NICE National Institute for Health and Care Excellence

PART 1

REDACTED for public observers

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

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Company: Daiichi Sankyo

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Abbreviations

Abbreviation	
ALI	Alirocumab
BA	Bempedoic acid
BA/EZE FDC	Bempedoic acid / ezetimibe (180mg/10mg tablet) fixed dose combination pill
CVD	Cardiovascular disease
EVO	Evolocumab
EZE	Ezetimibe
FDC	Fixed-dose combination
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
IS	Ischemic stroke

Abbreviation	
LDL-C	Low-density lipoprotein cholesterol
LLTs	Lipid lowering therapies
LS	Least squares
MI	Myocardial infarction
NA	Not applicable
NC	Not calculable
NMA	Network meta-analysis
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
SA	Stable angina
THIN	The Health Improvement Network
TIA	Transient ischemic attack
VLD	Very low dose
VLDL	Very low-density lipoprotein

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).

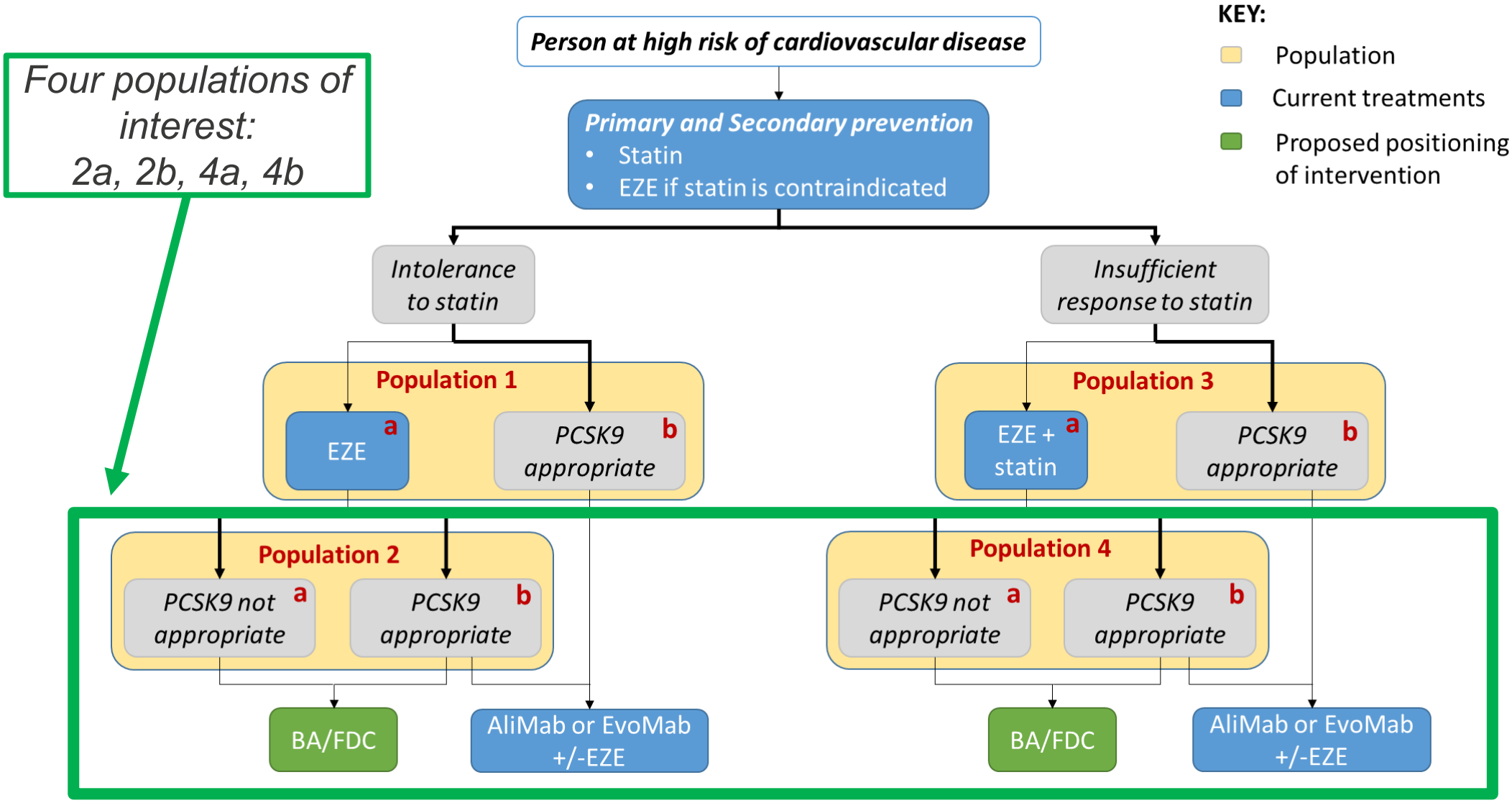
Bempedoic acid (Nilemdo/Nustendi, Daiichi Sankyo)

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)

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.

Recent NICE appraisals in mixed dyslipidaemia and primary hypercholesterolaemia

TA	Recommendation
385 – Ezetimibe (EZE) [a,*] [2016]	➢ Recommended as monotherapy in those for whom statin therapy is contraindicated. ➢ Recommended as monotherapy in those who are statin intolerant. ➢ Recommended with initial statin therapy if insufficient response to statin.
393 – Alirocumab (ALI) ** [2016]**	➢ Recommended for those who are statin intolerant, with or without previous EZE. ➢ Recommended for those who have had insufficient response to statin, with or without previous EZE + statin.
394 – Evolocumab (EVO) ** [2016]**	➢ Recommended for those who are statin intolerant, with or without previous EZE. ➢ Recommended for those who have had insufficient response to statin, with or without previous EZE + statin.

[a] Previously TA132 published in 2007

* Recommended for primary (heterozygous-familial or non-familial) hypercholesterolaemia.

**Recommended for primary hypercholesterolaemia or mixed dyslipidaemia.

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Recommendation of PCSK9i (EVO/ALI)

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	

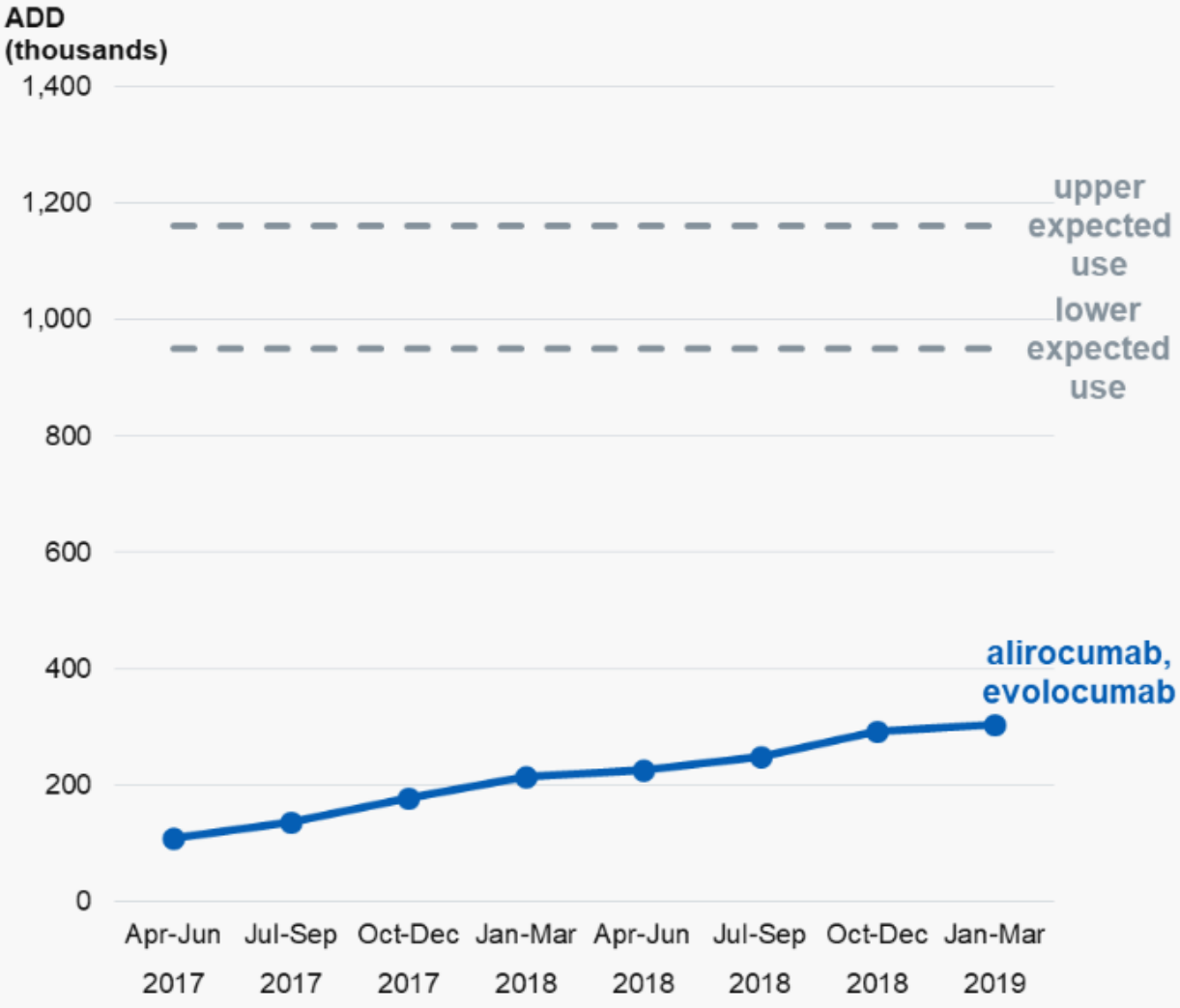
[1]High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial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

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

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 create vulnerable demographics.
- 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]

Clinical evidence: Overview of company's trials

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

Evidence Networks

Statin-intolerant population (population 2)
*networks for initial company submission

Maximally tolerated statin population (population 4)
*networks for initial company submission

- **Company initial submission NMAs: 44 studies in total** (Statin intolerant = 10 studies, Max dose statin = 36 studies; [note: 2 studies are included in both NMAs]).
- **Clarification stage: 31 studies in total** (Statin intolerant = 7 studies, Max dose statin = 25 studies; [note: 1 study is included in both NMAs]).
- **Technical engagement response NMA 5 (new company base case): 31 studies in total** (Statin intolerant = 7 studies, Max dose statin = 25 studies [1 study in both NMAs]).

Clinical evidence – Company's updated NMA results in maximally tolerated statin patients (population 4)

Treatment	Estimated difference in % change in LDL-C from baseline compared to ezetimibe at 12-weeks		
	Mean	95% CrIs	P value
BA + statin	[redacted]	[redacted]	0.6290
BA/EZE FDC + statin	[redacted]	[redacted]	0.1733
EVO + statin	[redacted]	[redacted]	< 0.0001
ALI (75mg) + statin	[redacted]	[redacted]	< 0.0001
ALI (150mg) + statin	[redacted]	[redacted]	< 0.0001
ALI (75mg) + statin + EZE	NA (only investigated in ODYSSEY Mono)		
ALI (150mg) + statin + EZE	NA (only investigated in ODYSSEY Mono)		

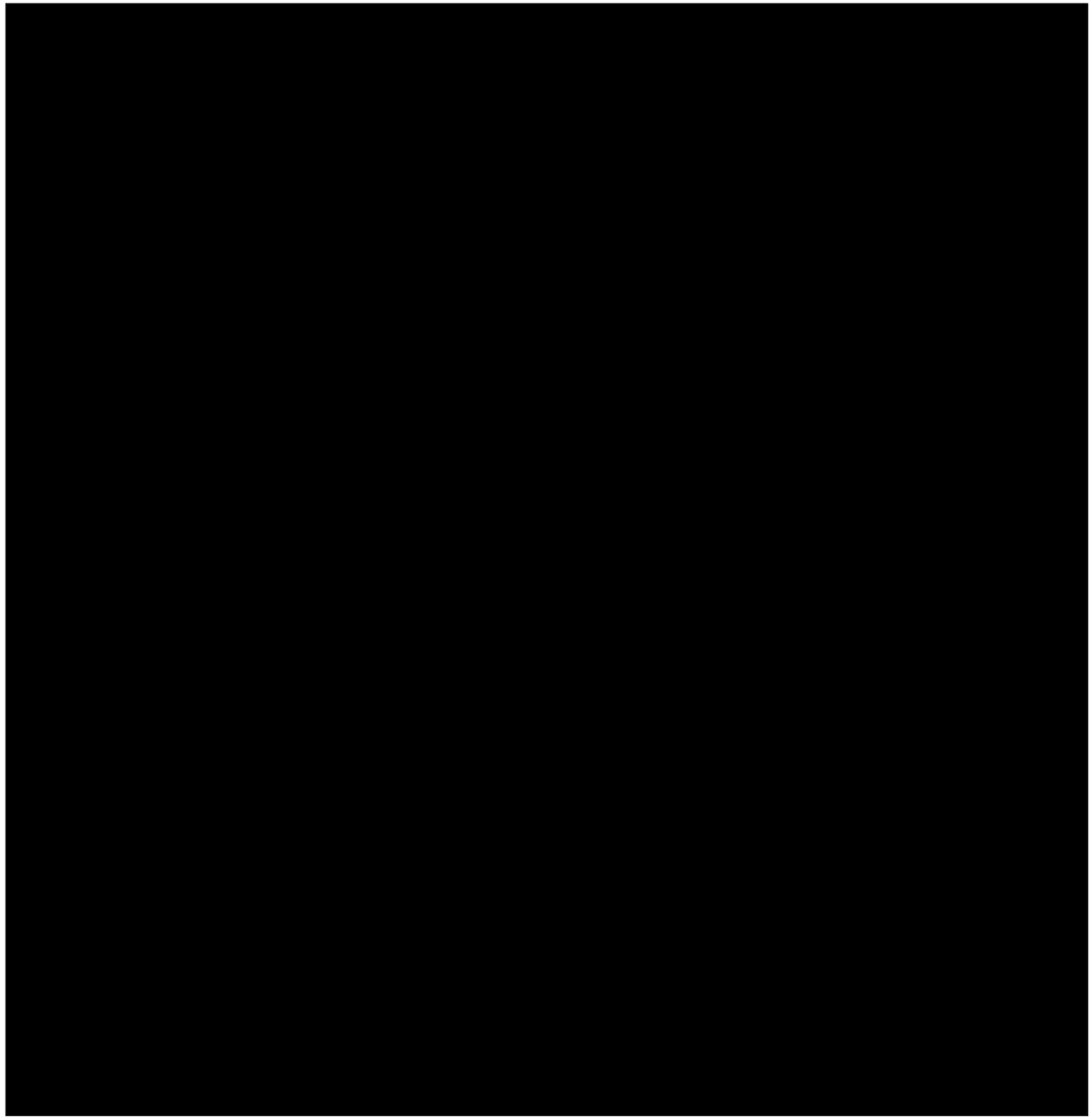
Updated base case following TE: NMA includes ODYSSEY LONGTERM (max dose with or without prior LLT and with prior EZE) and excludes ODYSSEY MONO (no prior LLT but should have been max dose).See Issue 6

Clinical evidence – Company's updated NMA results in statin-intolerant patients (population 2)

Treatment	Estimated difference in % change in LDL-C from baseline compared to ezetimibe at 12-weeks		
	Mean	95% CrIs	P value
BA	[redacted]	[redacted]	0.0985
BA+EZE	[redacted]	[redacted]	0.0024
EVO	[redacted]	[redacted]	0.0015
EVO+EZE	[redacted]	[redacted]	—
ALI (75mg)	[redacted]	[redacted]	0.0004
ALI (150mg)	[redacted]	[redacted]	0.0004

No update following TE, as no improvement observed in model fit in the new analyses conducted.

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 (Issue 5 resolved)

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
5	Consideration of subpopulation 2b, 4a and 4b as secondary prevention populations, and 2a as primary prevention (No FH)	The company agrees with changes to subpopulation.	The ERG's amendments are appropriate	**Yes**
5 (a)	Consistency of CV event history and risk data with the effectiveness data. Primary CV risks informed by Ward et al. 2007.	The company did not have full set of variables from CLEAR trials required to calculate primary CV risks.	The technical team agree with ERG that primary CV risks and event history should be taken from CLEAR trials.	**No**
8	HRQoL - across all populations (gender adjustment and multipliers)	The company agrees with the ERG's amendments	The ERG's amendments are appropriate	**Yes**
9	Costing of ALI/EVO administration and CV events	The company agrees with the ERG.	The ERG's suggested amendments in costing use for base case analysis are appropriate	**Yes**

Key issues

Unknown impact | Model driver | For discussion

Small impact | Resolved

Issue	Company base case	Technical team	Impact
1. The clinical pathway	Treatment additive, unlikely to be used as monotherapy	Issue informs larger issues 2,3 & 6	
2. Previous and/or concomitant therapy	No clinically significant impact on direction of effect	Clinical opinion that previous EZE will have impact but limited subgroup analysis by company	
3. Baseline LDL-C in subpopulations not eligible for ALI and EVO	Merged LDL-C reflective of current 'real world' uptake of PCSK9i	Potential overestimation of cost-effectiveness	
4. Subgroup analyses by CV risk and HeFH	Treatment effect is same across CV risk and HeFH	Data limitation – unclear if results are generalizable	
5. Primary and secondary prevention subpopulation	CLEAR studies previous CV event data	Impact on ICER for subpopulation 2a	
6. Methodological uncertainty in the NMA	Company NMA informs analysis across all subgroup	Poor model fit in Company NMA and high heterogeneity	
7. 12-week study data cut off and evaluation of treatment waning	24-week data cut off – no long term data provided	Longer timeframe data should be provided to determine impact on results	
8 and 9. HRQOL and costing of ALI/EVO, and CV events	Utilities and costs data required adjustments in line with previous changes	ERG modelling of utilities and costing of administration preferred	

Issue 2: Previous and/or concomitant therapy

TE questions on impact of previous EZE treatment and concomitant statin therapy

Background

- The impact of previous EZE therapy and concomitant therapy on the treatment effect of BA is uncertain
- With the exception of the CLEAR Tranquillity study, BA studies mainly include patients who were not previously treated with EZE at baseline or who have undergone a washout period of lipid lowering therapies

Company

- Pooled analysis of subpopulation 2 (CLEAR Tranquillity and CLEAR Serenity) and subpopulation 4 (CLEAR Harmony and CLEAR) showed mean percentage LDL-C reduction for the groups with and without previous EZE were [redacted] and [redacted]
- Direction of difference in effect was opposite for populations 2 and 4 – mechanistically difficult to explain

ERG

- considers the difference between the presence and absence of previous EZE at baseline ([redacted] and [redacted] to be clinically significant
- Consideration that analysis is based on *post-hoc* subgroups and lacking methodological detail

Tech team

- Uncertain if results of analyses presented by the company are generalisable to the subpopulations of interest.
- **The pooled analyses did not inform cost-effectiveness evidence**. The ERG's PSA results taking this uncertainty into account, indicate the ICER rises slightly.

Issue 2: Previous and/or concomitant therapy

Technical engagement response:

Company:

- No recognised threshold for the minimum clinically significant difference in LDL-C reduction. Therefore, it is not possible to comment on the clinical significance of these differences.

Clinical expert:

- Generalising clinical effectiveness of previous EZE depends on the length of time treated with EZE (impact on outcomes) and time since discontinued (impact on lipid profile) - **Adequate washout period before BA therapy may mitigate effect**
- Concomitant statin may attenuate the treatment effect of BA compared with BA monotherapy

Comparator company:

- The SmPC for BA reports pharmacokinetic interactions between BA and statins, noting that BA may potentially increase the risk of myopathy and concomitant use of BA is contraindicated in patients taking >40mg simvastatin

ERG:

- Does not consider the use of covariate adjustment for baseline EZE use to be appropriate given that BA is being positioned by the company in patients with prior EZE therapy

Is it acceptable to use clinical effectiveness results that are based on a population that may or may not have had previous EZE to people who have had previous EZE?

Issue 3: Baseline LDL-C in subpopulations not eligible for ALI and EVO

TE questions on access to PCSK9i and baseline LDL-C in non-eligible subpopulations

Background

- The CLEAR trials contained people who were *(subpopulations 2b/4b)* and were not *(subpopulations 2a/4a)* eligible for ALI and EVO
- The baseline LDL-C levels used in the company model were **not** separated by *non-eligible subpopulations*

Baseline characteristics based on CLEAR studies

Characteristic (mean baseline LDL-C (mmol/L))	Population 2 [a] (no or low dose statin)	Population 4 [b] (max dose statin)
Non-PCSK9i eligible (subpopulation a)	[redacted]	[redacted]
Non-PCSK9i eligible data used to inform the economic analysis (subpopulation a)	[redacted]	[redacted]
PCSK9i eligible data used to inform the economic analysis (subpopulation b)	[redacted]	[redacted]

[a] based on patients included in CLEAR Tranquility and CLEAR Serenity
[b] based on patients included in CLEAR Wisdom and CLEAR Harmony
[c] based on patients included in CLEAR Wisdom and CLEAR Harmony and 1002-FDC-053
Data source: Table 21 in ERG report

Issue 3: Baseline LDL-C in subpopulations not eligible for ALI and EVO

Company

- The approach to use LDL-C levels from all patients is appropriate because only limited numbers of patients eligible for ALI/EVO actually receive treatment
- Positioning eligible patients in positions 2a and 4a (non-eligible subpopulations) more accurately reflects NHS patients

Tech team

- Potential overestimation of cost-effectiveness of BA compared to EZE.
- Small impact on ICERs

ERG

- Cost effectiveness of BA should be modelled based on the appropriate LDL-C levels for the appropriate subpopulations.

TE response:

Company:

- Does not consider baseline LDL-C levels for positions 2a and 4a to be adequately reflected by the baseline LDL-C for patients not eligible for ALI/EVO

Clinical expert:

- PCSK9i use in clinical practice could be underutilised
- Baseline LDL-C levels will differ across subpopulations

Comparator company:

- Company's implementation of baseline LDL-C levels for comparison against EVO/ALI is inconsistent with levels at which EVO/ALI are recommended – as per NICE eligibility criteria

Is it appropriate to use the mean LDL-C data from all patients in the non-eligible subpopulations (2a & 4a)?

Issue 4: Subgroup analyses by HeFH

TE questions on subgroup analyses by HeFH

Background

- Scope identified that the subgroup of people with HeFH were important, as expected different baseline risks of mortality, CV events and HRQoL
- These subgroups inform the recommendations for ALI and EVO (TA394 and TA393)

Company

HeFH

- Number of HeFH patients included phase 3 studies are small - proportion of patients with HeFH was reported to be less than 6% in CLEAR Wisdom, less than 5% in CLEAR Harmony and less than 3% in CLEAR Serenity but not reported for CLEAR Tranquillity (Table 13 in company submission)
- A subgroup analysis for the pooled data from CLEAR Harmony and CLEAR Wisdom found interaction by presence of the HeFH status (HeFH vs. non-HeFH) was **not** significant ([redacted]); the treatment effect in terms of LDL-C reduction at 12 weeks was significant in both the HeFH group ([redacted]) and the non-HeFH group ([redacted])

Issue 4: Subgroup analyses by HeFH

ERG

- The subgroup analyses provided by the company have low patient numbers and are underpowered to detect between-subgroup differences in treatment effectiveness
- ERG prefers to assume all subpopulations are representative of patients *without* HeFH
- Analyses based on efficacy data directly relevant to the intended subpopulation should be conducted in order to provide reliable cost effectiveness estimates.

Tech team

- It is unclear if the analyses presented by the company or ERG are generalisable to a mixed cohort of primary and secondary prevention patients, with and without HeFH.

Technical engagement response:

Company: Presented 7 subgroup analyses according to CV/HeFH risk

Clinical expert 1:

- Patients with HeFH have a far greater risk of CVD, would expect far greater benefit from LLT

Clinical expert 2:

- Impact on HeFH depended on underlying genetic issue

Comparator company:

- Blended approach potential to mask differential cost-effectiveness across subgroups (HeFH and primary/secondary prevention) and not consistent with PCSK9i appraisals

ERG:

- Subgroup data provided by company assume same treatment effect – ICER correlated with baseline LDL-C levels

Is it appropriate to assume treatment effect is similar in people with/without HeFH?

Issue 4: Subgroup analyses by CV risk

TE questions on subgroup analyses by CV risk

Background

- The company did not present cost-effectiveness analyses in subgroups based on CV risk
- Cost-effectiveness results by CV risk should be provided in order to allow for consistent decision making with previous NICE appraisals

Company

CV Risk:

- The treatment effect for BA and BA/EZE FDC was consistent for patients with and without prior atherosclerotic cardiovascular disease, the P-values for the subgroup interaction were not significant
- The full set of variables required to reliably calculate risk using the QRISK3 algorithm is currently not available from the CLEAR studies – previous comparator TA's did not use studies to calculate QRISK2/3
- Model generalisable to patients with primary hypercholesterolaemia or mixed dyslipidaemia in the UK in terms of baseline characteristics and the treatment pathway (CLEAR trials included [redacted] UK study sites)

Issue 4: Subgroup analyses by CV risk

ERG

- High proportion of secondary prevention patients are included in the economic analyses and consider it unreliable to use estimates from the wider population to infer cost-effectiveness of the intervention for specific subgroups

Technical engagement response:

Company: Presented 7 subgroup analyses according to CV/HeFH risk

Clinical expert 1:

- Treatment effect likely to be higher in high CV risk and lower in low CV risk populations

Clinical expert 2:

- Appropriate to assumes similar treatment effect in CV risk given past TAs

Comparator:

- Blended approach potential to mask differential CE across subgroups and not consistent with PCSK9i appraisals

ERG:

- Baseline LDL-C levels were estimated for each subgroup based on analyses of the patient-level data in the CLEAR trials
- Subgroup data provided by company assume same treatment effect – ICER correlated with baseline LDL-C levels

Is it appropriate to assume treatment effect is similar in people with different CV risk?

Issue 6: Methodological uncertainty in the NMA

TE questions on the company's NMA vs ERG NMA for decision making

		ERG NMA			Company updated NMA (post TE)		
		Estimated difference in % change in LDL-C from baseline compared to EZE					
Treatment		Mean	95% CI	P value	Mean	95% CI	P value
Max tolerated statin (pop 4)	BA + EZE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ALI + EZE	[redacted]	[redacted]	[redacted]	NA (only investigated in ODYSSEY Mono)		
Statin intolerant (pop 2)	BA + EZE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ALI + EZE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: *p*- value relates to the difference in percentage change from baseline in LDL-C compared with placebo.
[a] These data are used in the economic model and are for ALI 150 mg alone versus EZE, they therefore can not be compared with the ERG NMA results as patients in only one arm of the company's NMA have received EZE whereas both treatment arms of the ERG's NMA have received EZE

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Issue 6: Methodological uncertainty in the NMA

Background

- Company NMA has been critiqued for not using generalisable evidence and for heterogeneity.
- The ERG NMA may not include all relevant studies and, whilst potentially more robust, offers evidence for only one comparison for each population.

ERG

- ERG NMA only considered studies or subgroups in patients with prior ezetimibe at baseline suitable for inclusion in its two NMAs
- ERG NMA to more closely reflect a population with prior ezetimibe therapy and to have substantially less clinical heterogeneity compared to the company's statin intolerant NMA.

Company

- In response to the ERG report, company performed further sensitivity and scenario analyses for the updated NMAs.
- Company update to maximally tolerated statin NMA: ODYSSEY LONGTERM included (with or without prior LLT and with prior EZE), ODYSSEY Mono excluded (no prior LLT), baseline LDL-C as a covariate

Tech team

- The technical team are concerned that results from both the company updated NMA and the ERG NMA have considerable uncertainty.
  - Company NMA includes patients with previous EZE and no previous EZE. High statistical and clinical heterogeneity
  - ERG NMA does not include all data from appropriate BA studies

Issue 6: Methodological uncertainty in the NMA

Technical engagement response:

Company:

- Presented 10 different NMAs for the maximally tolerated statin population
- Company preferred NMA 5 which included ODYSSEY LONGTERM and excluded ODYSSEY Mono, it also had baseline LDL-C as a covariate

ERG:

- In new company base case (NMA 5) for maximally tolerated statin population, there is poor model fit and high levels of statistical and clinical heterogeneity
- ERG prefers company's NMA 9b (scenario presented at technical engagement) which included ODYSSEY LONGTERM and excluded ODYSSEY Mono, had baseline LDL-C as a covariate, and 24-week data removed where 12-week data was included. However, ERG would prefer all covariate adjustments applied and to use only prior EZE subgroup
- The mean change in LDL-C with FDC (i.e. BA +EZE) suggest [redacted] in NMA 9b compared to NMA 5
- **Still considers the ERG's NMA to be the most appropriate (results exclusively in patients with prior EZE).** However, considerable uncertainty in whether results are optimistic or pessimistic with regards to the treatment effect of BA.

Should the company NMA or ERG NMA be used to inform results?

Issue 7: 12-week study data cut off and evaluation of treatment waning

TE questions on data cut off, stopping rule and potential waning effect with BA

Background

- Primary efficacy outcome of all relevant BA and FDC trials was percentage change from baseline LDL-C at 12 weeks

Tech team

- Impact on results unclear – comparator also subject to potential waning
- Evidence on waning effect may merit consideration of stopping rules

Is waning effect likely and substantial?

Company

- 24-week data not appropriate given primary endpoint for phase 3 studies was powered for measure at 12-weeks
- The open-label extension study (1002-050) reported improvements in LDL-C were durable through 52 weeks (−15.18 after 12 weeks and −15.82 after 52 weeks). [redacted] (EPAR report, Table 21)
- No waning of treatment effect is expected. Small observed differences in study expected to be discontinuation, which was accounted for in model (6.7%)

Technical engagement response:

Clinical expert:

- Stopping rule unlikely - only if experience AE or long-term benefit and lowering dose

Comparator company:

- Suboptimal BA+EZE in high-risk patients may preclude their access to optimal therapy (EVO/ALI)

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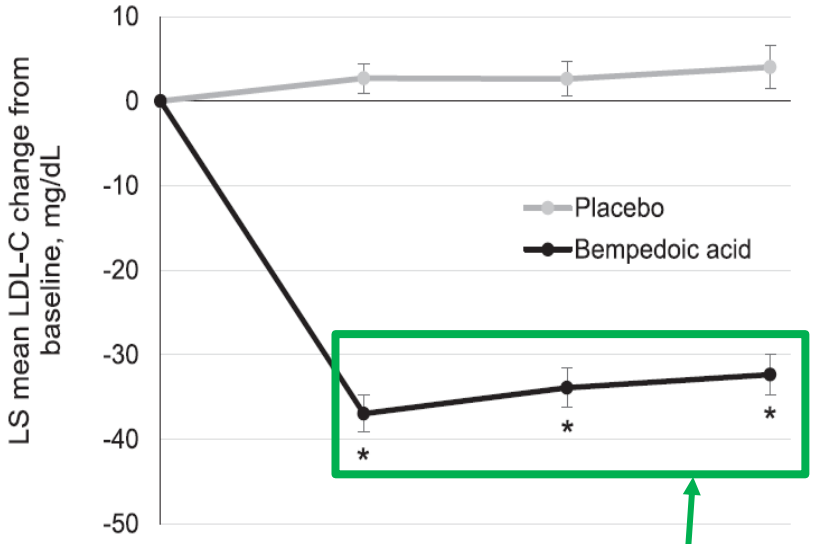
Issue 7: Potential waning effect in CLEAR Studies

CLEAR Tranquility (BA + EZE)
Statin Intolerant Population (2)

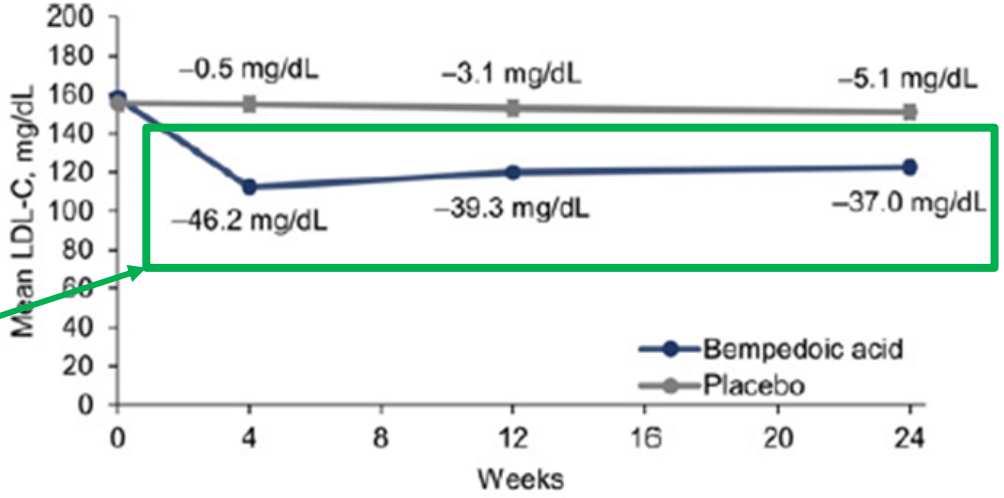


	Baseline	Week 4	Week 8	Week 12
Placebo, n	88	85	82	82
Bempedoic acid, n	181	180	173	175

ERG

- ERG suggested waning effect between 4 and 24 weeks in CLEAR Serenity and 4 and 12 weeks in CLEAR Tranquillity

CLEAR Serenity (BA)
Statin Intolerant Population (2)



Bempedoic acid, n	234	229	224	217
Placebo, n	111	106	107	106

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Cost effectiveness results: Overview

- Company presented results using price for both BA and EZE separately and BA/EZE FDC
- ERG presented results using the price the FDC only (cheaper combination)
- All results presented in the section consider the FDC price only

Issue*	Included in Company base case	Included in ERG base case
3: Baseline LDL-C levels	LDL-C from all patients	**Preferred**: LDL-C levels from patients not eligible for ALI/EVO in subpopulations 2a and 4a **Alternate**: LDL-C from all patients not eligible for ALI/EVO (i.e. company base case)
4. Subgroup based on HeFH/CV risk	No. Company included subgroup analyses	Not presented
5: Subpopulations 2b,4a, and 4b as secondary prevention	Relevant subpopulation enters the model in the 3-year+ post-event health state	Relevant subpopulation enters the model in the 3-year+ post-event health state
6: NMA	Company preferred	ERG preferred
8-9: Costs & health states	ERG preferred	ERG preferred

* Issues 1,2 and 7 were not considered in the modelling

Probabilistic ICERs for population 2a and 4a

	Population 2a Statin-intolerant	Population 4a Max dose
	FDC vs EZE	FDC vs EZE
Company revised base case	£23,969	£63,138
ERG base case[a] (Tech team preferred assumption)	£24,641	£62,874*
ERG alternative base case[b]	£24,264	£53,056*

Probabilistic ICERs were generated by the ERG
* Indicates deterministic value
[a] ERG NMA (Issue 6) and LDL-C levels from patients not eligible for ALI/EVO (Issue 3)
[b] ERG NMA (Issue 6) and LDL-C levels from all patients (Issue 3)

Probabilistic ICERs and NMB for population 2b (south-west quadrant)

At a £20,000 and £30,000 per QALY threshold, bempedoic acid FDC would be considered cost-effective in subpopulations 2b, as bempedoic acid FDC provided a positive NMB compared with ALI and EVO.

	Population 2b, Statin-intolerant					
	FDC vs ALI			FDC vs EVO		
	ICER	NMB £20,000	NMB £30,000	ICER	NMB £20,000	NMB £30,000
Company revised base case	£416,292	£24,158[b]	£23,555[b]	£290,094	£24,025[b]	£23,136[b]
ERG base case and Tech team preferred assumption[a]	£104,930*	£21,054[c]	£18,554[c]	NC	-	-

Company's probabilistic ICERs were generated by the ERG
ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs than comparators but is also less costly).
* Indicates deterministic value
[a] Company revised assumptions with the ERG NMA (Issue 6)
[b] ERG results reversed to show FDC vs ALI/EVO rather than ALI/EVO vs FDC
[c] Values calculated by NICE technical team using rounded incremental costs and QALY results

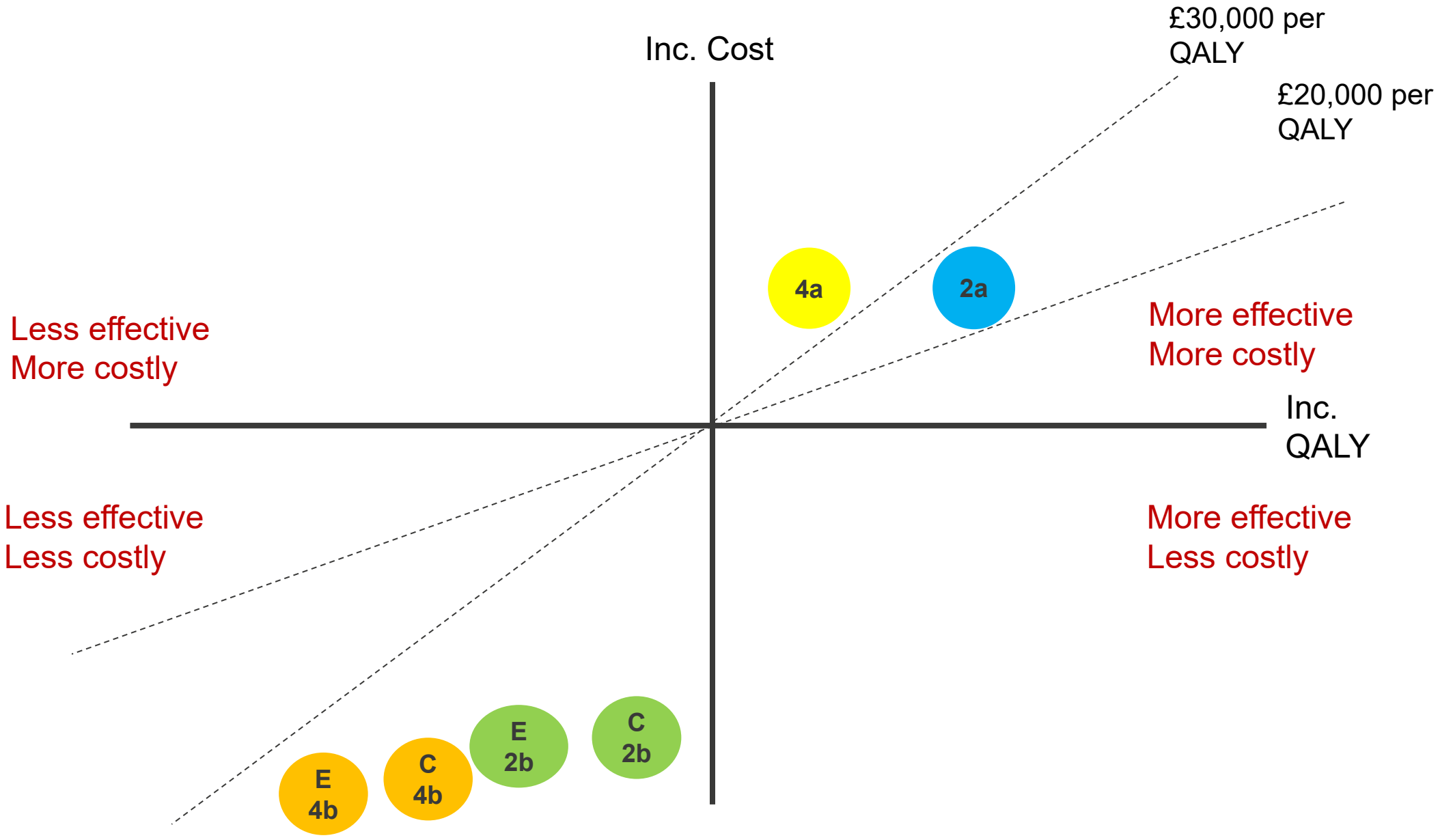
Probabilistic ICERs and NMB for population 4b (south-west quadrant)

At a £20,000 and £30,000 per QALY threshold, bempedoic acid FDC would be considered cost-effective in subpopulations 4b, as bempedoic acid FDC provided a positive NMB compared with ALI and EVO.

	Population 4b , Max dose					
	FDC vs ALI			FDC vs EVO		
	ICER	NMB £20,000	NMB £30,000	ICER	NMB £20,000	NMB £30,000
Company revised base case	£114,181	£20,518[b]	£18,376[b]	£69,088	£18,281[b]	£14,638[b]
ERG base case and Tech team preferred assumption[a]	£63,495*	£17,534[c]	£13,534[c]	NC	-	-

Company's probabilistic ICERs were generated by the ERG
ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs than comparators but is also less costly).
* Indicates deterministic value
[a] Company revised assumptions with the ERG NMA (Issue 6)
[b] ERG results reversed to show FDC vs ALI/EVO rather than ALI/EVO vs FDC
[c] Values calculated by NICE technical team using rounded incremental costs and QALY results

Cost-effectiveness plane



E is ERG preferred
C is Company preferred

Additional scenario analysis 1

- ERG assumed the same baseline treatment effect for EZE as the company has used (i.e. [redacted] in the max dose statin NMA and [redacted] in the statin intolerant NMA, respectively).
- The scenarios reported here assume all patients with prior EZE maintain their pre-existing benefit from EZE treatment but do not gain any additional benefit from EZE (i.e. the benefit is 0%, or no change from baseline).

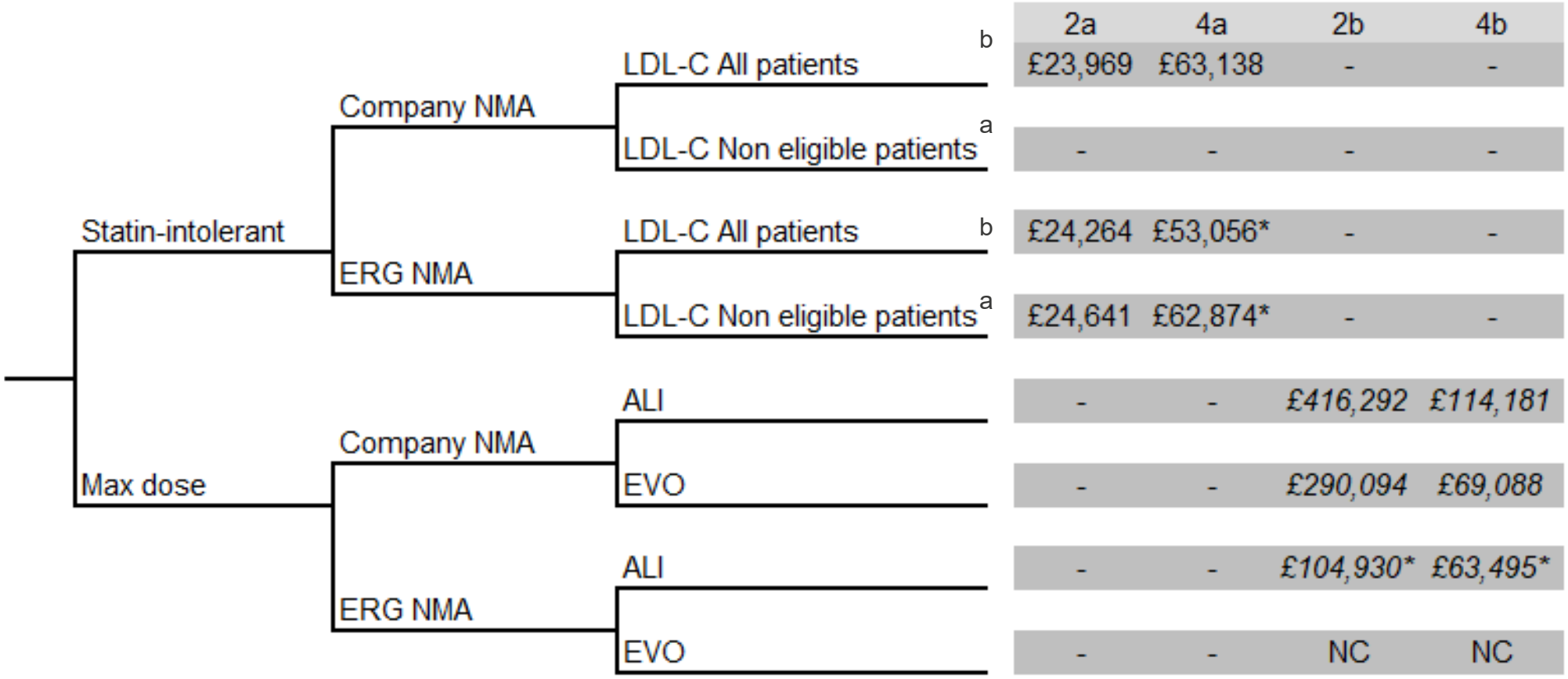
	Population 2a	**Population 4a**	**Population 2b** *South-west ICER*	**Population 4b** *South-west ICER*
	FDC vs EZE	**FDC vs EZE**	**FDC vs ALI**	**FDC vs ALI**
Company revised base case ([redacted] in the max dose statin NMA and [redacted] in the statin intolerant NMA)	£23,960	£65,293	£420,781	£115,783
ERG's preferred base case (ERGs NMA, and [redacted] in the max dose statin NMA and [redacted] in the statin intolerant NMA)	£23,948	£62,874	£104,930	£63,495
ERG's alternative base case (ERGs NMA, and 0%, or no change from baseline)	£21,851	£60,031	£97,398	£58,782

Additional scenario analysis 2 (Issue 5a)

- The ERG considers that the company's approach to estimate background CV risks is largely similar to other primary HC or mixed dyslipidaemia models appraised by NICE.
- The impact of varying the 10-year risk for MI, IS or CV death on the cost-effectiveness results was negligible in subpopulations 2b, 4a and 4b **but notable in 2a (due to the larger proportion of patients entering the model in primary prevention)**
- The company's base case analysis included a 10-year risk of around *30*% for MI, IS or CV death estimated using the SCORE risk algorithm in European Society of Cardiology [ESC] guidelines
- The company's scenario analysis provided during the clarification stage included a 10-year risk of *20*% for MI, IS or CV death to reflect CG181 and TA385
- The ERG considers that the true risk for primary CV events would lie somewhere in between the company's base case analysis and its alternative scenario

Population 2a Statin-intolerant	FDC vs EZE Deterministic ICER
Company revised base case 10-year risk of around 30%	£23,960
Company alternative scenario analysis 10-year risk of 20%	£31,806

ICER Decision Tree



	2a	4a	2b	4b
LDL-C All patients [b]	£23,969	£63,138	-	-
LDL-C Non eligible patients [a]	-	-	-	-
LDL-C All patients [b]	£24,264	£53,056*	-	-
LDL-C Non eligible patients [a]	£24,641	£62,874*	-	-
ALI	-	-	*£416,292*	*£114,181*
EVO	-	-	*£290,094*	*£69,088*
ALI	-	-	*£104,930**	*£63,495**
EVO	-	-	NC	NC

ICERs in *italics* are in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs than comparators but is also less costly).

* Indicates deterministic value

[a] ERG NMA (Issue 6) and LDL-C levels from patients not eligible for ALI/EVO (Issue 3)

[b] ERG NMA (Issue 6) and LDL-C levels from all patients (Issue 3)

Innovation & equality

Innovation

- The company considers bempedoic acid a first-in-class, non-statin, adenosine triphosphate citrate lyase (ACL) inhibitor with a targeted mechanism of action
  - The technical team considers that all relevant benefits associated with bempedoic acid are adequately captured in the model.

Equality

- The company submission does not identify any specific equalities considerations

Key issues

Unknown impact | Model driver | For discussion

Small impact | Resolved

Issue	Company base case	Technical team	Impact
1. The clinical pathway	Treatment additive, unlikely to be used as monotherapy	Issue informs larger issues 2,3 & 6	
2. Previous and/or concomitant therapy	No clinically significant impact on direction of effect	Clinical opinion that previous EZE will have impact but limited subgroup analysis by company	
3. Baseline LDL-C in subpopulations not eligible for ALI and EVO	Merged LDL-C reflective of current 'real world' uptake of PCSK9i	Potential overestimation of cost-effectiveness	
4. Subgroup analyses by CV risk and HeFH	Treatment effect is same across CV risk and HeFH	Data limitation – unclear if results are generalizable	
5. Primary and secondary prevention subpopulation	CLEAR studies previous CV event data	Impact on ICER for subpopulation 2a	
6. Methodological uncertainty in the NMA	Company NMA informs analysis across all subgroup	Poor model fit in Company NMA and high heterogeneity	
7. 12-week study data cut off and evaluation of treatment waning	24-week data cut off – no long term data provided	Longer timeframe data should be provided to determine impact on results	
8 and 9. HRQOL and costing of ALI/EVO, and CV events	Utilities and costs data required adjustments in line with previous changes	ERG modelling of utilities and costing of administration preferred	