without tafamidis (including diflunisal)'

Company

- Excluded due to lack RCTs for use of diflunisal in ATTR-CM
- Patients diagnosed more recently with ATTR-CM are no longer initiated on diflunisal as poorly tolerated
- Diflunisal is not licensed for treatment of ATTR-CM

EAG comments

- Do a breakdown of all comparators used in the NHS and a do SLR and an ITC for each of them

Other considerations

- NHSE comment that diflunisal is used for patients at end stage of disease, whereas tafamidis is used for patients at NYHA class 1 to 2

Is diflunisal an appropriate comparator for tafamidis?

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ITC, indirect treatment comparison; RCT, randomised controlled trial; SLR, systematic literature review

Key issue: No new comparative evidence

No updated systematic review in CS

Background

- No systematic review was presented or any comparative evidence (i.e. tafamidis versus any form of standard of care), only Kaplan-Meier curves based on the latest overall survival and time to discontinuation data and limited safety data from patients treated with tafamidis in the long-term extension (LTE) study. The SLR was not updated for model inputs

Company

- The intention for this CS was for it to be “abbreviated”. Company stated this was agreed during the DP meeting and that this abbreviated document would contain no clinical effectiveness evidence but: “New evidence which has become available since the original STA for tafamidis in ATTR-CM [TA6966] and where these data have been applied in the new economic base case”.

EAG comments

- The EAG requested a full systematic review and comparative evidence from the tafamidis trial, which were not provided.

Other considerations

- The FAD for TA696 concluded that the ATTR-ACT trials were appropriate for decision making and that, based on ATTR-ACT, tafamidis is more effective than placebo in both primary and secondary outcomes. However, it is not usual practice in an STA to not present comparative clinical effectiveness evidence.

Is the evidence appropriate for decision making?

Abbreviations: ATTR-CM, Transthyretin amyloidosis with cardiomyopathy, DP; decision point CS; company submission, FAD; final appraisal document, SLR; systematic literature review

Key issue: Extrapolation of tafamidis overall survival

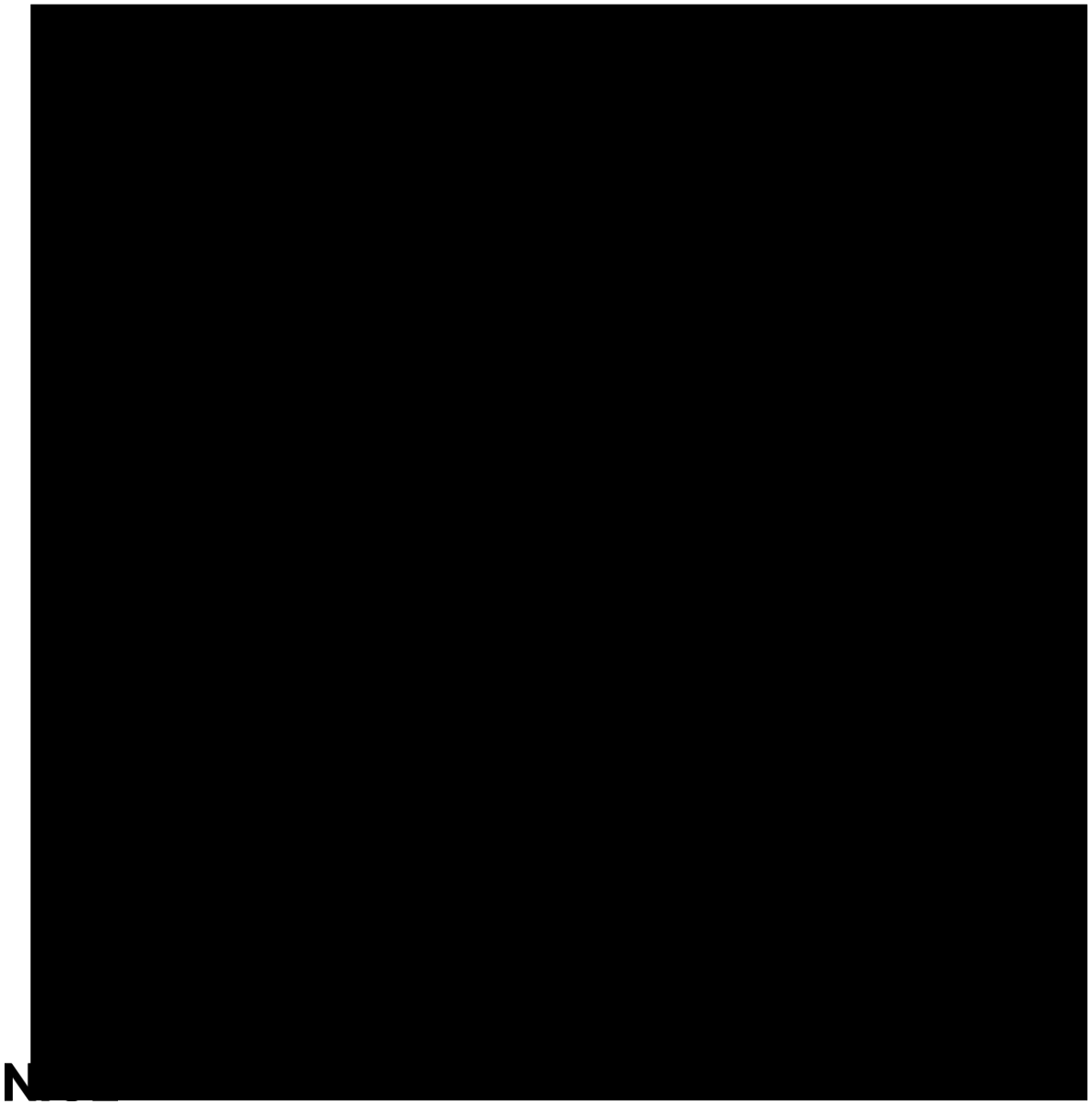

Figure: Possible parametric survival models of OS for tafamidis (fit over observed period)

EAG, Evidence assessment group; CMAD, Cardiac mechanical assist device; HT, Heart transplant; LT, Life table; OS, Overall survival

Key issue: Extrapolation of tafamidis overall survival

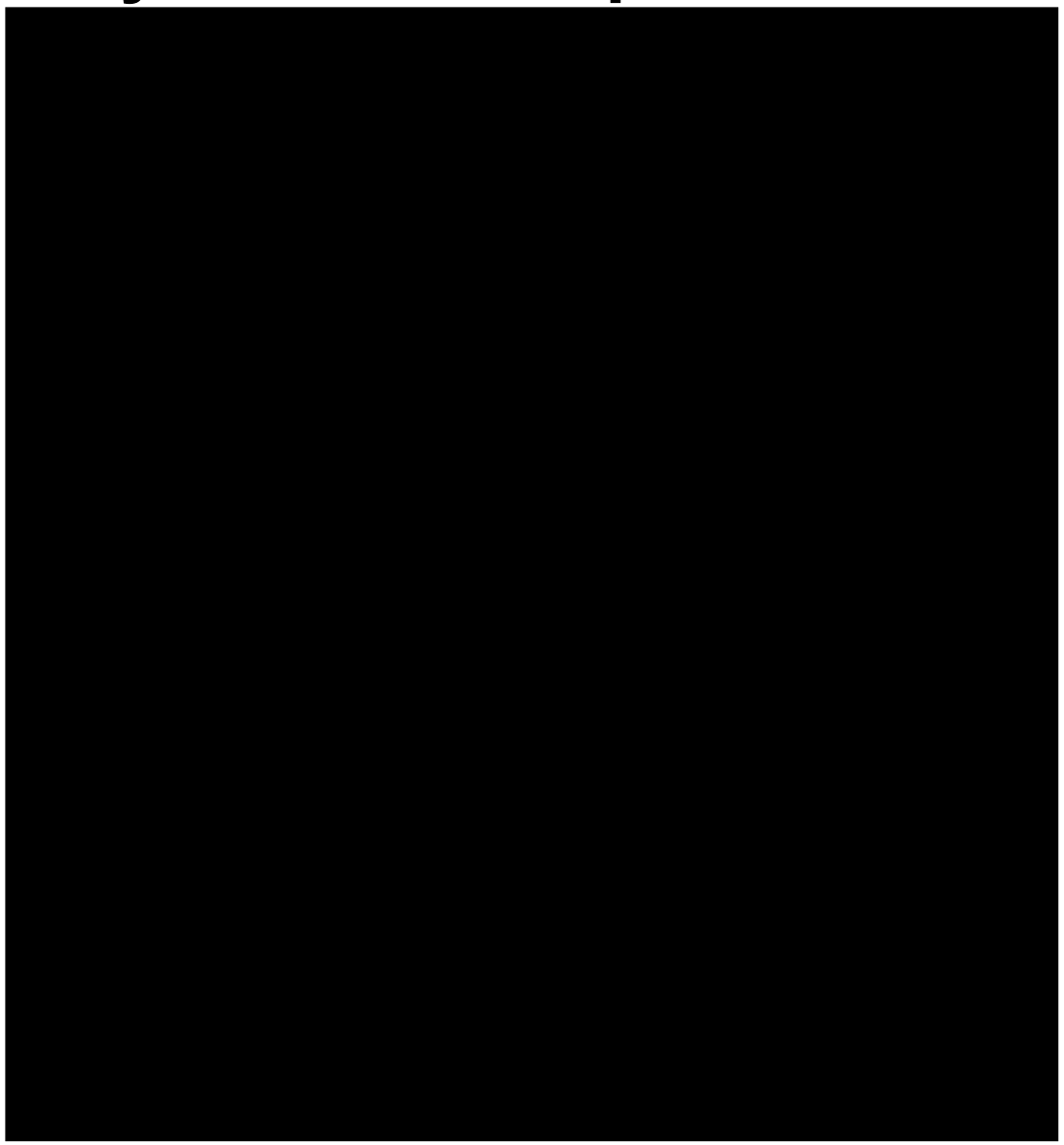

Figure: Hazards for OS for tafamidis in ATTR-ACT crossover and LTE (Augst 2021 data cut)

EAG, Evidence assessment group; CMAD, Cardiac mechanical assist device; HT, Heart transplant; LT, Life table; OS, Overall survival

Company deterministic scenario analysis

Included company scenario analyses (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£) versus Tafamidis	Incremental QALYs versus Tafamidis	ICER (£/QALY) versus Tafamidis
1	**Company base case**	[redacted]	[redacted]	[redacted]
2	Tafamidis OS extrapolation (log normal)	[redacted]	[redacted]	[redacted]
3	TTD extrapolation (log normal)	[redacted]	[redacted]	[redacted]
4	Treatment specific utilities in NYHA 4	[redacted]	[redacted]	[redacted]

Abbreviations: QALY; Quality adjusted life year ICER; Incremental cost effectiveness ratio BSC; best supportive care, OS; Overall survival, TTD; Time to treatment discontinuation, NYHA; New York heart association classification, CV; cardiovascular, AE; adverse event