PART 1

NICE National Institute for Health and Care Excellence

Slides for the public observer

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

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ERG: BMJ Technology Assessment Group (BMJ TAG)

Technical team: Stephen O'Brien, Victoria Kelly, Cameron Collins, Jasdeep Hayre

Company: Daiichi Sankyo

ACM 2 – 5th November 2020

Recap of the 1st committee meeting

- The appraisal committee was unable to develop recommendations for bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia due to:
  - considerable uncertainty in the company network meta-analysis (NMA)
- NICE paused this appraisal pending further analyses being completed
- Company submitted additional analyses which has been critiqued by the ERG

Mixed dyslipidaemia and primary hypercholesterolaemia

- Mixed dyslipidaemia is characterised by elevated LDL-C and triglycerides and/or reduced or elevated HDL-C.
- Primary hypercholesterolaemia, a type of dyslipidaemia, is defined when total plasma cholesterol concentration is approximately ≥ 3 mmol/L and falls into two categories: familial or non-familial.
- Hypercholesterolaemia and mixed dyslipidaemia are associated with many comorbidities, including diabetes and cardiovascular disease (CVD) such as atherosclerotic cardiovascular disease (ASCVD).

Bempedoic acid (Nilemdo/Nustendi, Daiichi Sankyo)

Marketing authorisation (received April 2020)	BA and BA/EZE FDC are indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet. **Insufficient response to statin population:** • BA with statin or statin + other lipid lowering therapies • BA/EZE FDC with statin (population has prior EZE therapy) **Statin intolerant population:** • BA alone or with other lipid lowering therapy • BA/EZE FDC alone (population has prior EZE therapy)
Description of technology	BA is a cholesterol synthesis inhibitor (inhibiting adenosine triphosphate citrate lyase). BA upregulates LDL receptors by suppression of cholesterol synthesis.
Administration	• BA – oral, once daily; 1 tablet containing 180 mg BA • FDC – oral, once daily; 1 tablet containing 180 mg BA FDC and 10 mg EZE.
Price	£55.44 (£1.98 per day, £723.20 per year) per 28-pack of BA £55.44 (£1.98 per day, £723.20 per year) per 28-pack of BA/EZE FDC £57.30 (£2.05 per day, £746.46 per year) per 28-pack of BA+EZE separate tablets

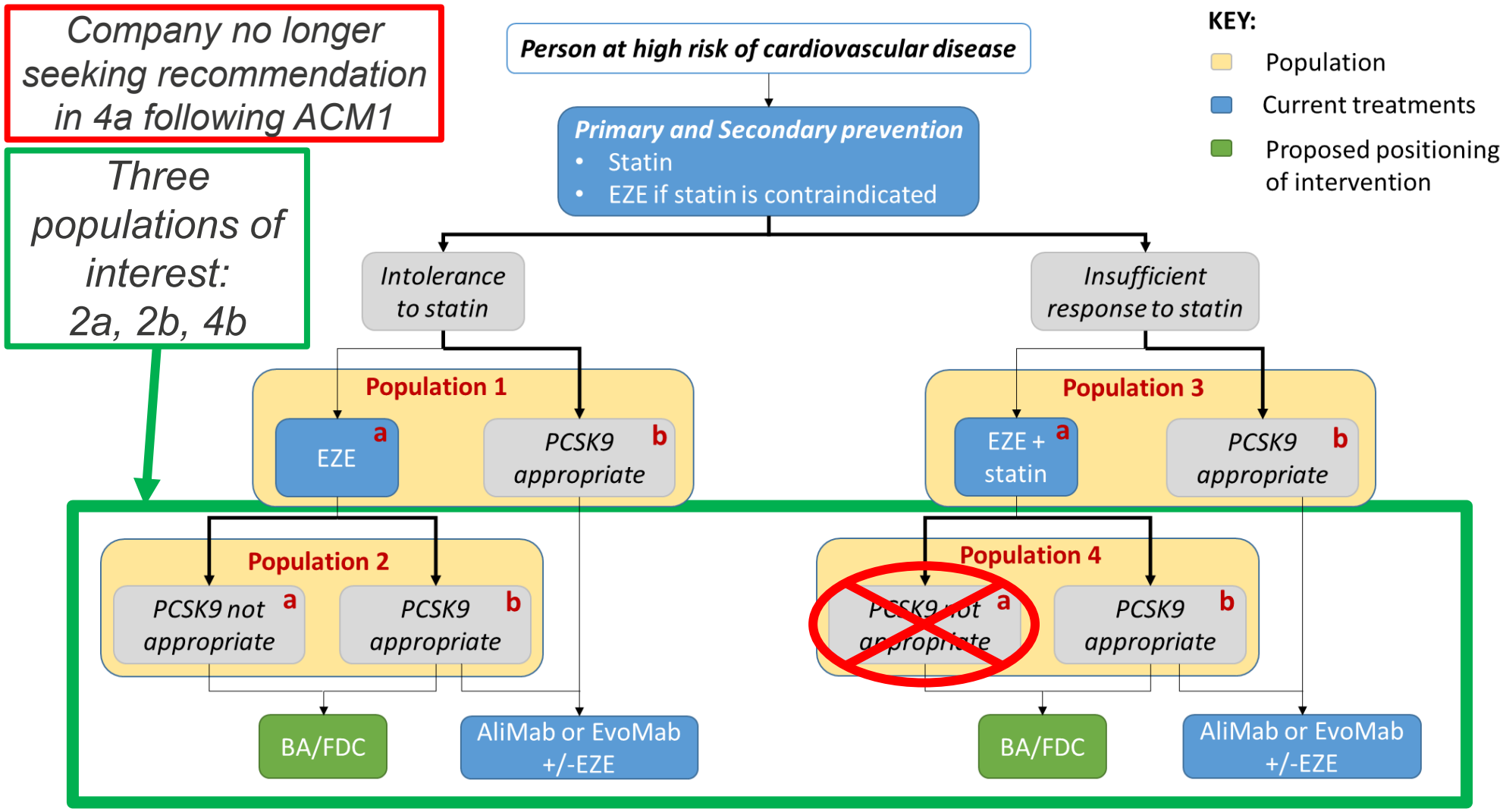
Bempedoic acid (BA), Bempedoic acid / ezetimibe fixed dose combination pill (BA/EZE FDC)

Patient and carer perspectives

- Cardiovascular disease is the underlying cause of 26% of all deaths in the UK. Approx. 160,000 deaths p.a. or 435 people each day. Approx. 42,000 of these deaths are premature and, in many cases, could be prevented.
- Associated with deprivation and other social determinants of health that amplify non-communicable diseases and multimorbidities associated with metabolic dysfunction for some demographics. COVID – further amplified by inequalities in digital access and digital health that is increasingly needed to manage LTC.
- Cholesterol management is a long-term strategy and key investment area for NHS England.
- NHS Health Checks. Initial clinical priority for NHSE's Universal Care Model.
- Unmet need for a safe, cheap oral preparation that would: (a) improve LDL-reduction in combination with statins or (b) be available for use in patients who are intolerant of statins. [Clinical Expert]
- Previously noted that patients are not navigated through the lipid management pathway appropriately and uptake of PCSK9i uptake is lower than expected.

Treatment pathway

Position of BA/FDC in treatment pathway for hypercholesterolaemia and mixed dyslipidaemia



Note: Subpopulations labelled with 'a' relate to situations when alirocumab (ALI) and evolocumab (EVO) are not appropriate and 'b' for when ALI and EVO are appropriate.

NICE

Question for committee: Is it appropriate to no longer consider population 4a?

Recap: Overview of company's trials (1)

Study title	CLEAR Tranquility (2018)	CLEAR Serenity (2019)	1002-008 (2016)	1002-009 (2016)	CLEAR Harmony (2019)	CLEAR Wisdom (2019)	1002FDC-053 (2019)
	Statin intolerant (population 2)			Insufficient response to statin (population 4)			
Size	n=269 *Phase 3*	n=345 *Phase 3*	n=223 *Phase 2*	n=90 *Phase 2*	n=2,230 *Phase 3*	n=779 *Phase 3*	n=382 *Phase 3*
Intervention(s)	BA with EZE	BA	BA with EZE or BA alone	BA	BA	BA	BA/EZE FDC or BA alone
Comparator(s)	Placebo with EZE	Placebo	EZE	Placebo	Placebo	Placebo	EZE, placebo
Background therapy	LMT + no/low dose statin and various others	LMT + no/low-dose statin or non-statin	No statin	Low-/moderate- intensity statin	LMT + moderate-/high-intensity statin, EZE	LMT + moderate-/high-intensity statin, PCSK9i and others	No/moderate-/high-intensity statin
Key results (LS mean % change LDL-C)	−21.4 (< 0.001)	−28.5 (< 0.001)	n/a	n/a	−18.1 (< 0.001)	−17.4 (< 0.001)	−19.0 (< 0.001)

LMT, lipid-modifying therapy; LS mean, Least Squares Mean

Key issues at the end of ACM1(1)

Issue	Background	Committee Conclusion
2. Previous and/or concomitant therapy	Apart from CLEAR Tranquillity the BA studies include patients not previously treated with EZE or have undergone washout	The impact of previous ezetimibe therapy on treatment effect is uncertain and the company analyses are likely to be underpowered
3. Baseline LDL-C in subpopulations not eligible for ALI and EVO	Company used mean baseline LDL-C levels from all patients in the CLEAR trials and did not distinguish between ALI/EVO eligibility	Committee agree with ERG that using LDL-C levels based on ALI/EVO eligibility is preferred
4. Subgroup analyses by CV risk and HeFH	Subgroup on HeFH and CV risk identified as important in NICE scope and align with subgroups that inform the recommendations for ALI and EVO (TA394 and TA393)	Not appropriate to assume no difference in treatment effect across CV risk and HeFH subgroups
5. Primary and secondary prevention subpopulation	Analyses did not include efficacy data directly relevant to the intended subpopulation (e.g. limiting to primary prevention without HeFH trials for population 2a)	Use appropriate CLEAR trials to inform treatment efficacy for primary and secondary prevention populations

Key issues at the end of ACM1(2)

Issue	Background	Committee Conclusion
5a. CV event history and risk data	The estimates of annual CV event risk in the model was informed by Ward et al., 2007, not consistent with effectiveness data	Use appropriate CLEAR trials to inform prior CV events
6. Methodological uncertainty in the NMA	• Company NMA has been critiqued for high levels of statistical and clinical heterogeneity • The ERG NMA was unable to include all relevant data from the BA studies and may be missing relevant comparator studies	Neither ERG or company NMA optimal - prefer to see improved statistical fit, reduced heterogeneity, and comparability with related TAs
7. 12-week study data cut off and evaluation of treatment waning	Company used percentage change from baseline LDL-C at 12 weeks. The company maintain that improvements in LDL-C were durable through 52 and 78 weeks. ERG suggested a waning effect between 2-24 weeks in SERENITY and 4-12 weeks in TRANQUILITY	Committee could not be certain without longer term data that there is no waning effect with BA

Reason for pausing the appraisal

Methodological uncertainty in the NMA (key issue) (referred to as Issue 6 in ACM1)

- Neither ERG or company network meta analyses (NMA) were fully acceptable
  - NMA results important as they provide the estimates of efficacy of BA and FDC vs EZE, ALI and EVO in population 2 and 4
  - Committee wanted analyses with improved statistical fit, reduced heterogeneity, and comparability to previous technology appraisals
- The committee expressed a preference for the approach taken by the ERG for conducting the NMAs.
- NICE recommended that the company:
  - conduct a **primary analysis** where they build upon the NMAs conducted by the ERG
  - conduct **scenario analyses** using studies that reflect PCKS9i eligibility
  - conduct a **sensitivity analysis** by relaxing the assumptions of the primary analysis
  - address several **additional considerations** relating to issues identified in ACM1

Request for Information: Primary Analysis

As part of the **primary analysis,** NICE asked the company to

- build upon the NMAs conducted by the ERG
- identify any additional studies in the wider group of trials included in the company's NMA that meet the following 4 points:

1. Have use of ezetimibe prior to randomisation
2. Have similar unadjusted baseline low-density lipoprotein cholesterol (LDL-C) levels
3. Use appropriate trials to inform treatment efficacy for primary prevention (population 2a) and secondary prevention (populations 2b and 4b)
4. Also have other similar baseline characteristics such as cardiovascular disease (CVD) risk, Heterozygous Familial Hypercholesterolemia (HeFH), type of statin, sex, and ethnicity

Company

The company presented 4 further NMAs, two for both population 2 and 4:

- Expanded ERG analysis post ACM1
- Company additional analysis post ACM1

Company's updated NMAs: Overview

Company's updated NMAs	Company comments	ERG comments
Expanded ERG analysis post ACM1	• Includes all available data for BA in patients receiving EZE at baseline from the CLEAR studies that the ERG did not have access to previously • No additional comparator data from other non-BA studies that could be included • Provides estimates for ALI+EZE (subgroup data)	• Agrees with the studies included by the company (all population with prior EZE) • Considers this to meet the primary analysis requested by the committee
Company additional analysis post ACM1	• Builds upon the ERG NMA and address committee's additional information request for the primary analysis (slide 14) • Provides estimates for ALI without EZE (full trial data)	• Considers this to be a sensitivity analysis • **Substantial unresolved clinical heterogeneity, and not suitable for decision making**

- It was agreed (company and ERG) that it is suitable to assume a class effect for the PCSK9i as no data on EVO suitable for inclusion in the NMAs was identified. I.e. the efficacy of EVO+EZE was assumed to be the same as ALI+EZE in the cost-effectiveness model
- Company feels both post ACM1 NMAs are relevant for decision-making (ALI without EZE is important intervention in routine practice)

Company

Company maintains that the NMA submitted at Tech Engagement is most robust source for decision making and makes most of available data

Company additional analysis post ACM1

Committee Request for Information	Relating issue from ACM1	Company response
Include trials with use of ezetimibe prior to randomisation (80% or more)	Issue 2. Previous and/or concomitant therapy	All trials reported less than 20% of patients on EZE at baseline, thus not feasible in network for population 4. If threshold relaxed to 60%, one study could be added to network for population 2
Select trials that have similar unadjusted baseline (LDL-C) levels	Issue 3. Baseline LDL-C in subpopulations not eligible for ALI and EVO	Removed four studies from network for population 4 and two studies removed from network for population 2
Consider trials that also have other similar baseline characteristics such as CVD risk, HeFH, type of statin, sex, and ethnicity.	Issue 4. Subgroup analyses by CV risk and HeFH	Five studies were removed from the NMA for population 4 because they were conducted in Asian populations. All ALI 75mg data were removed as this dose is not required. Statin control arms removed from two studies
Use appropriate trials to inform treatment efficacy for primary and secondary prevention populations	Issue 5. Primary and secondary prevention subpopulation	No changes to either NMA for population 2 or 4 were made in relation to this characteristic. Trials had mixed populations and reporting of CV risk and prior CV events was unclear

ERG

Still considers there to be substantial unresolved clinical heterogeneity between the trials included in the Company additional analysis post ACM1

ERG additional NMAs: Overview

ERGs additional NMAs	ERG comments
ERG NMA V2 (ERG preferred)	• The ERG replicated the company's expanded ERG analysis post ACM1 (same clinical data) but results were slightly different and could not be explained • **ERG considers the results from the ERG NMA V2 to be the most robust and to address the primary analysis requested in the NICE request for additional information**
ERG validation NMA	• The ERG validated the company additional analysis post ACM1 (with trial data supplied by the company) • Validation NMA demonstrated fixed effects vs random effects has similar model fit in NMA for position 2 • Validation NMA demonstrated fixed effects has a better model fit vs random effects in NMA for position 4

ERG

For the ERG and company versions of each analysis (excluding company Tech Engagement analyses), the mean change in LDL-C is similar but the credible intervals are considerably wider in the company's results

NMA results – Population 2

Population 2 (statin intolerant)	Estimated difference in % change in LDL-C from baseline compared with EZE		
	Mean	95% CIs	P value
Company's Expanded ERG NMA post ACM1			
BA+EZE	[redacted]	[redacted]	[redacted]
ALI (150mg) + EZE	[redacted]	[redacted]	[redacted]
ERG NMA V2 (ERG preferred)			
BA+EZE	[redacted]	[redacted]	[redacted]
ALI (150mg) + EZE	[redacted]	[redacted]	[redacted]
Company additional analysis post ACM1			
BA	[redacted]	[redacted]	[redacted]
BA+EZE	[redacted]	[redacted]	[redacted]
ALI (150mg)	[redacted]	[redacted]	[redacted]
ERG validation NMA (of company additional analysis post ACM1)			
BA	[redacted]	[redacted]	[redacted]
BA+EZE	[redacted]	[redacted]	[redacted]
ALI (150mg)	[redacted]	[redacted]	[redacted]
Tech engagement analysis 1 (Company preferred)			
BA	[redacted]	[redacted]	[redacted]
BA+EZE	[redacted]	[redacted]	[redacted]
EVO	[redacted]	[redacted]	[redacted]
EVO+EZE	[redacted]	[redacted]	[redacted]
ALI (75mg)	[redacted]	[redacted]	[redacted]
ALI (150mg)	[redacted]	[redacted]	[redacted]

NMA results – Population 4

Population 4 (maximum tolerated dose)	Estimated difference in % change in LDL-C from baseline compared with EZE		
	Mean	95% CIs	P value
Company's Expanded ERG NMA post ACM1			
BA+EZE+statin	[redacted]	[redacted]	[redacted]
ALI (150mg)+EZE+statin	[redacted]	[redacted]	[redacted]
ERG NMA V2 (ERG preferred)			
BA+EZE[b]	[redacted]	[redacted]	[redacted]
ALI (150mg)+EZE[b]	[redacted]	[redacted]	[redacted]
Company additional analysis post ACM1[a]			
EVO+statin	[redacted]	[redacted]	[redacted]
ALI (150mg)+statin	[redacted]	[redacted]	[redacted]
ERG validation NMA (of company additional analysis post ACM1)			
BA[b]	[redacted]	[redacted]	[redacted]
EVO[b]	[redacted]	[redacted]	[redacted]
ALI (150mg) [b]	[redacted]	[redacted]	[redacted]
Tech engagement analysis NMA 10a (Company preferred)			
BA+statin	[redacted]	[redacted]	[redacted]
FDC+statin	[redacted]	[redacted]	[redacted]
EVO+statin	[redacted]	[redacted]	[redacted]
ALI (75mg)+statin	[redacted]	[redacted]	[redacted]
ALI (150mg)+statin	[redacted]	[redacted]	[redacted]

[a] Results for BA+EZE are not available as 1002FDC-053 was not included in the network due to very few patients on EZE at baseline
[b] Patients also on background maximally tolerate dose statin

Overview of additional analyses

Methodological uncertainty in the NMA (referred to as Issue 6 in ACM1)

This issue is central to the results as the NMAs have been performed to provide estimates of the efficacy of BA and FDC versus EZE, ALI and EVO in populations 2 and 4 (given lack of direct evidence).

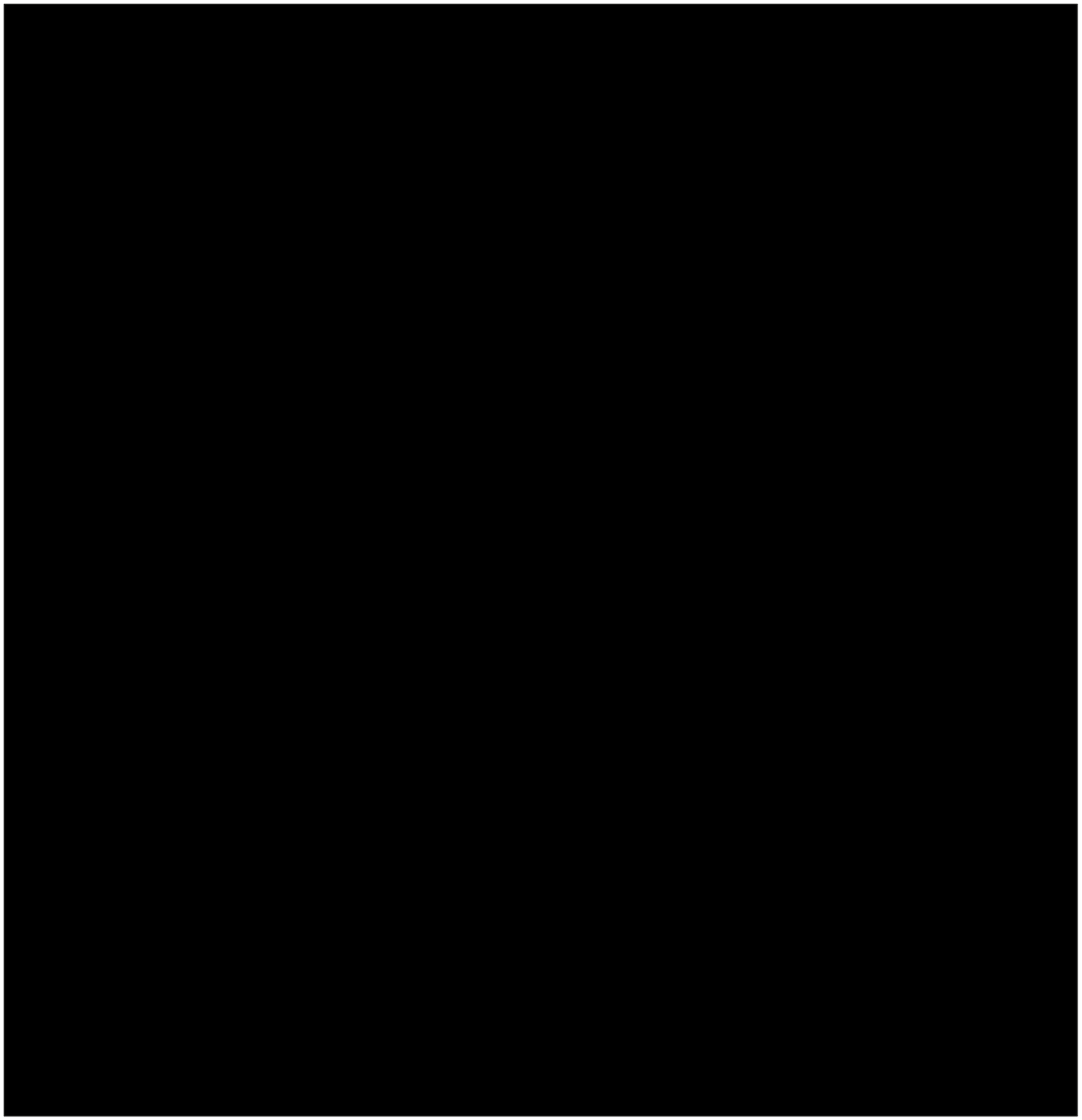
Preferred NMAs	Company comments	ERG comments
ERG NMA V2 (SI and MTD) **ERG preferred**	-	• Includes all available data for BA in patients receiving EZE at baseline from the CLEAR studies • Most robust and addresses the primary analysis requested in the NICE request for additional information
Tech engagement NMA (analysis 1 and 10a) **Company preferred**	• Most robust for decision-making and makes most use of the available data	• Includes patients with **no** prior EZE • Maintains these analyses were associated with high levels of clinical and statistical heterogeneity and are thus unreliable

Question for Committee:

What is the most appropriate NMA to inform the analysis?

Cost effectiveness results

Summary of company model

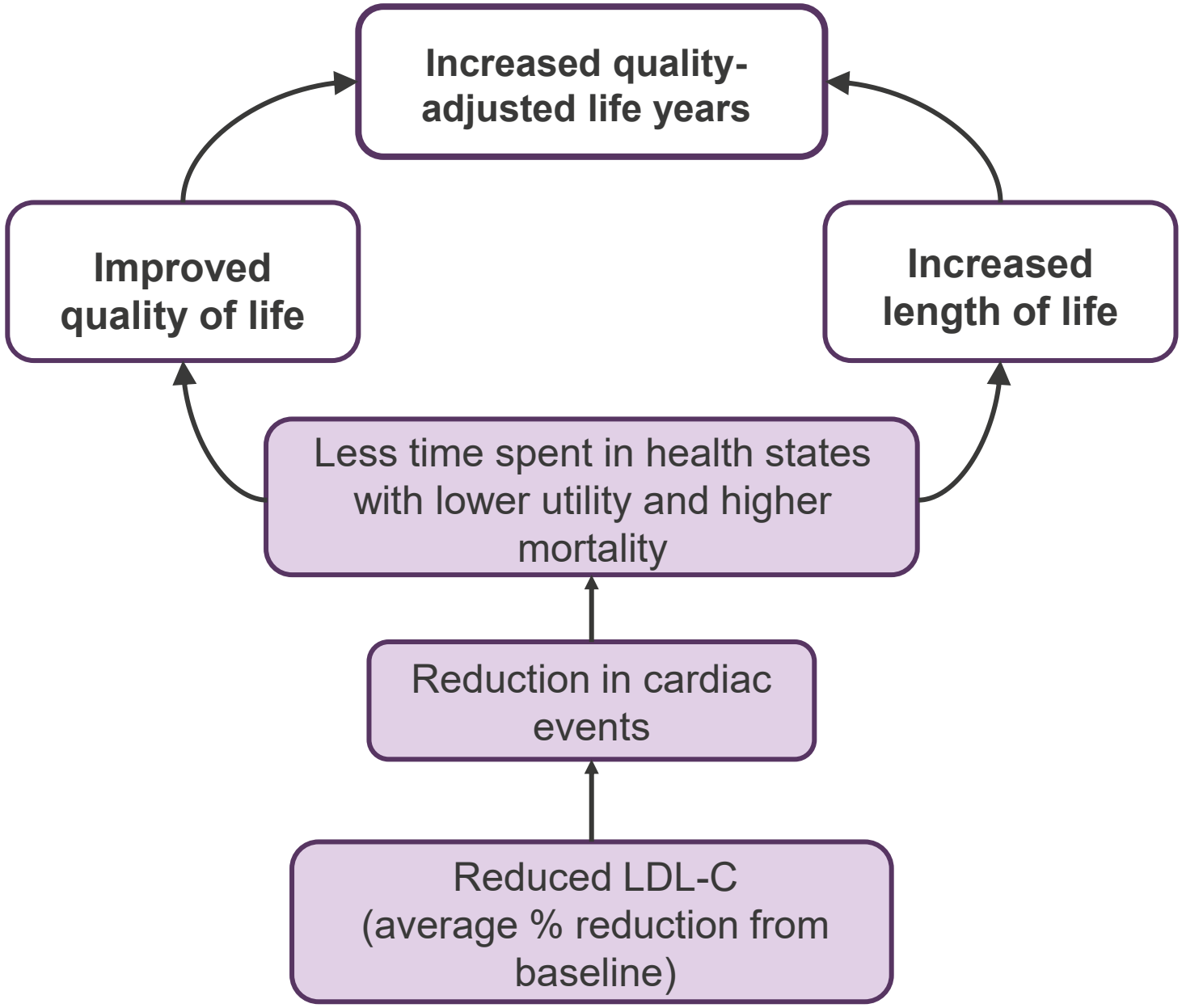


- Time horizon set to lifetime (55 years)
- Health states are myocardial infarction (MI), unstable angina (UA), stable angina (SA), ischaemic stroke (IS), and transient ischaemic attack (TIA).
- Each CV event also includes post-event tunnel states: 0 to 1-year post-CV event; 1 to 2-year post-CV event; and, > 2 years post-CV event.
- Transitions from the IS health state to other CV health states are blocked as moving to these health states would result in an increase in a patient's quality of life which is clinically implausible
- Primary prevention cohort enter in the "High risk for ASCVD" health state
- Secondary prevention cohort to enter the model in the 3-year+ post-event state

Summary of company model

Overview of how quality-adjusted life years accrue in the model

- No HRQoL data was collected in the bempedoic acid or FDC trials
- HRQoL estimates were based on published literature and regression equations
- HRQoL in the model varied according to CV events, health state, age and gender
- No adverse events were included in the model.



Cost effectiveness results: Overview

Relating issue from ACM1	Included in Company preferred analysis	Included in ERG preferred analysis
Issue 2. Previous and/or concomitant therapy	Patients with prior EZE and without prior EZE	Only patients with prior EZE
Issue 3. Baseline LDL-C from PCSK9i eligibility	From all patients No adjustment for PCKS9i eligibility	From all patients No adjustment for PCKS9i eligibility but has been presented in scenario analysis
Issue 4. Subgroup analyses by CV risk and HeFH	Not presented in primary or scenario analysis*	Not presented in primary or scenario analysis
Issue 5. Primary and secondary prevention subpopulation	Not possible for primary analysis Not presented in scenario analysis	Not presented in primary or scenario analysis
Issue 5a. CV event history and risk data	No additional data provided	Not presented in primary analysis Presented in scenario analysis
Issue 6: Preferred NMA	Tech engagement analyses • Analysis 1 for population 2 • Analysis10a for population 4	ERG NMA V2 • SI V2 for population 2 • MTD V2 for population 4
Issue 7. 12-week study data cut off and evaluation of treatment waning	No additional data provided	No additional data provided

* Presented at ACM1 but not updated at ACM2

Summary probabilistic ICER results for BA FDC

- Results provided for BA/EZE FDC (cheaper combination and efficacy assumed equivalent)
- Results for EVO have not been presented, as a class-effect has been assumed and ALI is the cheaper PCKS9i (£4,437.79 for EVO and £4,383 for ALI)

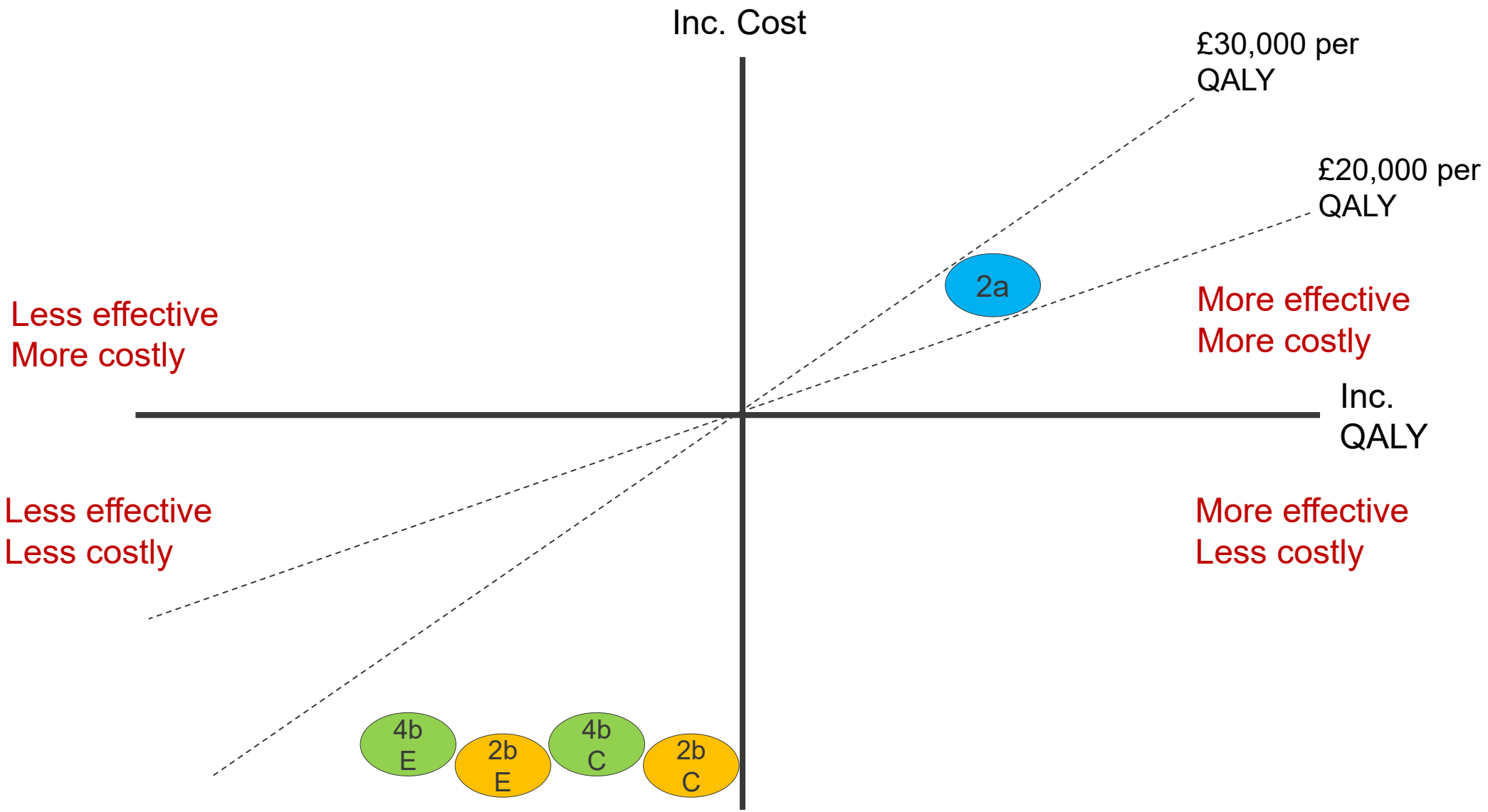
Probabilistic results from ERG and Company for Company analyses (£/QALY)

Analysis	PSA estimate	Statin intolerant		Maximally tolerated statin
		Position 2a	Position 2b (south-west quadrant)	Position 4b (south-west quadrant)
ERG NMA V2 (ERG preferred)	ERG	£23,824	£84,531*	£55,388*
Tech engagement analysis (Company preferred)	Company	£23,969	£416,292 *	£114,181 *

Position 2a = FDC vs EZE
Position 2b and 4b = FDC vs ALI

*using list price for ALI and EVO

Cost-effectiveness plane



E is ERG preferred
C is Company preferred

Scenario and Additional analysis

Committee's request: Scenario Analysis

Committee concerns at ACM1: Populations eligible for ALI or EVO not informed by studies that only reflect patients eligible for PCSK9i. Populations not eligible for ALI or EVO were not informed by studies that only reflect patients ineligible for PCSK9 inhibitors

Committee preference/request	Relating issue from ACM1	Company response
Provide a scenario analysis using a network of studies that reflects the eligibility criteria for PCSK9i (2a = ineligible) (2b&4b = eligible)	Issue 3. Baseline LDL-C in subpopulations not eligible for ALI and EVO Issue 6. Preferred NMA	The baseline characteristics and efficacy data for equivalent patient subpopulations are not available from the PCSK9i NICE appraisals or any other published sources for use in the company NMAs. However, have provided % change in LDL-C for patients in BA studies meeting these criteria
Provide results where baseline LDL-C levels to reflect the intended positioning for bempedoic acid (from patients who received prior EZE and according to PCSK9i eligibility)		LDL-C levels are provided but no statistical tests for differences between 'prior EZE patients' and 'all patients' were performed

Recap: PCSK9i (EVO/ALI) recommendations

LDL-C concentrations above which ALI and EVO are recommended	Without CVD	With CVD	
		High risk of CVD[1]	Very high risk of CVD[2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l	

[1]High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease.

[2]Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

PCSK9i eligibility

Committee concerns at ACM1: Populations eligible for ALI or EVO not informed by studies that only reflect patients eligible for PCSK9i. Populations not eligible for ALI or EVO were not informed by studies that only reflect patients ineligible for PCSK9 inhibitors

Company: Across the trials, the percentage reduction was similar in patients meeting the criteria for PCSK9i therapy and those who do not

Study	PCSK9i non-eligible		PCSK9i eligible	
	N	Percentage reduction in LDL-C at 12 weeks vs placebo	N	Percentage reduction in LDL-C at 12 weeks vs placebo
Clear Wisdom (pop 4)	596	[redacted]	183	[redacted]
Clear Harmony (pop 4)	2030	[redacted]	200	[redacted]
1002-FDC	192	[redacted]	190	[redacted]
Clear Tranquillity (pop 2)	251	[redacted]	18	[redacted]
Clear Serenity (pop 2)	278	[redacted]	67	[redacted]

ERG

- The percentage reduction for [redacted] was similar in patients meeting the criteria for PCSK9i therapy compared to in those who do not.
- However, the [redacted].
- The ERG therefore does not consider it possible to conclude that the impact of BA is independent of the PCSK9i eligibility status of patients.

PCSK9i eligibility – prior EZE vs all patients

Committee request

- Provide results where baseline LDL-C levels reflect the intended positioning for bempedoic acid (from patients who received prior EZE and according to PCSK9i eligibility) (Issue 2 and 3)

ERG

- Except for CLEAR Serenity, baseline LDL-C levels are generally higher in patients with prior EZE use

Data must be interpreted with caution due to the small patient numbers receiving prior EZE and the limited data used to determine PCSK9i eligibility.

- From baseline (LDL-C from all patients) the ICER increased by around £4,000 in position 2a (patients with prior EZE and ineligible for PCKS9i)
- From baseline (LDL-C from eligible for PCSK9i) the ICER increased by around £1,000 in position 2b and decreased by around £4,000 in position 4b (patients with prior EZE and eligible for PCSK9i)

The ERG does not consider these scenarios to be reliable for decision making.

Question for Committee:

Should the cost-effectiveness of BA be modelled based on appropriate LDL-C levels, and does the additional analysis sufficiently support recommendation under current PCSK9i criteria?

Committee's request: Additional Analysis

Committee concerns at ACM1: Patient characteristic being used to inform prior CV events were not taken from CLEAR trials.

Committee preference/request	Relating issue from ACM1	Company response
Use data from CLEAR trials to inform baseline risk (QRISK3)	Issue 5a. CV event history and risk data	Parameters required to estimate QRISK3 score not captured in trial datasets.
Use prior CV events from the CLEAR trials to estimate prior events in the model		These data are not available from the CLEAR studies

ERG

- ERG consider using prior CV event types from Ward et al., 2007 instead of CLEAR trials a reasonable alternative

ERG additional analysis – Patient characteristics from the CLEAR trials

ERG scenario analysis using baseline CV risk for primary prevention accepted in CG181 (and TA385 (population 2a)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALYs)
ERG SI NMA V2 (ERG **preferred)** a 10-year risk of **30%** for MI, IS or CV death					
EZE	£10,082	9.03	-	-	-
BA/EZE FDC	£14,658	9.22	£4,576	0.19	**£23,824**
ERG SI NMA V2 (using a 10-year risk of **20%** for MI, IS or CV death)					
EZE	£7,904	9.57	-	-	-
BA/EZE FDC	£12,724	9.72	£4,821	0.15	**£31,469**

ERG

- Using ERG NMA SI V2 – ICER increases by approx. £7,500
- Should be viewed as conservative as it is not an unreasonable assumption that the baseline risk in the company model (a 10-year risk of 30% for MI, IS or CV death) would be higher than in CG181 (CVD guideline) and TA385 (EZE guideline) because the proposed position of bempedoic acid is after EZE where patients are likely to be at a higher CV risk.

Question for Committee:

Is it reasonable to use sources other than the CLEAR trials to inform:

a) Baseline CV risks in a primary prevention population

b) CV event history in a secondary prevention population

Key issues to be resolved

Issue	Committee Decision
2. Previous and/or concomitant therapy	The impact of previous ezetimibe therapy on treatment effect is uncertain and the subgroup analyses are likely to be underpowered
3. Baseline LDL-C in subpopulations not eligible for ALI and EVO	Committee agree with ERG that using LDL-C levels based on alirocumab/evolocumab eligibility is preferred
4. Subgroup analyses by CV risk and HeFH	Not appropriate to assume no difference in treatment effect across CV risk and HeFH subgroups
5. Primary and secondary prevention subpopulation	Use appropriate trials to inform treatment efficacy for primary and second prevention
5a. CV event history and risk data	Use appropriate CLEAR trials to inform prior CV events
6. Methodological uncertainty in the NMA	Neither ERG or company NMA optimal - prefer to see improved statistical fit, reduced heterogeneity, and comparability with related TAs
7. 12-week study data cut off and evaluation of treatment waning	If available, the latest data informing treatment effect should be used

Question for Committee:

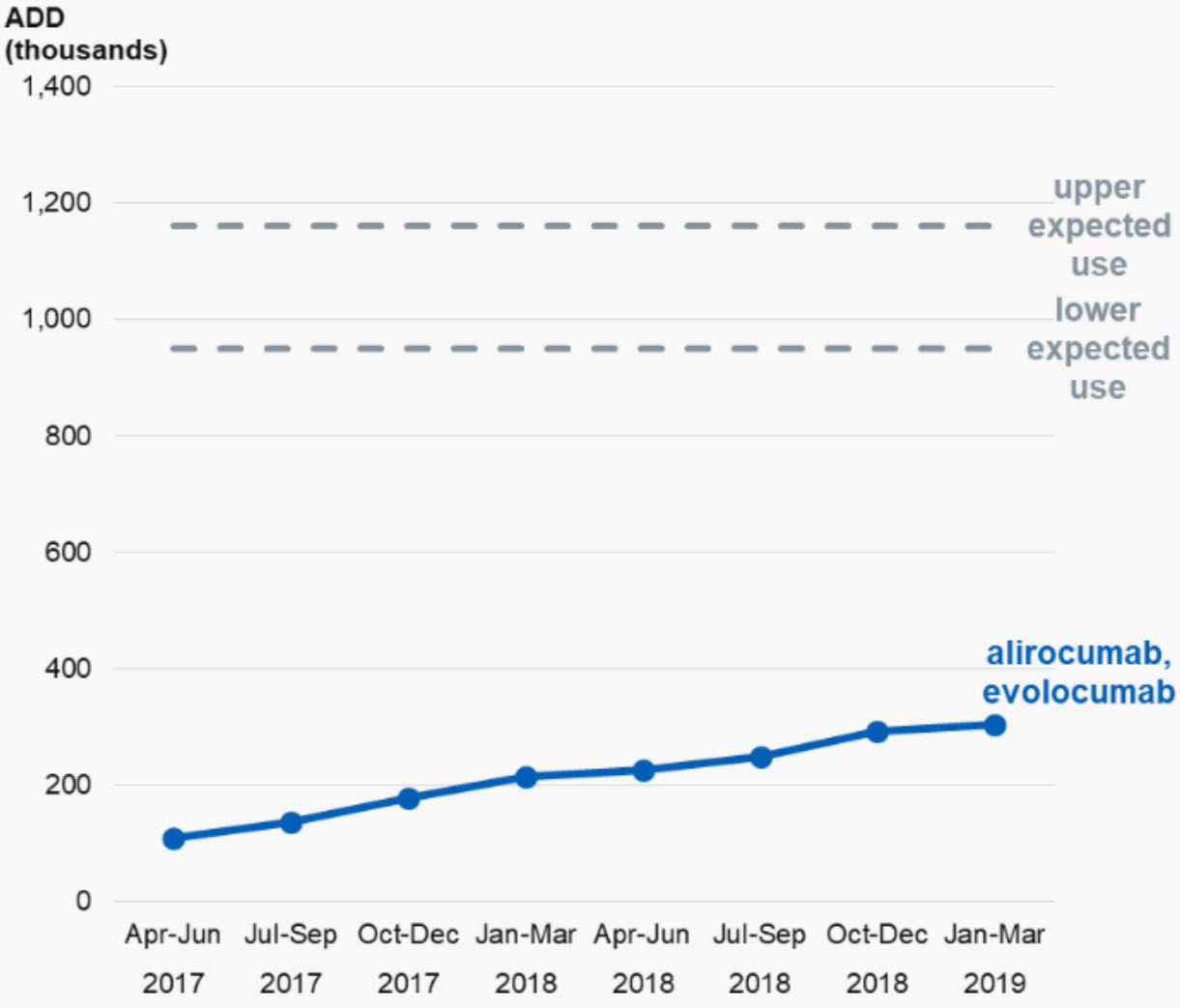
Have the primary and scenario analysis conducted by the company sufficiently resolved the uncertainties raised in ACM1?

Back-up slides

Access to PCSK9i

- October 2018 to September 2019, the annual volume of ALI/EVO used was between 65% and 72% lower than expected.
- The NHS accelerated access collaborative Rapid Uptake Working Group suggest patients are not navigated through the lipid management pathway appropriately and therefore very few actually get to the stage where PCSK9i's are considered.

Chart 7a: Alirocumab and evolocumab - observed use and range of expected use in primary and secondary care prescribing from April 2017 to March 2019



Source: NHS Digital