Slides for screen sharing– fully redacted

NICE National Institute for Health and Care Excellence

Tafamidis for treating transthyretin amyloid cardiomyopathy

Lead team presentation

Lead team: Alex Cale, Iain McGowan, Stella O'Brien

ERG: University of Sheffield, ScHARR

Technical team: Stephen O'Brien, Thomas Paling, Nicola Hay, Jasdeep Hayre

Company: Pfizer

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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
- ATTR cardiomyopathy (ATTR-CM) is a type of transthyretin amyloidosis in which most amyloid deposits accumulate in the heart → heart tissue to thicken and stiffen → 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** affects people born with inherited mutations in the TTR gene. Thought to be less stable than the wildtype and so are more likely to form very small amyloid fibres (fibrils).
- ATTR-CM symptoms include: shortness of breath, palpitations and abnormal heart rhythms (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 60 years in people with hereditary ATTR-CM
- Death in most people with ATTR-CM is from sudden death or progressive heart failure

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**
- Liver transplantation or heart transplantation, are options for some people with ATTR-CM and a specific genetic mutation. However, transplants are rare because:
  - This mutation is uncommon in England
  - Transplantation can only take place early in the course of the disease
- A small proportion of people with cardiomyopathy caused by transthyretin amyloidosis also have polyneuropathy.

NICE recommendations for polyneuropathy	
HST9	Inotersen is recommended as an option for treating stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis
HST10	Patisiran is recommended as an option for treating hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy

Assessment of heart failure

New York Heart Association (NYHA) 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

Tafamidis (Vyndaqel, Pfizer)

Description of technology	Tafamidis binds to transthyretin (TTR) in the blood. This binding stabilises the shape of TTR and prevents the formation of abnormal proteins. This then stops the formation of amyloid deposits
Marketing authorisation	The treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)
Dosage and administration	Tafamidis is administered orally. The dose is 61 mg once a day*
List price	The list price of tafamidis is £10,685 Estimated annual cost at list price £130,089.88 *Confidential commercial arrangement (simple discount PAS)*

Notes: *tafamidis doses used in main trial (20 mg and 80 mg) different to licensed dose (61 mg)

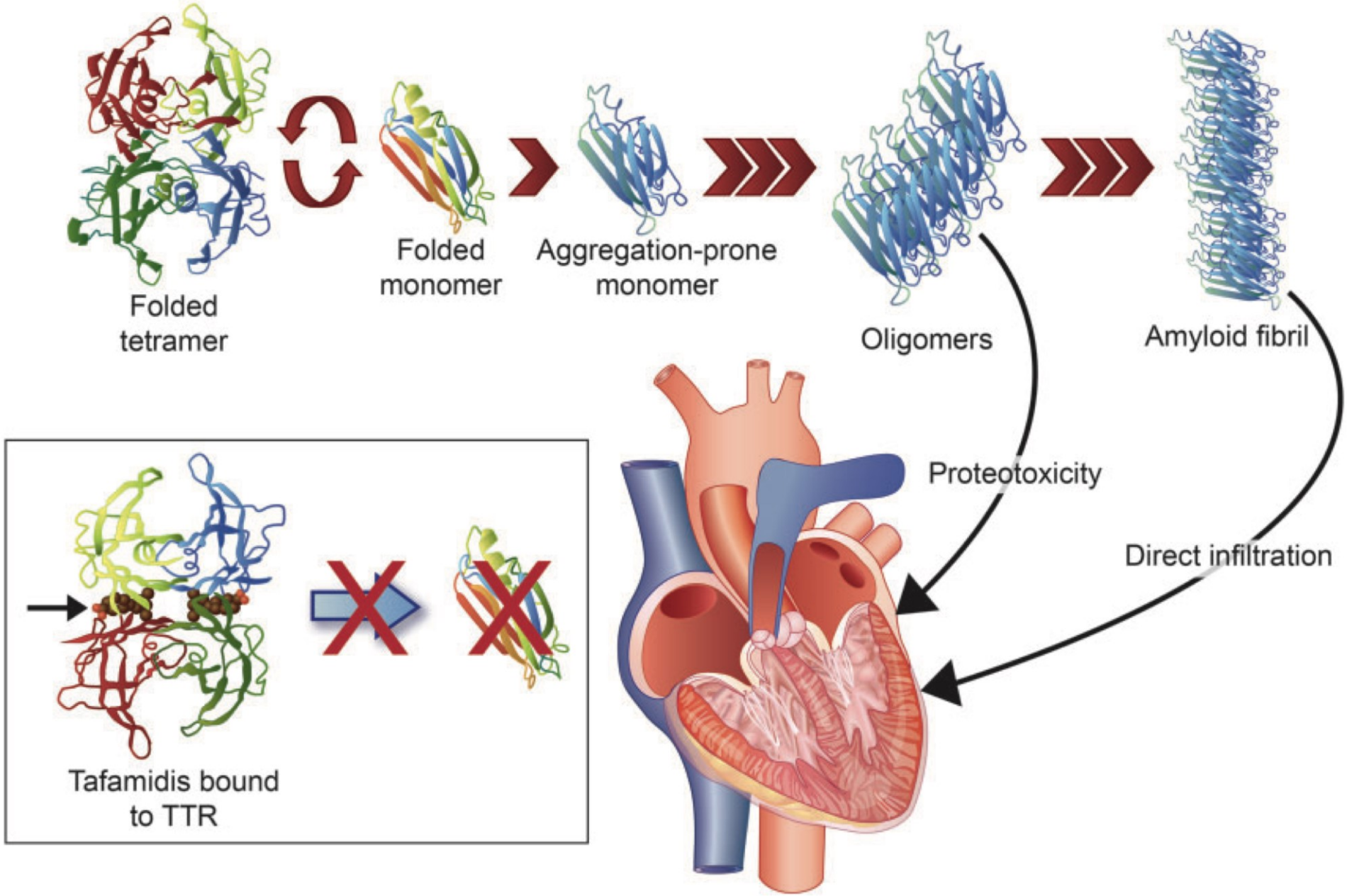
Tafamidis dose and formulation

There is a discrepancy between the tafamidis dose and formulation used in the main clinical trial trials and the licensed dose and formulation

Drug	Formulation	Adult daily dose	Information
Tafamidis meglumine	20mg capsules	80mg Four capsules	Used in clinical trials
Tafamidis (free acid form)	61mg capsules	61mg One capsule	Licensed dose and formulation

- **Clinical trial evidence is based on Vyndaqel**
  - 80mg, 20mg, placebo; (2:1:2 randomization)
- **Bioequivalence study: Study B3461056**
  - Bioequivalence between 61 mg Tafamidis free acid and 80 mg Tafamidis meglumine was proven at steady state (fasted)
- **Some reservations expressed by regulator (EMA (EPAR, p28)**
  - *"…[bioequivalence] could not be proven after single dose"*
  - "… *it cannot be considered that bioequivalence has strictly been proven*"

How does tafamidis work?



NICE Source: European Heart Journal (2019) 40, 1009–1012 doi:10.1093/eurheartj/ehy697

Background

Comparators	Best supportive care
Subgroups	Wild-type and hereditary (familial amyloid cardiomyopathy) ATTR-CM
Clinical trial	• ATTR-ACT: phase III, placebo-controlled trial evaluating the efficacy, safety and tolerability tafamidis in adults • ATTR-ACT extension study: including people who completed ATTR-ACT and another cohort of people with ATTR-CM diagnosis who did not participate in ATTR-ACT
Key results	Tafamidis demonstrated statistically significant improvements in the primary outcome (reduced all-cause mortality and cardiovascular related hospitalisations)
Model	The company's economic model is a cohort-level Markov state-transition model, incorporating 5 health states: 4 based on NYHA classifications and death
Company ICER	£[redacted] per QALY gained (with PAS figures)
Technical team preferred ICER	£[redacted] per QALY gained (with PAS figures)

Patient and carer perspectives

UK ATTR Amyloidosis Patients' Association

The condition: ATTR-CM

- An underdiagnosed, debilitating disease associated with loss of mobility and declining quality of life

Physical effects

- Fatigue → walking short distances is a struggle
- Breathlessness → distressing, associated with anxiety, limits usual daily activities
- Pain → some can experience pain in the chest and/or limbs
- Unstable blood pressure → dizziness, falling and fainting is common
- Abnormal heart rhythms → pacemakers or other devices needed

Psychological effects

- Loss of independence → increased reliance on caregivers
- Hereditary ATTR-CM can affect multiple family members

Key trial results
ATTR-ACT (30 month)

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

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	

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

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

Key trial results
ATTR-ACT and ATTR-ACT extension

Secondary endpoints: All-cause mortality

Figure redacted - AIC

Combined hazard ratio (95% CI) Tafamidis v placebo	0.64 (0.47, 0.85)

Everyone treated with placebo in ATTR-ACT swapped to tafamidis in the extension study → substantial crossover confounding the combined hazard ratio

NICE Source: adapted from figure 19 and table 24 CS

Key issues:	Status
Key issues from technical engagement	
Issue 1. Starting and stopping rules (s16/17)	For discussion
• Uncertainty around whether proposed rules could be implemented in practice	
Issue 2. Continued treatment benefit ★◇ (s18/19)	Partially resolved: For discussion
• Will tafamidis treatment benefit continue after discontinuation? • Will people discontinue tafamidis in NYHA I-III health states? • Will people receive BSC after discontinuing tafamidis?	
Issue 3. Health state utility values	Issue resolved
Issue 4. Hereditary ATTR-CM (s20/21)	For discussion
• Is the clinical effectiveness of tafamidis different in people with hereditary ATTR-CM compared with those with wild-type ATTR-CM?	
Issue 5. Early diagnosis of ATTR-CM ★ (s22/23)	For discussion
• Would the introduction of tafamidis reduce time to diagnosis? • Are most people likely to start tafamidis in NYHA I/II? • Will earlier diagnosis lead to cost savings and avoided QALY loss?	
Other issues for consideration	
What is the most plausible ICER?	For discussion
Does tafamidis represent a step-change in the management of ATTR-CM?	For discussion
Equality considerations	For discussion

Key: high ICER impact: ★, structural uncertainty: ◇

Issue partially resolved after technical engagement

Issue	Summary	Stakeholder responses	Technical team consideration	Included in preferred analysis?
2 ***Part resolved***	***NYHA I-III tafamidis discontinuation*** Company model included a time to treatment discontinuation function: the number of people remaining on tafamidis in health states NYHA I-III reduced over time. After treatment stops: benefits are maintained and treatment cost stop. ERG: this was overly optimistic and instead assumed nobody in NYHA I-III stopped treatment after the trial period.	***Company*** • Tafamidis well tolerated and likely that people will remain on treatment when their disease is classified NYHA I-III. ***Clinical*** • Withdrawing people from tafamidis in any health state could be challenging.	After [redacted] months (observed trial period) it is reasonable to assume that people on tafamidis will remain on treatment in health states NYHA I-III.	Company ✗ ERG ✓

Issue resolved after technical engagement

Issue	Summary	Stakeholder responses	Technical team consideration	Included in preferred analysis?
3a	***Age adjusted utility values*** • Utility values not adjusted to account for the effect of increasing age → utility values for tafamidis and BSC were higher than that of the general population from ages 82 and 84 years onwards respectively	***Company*** • Accepts the application of age adjusted utility values → model age adjustment after the observed period (30 months) ***Professional organisation*** • People with ATTR-CM will have a significantly worse QoL than the general population	Reasonable to apply age-adjustment to model utility values after the observed trial period (30 months)	Company ✓ ERG ✓
3b	***Utility values in NYHA IV*** • Treatment dependent utility values modelled for tafamidis and BSC • Discrepancy in NYHA IV inconsistent with assumed stopping rule	***Company*** • Agrees with the application of BSC utility values for treatment groups in NYHA IV	BSC utility values should be applied for everyone in the NYHA IV health state	Company ✓ ERG ✓

Issue 1: Starting and stopping rules (1)

Background: *stopping rule*

- **Company:** assumed that on progression to NYHA IV people would stop tafamidis and have no further treatment costs
- **ERG:**
  - In ATTR-ACT, [redacted] progressed to NYHA IV before stopping treatment
  - No stopping rule in the draft SmPC

ERG comment

- Difficult to implement NYHA IV stopping rule in practice
  - NYHA is self reported
- People will receive BSC after stopping tafamidis → move on to BSC costs

Stakeholder comments

Company:

- Given the lack of evidence of tafamidis benefit in NYHA IV experts suggested it could be a suitable stopping rule
- Experts noted possible challenges withdrawing tafamidis
- Tafamidis stopping in NYHA IV was observed in ATTR-ACT without an explicit rule → feasible in clinical practice
- Included BSC costs after stopping tafamidis

Clinical experts:

- It would be challenging to:
  - Define exact progression to NYHA IV
  - Withdraw tafamidis on progression to NYHA IV
- Majority will continue tafamidis in NYHA IV
- BSC would be offered after tafamidis is stopped

NHSE

- Poor evidence supporting tafamidis use in NYHA IV
- BSC would be offered after tafamidis is stopped

Technical team judgements:

- Unclear if proposed stopping rule would be adhered to in practice → some may continue
- Unrealistic to assume no further treatment costs after stopping tafamidis → include BSC cost post tafamidis

Issue 1: Starting and stopping rules (2)

Background: *starting rule*

- **Company:** presented a subgroup analysis incorporating NYHA starting/stopping rules
- **ERG:** unclear if people would continue but not start tafamidis in NYHA III

Tafamidis treatment	NYHA starting/stopping rules			
	I	II	III	IV
Initiate	✓	✓		
Continue	✓	✓	✓	
Stop				✓

Stakeholder comments

Company:

- Acknowledge that it may not be clinically appropriate assuming people continue tafamidis but don't start in NYHA III
- If tafamidis is recommended time to diagnosis could fall → more start tafamidis in NYHA I/II
  - Trend towards earlier diagnosis observed in Early Access to Medicines Scheme (EAMS)

Clinical experts:

- Limited evidence of tafamidis benefit in NYHA III → stop treatment in NYHA III

NHSE:

- Limited evidence of tafamidis benefit in NYHA III and IV → consider subgroups (I,II & III,IV)

ERG comment

- Concerns regarding the clinical relevance of the treatment pathway implied by the NYHA I/II subgroup analysis
- Unclear if a positive recommendation would reduce diagnostic delays

Technical team judgements:

- Unlikely in clinical practice people would be ineligible to start tafamidis in NYHA III, but could continue on progression from NYHA II to III
- The extent to which future diagnosis delays will change is uncertain

Issue 2: Continued treatment benefit (1)

Background: *Continued treatment benefit*

- Model includes a function where number of people remaining on tafamidis in health states NYHA I-III reduced over time
  - After tafamidis is stopped benefits are maintained and treatment costs stop
- ERG: company approach is overly optimistic → alternative approach assuming nobody in NYHA I-III stops tafamidis after the trial period → ***treatment benefits and costs continue***

Stakeholder comments

Company:

- Revised analysis models tafamidis stopping in NYHA I-III after the trial period (month [redacted])
  - Use conservative extrapolation (log-normal) to limit uncertainty

Figure redacted - AIC

Treatment discontinuation – Overall population parametric survival models with Kaplan-Meier from [redacted] LTE data

Source: company TE response appendix B figure 1

Issue 2: Continued treatment benefit (2)

Stakeholder comments (continued)

Company:

- Acknowledged that because of the lack of alternative treatments, people would unlikely stop tafamidis treatment in NYHA I-III

Clinical experts:

- After stopping tafamidis ATTR is expected to accumulate at the same rate as BSC
- No data to support the maintenance of tafamidis benefit after treatment is stopped

ERG comment

- After the observed trial period ([redacted] months) the ERG's revised analysis assumes everyone in NYHA I-III continues tafamidis treatment
  - Most health outcomes are modelled from month 30 → unclear if the treatment effects would be equivalent when increased discontinuation is accounted for (month 30 → [redacted])
- Company's approach is not 'conservative' → assumes continued benefits at zero cost

Technical team judgements:

- Modelling a discontinuation function in NYHA I-III means a proportion of people stop tafamidis while maintaining benefits at zero costs → 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
  - The ERG's approach - modelling a 'discontinuation plateau' where nobody discontinues tafamidis in NYHA I-III after the observed trial period (month [redacted]) - is acceptable to limit the uncertainty associated with assuming continued treatment benefit

Issue 4: Hereditary ATTR-CM

Background:

- ATTR-CM can be classified as hereditary or wild-type
- Tafamidis treatment effects are driven by people with wild-type ATTR-CM
- Tafamidis benefits are not statistically significant in the hereditary ATTR-CM subgroup

ERG comment

- Tafamidis benefits over placebo are mainly driven by wild-type ATTR-CM
  - Statistically significant results in primary outcome (CV-hospitalisations and all-cause mortality) for people with wild-type ATTR-CM were driven by reducing CV-hospitalisations

Stakeholder comments

Company

- ATTR-ACT was not powered to assess the effect of subgroups
- Hereditary ATTR-CM subgroup analysis found treatment effect numerically favoured tafamidis in primary and secondary outcomes

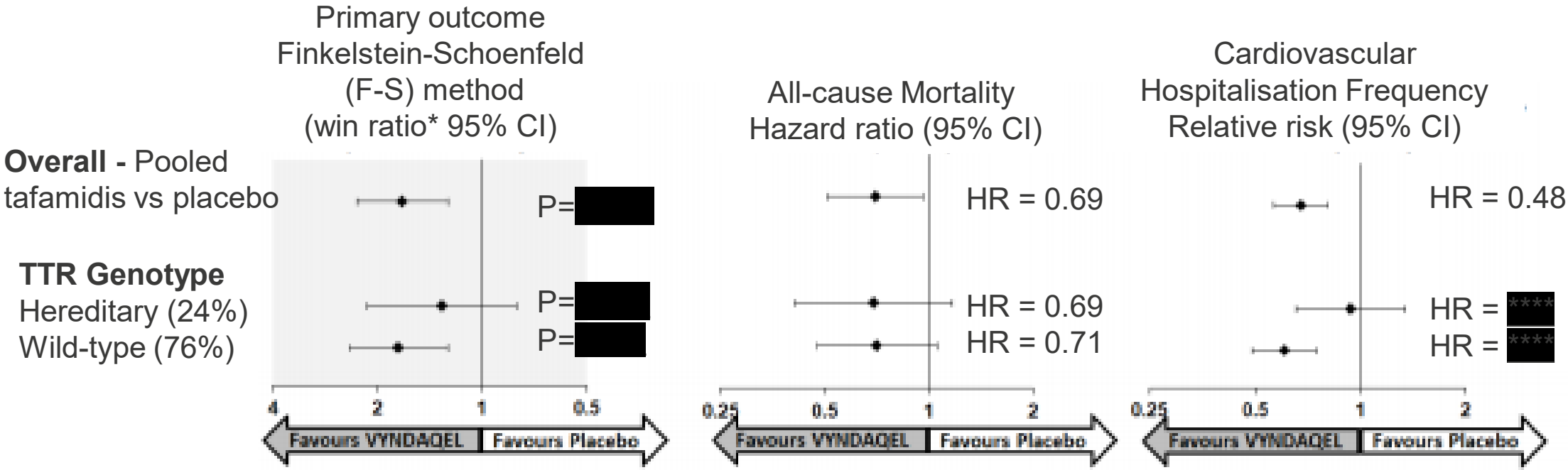
Clinical experts:

- Not enough available data to understand this
- Gene silencing treatments are more effective than tafamidis in hereditary ATTR-CM

Professional group:

- Tafamidis appears more effective in wild-type
- Statistically significant benefits in terms of symptomatic status observed in hereditary subgroup

Issue 4: Hereditary ATTR-CM



Source: adapted from figure 2 tafamidis SPC
Note: * F-S results presented using win ratio (based on all-cause mortality and frequency of cardiovascular hospitalisation). The win ratio is the number of pairs of treated-patient "wins" divided by number of pairs of placebo patient "wins."

Technical team judgements:

- Tafamidis benefits for people with hereditary ATTR-CM are unclear
  - Acknowledges small patient numbers as a limitation

Issue 5: ATTR-CM early diagnosis (new issue)

Background:

Company

- Patients with ATTR-CM experience an average delay from presentation of symptoms to diagnosis of >3 years → more advanced disease state at diagnosis
- Avoidable health care costs are incurred during delay to diagnosis

Stakeholder comments

Company

- The availability of tafamidis will result in earlier detection of ATTR-CM through greater awareness among cardiologists
  - May improve equity in access to diagnostics in England
- Trend of earlier diagnosis in EAMS data, [redacted]% diagnosed in NYHA I/II compared to 64% in ATTR-ACT
- New analysis presented, including:
  a) £20,000 cost saving
  b) avoiding QALY losses associated with anxiety and depression by reducing diagnosis time by 2.5 years
  c) earlier age at diagnosis (71.95 years)

NHS England

- ATTR-CM is often misdiagnosed
- Heart failure is a common presentation which increases in prevalence with age
- Early diagnosis and treatment are key to improve survival
- Recommending tafamidis and increasing awareness through educational campaigns could improve diagnosis rates

Issue 5: ATTR-CM early diagnosis (new issue)

ERG comment

- No empirical evidence to support claims that introducing tafamidis will reduce diagnosis time
- The awareness of ATTR-CM has increased because of the introduction of patisiran and inotersen → the introduction of tafamidis is unlikely to substantially change time to diagnosis
- Earlier diagnosis observed in EAMS could be explained by improved diagnostics
- Unclear how the company's estimated the potential reduction in diagnosis time at 2.5 years or exactly how it derived cost savings of £20,000
- The QALY gains from reduced anxiety/depression are not reasonable

Technical team judgements:

- All of the assumptions included in the early diagnosis analyses are highly uncertain and therefore should not be incorporated in the technical team's preferred ICER
  - Assuming the introduction of tafamidis could lead to a reduction of diagnosis delays of 2.5 years is not supported by the evidence
  - No details of how cost savings achieved by earlier diagnosis were estimated → unclear if £20,000 savings is realistic
  - No evidence to support the assumption that all patients would experience 'some' or 'extreme' problems in relation to anxiety/depression resulting from delayed diagnosis

Additional areas of uncertainty

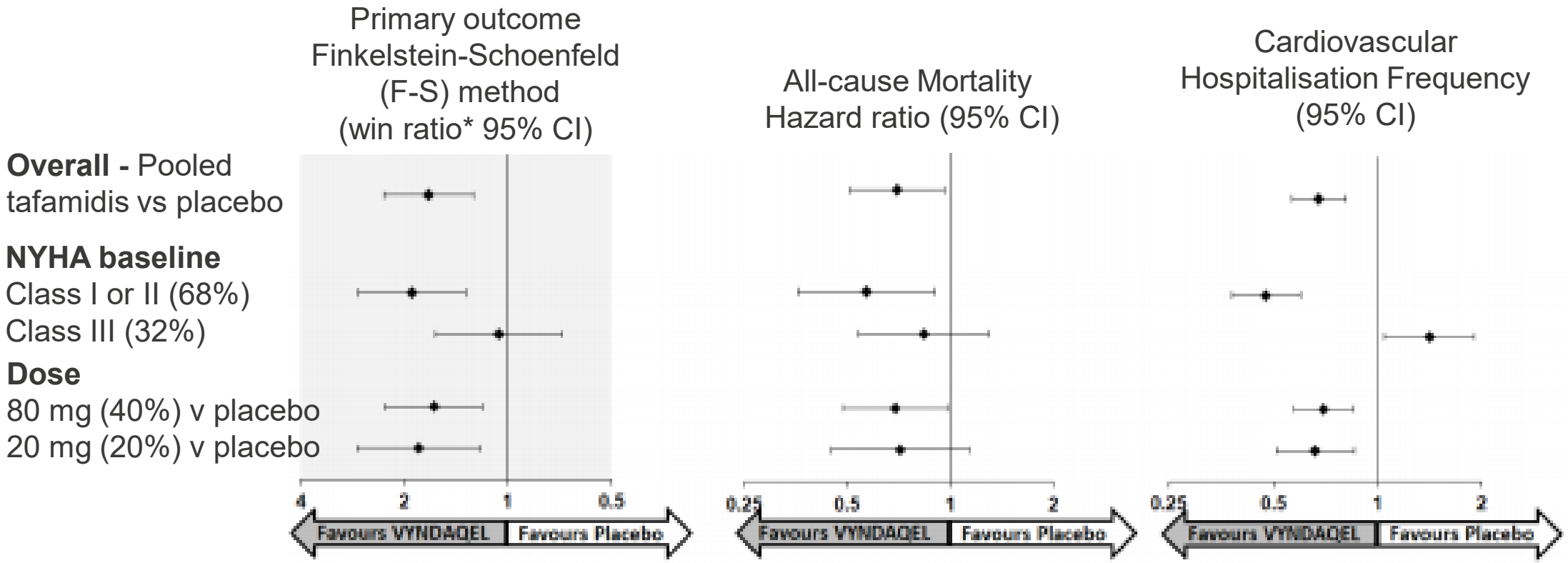
Issue	Why issue is important	Impact on ICER
Clinical effectiveness of tafamidis beyond NYHA classes I/II	• There is a lack of evidence of tafamidis treatment benefit over placebo in people whose disease has progressed to NYHA III. - Tafamidis benefits in the primary outcome are not statistically significant - Increased rates of CV hospitalisations compared to placebo	Impact on ICER unknown *Impact on key clinical outcomes can be seen on s21*
Clinical equivalence of tafamidis dosing regimens	The effectiveness of tafamidis is modelled using pooled data from the 20 mg and 80 mg doses used in ATTR-CM, whereas the licensed dose/formulation of tafamidis specified in the SmPC 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 to be used in clinical practice. ***Regulator comments* (EPAR p28):*** "*… it cannot be considered that bioequivalence has strictly been proven*".	Impact on ICER unknown *Impact on key clinical outcomes can be seen on s21*

Notes:* full comment in back up slides

Additional areas of uncertainty

Subgroup analyses

Subgroup analyses:
baseline disease classification and tafamidis dose



Source: adapted from figure 2 tafamidis SPC

Note: * F-S results presented using win ratio (based on all-cause mortality and frequency of cardiovascular hospitalisation). The win ratio is the number of pairs of treated-patient “wins” divided by number of pairs of placebo patient “wins.”

Cost effectiveness results

Updated analyses post-TE (including updated PAS)

Scenario	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Tech team preferred ICER* (aligns with ERG1 but without drug wastage)			
• No discontinuation in NYHA I-III after observed trial period (month [redacted]): ***continued costs and benefits*** • Age adjusted utility values after trial period (month 30) • Everyone achieves BSC utilities in NYHA IV • BSC costs after discontinuation	[redacted]	[redacted]	[redacted]
ERG preferred ICER* (ERG1)			
Amendments from tech team ICER • Inclusion of drug wastage	[redacted]	[redacted]	[redacted]
Company revised analysis*			
Amendments from tech team ICER* • Discontinuation modelled (exponential) in NYHA I-III after observed trial period: ***after discontinuation tafamidis benefits continue and costs are stopped*** • Generalised gamma OS distribution (tafamidis & BSC)	[redacted]	[redacted]	[redacted]

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Source: table 5 company TE response appendix D and table 5 ERG comment on company TE response, produced by tech team checked by ERG
Notes:*table of assumptions for each analysis included in backup slides

Cost effectiveness results

Early diagnosis analyses (including updated PAS)

Scenario	Incremental QALYs		ICER (£/QALY)	
	Tech team	Company	Tech team	Company*
Preferred ICER / revised analysis	[redacted]	[redacted]	[redacted]	[redacted]
1. Post-engagement early diagnosis analyses: ***company preferred assumptions***				
• £20,000 cost saving • QALY loss from depression/anxiety = 0.18 • Lower diagnosis age by 2.5 years	[redacted]	[redacted]	[redacted]	[redacted] **Company preferred**
2. NYHA I/II subgroup (see slide 17 for full subgroup definition)				
Subgroup analysis assuming: • People are diagnosed and start tafamidis in less severe NYHA states (I&II only) • Continue on progression to NYHA III • Stop in NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
3. Post-engagement early diagnosis assumptions in the NYHA I/II subgroup				
Combined scenario 1 and 2	[redacted]	[redacted]	[redacted]	[redacted]

Source: generated by tech team checked by ERG and tables 4 and 5 company TE response appendix D
Notes:*company ICERs include discontinuation function acknowledged to be unreflective of clinical practice at TE

Cost effectiveness results

Scenario analyses (including updated PAS)

Scenario	ICER (£/QALY)	
	Full population	NYHA I/II subgroup
Tech team preferred ICER	[redacted]	[redacted]
Issue 1: Treatment starting and stopping rules		
Removing NYHA IV stopping rule	[redacted]	[redacted]
Issue 2: Continued treatment benefit		
a) Log-normal discontinuation function in NYHA I-III *Treatment benefits continue and costs stops*	[redacted]	[redacted]
b) Exponential discontinuation function in NYHA I-III *Treatment benefits continue and costs stops*	[redacted]	[redacted]
c) Exponential discontinuation function in NYHA I-III *BSC outcomes applied after tafamidis discontinuation*	[redacted]	[redacted]
Issue 5: early diagnosis (new issue post-engagement)		
a) Reduce age of diagnosis 2.5 years to 71.95	[redacted]	[redacted]
b) QALY loss of 0.18: reduced anxiety/depression	[redacted]	[redacted]
c) Including £20,000 cost savings	[redacted]	[redacted]

Source: generated by tech team, checked by ERG

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Notes:* company acknowledge that there will be a discontinuation plateau in NYHA I-III, no analyses presented to address issue 4

Issues for information

Issue	Why issue is important
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.
Innovation	**Company:** • Tafamidis is a breakthrough treatment for ATTR-CM • It represents a step-change in the management of ATTR-CM • High QALY gains (~[redacted]) represent a paradigm shift • Reduced burden on patients and carers in an area of substantial unmet need → not captured in costs and QALYs **Technical team:** considered that the relevant benefits associated with tafamidis are adequately captured in the economic model.
Equality considerations	• 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. • 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.

Key issues:	Status
Key issues from technical engagement	
Issue 1. Starting and stopping rules (s16/17)	For discussion
• Uncertainty around whether proposed rules could be implemented in practice	
Issue 2. Continued treatment benefit ★◇ (s18/19)	Partially resolved: For discussion
• Will tafamidis treatment benefit continue after discontinuation? • Will people discontinue tafamidis in NYHA I-III health states? • Will people receive BSC after discontinuing tafamidis?	
Issue 3. Health state utility values	Issue resolved
Issue 4. Hereditary ATTR-CM (s20/21)	For discussion
• Is the clinical effectiveness of tafamidis different in people with hereditary ATTR-CM compared with those with wild-type ATTR-CM?	
Issue 5. Early diagnosis of ATTR-CM ★ (s22/23)	For discussion
• Would the introduction of tafamidis reduce time to diagnosis? • Are most people likely to start tafamidis in NYHA I/II? • Will earlier diagnosis lead to cost savings and avoided QALY loss?	
Other issues for consideration	
What is the most plausible ICER?	For discussion
Does tafamidis represent a step-change in the management of ATTR-CM?	For discussion
Equality considerations	For discussion

Key: high ICER impact: ★, structural uncertainty: ◇

Back up slides

Backup slides: *bioequivalence of doses*

Regulator comment on bio-equivalence of tafamidis doses

*"At steady state under fasted condition, however, with Study B3461056, bioequivalence could be proven between 61 mg Tafamidis free acid and 80 mg Tafamidis meglumine. Bioequivalence between 61 mg Tafamidis free acid and 80 mg Tafamidis meglumine was proven at steady state (fasted). However, it could not be proven after single dose, which is the most relevant and discriminant according to the guideline for evaluation of bioequivalence. Therefore, it cannot be considered that bioequivalence has strictly been proven (and this term should be taken off in the SmPC), which is a serious concern since most efficacy data come from 4*20 mg Tafamidis meglumine treatments. Please refer to the B/R discussion for relevance of this non-bioequivalence on benefit-risk."*

p28 Tafamidis EMA EPAR

Backup slides: *key ICER assumptions*

Summary of assumptions in key ICERs

	Tech team preferred ICER	ERG preferred ICER (ERG1)	Company revised analysis*
Updated [redacted] extrapolation for discontinuation and overall survival	✓	✓	✓
Exponential TTD extrapolation	✓	✓	✓
Discontinuation plateau at month [redacted]	✓	✓	
Log-normal OS for Tafamidis	✓	✓	
Generalised gamma OS for Tafamidis and BSC			✓
Age adjusted utility decrements after month 30	✓	✓	✓
BSC utilities in NYHA IV	✓	✓	✓
BSC costs after discontinuation	✓	✓	✓
Drug wastage included		✓	

Notes: * The company did not explicitly state a revised base-case. However, they presented an analysis which examined the cumulative impact on the ICER which is presented here and referred to as the company revised analysis.

Back up slides: *End of life*

- No case put forward

Back up slides: *Innovation*

The company considers tafamidis to be an innovative technology

- The company states tafamidis is the 1st treatment to:
  - Reduce mortality and morbidity in ATTR-CM.
  - Reduce all-cause mortality and CV-related hospitalisations in patients with HFpEF.
  - 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
- They highlight that the high QALY gains (~[redacted] in tech team analysis) represents a paradigm shift in the management of ATTR-CM disease
- They suggest benefits relating to service transformation and impact on carers and families are not captured in the costs and QALYs
- Tafamidis received a Promising Innovative Medicine designation from the MHRA

Back up slides: *Equality*

- 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.