NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

The following documents are made available to the Company:

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

1. **Company submission** from Daiichi Sankyo UK

2. **Clarification questions and company responses** from Daiichi Sankyo UK

3. **Patient group, professional group and NHS organisation submissions** from:
   a. HEART UK
   b. British Cardiovascular Society

4. **Expert personal perspectives** from:
   a. Dr Kathryn Ryan – clinical expert, nominated by Royal College of Pathologists

5. **Evidence Review Group report** prepared by BMJ Group
   a. Erratum

6. **ERG report – factual accuracy check** prepared by BMJ Group

7. **Technical report** prepared by NICE

8. **Technical engagement response from company** from Daiichi Sankyo UK

9. **Technical engagement responses from consultees and commentators:**
   a. Association of British Clinical Diabetologists
   b. British Cardiovascular Society
   c. Amgen
   d. Sanofi

10. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ Group

11. **Request for additional evidence post ACM1** prepared by NICE

12. **Company additional evidence response** from Daiichi Sankyo UK
    a. Clinical and cost effectiveness data
    b. NMA data

13. **Evidence Review Group critique of company additional evidence response** prepared by BMJ Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bempedoic acid and bempedoic acid plus ezetimibe fixed-dose combination for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Document B

Company evidence submission

March 2020

File name	Version	Contains confidential information	Date
ID1515 Document B	1.0	No	29 November 2019
ID1515 Document B	2.0	No	27 March 2020

Contents

Tables and figures

Abbreviations

AAT	aspartate aminotransferase
ACL	adenosine triphosphate citrate lyase
ACS	acute coronary syndromes
ACSVL1	acyl-CoA synthetase 1
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo A-1	apolipoprotein A-1
Apo B	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BA	bempedoic acid
BMI	body mass index
BP	blood pressure
BP	blood pressure
CABG	coronary artery bypass graft
CE	cost-effectiveness
CETP-I	cholesteryl ester transfer protein inhibitor
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
CoA	coenzyme A
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CSR	clinical study report
CTT	Cholesterol Treatment Trialists
CTTC	Cholesterol Treatment Trialists Collaboration
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
DM	diabetes mellitus
EAS	European Atherosclerosis Society
ECG	electrocardiograms
eGFR	estimated glomerular filtration rate
ERFC	Emerging Risk Factors Collaboration
ESC	European Society of Cardiology
EZE	ezetimibe 10 mg once daily

FDC	Bempedoic acid plus ezetimibe fixed-dose combination
FH	familial hypercholesterolaemia
GI	gastrointestinal
GP	general practitioner
HbA1c	glycosylated haemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HMG-CoA	3-hydroxy-3-methylglutaryl–coenzyme A
HoFH	homozygous familial hypercholesterolemia
hsCRP	high-sensitivity C-reactive protein
HTN	hypertension
IDL	intermediate-density lipoproteins
IMP	investigational medicinal product
IQR	interquartile range
ITT	intention to treat
IV	intravenous
IWRS	interactive web-response system
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
LMT	lipid-modifying therapy
LOS	length of stay
Lp(a)	lipoprotein(a)
LS	least squares
LY	life-year
MACE	major adverse cardiovascular events
MI	myocardial infarction
mITT	modified intention to treat
NA	not applicable
NCEP ATP-III	National Cholesterol Education Program adult treatment panel III
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit at £30,000 per QALY
NR	not reported
OLE	open-label extension
PBO	placebo
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin / kexin type 9
PCSK9i	proprotein convertase subtilisin / kexin type 9 inhibitor

PK	pharmacokinetic
PMM	pattern-mixture model
Q2W	every 2 weeks
QALY	quality-adjusted life year
QD	once daily
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
siRNA	small interfering RNA
SLR	systematic literature review
SmPC	summary of product characteristics
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBD	to be determined
TC	total cholesterol
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
THIN	The Health Improvement Network
TIA	transient ischaemic attack
UK	United Kingdom
ULN	upper limit of normal
VLDL	very low-density lipoprotein
WHO	World Health Organization

Treatment Combination Abbreviations

AliMab (75 mg)	Alirocumab 75 mg subcutaneous injection every 2 weeks
AliMab (75 mg)+statin	Alirocumab 75 mg subcutaneous injection every 2 weeks in combination with a statin
AliMab (150 mg)	Alirocumab 150 mg subcutaneous injection every 2 weeks
AliMab (150 mg)+statin	Alirocumab 150 mg subcutaneous injection every 2 weeks in combination with a statin
AliMab (75/150 mg)	Alirocumab 75 mg with possible uptitration to 150 mg subcutaneous injection every 2 weeks
AliMab (75/150 mg)+statin	Alirocumab 75 mg with possible uptitration to 150 mg subcutaneous injection every 2 weeks in combination with a stain
BA	Bempedoic acid 180 mg oral once daily
BA+statin	Bempedoic acid 180 mg oral once daily in combination with a statin
FDC	Bempedoic acid 180 mg plus ezetimibe 10 mg fixed-dose combination tablet once daily
BA+EZE	Bempedoic acid 180 mg oral once daily in combination with ezetimibe 10 mg once daily (separate tablets)
FDC+statin	Bempedoic acid 180 mg plus ezetimibe 10 mg fixed-dose combination tablet once daily in combination with a statin
BA+EZE+statin	Bempedoic acid 180 mg oral once daily in combination with ezetimibe 10 mg once daily (separate tablets) in combination with a statin
EvoMab(140 mg)	Evolocumab 140 mg subcutaneous injection every 2 weeks
EvoMab(140 mg)+statin	Evolocumab 140 mg subcutaneous injection every 2 weeks in combination with a statin
EvoMab(420 mg)	Evolocumab 420 mg subcutaneous injection every month
EvoMab(420 mg)+statin	Evolocumab 420 mg subcutaneous injection every month in combination with a statin
EZE	Ezetimibe 10 mg once daily
EZE+statin	Ezetimibe 10 mg once daily with a statin

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

B.1.1.1 Decision problem

The clinical effectiveness submission covers the technology's full marketing authorisation for this indication. To note, two technologies are covered: bempedoic acid and bempedoic acid fixed-dose combination with ezetimibe.

The proposed positions in the treatment pathway are as follows:

- When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control low-density lipoprotein cholesterol (LDL-C)
- When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C

The proposed position is narrower than the anticipated marketing authorisation because it would not be used prior to ezetimibe in the treatment pathway in the National Health Service (NHS).

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with primary hypercholesterolaemia or mixed dyslipidaemia	Patients with primary hypercholesterolaemia or mixed dyslipidaemia	NA
Intervention	Bempedoic acid, alone or with a statin, with or without other lipid-lowering therapy Bempedoic acid in an FDC with ezetimibe, alone or with a statin	Bempedoic acid alone or with a statin, with or without other lipid-lowering therapy Bempedoic acid in an FDC with ezetimibe, alone or with a statin	NA
Comparator(s)	When statins are contraindicated or not tolerated: • Ezetimibe • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering therapy) When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C: • Ezetimibe (when evolocumab and alirocumab are not appropriate) • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering therapy) When maximally tolerated statin dose does not appropriately control LDL-C: • Ezetimibe with a statin	When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C: • No additional treatment on background ezetimibe (when evolocumab and alirocumab are not appropriate) • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering therapy) When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: • No additional treatment on background ezetimibe and statin (when evolocumab and alirocumab are not appropriate)	Comparisons are only presented when ezetimibe does not appropriately control LDL-C, because bempedoic acid and FDC are not expected to be used prior to ezetimibe in the treatment pathway. The comparator when ezetimibe does not appropriately control LDL-C and evolocumab and alirocumab are not appropriate has been clarified as “no additional treatment on background ezetimibe”, as patients are already receiving ezetimibe.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Evolocumab with a statin (with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy) When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: • Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate) • Evolocumab with a statin (with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy)	• Evolocumab with a statin (with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy)	
Outcomes	The outcome measures to be considered include: • Plasma lipid and lipoprotein levels, including LDL-C, non–HDL-C, apolipoprotein B and lipoprotein a • Requirement of procedures including LDL apheresis and revascularisation • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Plasma lipid and lipoprotein levels, including LDL-C, non–HDL-cholesterol, apolipoprotein B, triglycerides, and total cholesterol • Inflammatory marker high-sensitivity C-reactive protein • Requirement of procedures including LDL apheresis and revascularisation • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life	hsCRP was included as a secondary endpoint in the phase 3 clinical trial programme for bempedoic acid and FDC. hsCRP is an inflammatory marker associated with increased cardiovascular risk (see Section B.2.3.2.1) and is presented as supporting scientific evidence of a biological effect (it is not used in the economic evaluation). Total cholesterol and triglycerides are lipid endpoints included in clinical guidelines (Mach et al., 2019), often reported in trials and included in the bempedoic acid trials. Lipoprotein a and apheresis data were not reported in the bempedoic acid or FDC trials.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Presence or risk of CVD • People with HeFH • People with statin intolerance • Severity of hypercholesterolaemia	Where the evidence allows the following subgroups will be considered: • Presence or risk of CVD • Patients with HeFH • Patients with statin intolerance • Severity of hypercholesterolaemia	NA
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	Evidence is presented for treatment combinations in accordance with the anticipated wording of the marketing authorisation	NA

AliMab = alirocumab; CVD = cardiovascular disease; EvoMab = evolocumab; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PCSK9 = proprotein convertase subtilisin/ kexin type 9.

B.1.2 Description of the technology being appraised

In Appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

Table 2. Technology being appraised

UK approved name and brand name	The below names are used: • Bempedoic acid (Nilemdo®) • Bempedoic acid fixed-dose combination with ezetimibe (Nustendi®)
Mechanism of action	Bempedoic acid (ETC-1002) is an oral, once daily, first-in-class small molecule cholesterol synthesis inhibitor. With a targeted mechanism of action, bempedoic acid is an adenosine triphosphate (ATP) citrate lyase (ACL) inhibitor that lowers LDL-C by reducing cholesterol biosynthesis and up-regulating the LDL receptor. Bempedoic acid is a pro-drug and thus requires coenzyme A activation by very long-chain ACSVL1, which is expressed primarily in the liver and not in skeletal muscle. Although bempedoic acid (via ACL inhibition) and statins (via HMG-CoA reductase inhibition) both inhibit cholesterol synthesis in the liver, a differentiating factor is that, unlike statins, bempedoic acid is inactive in skeletal muscle. Ezetimibe is an NPC1L1 (sterol transporter) inhibitor, which inhibits gastrointestinal cholesterol absorption and upregulates LDL receptors. The fixed-dose combination (FDC) pill contains 180 mg bempedoic acid and 10 mg ezetimibe, two LDL-C–lowering compounds with complementary mechanisms of action in cholesterol lowering; bempedoic acid via inhibition of cholesterol synthesis, and ezetimibe via inhibition of cholesterol absorption in the intestine.
Marketing authorisation/CE mark status	EMA, centralised procedure, standard review, full submission • EMEA/H/C/004958 (bempedoic acid [Nilemdo]) and • EMEA/H/C/004959 (bempedoic acid + ezetimibe FDC [Nustendi]) Marketing authorisation for Nilemdo was granted by the European Medicines Agency on 1 April 2020 Marketing authorisation for Nustendi was granted by the European Medicines Agency on 27 March 2020
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Indication for bempedoic acid (Nilemdo):** Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin or a statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, • alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated.

	Indication for bempedoic acid and ezetimibe FDC (Nustendi): Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe, • alone in patients who are either statin intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone, • in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin
Method of administration and dosage	Bempedoic acid • Oral, once daily, 1 tablet containing 180 mg bempedoic acid FDC • Oral, once daily; 1 tablet containing 180 mg bempedoic acid and 10 mg ezetimibe Each tablet should be taken orally with or without food. Tablets should be swallowed whole.
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	Bempedoic acid • List price: [redacted] per pack of 28 tablets • Cost per year: [redacted] FDC • List price: [redacted] per pack of 28 tablets • Cost per year: [redacted]
Patient access scheme (if applicable)	Not applicable

ACL = adenosine triphosphate citrate lyase; ACSVL1 = acyl-CoA synthetase 1; CE = cost-effectiveness; CHMP = Committee for Medicinal Products for Human Use; CVD = cardiovascular disease; EMA = European Medicines Agency; FDC = bempedoic acid and ezetimibe fixed-dose combination; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/ kexin type 9; SmPC = summary of product characteristics; UK = United Kingdom.

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

- Mixed dyslipidaemia is a lipid disorder, commonly termed as combined hyperlipidemia, that is characterised by elevated LDL-C and triglycerides (< 1.7 mmol/L) and/or reduced or elevated high-density lipoprotein cholesterol (HDL-C) (Carroll et al., 2017).
- Primary hypercholesterolemia, a type of dyslipidaemia, is defined when total plasma cholesterol concentration in the blood is excessive (approximately ≥ 3 mmol/L) and falls into two categories:
- Familial hypercholesterolaemia (FH), an autosomal codominant hereditary disease, is caused by mutations in genes for the catabolism of LDL-C resulting in patients having premature cardiovascular disease (CVD) due to lifelong elevation of plasma levels of LDL-C (Beliard et al., 2018; Landmesser et al., 2017; Palma et al., 2016).
- Non-FH, defined as elevated LDL-C caused by a combination of genetic, diet, and lifestyle factors (Carroll et al., 2017).
- There is consistent evidence from multiple types of clinical and genetic studies that clearly establish that LDL-C is a causal factor of atherosclerotic cardiovascular disease (ASCVD) and that cumulative LDL burden is a determinant for initiation and progression of ASCVD (Agabiti Rosei and Salvetti, 2016; Ciccarelli et al., 2018; Ference et al., 2017; Graham et al., 2012; Herrington et al., 2016).
- High concentrations of LDL-C in the blood are associated with poor clinical outcomes in patients with FH, including in patients who are treated with lipid-lowering therapy (Beliard et al., 2018; Galema-Boers et al., 2018; Santos et al., 2016).
- Patients with hypercholesterolaemia/dyslipidemia have an increased risk of CVD, which is the leading cause of death in the World Health Organization (WHO) European region (Rayner et al., 2009) and is the number one cause of death globally (Lindh et al., 2019).
- Hypercholesterolemia/dyslipidaemia is associated with a high economic burden as patients in the UK are reported to have large hospitalisation and general practitioner visit costs (Danese et al., 2017).
- European guidelines state that when lowering LDL-C for the prevention of ASCVD, the method used should relate to an individual's total cardiovascular (CV) risk: the higher the risk, the more intense the LDL-C intervention should be (Mach et al., 2019).
- Much evidence has been generated showing that reducing plasma LDL-C levels with lipid-lowering therapies, including statins, leads to dose-dependent reductions in the risk of major CV events, including the incidence of heart attack, revascularisation, and ischaemic stroke (Cholesterol Treatment Trialists et al., 2010; Ference et al., 2017).
- Current guidelines for the prevention of ASCVD recommend that the decision on which LDL-C–lowering therapy to use be based on the total CV risk. The European Guidelines on CVD prevention in clinical practice (both the 2019 and 2016 versions) recommend the use of the SCORE system to establish CV risk (Mach et al., 2019).
- Once the level of CV risk is established, patients are recommended to be treated with lifestyle interventions and lipid-lowering therapy depending on the level of CV risk (Mach et al., 2019).
- National Institute for Health and Care Excellence (NICE) recommends that patients at risk of CVD and with FH be treated with statins of high intensity and low cost (NICE, 2016a; NICE, 2016b; NICE, 2016c; NICE, 2017).
  - For primary prevention therapy, atorvastatin 20 mg is recommended, and for secondary prevention, atorvastatin 80 mg is recommended.
  - If patients are intolerant to high-intensity statins, they are recommended to be treated with the maximum tolerated dose.
- For patients who do not reach therapeutic targets on statin therapy after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial

statin therapy, combination therapy with ezetimibe is recommended (Menzin et al., 2017; Volpe et al., 2017).

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a newer class of drugs administered as subcutaneous injection and indicated for patients with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet. NICE guidelines recommend that the PCSK9 inhibitors alirocumab and evolocumab can be considered in certain circumstances as follows (NICE, 2017; Volpe et al., 2017):
  - Patients with primary heterozygous-familial hypercholesterolaemia and LDL-C persistently above 5.0 mmol/L, or 3.5 mmol/L if patients have a high or very high risk of CVD
  - Patients with primary non-familial hypercholesterolaemia and LDL-C persistently above 4.0 mmol/L if patients have a high risk for CVD, or 3.5 mmol/L if patients have a very high risk of CVD
- Although a range of effective therapies are available, there are certain patient groups with high unmet need, particularly the following:
  - Where statin therapy is contraindicated or not tolerated and ezetimibe does not adequately control LDL-C, particularly where alirocumab and evolocumab are not appropriate
  - When maximally tolerated statin dose with ezetimibe does not adequately control LDL-C, particularly where alirocumab and evolocumab are not appropriate.

B.1.3.1 Disease overview

B.1.3.1.1 Association between cholesterol and CVD risk

Atherosclerosis develops as a consequence of LDL-C (lipoprotein particles produced in the metabolic pathway of cholesterol) deposition in arterial walls, which develops into plaques. When left untreated, this leads to ASCVD, which is a major cause of morbidity, mortality, and disability (Abizanda et al., 2010; Ciccarelli et al., 2018; Ference et al., 2017; Lepor and Kereiakes, 2015). Of the risk factors for ASCVD, LDL-C has been the most extensively studied, and a long history of comprehensive research has found that high LDL-C levels are closely linked to atherosclerosis and CVD (Ciccarelli et al., 2018; Lepor and Kereiakes, 2015). A close link also exists between diabetes mellitus and CVD as this is the most common form of morbidity and mortality in diabetic patients. Risk factors for CVD such as obesity, hypertension, and dyslipidemia are common in patients with diabetes mellitus, which places them at an increased risk for cardiovascular events (Leon and Maddox, 2015). Some of the multiple risk factors for ASCVD are shown in Table 3.

Table 3. Major atherosclerotic cardiovascular disease risk factors

Major Risk Factors	Additional Risk Factors	Nontraditional Risk Factors
• Advancing age • Increased total cholesterol level • Increased non–HDL-C • Increased LDL-C • Low HDL-C • Diabetes mellitus • Hypertension • CKD	• Obesity, abdominal obesity • Family history of hyperlipidemia • Increased small, dense LDL-C • Increased Apo B • Increased LDL particle concentration	• Increased lipoprotein (a) • Increased clotting factors • Increased inflammation markers (hsCRP, Lp-PLA2) • Increased homocysteine levels • Apo E4 isoform • Increased uric acid

Major Risk Factors	Additional Risk Factors	Nontraditional Risk Factors
• Cigarette smoking • Family history of ASCVD	• Fasting/post-prandial hypertriglyceridemia • PCOS • Dyslipidemic triad	• Increased triglyceride-rich remnants

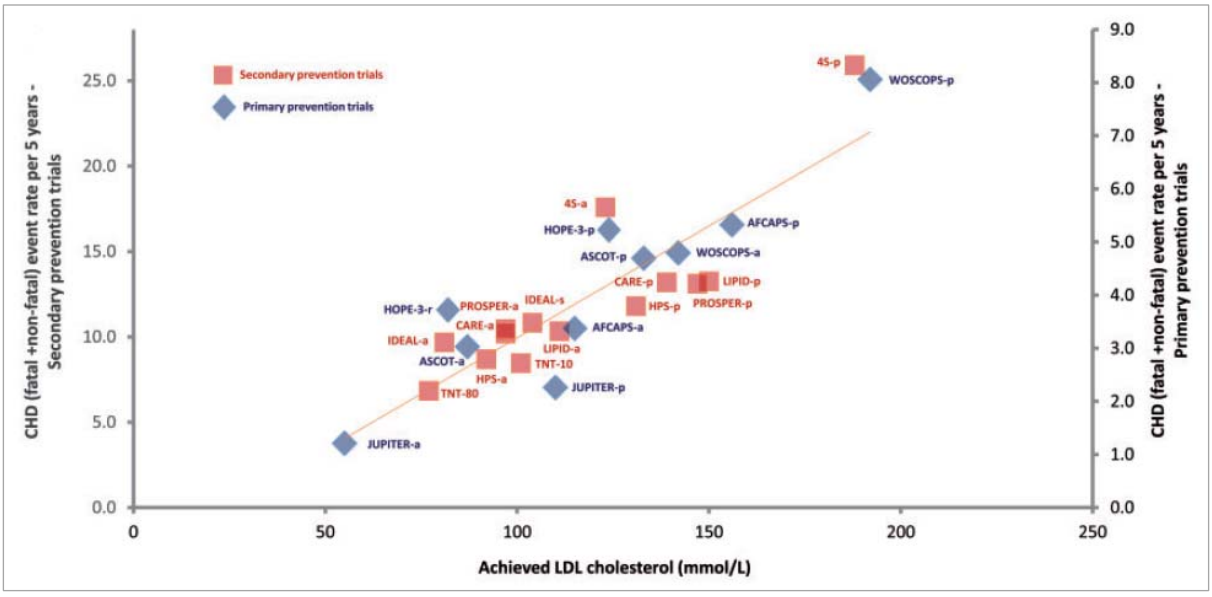
Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA2 = lipoprotein-associated phospholipase; PCOS = polycystic ovary syndrome.

Source: Jellinger et al. (2012).

An independent study of over 200 prospective cohort studies, Mendelian randomisation studies, and randomised trials including more than 2 million participants with over 20 million person-years of follow-up and over 150,000 CV events by Ference et al. (2017) demonstrated that there is a dose-dependent log-linear association between LDL-C burden and risk of ASCVD.

Figure 1 presents the association between LDL-C level and absolute coronary heart disease (CHD) event rate for both primary and secondary prevention patients. The absolute yearly CHD event rate observed was found to be strongly and linearly associated with the level of LDL-C achieved by the patients (Ference et al., 2017). This helps to demonstrates that lowering LDL-C levels has the potential to lower the risk of ASCVD.

Figure 1. Association between achieved LDL-C level and absolute CHD event rate in randomised statin trials



CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

Note: Achieved LDL-C in trials of primary prevention and secondary prevention in stable CHD was related to the endpoint of CHD event (fatal plus non-fatal myocardial infarction, sudden CHD death) proportioned to 5 years assuming linear rates with time. Trend lines for primary and secondary prevention associations are virtually superimposable.

Source: Ference et al. (2017).

Methods for lowering LDL-C in patients at risk of ASCVD include lifestyle modifications (such as diet

and exercise) and therapeutic options. Whichever method of ASCVD prevention is taken, European guidelines state that it should relate to an individual's total CV risk: the higher the risk, the more intense the LDL-C intervention should be (see Section B.1.3.3 for detail on treatment depending on CV risk estimation) (Mach et al., 2019). The European Atherosclerosis Society (EAS)/ European Society of Cardiology (ESC) guidelines proposed levels for the total CV risk which are shown in Table 4. Hypercholesterolemia and high levels of total cholesterol were reported to be closely linked to the level of CV risk.

Table 4. Cardiovascular risk categories

Risk category	Criteria
Very high risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging – Documented ASCVD includes previous acute coronary syndrome (myocardial infarction or unstable angina), stable angina, coronary revascularisation (percutaneous coronary intervention, coronary artery bypass graft, and other arterial revascularisation procedures), stroke and transient ischaemic attack, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography, computed tomography scan (multivessel coronary disease with two major epicardial arteries having > 50% stenosis), or carotid ultrasound. • DM with target organ damage, at least three major risk factors, or early onset of T1DM of long duration (> 20 years) • Severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2) • A calculated SCORE ≥ 10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor
High risk	People with: • Markedly elevated single-risk factors, in particular total cholesterol > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL), or blood pressure > 180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage, with DM duration ≥ 10 years or another additional risk factor • Moderate chronic kidney disease (eGFR 30-59 mL/min/1.73 m^2) • A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD
Moderate risk	Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors. Calculated SCORE ≥ 1 % and < 5% for 10-year risk of fatal CVD
Low risk	Calculated SCORE < 1% for 10-year risk of fatal CVD

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Source: Mach et al. (2019).

There is convincing evidence to show a causal association between diet and therapeutic methods for

lowering LDL-C and the risk of ASCVD. Furthermore, it has also been demonstrated that the causal effect of LDL-C on ASCVD is largely independent of the manner in which LDL levels are lowered (Ference et al., 2017). The recent study by Ference et al. (2017) demonstrated similar plasma LDL-C–lowering effects between genetic variants of ATP citrate lyase and 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase. In addition to decreased LDL-C levels, ATP citrate lyase variants were also associated with a decreased risk of CV event, thus genetically validating ATP citrate lyase as a therapeutic target.

A study by the Cholesterol Treatment Trialists (CTT) Collaboration evaluated 26 randomised clinical trials in 170,000 patients receiving more intensive statin therapy and showed that across all 26 trials, all-cause mortality was reduced by 10% per 1.0 mmol/L LDL reduction (RR, 0.90; 95% confidence interval [CI], 0.87-0.93; $P < 0.0001$), largely reflecting significant reductions in deaths due to CHD (RR, 0.80; 95% CI, 0.74-0.87; $P < 0.0001$) and other cardiac causes (RR, 0.89; 95% CI, 0.81-0.98; $P = 0.002$), with no significant effect on deaths due to stroke (RR, 0.96; 95% CI, 0.84-1.09; $P = 0.5$) or other vascular causes (RR, 0.98; 95% CI, 0.81-1.18; $P = 0.8$) (Cholesterol Treatment Trialists et al., 2010). In addition, a meta-regression analysis of 49 clinical trials in 312,175 patients found that for nearly all therapeutic approaches for lowering LDL-C, each 1 mmol/L (387 mg/dL) reduction in LDL-C level was associated with a consistent 20% to 25% proportional reduction in vascular events (Ference et al., 2019). Therefore, control of LDL-C levels is an effective method for reducing the risk of CVD (Agabiti Rosei and Salvetti, 2016; Graham et al., 2012).

A recent meta-analysis evaluated the association of baseline LDL-C levels with total and CV mortality risk reductions, including a total of 34 trials in 134,299 patients who received more intensive LDL-C–lowering therapies and 133,989 who received less intensive LDL-C–lowering therapies (Navarese et al., 2018). All-cause mortality was reported to be lower in patients receiving more intensive therapies as was CV mortality (3.48% vs. 4.07%; RR, 0.84; 95% CI, 0.79-0.89), and this varied with baseline LDL-C levels. Meta-regression analysis showed that, for patients receiving more intensive LDL-C–lowering therapy, the reduction in CV mortality was greater in patients with higher baseline LDL-C levels but only when baseline LDL-C levels were ≥ 100 mg/dL ($P < 0.001$) (Navarese et al., 2018). Another meta-analysis compared PCSK9 inhibitor treatment versus no PCSK9 inhibitors in adults with hypercholesterolaemia from 24 RCTs including 10,159 patients (Navarese et al., 2015). The study found that, compared with no PCSK9 treatment, PCSK9 inhibitor treatment led to a statistically significant reduction in LDL-C (mean difference, −47.49%; 95% CI, −69.64% to −25.35%; $P < 0.001$) and a statistically significant reduction in all-cause mortality (OR, 0.45; CI, 0.23-0.86; $P = 0.015$; heterogeneity $P = 0.63$; $I^2 = 0\%$) and CV mortality (OR, 0.50; CI, 0.23-1.10; $P = 0.084$; heterogeneity $P = 0.78$; $I^2 = 0\%$) (Navarese et al., 2015). These studies show that lowering LDL-C levels can reduce CV-related mortality in some patients and that greater LDL-C reductions correspond to greater reductions in CV-related mortality. This helps to demonstrate the role LDL-C has in causing potentially fatal CVD (Navarese et al., 2015; Navarese et al., 2018).

An analysis by Ference et al. (2018) aimed to compare the results of the FOURIER and SPIRE trials with the results of the CTT meta-analysis to evaluate the efficacy of LDL-C–lowering therapies (PCSK9

inhibitors and statins) for reducing CVD risk. The FOURIER (evolocumab) and SPIRE (bococizumab) cardiovascular outcomes trials reported that lowering LDL-C with PCSK9 inhibitors reduced the risk of patients experiencing major CV events to the same extent as statins per mmol/L reduction in LDL-C. Similarly, the CTT meta-analysis also reported that PCSK9 inhibitors and statins have almost identical effects on CVD risk per unit change in LDL-C. Moreover, the magnitude of the observed risk reduction in CV events in the FOURIER and SPIRE trials was the same as the observed risk reduction reported in the CTT meta-analysis either by total duration of treatment or by the observed effect during each year of treatment. This consistency in results for the effects of PCSK9 inhibitors and statins in lowering CV risk across different studies and analysis types strongly demonstrates that PCSK9 inhibitors and statins reduce the risk of CV events and that this reduction is proportional to the absolute LDL-C reduction achieved and the total duration of therapy (Ference et al., 2018).

B.1.3.1.2 Hypercholesterolaemia and mixed dyslipidaemia

Mixed dyslipidaemia is a lipid disorder, commonly termed as combined hyperlipidemia that is characterised by elevated LDL-C and triglycerides (< 1.7 mmol/L) and/or reduced or elevated high-density lipoprotein cholesterol (HDL-C).(Carroll et al., 2017) Hypercholesterolaemia, a type of dyslipidaemia, is defined when total plasma cholesterol concentration in the blood is excessive (approximately ≥ 3 mmol/L). Primary hypercholesterolaemia can be classified into two broad categories, hypercholesterolaemia familial and non-familial (Carroll et al., 2017). (For UK-specific epidemiology information on FH, see Section B.1.3.1.3).

Familial hypercholesterolaemia

Familial hypercholesterolaemia is an autosomal dominant hereditary disease that occurs as a consequence of mutations in genes for the catabolism of LDL-C (Beliard et al., 2018). The mutations that cause FH are mostly loss-of-function mutations in the LDL receptor gene and, currently, there are more than 1,200 mutations of the LDL receptor documented. Three other genes are known to result in FH and these are the genes encoding apolipoprotein B-100, PCSK9, and autosomal recessive hypercholesterolaemia adaptor protein (Bandeali et al., 2014; Palma et al., 2016). The mutations described cause patients to have defective LDL receptors in the liver and thus insufficient clearance of LDL particles from the plasma, resulting in patients having substantially elevated LDL-C levels from birth and often causing premature CVD (Mach et al., 2019). During the lifetime of a patient with FH, LDL-C elevations persist and deposits of LDL-C are retained in the arterial wall leading to foam cell formation within arteries and the development of plaques that can then progress to occlusive atherosclerosis (Palma et al., 2016).

Familial hypercholesterolaemia can be heterozygous or homozygous, depending on the presence of one or two affected alleles in the genes encoding the LDL receptor, apolipoprotein B-100, or PCSK9 (Landmesser et al., 2017). Most patients with FH have the heterozygous form, and it is most commonly diagnosed using the Simon Broome criteria and confirmed with genetic mutation tests. Patients with heterozygous familial hypercholesterolaemia (HeFH) have LDL receptor activity level reduced by around 50%, with baseline LDL-C levels of two to three times (200-350 mg/dL) that of a healthy patient.

Early diagnosis is paramount in patients with HeFH because if it is left untreated, patients have a high chance of developing CHD before the age of 55 years in men and 60 years in women (Carroll et al., 2017; Volpe et al., 2017). In patients with homozygous familial hypercholesterolaemia, LDL receptor function is almost completely suppressed, and LDL-C levels are around 500 to 1,200 mg/dL. In these cases, a diagnosis is usually made early (in childhood) and signs of CV damage are generally observed in the first decade of life with death before 20 years of age (Volpe et al., 2017).

Non-familial hypercholesterolaemia

Non-familial primary hypercholesterolaemia is defined as elevated LDL-C caused by a combination of genetic, diet, and lifestyle factors and is the most common form of primary hypercholesterolaemia in the UK. The exact role that genetic inheritance plays in producing high LDL-C in non-FH is unclear (Carroll et al., 2017).

B.1.3.1.3 Epidemiology in the UK

The prevalence of hypercholesterolaemia has been estimated as 15.4% in the adult UK population in 2018, based on a Clinical Practice Research Database study (Daiichi Sankyo Europe data on file, 2019c). Among all patients requiring lipid-lowering therapy, approximately 15% are unable to receive statin therapy because it is contraindicated, not tolerated or considered unsuitable (Daiichi Sankyo Europe data on file, 2019c; NICE, 2016d). In a further 29% of patients, maximally tolerated statin dose does not appropriately control LDL-C levels (Daiichi Sankyo Europe data on file, 2019b).

For patients who do not reach therapeutic targets on statin therapy after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy, therapy with ezetimibe is recommended (Menzin et al., 2017; Volpe et al., 2017). In more than 20% of patients, ezetimibe does not appropriately control LDL-C (Daiichi Sankyo Europe data on file, 2019b).

B.1.3.2 Disease burden

Hypercholesterolaemia and mixed dyslipidemia are associated with many comorbidities such as diabetes or CV disease; therefore, patients can experience substantial clinical burden (Agabiti Rosei and Salvetti, 2016; Graham et al., 2012; Hovland et al., 2017). Patients with high concentrations of LDL-C in the blood (e.g., patients with dyslipidemia, especially hypercholesterolaemia) who are left untreated are reported to be at risk of developing CVD, which is associated with poor clinical outcomes (Santos et al., 2016). Atherosclerotic CVD includes two major conditions, ischaemic heart disease and cerebrovascular disease (mainly ischaemic stroke). Ischaemic heart disease and stroke both pose substantial clinical burdens for patients and are the world's first and third causes of death, respectively, representing 28.2% of all-cause mortality in 2013 (Barquera et al., 2015). Cardiovascular disease as a whole is the leading cause of death in the WHO European region, accounting for approximately 4.3 million deaths per year (48% of all deaths), and is the number one cause of death globally, with nearly 18 million deaths in 2013 reported worldwide (7.4 million and 6.7 million were related to CHD and stroke, respectively) (Lindh et al., 2019; Rayner et al., 2009). Cardiovascular disease is also reported as a major cause of disability in western countries, and it is becoming increasingly common in

developing countries (Agabiti Rosei and Salvetti, 2016). An analysis by Wong et al. (2016) estimated that approximately 63.7% of patients with ASCVD who were ≥ 21 years old were receiving statin therapy, and of these patients, 83.5% were not at the desired LDL-C goal and therefore remained at a high risk for CVD. Of the statin-eligible patients analysed (N = 5,206), 43.7% were treated with statins, and 70.7% of patients treated with statins were not at the LDL-C goal.

Other real-world studies have also demonstrated that there is still a significant proportion of the population at high risk for CV events that remain suboptimally treated with statins, have a high rate of discontinuation of therapy, and have low rates of adherence. A study by Tran et al. (2016) examined 610,535 patients with ASCVD or type 1 diabetes mellitus (T1DM) and the effect of cholesterol guidelines on treatment patterns. Overall, there was no change noted in statin treatment rates in patients with ASCVD (48% prior to guidelines vs. 47.3% after guidelines) or T1DM (50% prior to guidelines vs. 51.5% after guidelines). Among patients on statin therapy 1 year after the guidelines were issued, 80% of patients with ASCVD and aged ≤ 75 years were not receiving guideline-recommended high-intensity statin therapy, while most patients with ASCVD and aged > 75 years or with diabetes mellitus were on moderate- or high-intensity statin therapy. This demonstrates that regardless of the guidance on treatment for LDL-C lowering, many patients at high risk of ASCVD remain either untreated or undertreated (Tran et al., 2016). The undertreatment of high-risk patients means that there is a large proportion of patients with raised LDL-C plasma levels, and this increases a patient's risk of developing atherosclerotic plaques and, therefore, developing ASCVD (Abizanda et al., 2010).

Costs for CVD include direct and indirect costs. The direct medical costs related to CVD are generally more extensive than medical costs related to any other disease, including Alzheimer's and diabetes (AHAAS Association, 2017). The economic burden associated with the cost of hospitalisations, prescriptions, and general practitioner and specialist visits for patients in the UK who have hyperlipidemia and experience CV events is substantial (Danese et al., 2017). Hospitalisation costs and general practitioner visit costs make up the largest components of the total direct medical cost in patients with dyslipidemia (Danese et al., 2017).

B.1.3.3 Management and unmet needs

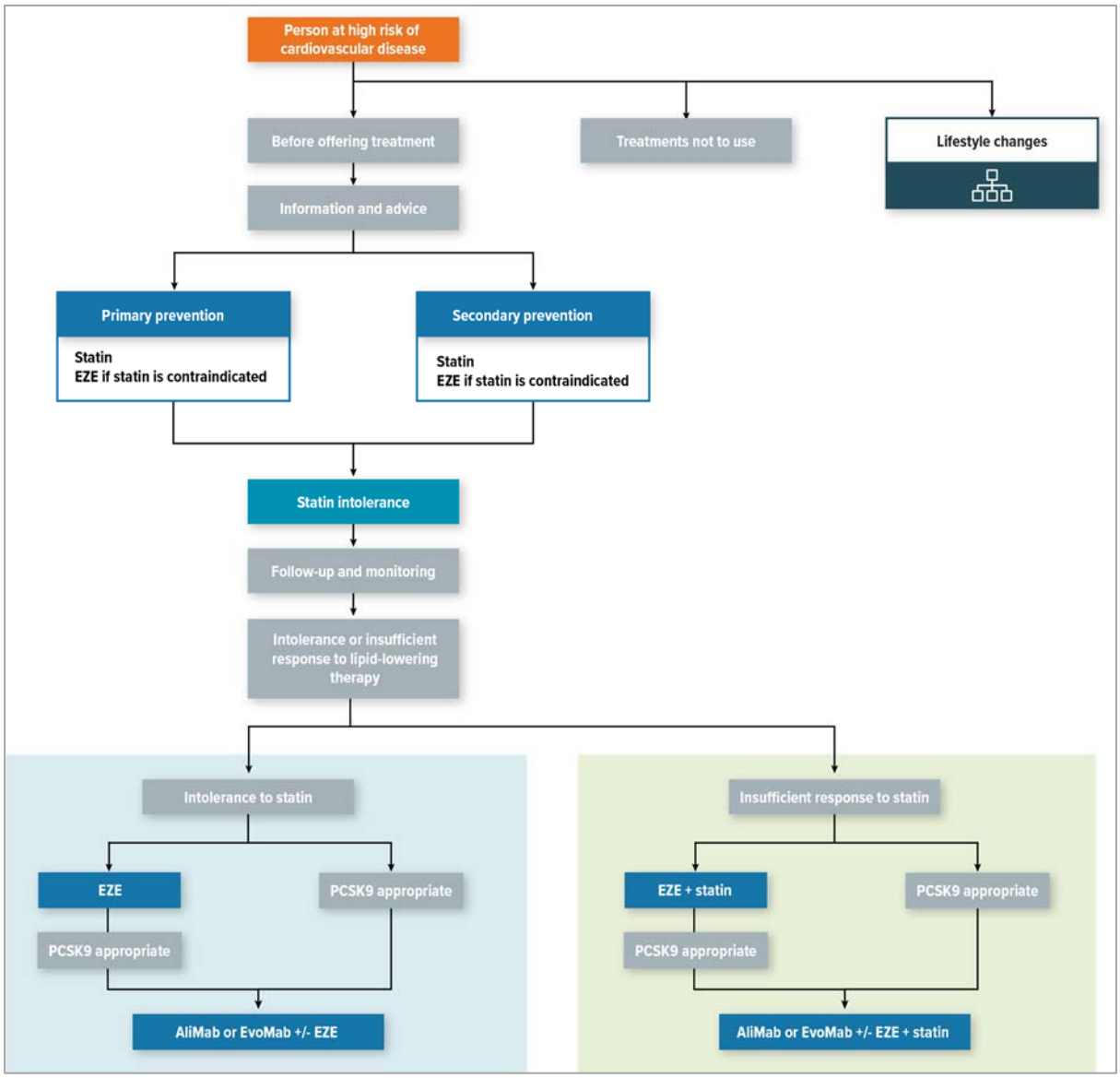
B.1.3.3.1 Current treatment

Current guidelines on the prevention of ASCVD in clinical practice recommend the assessment of total CV risk. Every method of ASCVD prevention used should relate to an individual's total CV risk, with more intense LDL-C interventions given to patients with higher CVD risk. Persons with documented ASCVD (namely secondary prevention), type 1 or type 2 diabetes mellitus (T1DM or T2DM), very high levels of individual risk factors, or chronic kidney disease (CKD) are generally at very high or high total CV risk. No risk estimation models are needed for such persons, and they all should receive active pharmacological management. For other, apparently healthy people, the use of a risk estimation system is recommended to estimate total CV risk, because many people have several risk factors that, in combination, may result in high levels of total CV risk.

Many assessment systems are available, but the European Guidelines on CVD prevention in clinical practice (both the 2019 and 2016 versions) recommend the use of the SCORE system, which estimates the 10-year cumulative risk of a first fatal atherosclerotic event (see Table 4 in Section B.1.3.1.1 for CV risk categories) (Mach et al., 2019). The guidelines recommend that patients of all CV risk levels should receive lifestyle advice and interventions such as diet modifications, smoking cessation, and body weight management, while pharmacological interventions should be administered in patients with higher LDL-C levels and in patients of higher total CV risk (according to SCORE). The higher the total CV risk and LDL-C levels, the greater the need for therapeutic intervention (Mach et al., 2019). The QRISK2 is another CVD risk assessment tool that NICE recommends for people up to and including the age of 84 years. This tool should be used when estimating the level of risk when making decision on lipid-modification therapy for primary and secondary prevention of CVD and when assessing CVD risk in people with T2DM (NICE, 2016b).

Pharmacological lipid-lowering therapy is recommended as soon as possible in adults with ASCVD or those at risk of ASCVD with raised LDL-C (Table 5). Therapy is generally maintained for life with LDL targets of < 135 mg/dL in children and < 55-70 mg/dL in adults depending on CV risk level (55 mg/dL is the target for very high-risk patients) (Mach et al., 2019; Volpe et al., 2017). Within the UK, statins and ezetimibe are currently the most common pharmacological treatments for lowering LDL-C levels in patients with hypercholesterolaemia but, despite their efficacy, there are still patients who do not reach their lipid targets (Agabiti Rosei and Salvetti, 2016). Figure 2 presents the pathway for use of the currently available treatments in the UK for LDL-C lowering according to NICE.

Figure 2. Current NICE pathway and recommendations for LDL-C lowering



AliMab = alirocumab; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; NICE = National Institute for Health and Care Excellence; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Sources: NICE (2016a); NICE (2016b); NICE (2016c); NICE (2017).

Statins

Statins are the preferred treatment for prevention of ASCVD in patients with hypercholesterolaemia or dyslipidemia (Agabiti Rosei and Salvetti, 2016). Patients begin treatment with high doses of highly effective statins (e.g., atorvastatin 80 mg, rosuvastatin 40 mg). However, there are reports that more than 40% of patients who receive high-dose statin therapy do not achieve the LDL-C target of < 70 mg/dL and this proportion is thought to be even higher in clinical practice (Mach et al., 2019; Volpe et al., 2017). Patients usually receive the maximum doses of atorvastatin (80 mg) or rosuvastatin (40 mg) that they can tolerate to achieve the reduction in LDL-C as close to < 70 mg/dL as possible

without any side effects, but, despite this, only a small proportion of patients achieve their LDL-C targets (Agabiti Rosei and Salvetti, 2016). Adherence is a significant problem in patients taking statins (up to 60% of patients may stop their statin therapy). The reasons for nonadherence are unclear, but the nonsymptomatic nature of the disease is a contributing factor as are the side effects (e.g., myopathy and statin myositis) associated with treatment (Agabiti Rosei and Salvetti, 2016).

Although therapy with statins can lower LDL-C levels in some patients, many patients can present with a very high-risk profile for ASCVD or with LDL-C higher than recommended goals, despite receiving maximally tolerated statins and being maintained on this treatment. One real-world study reported that after 24 months of receiving statin therapy for primary prevention of CVD, over half of the patients did not experience an optimal reduction in their LDL-C levels. These patients had a significantly greater risk of future CVD than patients with optimal therapeutic response (Akyea et al., 2019). There are also patients who are unable to tolerate statin therapy because they can experience muscle symptoms such as myopathy or rhabdomyolysis due to statins. Such intolerance is frequently encountered by practitioners and can be difficult to manage (Mach et al., 2019).

Other lipid-lowering therapies

Patients with hypercholesterolemia who do not reach therapeutic targets on statins alone are generally given combination therapy with ezetimibe, and the current ESC/EAS guidelines recommend that, for most cases of FH, treatment is initiated with ezetimibe (in combination with statins). However, many patients still do not reach therapeutic targets despite maximum combination therapy with statins and ezetimibe, as data from a real-world setting have been reported to show that statin and ezetimibe combination therapy for patients with ASCVD or HeFH results in only a small percentage (26%) of patients (N = 125,330) achieving LDL-C goals (< 70 mg/dL) (Mach et al., 2019; Menzin et al., 2017; Volpe et al., 2017).

Proprotein convertase subtilisin/Kexin type 9 inhibitors (PCSK9i) evolocumab and alirocumab have become available for high-risk patients with primary hypercholesterolaemia and mixed dyslipidaemia who are either intolerant to statins or despite statin (and ezetimibe) therapy and fail to meet target LDL-C levels. NICE has recommended PCSK9i in those patients against a clear set of criteria (see Figure 2). PCSK9 is an enzyme that binds to the LDL receptor causing it to be internalised, leading to higher LDL-C levels in the blood. Both alirocumab and evolocumab are monoclonal antibodies that target PCSK9 and inhibit its action, leading to lower LDL-C in the plasma (Agabiti Rosei and Salvetti, 2016; Mach et al., 2019; NICE, 2016a; NICE, 2016c; Volpe et al., 2017).

However, alirocumab and evolocumab are administered by subcutaneous injection and are very costly, there is a lack of long-term safety data for these treatments, and they are associated with injection-site reactions. Treatment-emergent adverse events are reported in up to 80% of patients receiving alirocumab and, despite the positive findings, not all patients achieve their LDL-C–reduction targets (Catapano et al., 2017; Mach et al., 2019; Volpe et al., 2017).

In 2016, NICE approved PCSK9 inhibitors for the treatment of patients with hypercholesterolaemia or

mixed dyslipidaemia who have LDL-C concentrations persistently above specified thresholds despite receiving maximal doses of stains and ezetimibe. The thresholds for patients to receive PCSK9 inhibitors are as follows (Mach et al., 2019; NICE, 2016a; NICE, 2016c; Volpe et al., 2017):

- For primary prevention, treatment with PCSK9 inhibitors is recommended only for patients with primary HeFH and when LDL-C concentration is persistently above 5.0 mmol/L.
- For secondary prevention, treatment with PCSK9 inhibitors is recommended for patients at high risk of further CVD (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) and LDL-C concentrations persistently above 4.0 mmol/L; and for patients at very high risk (with primary HeFH or recurrent CV events or CV events in > 1 vascular bed [i.e., polyvascular disease]) with LDL-C persistently above 3.5 mmol/L.

For very high-risk patients with FH (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe in a combination with a PCSK9 inhibitor, the ESC/EAS recommend considering treating patients with a statin and bile acid sequestrant combination.

Bile acid sequestrant drugs including cholestyramine, colestipol, and colesevelam, bind bile acids that have been synthesised in the liver from cholesterol and prevent reabsorption of cholesterol in the process. They have been reported to lower LDL-C and reduce CV events in patients with hypercholesterolaemia. However, bile acid sequestrants are frequently associated with gastrointestinal adverse effects (e.g., constipation, dyspepsia, and nausea) and have major drug interactions, even at low doses. This limits their practical use and means they are generally a treatment option for lowering LDL-C only in extreme cases (Mach et al., 2019).

In extreme cases, patients with high levels of LDL-C despite drug therapy, or with homozygous or heterozygous forms of dyslipidaemia and previous CV events, can be considered for aphaeresis, which has been reported to have the potential to reduce levels of LDL-C by around 50% to 75% (Volpe et al., 2017). However, apheresis is characterised by rapid increases of LDL-C towards the pre-apheresis levels, which can cause negative effects over the long-term (Catapano et al., 2017). The processes involved in apheresis are very expensive and time consuming for the patient and health services, presenting an unmet need for a more-accessible and less-intrusive treatment for patients with high LDL-C levels unsuccessful on current pharmacological treatment (Waldmann and Parhofer, 2019).

Unmet need

The many issues associated with statin treatment for LDL-C lowering presents an unmet need for additional LDL-C–lowering agents for patients with hypercholesterolaemia and statin intolerance, and for patients receiving maximally tolerated stain doses but not achieving LDL-C goals (Lepor and Kereiakes, 2015). Although ezetimibe is a further treatment option for these patients, many patients still do not reach therapeutic targets despite maximum combination therapy with statins and ezetimibe, and

also do not reach the LDL-C threshold specified by NICE to allow treatment with a PCSK9 inhibitor. As verified in clinical expert panels, there are currently no further treatment options for these patients because other therapies such as bile acid sequestrant drugs and aphaeresis are only recommended in extreme circumstances. This group of patients has been identified by clinical experts as having high unmet need (Daiichi Sankyo Europe data on file, 2019c). PCSK9 inhibitors are injected subcutaneously and can lead to patients experiencing itching around the injection site and flu-like symptoms. There is also no long-term safety data for PCSK9 inhibitors and due to their high cost, they are only considered cost-effective in very high-risk patients (Mach et al., 2019; NICE, 2016a; NICE, 2016c; Volpe et al., 2017). This presents a need for a more cost-effective, better tolerated and easily administered treatment for patients with uncontrolled LDL-C levels after maximum combination therapy with statins and ezetimibe.

B.1.3.3.2 Current UK guidelines

NICE has published guidelines for the management of CVD (CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification) and for the management of FH (CG71: Familial hypercholesterolaemia: identification and management) (Section B.1.3.3.4) (NICE, 2016b; NICE, 2017). Statins of high intensity and low cost are recommended for patients at risk of CVD and in patients with FH, and at least a 50% reduction in LDL-C concentration from baseline is recommended as a target for therapy (NICE, 2016b; NICE, 2017). For primary prevention therapy, atorvastatin 20 mg is recommended and for secondary prevention, atorvastatin 80 mg is recommended unless there is a risk of potential drug interactions or high-risk adverse events. If patients are intolerant to high-intensity statins, they are recommended to be treated with the maximum tolerated dose (NICE, 2016b; NICE, 2017).

In patients with primary HeFH or non-hypercholesterolaemia FH who cannot tolerate statins or for whom initial statin therapy is contraindicated, treatment with ezetimibe monotherapy should be considered (NICE, 2016b; NICE, 2017). Co-administration of ezetimibe with initial statin therapy is also recommended for treating primary hypercholesterolaemia in adult patients who have started statin therapy for the following reasons (NICE, 2016d):

- When serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy
- When a change from initial statin therapy to an alternative statin is being considered

For patients who are not adequately controlled on statins and ezetimibe therapy, NICE guidelines recommend that alirocumab and evolocumab can be considered. For patients with homozygous familial hypercholesterolemia, LDL apheresis is an option in exceptional circumstances depending on the response to lipid-modifying treatment and if this fails, liver transplantation can be considered (NICE, 2017).

Table 5 presents the NICE recommendations for alirocumab and evolocumab in patients with

hypercholesterolaemia and mixed dyslipidaemia where LDL concentrations are persistently above the thresholds (specified in Table 5) despite maximal tolerated lipid-lowering therapy. Both are given by subcutaneous injection. The recommended dose of alirocumab is either 75 mg or 150 mg every 2 weeks, and the recommended dose for evolocumab is either 140 mg every 2 weeks or 420 mg once monthly (NICE, 2016a; NICE, 2016c).

Both alirocumab and evolocumab are recommended on the basis of a discount agreed with the manufacturing company in a patient access scheme (NICE, 2016a; NICE, 2016c).

Table 5. Low-density lipoprotein cholesterol concentrations above which alirocumab and evolocumab are recommended

	Alirocumab and evolocumab		
	Without CVD	**With CVD**	
		High risk of CVD[a]	**Very high risk of CVD[b]**
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 HeFH	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	

CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolaemia.

Sources: NICE (2016a); NICE (2016c).

B.1.3.3.3 Other guidelines

The ESC/EAS released guidelines for the management of dyslipidaemias in 2016 that were updated in 2019 owing to the emergence of new evidence, particularly surrounding the efficacy of PCSK9 inhibitors in reducing LDL-C levels beyond those attained on intensive statin treatment. PCSK9 treatment should be targeted to patients with the highest CVD risk in clinical practice with an emphasis on very high-risk patients with recurrent events, more extensive ASCVD, or higher global CVD risk scores (Mach et al., 2019).

The guidelines state that lowering LDL-C levels is the best way to prevent CVD outcomes in high-risk patients (see Table 4 in Section B.1.3.1.1 for risk categories). LDL-C levels should be lowered as much as possible to prevent CVD, especially in high and very high-risk patients (Table 6). In very high-risk patients, recommendations are that both a goal LDL-C level of < 55 mg/dL or < 1.4 mmol/L and at least a 50% reduction from baseline LDL-C levels should be achieved through treatment. In high-risk patients, the LDL-C goal is < 70 mg/dL or < 1.8 mmol/L and at least a 50% reduction from baseline LDL-C levels should be aimed for (Mach et al., 2019).

Table 6. High-risk and very high-risk patients included in 2019 ESC/EAS dyslipidaemia guidelines

Very high risk	Documented ASCVD, either clinical or unequivocal on imaging (i.e., previous ACS, stable angina, coronary revascularisation, stroke and transient ischaemic attack, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan defined by multivessel coronary disease with two major epicardial arteries having > 50% stenosis) or on carotid ultrasound).
	DM with target organ damage, ≥ 3 major risk factors or early onset of type 1 DM of long duration (> 20 years).
	Severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2).
	Calculated SCORE ≥ 10% for 10-year risk of fatal CVD.
	FH with ASCVD or with another major risk factor.
High risk	Markedly elevated single-risk factors, in particular total cholesterol > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL), or blood pressure ≥ 180/110 mmHg.
	Patients with FH without other major risk factors.
	Patients with DM without target organ damage, with DM duration ≥ 10 years or another additional risk factors.
	Moderate CKD (eGFR 30-59 mL/min/1.73 m^2).
	A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD.

ACS = acute coronary syndromes; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; EAS = European Atherosclerosis Society; eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

Source: Mach et al. (2019).

The ESC/EAS recommend that to achieve the low LDL-C targets they have set for high-risk patients, combination treatment of statins with first ezetimibe and then a PCSK9 should be administered. Recommendations from the ESC/EAS guidelines for pharmacologically lowering LDL-C in patients at risk of CVD are summarised in (Mach et al., 2019).

Table 7. Recommendations for pharmacological low-density lipoprotein cholesterol lowering

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended	I	B
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered	IIb	C
For secondary prevention, patients at very high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended	I	A

Recommendations	Class[a]	Level[b]
For very high risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered	IIb	C
If the goal is not achieved, statin combination with a bile acid sequestrant may be considered	IIb	C

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/ kexin type 9.

[a] Class of recommendation: I, recommended or is indicated; IIa, should be considered; IIb, may be considered; III, is not recommended.

[b] Level of evidence: A, data derived from multiple randomised clinical trials or meta-analyses; B, data derived from a single randomised clinical trial or large nonrandomised studies; C, consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Source: Mach et al. (2019).

For the management of high triglycerides (> 200 mg/dL or 2.3 mmol/L), statins remain the first choice but the ESC/EAS also recommend n-3 PUFAs (particularly icosapent ethyl 2 × 2 g daily) in high-risk patients with persistently elevated triglycerides (between 135-499 mg/dL or 1.5-5.6 mmol/L) despite statin treatment. In high-risk patients who have achieved their LDL-C goal but have triglycerides > 200 mg/dL or > 2.3 mmol/L, fenofibrate or bezafibrate may be considered in combination with statins. The guidelines also emphasise the importance of managing lipoprotein(a) (Lp(a)) and recommend measurement of Lp(a) at least once in all adult patients. Options for treatment of high Lp(a) are limited to the PCSK9 inhibitors which have been shown to, on average, reduce levels by 25% to 30% alone or in combination with background statin therapy (Mach et al., 2019).

B.1.3.3.4 NICE guidance and clinical guidelines

Current clinical practice in England and Wales is driven by NICE guidance. The key guidance and technology appraisals in hypercholesterolaemia are as follows:

- Related guidelines and pathways:
  - NICE guideline CG181 (2014). Reviewed 2018 - update to be scheduled. https://www.nice.org.uk/guidance/cg181.
  - NICE guideline CG71 (2008). Review date to be confirmed. https://www.nice.org.uk/guidance/cg71.
  - NICE Pathway for cardiovascular disease prevention (2017). https://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention.
  - NICE Pathway for familial hypercholesterolaemia (2017). https://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia.

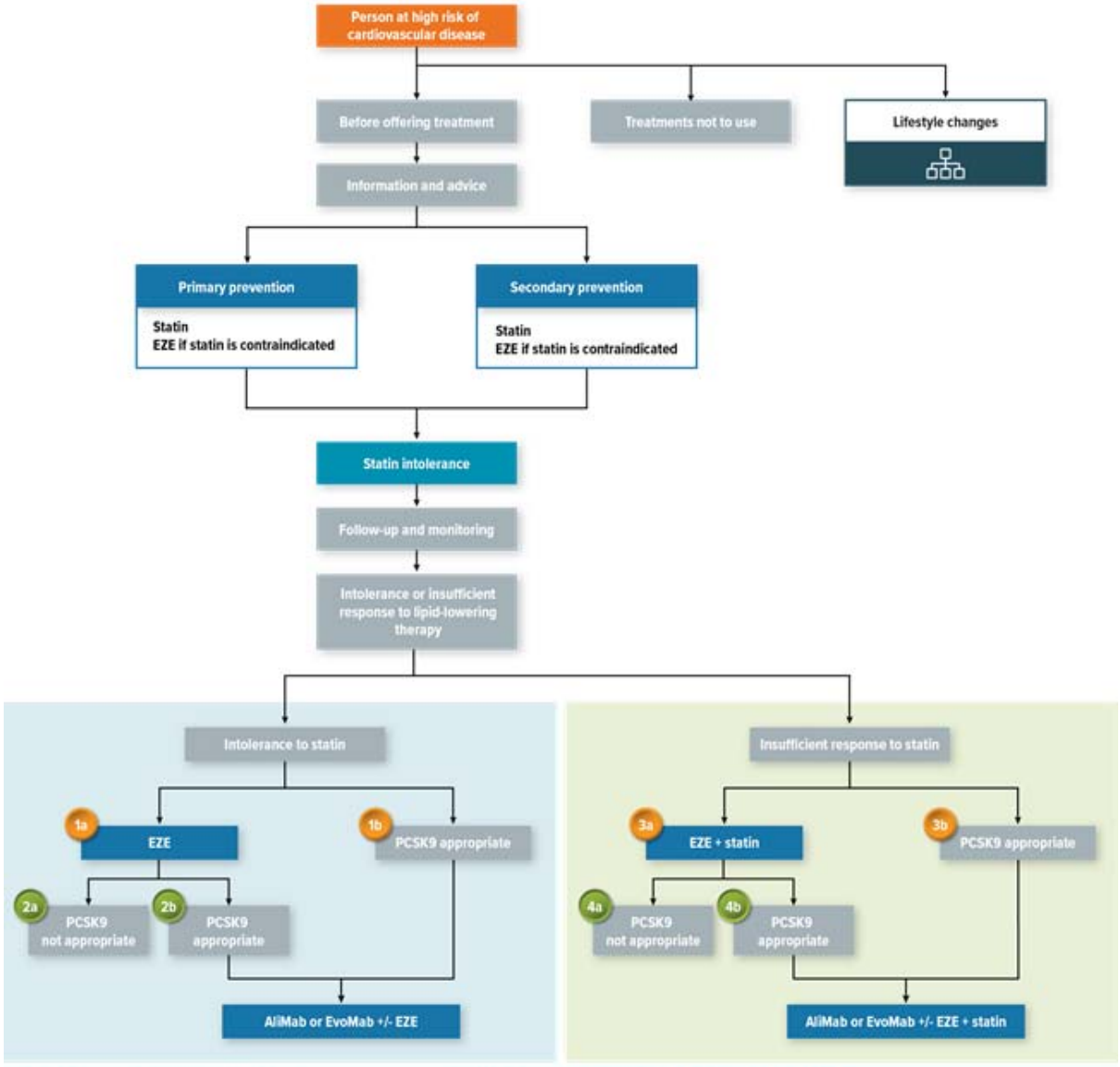
- Related NICE technology appraisals
  - NICE technology appraisal 393 (2016). Review date 2018 (awaiting results of trial). https://www.nice.org.uk/guidance/ta393.
  - NICE technology appraisal 394 (2016). Review date 2018 (awaiting results of trial). https://www.nice.org.uk/guidance/ta394.
  - NICE technology appraisal 385 (2016). Review date February 2019. https://www.nice.org.uk/guidance/ta385.
  - Related quality standards:
  - NICE quality standard 100 (2015). https://www.nice.org.uk/guidance/qs100.
  - NICE quality standard 41 (2013). https://www.nice.org.uk/guidance/qs41.

B.1.3.3.5 Treatment pathway: anticipated place of therapy of bempedoic acid in UK practice

Figure 3 summarises the treatment pathway for hypercholesterolaemia and the possible placement of bempedoic acid and ezetimibe fixed-dose combination (FDC) as outlined in the NICE scope, shown in Table 8.

Bempedoic acid and FDC provide additional oral therapy options for patients with hypercholesterolaemia or mixed dyslipidaemia when statins are contraindicated or not tolerated, and when maximally tolerated statin dose does not appropriately control LDL-C. In particular, the products provide effective lipid-lowering therapy when statins and ezetimibe do not appropriately control LDL-C (positions 2 and 4 in Figure 3), and these are the target positions for bempedoic acid and FDC. As shown in Sections B.1.3.3.1 and B.1.3.3.4, clinical experts have highlighted that patients in this situation and for whom alirocumab and evolocumab are not appropriate have particularly high unmet needs and no further treatment options (positions 2a and 4a in Figure 3).

Figure 3. Current NICE pathway and recommendations and proposed placement of bempedoic acid and FDC



Position	Background therapy	Intervention	Phase 3 trial evidence for BA / FDC
1	None	BA	CLEAR Serenity (1002-046)
		FDC	Position not clinically relevant
2	Ezetimibe	BA	CLEAR Tranquility (1002-048)
		FDC[a]	CLEAR Tranquility (1002-048) [SE]
3	Maximally tolerated stain	BA	CLEAR Harmony (1002-040); CLEAR Wisdom (1002-047)
		FDC	Position not clinically relevant
4	Maximally tolerated stain and ezetimibe	BA	CLEAR Harmony (1002-040); CLEAR Wisdom (1002-047); 1002FDC-053
		FDC[a]	1002FDC-053

BA = bempedoic acid 180 mg oral once daily; EZE = ezetimibe 10 mg once daily; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/ kexin type 9.

Table 8. Situations defined in the NICE scope and corresponding positions shown in Figure 3

Situation	Comparator	Position (Figure 3)[a]
When statins are contraindicated or not tolerated	Ezetimibe	1a
	Evolocumab (with or without another lipid-lowering therapy)	1b
	Alirocumab (with or without another lipid-lowering therapy)	
When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C	No additional treatment on background ezetimibe (when evolocumab and alirocumab are not appropriate)	2a 2b
	Evolocumab (with or without another lipid-lowering therapy)	
	Alirocumab (with or without another lipid-lowering therapy)	
When maximally tolerated statin dose does not appropriately control LDL-C	Ezetimibe with a statin	3a
	Evolocumab with a statin (with or without another lipid-lowering therapy)	3b
	Alirocumab with a statin (with or without another lipid-lowering therapy)	
When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C	No additional treatment on background ezetimibe and statin (when evolocumab and alirocumab are not appropriate)	4a
	Evolocumab with a statin (with or without another lipid-lowering therapy)	4b
	Alirocumab with a statin (with or without another lipid-lowering therapy)	

LDL-C = low-density lipoprotein cholesterol.

[a] Positions ending "a" relate to situations when alirocumab or evolocumab are not appropriate. Positions ending "b" relate to situations when alirocumab or evolocumab are appropriate.

B.1.4 Equality considerations

No equality issues are foreseen.

B.2 Clinical effectiveness

Bempedoic acid trials

- Across four completed phase 3 trials (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, and CLEAR Tranquility) and two phase 2 RCTs investigating the efficacy of bempedoic acid 180 mg at 12 weeks (Study 1002-008 and Study 1002-009), treatment with bempedoic acid resulted in significant LDL-C reductions at 12 weeks versus placebo in patients with hypercholesterolaemia on maximally tolerated statin dose or with statin intolerance. These reductions were observed at the first post-baseline study visit (week 4) and were maintained throughout the duration of the studies.
- Bempedoic acid lowered LDL-C levels similarly across subgroups in the phase 3 trials. Patients treated with maximally tolerated statins received additional LDL-C reductions with the addition of bempedoic acid, while larger reductions in LDL-C were observed in patients not taking statins. In post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use.
- Compared with placebo, treatment with bempedoic acid added to background lipid-lowering therapy significantly reduced levels of apolipoprotein (apo B), non–HDL-C, and total cholesterol (TC).

FDC trial

- The FDC of bempedoic acid and ezetimibe has been studied in one, double-blind phase3 study (1002FDC-053) with adult patients at high risk of CVD due to ASCVD, HeFH, or multiple CVD risk factors receiving maximally tolerated statin therapy. Treatment with FDC resulted in significant reductions in LDL-C at week 12 from baseline compared with placebo.
- The FDC lowered LDL-C levels similarly across subgroups.
- Supporting evidence for FDC in statin-intolerant patients is available from the CLEAR Tranquility study which investigated bempedoic acid and ezetimibe given as separate tablets. Pharmacokinetic studies have shown the two presentations to be equivalent (Esperion Therapeutics data on file, 2019e; Esperion Therapeutics data on file, 2019f)

B.2.1.1 Identification and selection of relevant studies

A systematic literature review (SLR) was performed in May 2019 according to a pre-specified protocol to identify efficacy and safety studies of bempedoic acid and its comparator treatments for patients with primary hypercholesterolaemia or mixed dyslipidaemia when optimised lipid-lowering therapy including statins does not appropriately control LDL-C or when statins are contraindicated or not tolerated. Literature searches encompassed electronic databases (MEDLINE, MEDLINE In-Process, Embase, BIOSIS and The Cochrane Library) and the Internet. In addition, the bibliographies of systematic reviews and key articles were reviewed to identify other relevant articles that were appropriate for inclusion. The electronic database searches were not limited by language, date, or geographical location. All citations were double screened at level 1 and level 2 phases using pre-specified inclusion and exclusion criteria by independent researchers. Once relevant studies were identified, study characteristics, efficacy, and safety data were extracted, and methodologies were critically appraised according to NICE requirements.

See Appendix D for full search strategies, study inclusion and exclusion criteria, details of the process and methods to identify and select the clinical evidence relevant to the submission, and results.

The clinical studies investigating bempedoic acid and FDC identified in the SLR as relevant for the NICE

decision problem are listed in Section B.2.2. Studies investigating comparator interventions are presented in Section B.2.9.

B.2.2 List of relevant clinical effectiveness evidence

Completed phase 3 trials that provide evidence of the clinical efficacy and safety of bempedoic acid and FDC are summarised in Table 9.

The phase 3 bempedoic acid programme evaluated over 3,600 unique patients including over 3,000 high-risk patients with LDL-C ≥ 70 mg/dL (1.8 mmol/L) who had ASCVD and/or HeFH, or presence of other CVD risk factors, and were receiving maximally tolerated statin therapy. An additional 614 patients included those with hypercholesterolaemia who had a history of statin intolerance with a broader range of risk factors for CV events. Study 1002FDC-053 was a randomised, double-blind, parallel-group, multicentre study of the bempedoic acid/ezetimibe FDC compared with bempedoic acid, ezetimibe, and placebo as individual components once daily added to current LMT in patients with high CV risk and hyperlipidaemia. Patients had underlying ASCVD, HeFH, and/or multiple CV risk factors and were not adequately controlled with their current maximally tolerated statin therapy; which allowed statin doses lower than the lowest approved dose as well as no statin at all.

An ongoing open label extension (OLE) study (1002-050) for safety, enrolled patients who received bempedoic acid 180 mg QD for 78 weeks after completion of the 52-week CLEAR-HARMONY study (the parent 1002-040 study). The OLE study is expected to report in [redacted]. A further phase 3 global, CV outcomes trial is ongoing (CLEAR CVOT, 1002-043) which investigates bempedoic acid compared with placebo in patients with, or at high risk of, CVD who are statin intolerant. The primary outcome is time-to-first major adverse cardiovascular event (MACE), where MACE is an adjudicated composite endpoint of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and coronary revascularisation. The CLEAR CVOT study is expected to report in [redacted].

The phase 2 trials investigating bempedoic acid are summarised in Table 10. Of the phase 2 trials, only studies 1002-008 and 1002-009 investigated LDL-C lowering for bempedoic acid 180 mg at 12 weeks and are included in the submission. Excluded phase 2 studies had small sample sizes ranging from 52 to 68 patients, did not include 180 mg dose or a 12-week endpoint, or enrolled only patients with hypertension (143 patients) and therefore would not be expected to influence overall meta-analysis results.

Table 9. Completed phase 3 trials providing clinical efficacy and safety evidence for bempedoic acid and FDC of bempedoic acid with ezetimibe

	Bempedoic acid trials				FDC trial
Study	**CLEAR Harmony 1002-040 (Ray et al., 2019b)**	**CLEAR Wisdom 1002-047 (Goldberg et al., 2019)**	**CLEAR Serenity 1002-046 (Laufs et al., 2019)**	**CLEAR Tranquility 1002-048 (Ballantyne et al., 2018)**	**1002FDC-053 (Ballantyne et al., 2019a)**
Study design	RCT	RCT	RCT	RCT	RCT
Population	Adults with ASCVD, HeFH, or both	Adults at high CV risk due to ASCVD, HeFH, or both	Adults with hypercholesterolaemia and a history of intolerance to at least 2 statins	Adults with a history of statin intolerance who require additional LDL-C lowering	Adults at high CV risk due to ASCVD, HeFH, or multiple CVD risk factors
Background therapy	LMT including moderate-/high-intensity statin, ezetimibe, or fibrate	LMT including moderate-/high-intensity statin, cholesterol absorption inhibitors, bile acid sequestrants, fibrates, proprotein convertase subtilisin/kexin type 9 inhibitors, or niacin, either alone or in combination	LMT including no/low-dose statin or non-statin	LMT including no/ low-dose statin, fibrate, nicotinic acid, bile acid sequestrant, fish oil, eicosapentaenoic acid ethyl ester, omega-3 fatty acids, salmon oil, or sitosterol	No/moderate-/high-intensity statin
Intervention(s)	Bempedoic acid	Bempedoic acid	Bempedoic acid	Bempedoic acid with background ezetimibe (separate pills)	Bempedoic acid and ezetimibe FDC
Comparator(s)	Placebo	Placebo	Placebo	Placebo with background ezetimibe	Bempedoic acid, ezetimibe, placebo
Trial supports marketing authorisation application	Yes, for bempedoic acid	Yes, for bempedoic acid	Yes, for bempedoic acid	Yes, for bempedoic acid and FDC	Yes, for bempedoic acid+ezetimibe FDC

	Bempedoic acid trials				FDC trial
Study	**CLEAR Harmony 1002-040 (Ray et al., 2019b)**	**CLEAR Wisdom 1002-047 (Goldberg et al., 2019)**	**CLEAR Serenity 1002-046 (Laufs et al., 2019)**	**CLEAR Tranquility 1002-048 (Ballantyne et al., 2018)**	**1002FDC-053 (Ballantyne et al., 2019a)**
Trial used in the economic model	Yes	Yes	Yes	Yes	Yes
Rationale for use/non-use in the model	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks
Reported outcomes specified in the decision problem	**% change LDL-C**, non–HDL-C, TC, apo B, adverse effects	**% change LDL-C**, non–HDL-C, TC, apo B, adverse effects	**% change LDL-C**, non–HDL-C, TC, apo B, adverse effects	**% change LDL-C**, non–HDL-C, TC, apo B, adverse effects	**% change LDL-C**, non–HDL-C, TC, apo B, adverse effects
All other reported outcomes	hsCRP	hsCRP	hsCRP	hsCRP	hsCRP

apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; RCT = randomised controlled trial; TC = total cholesterol.

Note: bold text indicates outcomes which are used in the economic model.

Table 10. Completed phase 2 trials providing clinical efficacy and safety evidence for bempedoic acid and/or FDC

Study	1002-003 (Ballantyne et al., 2013)	1002-007 (Esperion Therapeutics data on file, 2014)	1002-009 (Ballantyne et al., 2016)	1002-035 (Esperion Therapeutics data on file, 2016)	1002-038 (Esperion Therapeutics data on file, 2017a)	1002-039 (Esperion Therapeutics data on file, 2018a)	1002-006 (Thompson et al., 2015)	1002-008 (Thompson et al., 2016)	1002-014 (Esperion Therapeutics data on file, 2015)	1002-005 (Gutierrez et al., 2014)
Study design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Population	Hyper-cholesterol-aemia (Elevated LDL-C +/- high TG)	Hyper-cholesterol-aemia	Hyper-cholesterol-aemia	Hyper-cholesterol-aemia (fasting TG ≤ 400 mg/dL)	Fasting elevated LDL-C (130-189 mg/dL)	Elevated LDL-C	Hyper-cholesterol-aemia + statin intolerant	Hyper-cholesterol-aemia +/- statin-related muscle symptoms	Elevated LDL-C + hypertension	Elevated LDL-C + T2DM
Background therapy	None	Atorva 10	Low-/ moderate-intensity statin	Atorva 80	Ezetimibe + Atorva 20	Evolocumab(420)	No/statin	No statin	None	None
Intervention	Bempedoic acid 40, 80, and 120 mg	Bempedoic acid + Atorva 10 mg	Bempedoic acid 120 or 180 mg + statin	Bempedoic acid 180 mg + Atorva 80 mg	Bempedoic acid 180 mg + ezetimibe 10 mg + Atorva 20 mg	Bempedoic acid 180 mg + PCSK9 inhibitor	Bempedoic acid	Bempedoic acid or bempedoic acid + ezetimibe	Bempedoic acid	Bempedoic acid 80-120 mg
Comparator(s)	PBO	PBO + atorvastatin 10 mg	PBO + statin	PBO + atorvastatin 80 mg	PBO	PBO+ PCSK9 inhibitor	PBO	Ezetimibe	PBO	PBO
Trial supports marketing authorisation application	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Trial used in the economic model	No	No	Yes	No	No	No	No	Yes	No	No

Study	1002-003 (Ballantyne et al., 2013)	1002-007 (Esperion Therapeutics data on file, 2014)	1002-009 (Ballantyne et al., 2016)	1002-035 (Esperion Therapeutics data on file, 2016)	1002-038 (Esperion Therapeutics data on file, 2017a)	1002-039 (Esperion Therapeutics data on file, 2018a)	1002-006 (Thompson et al., 2015)	1002-008 (Thompson et al., 2016)	1002-014 (Esperion Therapeutics data on file, 2015)	1002-005 (Gutierrez et al., 2014)
Rationale for use/non-use in the model	Bempedoic acid was not investigated at 180 mg	No 12-week time point	Bempedoic acid 180 mg was investigated at 12 weeks in patients receiving statin therapy	No 12-week time point	No 12-week time point	No 12-week time point	No 12-week time point	Bempedoic acid 180 mg was investigated at 12-weeks in statin-intolerant patients (subgroup)	No 12-week time point	No 12-week time point
Reported outcomes specified in the decision problem	% change LDL-C, non–HDL-C, apo B, Lp(a), and AEs	% change in LDL-C, non–HDL-C, apo B, Lp(a)	**% change in LDL-C**, non–HDL-C, apo B, AEs	% change in LDL-C, non–HDL-C, apo B, AEs	% change in LDL-C, non–HDL-C, apo B, AEs	% change in LDL-C, non–HDL-C, apo B, AEs, change in LDL-C	% change in LDL-C, non–HDL-C, apo B, Lp(a)	**% change in LDL-C**, non–HDL-C, apo B	% change in LDL-C, non–HDL-C, apo B	% change in LDL-C, non–HDL-C

Study	1002-003 (Ballantyne et al., 2013)	1002-007 (Esperion Therapeutics data on file, 2014)	1002-009 (Ballantyne et al., 2016)	1002-035 (Esperion Therapeutics data on file, 2016)	1002-038 (Esperion Therapeutics data on file, 2017a)	1002-039 (Esperion Therapeutics data on file, 2018a)	1002-006 (Thompson et al., 2015)	1002-008 (Thompson et al., 2016)	1002-014 (Esperion Therapeutics data on file, 2015)	1002-005 (Gutierrez et al., 2014)
All other reported outcomes	% change TC, TG, LDL particle number, apo A1, HDL particle number, FFA, hsCRP; changes in fasting insulin, DBP and SBP, physical examinations and clinical laboratory tests	% change in TC, HDL-C, TGs, Apo A1, FFA, hsCRP, homocysteine and adiponectin; TEAEs, physical examination, vital signs, ECGs, clinical laboratory values, weight, and ankle and waist circumferences; PK	% change TC, TG, LDL and HDL particle number, HDL-C, Apo A1, hsCRP, very LDL particle number; TEAEs, physical examination, vital signs, ECGs, clinical laboratory values, weight, and ankle and waist circumferences	PK, % change in TC, HDL-C, TGs, Apo A1, and hsCRP, blood biochemistry, haematology values, vital signs, ECG, and weight	% change in TC, HDL-C, TGs, apo A1, hsCRP, TEAEs, physical examination, vital signs, and clinical laboratory results	% change in TC, TG, Lp(a), HDL-C, hsCRP, clinical laboratory values, bempedoic acid concentration	% change in TC, TG, HDL-C, hsCRP, apo A1, FFA, lipids; number of patients achieving NCEP ATP-III 2004 goal for LDL-C	% change in TC, TG, HDL-C, LDL and HDL particle number, hsCRP, apo A1, LDL particle number, VLDL particle number; dose-response; TEAEs, physical examination, vital signs, ECGs, clinical laboratory values, weight, and ankle and waist circumferences	Change in SBP and DBP, % change in TC, HDL-C, TGs, FFA, hsCRP, insulin, homocysteine and adiponectin; TEAEs, physical examination, vital signs, ECGs, clinical laboratory values, weight, and ankle and waist circumferences; PK	% change in HDL-C

AE = adverse events; Apo B = apolipoprotein B; Atorva = atorvastatin; CSR = clinical study report; DBP = diastolic blood pressure; ECG = electrocardiograms; FDC = bempedoic acid and ezetimibe fixed-dose combination; FFA = free fatty acids; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); NCEP ATP-III = National Cholesterol Education Program Adult Treatment Panel III; PCSK9 = proprotein convertase subtilisin kexin type 9; PBO = placebo; PK = pharmacokinetics; RCT = randomised controlled trial; SBP = systolic blood pressure; TC = total cholesterol; TEAE = treatment-emergent adverse event; TG = triglyceride; T2DM = type 2 diabetes mellitus; VLD = very low dose; VLDL = very low-density lipoprotein.

Note: bolded header text indicates that the phase 2 trial reports 12-week LDL-C data for bempedoic acid 180 mg and is detailed further in the submission.

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

B.2.3.1 Bempedoic acid clinical development programme

The clinical development programme for bempedoic acid evaluated the efficacy of bempedoic acid in reducing LDL-C as an add-on therapy to other lipid-modifying therapies (LMTs), including maximally tolerated statins (which may mean no or low statin dose) or ezetimibe or PCSK9 inhibitors, for the treatment of patients whose LDL-C levels are not currently controlled with current standard of care for dyslipidemia.

The programme includes 15 phase 1, 10 phase 2, and 5 phase 3 studies to support the LDL-C reduction indication; 1 ongoing open-label extension (OLE) safety study; and 1 ongoing phase 3 CV outcomes trial. Efficacy was evaluated in a total 16 phase 3 and phase 2 studies in over 4,500 patients with elevated LDL-C. Among these studies were 5 pivotal phase 3 studies, 10 supportive phase 2 studies, and 1 ongoing phase 3 OLE study. The 5 completed phase 3 studies (CLEAR Harmony, Wisdom, Serenity, Tranquility, and Study 1002FDC-053) were double-blind, placebo-controlled, randomised (2:1 ratio of bempedoic acid: placebo), parallel-group, multicentre studies of bempedoic acid 180 mg either as monotherapy or in combination with stable background LMTs for 12 to 52 weeks. The 10 completed phase 2 studies included 4 studies of bempedoic acid monotherapy (Studies 1002-003, 1002-005, 1002-006, and 1002-014), 1 study of bempedoic acid monotherapy and bempedoic acid+ezetimibe combination therapy (Study 1002-008), 1 study of bempedoic acid+ezetimibe+atorvastatin combination therapy (Study 1002-038), 3 studies of bempedoic acid with background statin therapy (Studies 1002-007, 1002-009, and 1002-035), and 1 study of bempedoic acid with background PCSK9 inhibitor therapy (Study 1002-039). A total of 766 patients were exposed to bempedoic acid, 299 patients to placebo, and 99 patients to ezetimibe in the phase 2 studies. For this submission, bempedoic acid monotherapy trials and bempedoic acid+ezetimibe combination trials are presented separately.

B.2.3.2 Bempedoic acid trials: methodology and patient characteristics

B.2.3.2.1 Methodology

Phase 3 bempedoic acid trials

The clinical effectiveness and safety evidence from four phase 3 trials investigating bempedoic acid as relevant to the NICE decision problem and included in the economic model are summarised below and in Table 11. Note that CLEAR Tranquility provides evidence for bempedoic acid single-agent pill compared with placebo when given with background ezetimibe therapy in statin-intolerant patients and is described in this section.

CLEAR Harmony is a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study. It was designed to assess the long-term safety, tolerability, and efficacy of bempedoic acid over 52 weeks in patients with hyperlipidaemia who were at high risk for CV events (defined as patients

with underlying HeFH and/or ASCVD) and had elevated LDL-C despite treatment with stable background LMT, including maximally tolerated statin therapy (Esperion Therapeutics data on file, 2018b; Ray et al., 2019b).

Patients were randomised 2:1 to receive either bempedoic acid 180 mg or placebo (PBO) orally once daily (QD) for 52 weeks using an interactive web-response system (IWRS). Randomisation was stratified by CV risk (whether the patient had a diagnosis of HeFH) and baseline statin intensity (low-, moderate-, or high-intensity statins), for a total of six strata. Treatment was administered in a double-blind fashion. The Sponsor, all clinical site personnel (e.g., investigator, pharmacist), and other vendor personnel were blinded to the treatment group for each patient. Patients were also blinded to the treatment they received (Esperion Therapeutics data on file, 2018b; Ray et al., 2019b).

CLEAR Wisdom is a phase 3, long-term, randomised, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and long-term safety of bempedoic acid 180 mg over 52 weeks in patients with hyperlipidemia who were at high risk for CV events (defined as patients with underlying HeFH and/or ASCVD) and who had elevated LDL-C despite treatment with stable background LMT, including maximally tolerated statin therapy. The study consisted of a 1-week screening period, a 4-week single-blind placebo run-in period, and a 52-week double-blind, randomised treatment period. The extended treatment duration (52 weeks) and large patient number were chosen to obtain robust efficacy and safety data in this population of patients who have an unmet medical need for additional lipid-lowering therapy (Goldberg et al., 2019).

Patients were randomised 2:1 to receive either double-blind bempedoic acid 180 mg or PBO QD using IWRS. Randomisation was stratified based on the patient's CV risk (ASCVD alone; HeFH with or without ASCVD) and baseline statin intensity (high-, moderate-, or low-intensity statin) for a total of six strata. Patients, all clinical site personnel, the Sponsor, and other vendor personnel were blinded to the treatment group (Goldberg et al., 2019).

CLEAR Serenity is a phase 3, randomised, double-blind, placebo-controlled, parallel-group study that investigated the efficacy, safety, and tolerability of bempedoic acid versus PBO in statin-intolerant patients with elevated LDL-C requiring lipid-lowering therapy for primary or secondary prevention of CV events. The study consisted of a 5-week screening period, which included a 4-week, single-blind, placebo run-in period, and a 24-week double-blind, randomised treatment period (Laufs et al., 2019).

Patients were stratified by treatment indication (primary vs. secondary prevention and/or HeFH) then randomised 2:1 to receive treatment with oral bempedoic acid 180 mg or PBO. Patients and study personnel were blinded to the treatment assignments and to post-randomisation values for lipid and biomarker measures that may have inadvertently revealed treatment assignment (Laufs et al., 2019).

CLEAR Tranquility was a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of bempedoic acid 180 mg when added to background LMT in patients with a history of statin intolerance who required additional LDL-C lowering. The study comprised three phases: a 1-week screening period; a 4-week, ezetimibe 10 mg/day single-

blind run-in period; and a 12-week, double-blind treatment period (Ballantyne et al., 2018). Patients were randomised 2:1 to receive either double-blind treatment with oral bempedoic acid 180 mg or PBO QD, added to ezetimibe 10 mg/day for 12 weeks. Randomisation for treatment assignments was determined using IWRS. Patients, pharmacists, investigators, and study personnel remained blinded to treatment group assignments through the duration of the study (Ballantyne et al., 2018).

Table 11. Methodology of phase 3 bempedoic acid trials

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
Location	114 multinational clinical sites	86 multinational clinical sites	67 multinational clinical sites	90 multinational clinical sites
Trial design	Phase 3 randomised, double-blind, placebo-controlled, multicentre, parallel-group study to assess the long-term (52-week) safety, tolerability and efficacy of bempedoic acid in patients with hyperlipidemia at risk of CV events who have elevated LDL-C despite receiving background LMT, including maximally tolerated statin therapy. Randomisation was stratified according to the intensity of statin therapy at baseline (low, moderate, or high) and the presence or absence of HeFH.	Randomised, double-blind, placebo-controlled study to evaluate the 52-week efficacy of bempedoic acid in patients with hyperlipidemia who are at high risk for CV events and treated with stable background LMT including maximum tolerated statin therapy. Randomisation was stratified based on the patient's CV risk (ASCVD alone; HeFH with or without ASCVD) and baseline statin intensity (high-intensity statin; moderate-intensity statin; low-intensity statin), for a total of 6 strata.	Phase 3 randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of bempedoic acid in patients with ASCVD or HeFH who are statin intolerant and require lipid-lowering therapy for prevention of CV events. Patients were stratified by treatment indication (primary prevention vs. secondary prevention and/or HeFH).	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of bempedoic acid when added to background therapy with ezetimibe in patients with a history of not tolerating at least 1 statin and who required additional LDL-C lowering. This study enrolled eligible patients with documented ASCVD, HeFH, and/or multiple CV risk factors that put the patients at elevated risk for CVD, and who had elevated LDL-C and were unable to tolerate a statin at more than its lowest dose. Patients were randomised 2:1 to double-blind treatment with bempedoic acid or PBO using an IWRS. Stable background LMT (inclusive of a low-dose or very low-dose statin and/or permitted non-statin agents) and study-provided open-label ezetimibe were maintained throughout the study.

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
Eligibility criteria for participants	Age ≥ 18 years and fasting LDL-C ≥ 70 mg/dL at least 2 weeks before screening visit; high CV risk[a]; on maximally tolerated LMT, defined as maximally tolerated statin either alone or in combination with other LMTs, at stable doses for at least 4 weeks before screening.	Age ≥ 18 years with fasting LDL-C at week −5 ≥ 100 mg/dL and fasting LDL-C value at week −1 ≥ 70 mg/dL; high CV risk[a]; on maximally tolerated LMT, defined as maximally tolerated statin either alone or in combination with other LMTs, at stable doses for at least 4 weeks before screening.	Adult patients who had a history of statin intolerance[c] with fasting LDL-C ≥ 130 mg/dL (for primary prevention patients[d]) and ≥ 100 mg/dL (for those with HeFH) and/or had a secondary prevention indication.[e]	Inclusion criteria: Age ≥ 18 years with a history of statin intolerance, treated with no more than low-dose statin therapy[a] (which could also include no statin), and required additional LDL-C lowering; fasting LDL-C ≥ 100 mg/dL or ≥ 120 mg/dL if not on ezetimibe at baseline.
Settings and locations where the data were collected	114 clinical sites in 6 countries (Canada, Germany, Netherlands, Poland, UK, US).	86 clinical sites in 6 countries (Canada, Germany, Poland, Ukraine, UK, US.)	67 sites in 2 countries (Canada and US).	90 sites in 3 countries (Canada, Europe, and US)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n = [x]) and comparator(s) (n = [x])**	Patients were randomly assigned in a 2:1 ratio to receive either bempedoic acid (n = 1,488) or matching placebo (n = 742) for 52 weeks. Follow-up visits were conducted at weeks 4, 8, 12, 24, 36, and 52 and included the obtaining of fasting blood samples for biomarker measurement.	Patients were randomised 2:1 to bempedoic acid (n = 522) or matching placebo (n = 257) orally QD for 52 weeks. Follow-up visits were conducted at weeks 4, 8, 12, 24, 36, and 52.	Patients were randomised in a 2:1 ratio to receive either bempedoic acid (n = 234) or matching placebo (n = 111) OD for 24 weeks. Clinical laboratory samples were collected at weeks 4, 8, 12, and 24 for fasting lipids assessment and at weeks 12 and 24 for biomarker assessment.	Patients were randomised in a 2:1 ratio to receive either oral bempedoic acid 180 mg + ezetimibe 10 mg (n = 181) or matching PBO+ezetimibe 10 mg (n = 88) QD for 12 weeks. Follow-up visits were conducted at weeks 4, 8, and 12.

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
Permitted and disallowed concomitant medication	**Permitted medications:** Patients were required to be on stable LMT, including a maximally tolerated statin, for at least 4 weeks before screening. Stable LMT included, but was not limited to, monotherapies or combination therapies of the following treatments: • Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin)[b] • Selective cholesterol and/or bile acid absorption inhibitors (cholestyramine/cholestyramine, colestipol, colesevelam hydrochloride, ezetimibe) • Fibrates (fenofibrate, bezafibrate, ciprofibrate) • PCSK9 inhibitors (alirocumab, ezetimibe [prohibited within 4 weeks before screening but allowed as adjunctive therapy starting at week 24]) • Other (ezetimibe+simvastatin combination, where simvastatin dose was < 40 mg/day;	**Permitted medications:** Patients were required to be on maximally tolerated LMT, including a maximally tolerated statin either alone or in combination with other LMTs, at stable doses for at least 4 weeks before screening. Stable LMT included but was not limited to, monotherapies or combination therapies of the following treatments: • Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin)[b] • Selective cholesterol and/or bile acid absorption inhibitors (cholestyramine/cholestyramine, colestipol, colesevelam hydrochloride, ezetimibe) • Fibrates (fenofibrate, bezafibrate, ciprofibrate; at least 6 weeks before screening) • PCSK9 inhibitors (alirocumab, ezetimibe; patient must have received 3 stable doses) • Other (ezetimibe+simvastatin combination, where simvastatin dose was < 40 mg/day;	**Permitted medications:** Patients could continue stable LMT, when used for ≥ 4 weeks before screening and LMT could be combined with the following therapies: • Selective cholesterol absorption inhibitors • Bile acid sequestrants • Fibrates • PCSK9 inhibitors (if ≥ 3 doses were received before screening) • Niacin, either alone or in combination Patients tolerating very low-dose statin therapy[e] were permitted to continue statin therapy throughout the study, provided that the drug and dose were stable and well tolerated. **Disallowed medications:** • Gemfibrozil (in patients receiving a very low-dose statin)	**Permitted medications:** Patients on low or very low-dose statin[a] at screening could continue statin therapy throughout the study provided that the dose was stable (≥ 4 weeks) and well tolerated. Other allowed medications were: • Stable LMT (for at least 4 weeks before screening) • Fibrates (if stable for at least 6 weeks before screening) Use of any of the following medications were allowed if started before the randomisation visit as defined below and were expected to remain stable through completion of the study: hormone replacement therapy (≥ 6 weeks before day 1); thyroid replacement therapy (≥ 6 weeks before day 1); diabetes medications (≥ 4 weeks before day 1); obesity medications (≥ 4 weeks before day 1). Other concomitant medications and doses had to have been stable for 2 weeks before screening and, if possible, were not to be adjusted during the study except for reasons of safety.

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
	atorvastatin+ezetimibe combination) **Disallowed medications:** • Gemfibrozil • Simvastatin ≥ 40 mg/day	atorvastatin+ezetimibe combination) **Disallowed medications:** • Gemfibrozil • New or planned dose changes of systemic corticosteroids • Cholesteryl ester transfer protein inhibitors within the last 2 years before screening except for evacetrapib within the last 3 months before screening • Mipomersen (6 months before screening) • Simvastatin ≥ 40 mg/day (4 weeks before screening) • Red yeast rice extract-containing products are not allowed (2 weeks before screening) • Hormone or thyroid replacement (6 weeks before randomisation) • Diabetes or obesity medications (4 weeks before randomisation)		**Disallowed medications:** Patients were not to use the following medications (monotherapies or combination therapies) before screening or at any time during the study: • Gemfibrozil (within 6 weeks prior to screening) • PCSK9 inhibitors (within 4 months prior to screening) • Cholestin or red yeast rice-containing products (within 2 weeks prior to screening) • Statin dose exceeding the dose defined above; or any new or planned dose changes of systemic corticosteroids (within 4 weeks prior to screening) • Lomitapide or apheresis therapy; probenecid or cyclosporine (within 3 months prior to screening) • Mipomersen (within 6 months prior to screening) • CETP inhibitors within the last 2 years before screening except for evacetrapib within the last 3 months prior to screening

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
				• New or planned antiarrhythmia medication(s) within 3 months prior to screening • Any experimental or investigational drugs within 30 days before screening **Patients who enrolled in a study of an experimental siRNA inhibitor of PCSK9 were excluded.**
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was overall safety, which was assessed according to the incidence of AEs, changes in safety laboratory variables, severity of AEs, and relation to the trial agent.	The primary endpoint was percentage change from baseline to week 12 in LDL-C.	The primary endpoint was percentage change from baseline to week 12 in LDL-C.	The primary endpoint was percentage change from baseline to week 12 in LDL-C. LDL-C was calculated directly using the Friedewald formula, except in cases of TG > 400 mg/Dl or calculated LDL-C ≤ 50 mg/dL in these instances, a direct measure of LDL-C was conducted.

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
Other outcomes used in the economic model/specified in the scope	The principal secondary endpoint (principal efficacy endpoint) was the percentage change in the LDL-C level from baseline to week 12. Additional key secondary endpoints were the percentage changes in the levels of non–HDL-C, TC, apo B, and hsCRP from baseline to week 12; percentage change from baseline to week 24 in LDL-C.	Secondary endpoints were percentage change from baseline to week 24 in LDL-C; percentage change from baseline to week 12 in non–HDL-C, TC, apo B, hsCRP; absolute change from baseline to weeks 12 and 24 in LDL-C. Tertiary endpoints were absolute change and percentage change from baseline to week 52 in LDL-C; percentage change from baseline to weeks 24 and 52 in non–HDL-C, TC, apo B, and hsCRP; percentage change from baseline to weeks 12, 24, and 52, in TGs and HDL-C. Additional analyses included the proportion of patients who achieved hsCRP < 2 mg/L at weeks 12, 24, and 52 for whom baseline hsCRP was > 2 mg/L. Safety endpoints included TEAEs, clinical safety laboratories and vital signs, and adjudicated CV event rates.	Secondary endpoints were percentage change from baseline to week 24 in LDL-C; percentage change from baseline to weeks 12 and 24 in non–HDL-C, TC, apo B, hsCRP, triglycerides, and HDL-C; absolute change from baseline to weeks 12 and 24 in LDL-C; AEs.	Secondary endpoints included percentage changes from baseline to week 12 in non–HDL-C, TC, apo B, hsCRP, TGs, and HDL-C. Tertiary endpoints included percentage and absolute changes from baseline to weeks 4 and 8 in LDL-C, non–HDL-C, TC, TG, and HDL-C; and absolute changes from baseline to week 12 in LDL-C, non–HDL-C, TC, TG, and HDL-C. Safety included TEAEs, clinical safety laboratory results, physical examination findings, vital sign measurements, ECG readings, and weight measurements.

Trial number (acronym)	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)	CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)	CLEAR Serenity (1002-046) (Laufs et al., 2019)	CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)
Preplanned subgroups	Percentage change from baseline in LDL-C at week 12 was analysed within the following subgroups: sex (male vs. female), age (< 65 years vs. ≥ 65 years and < 75 years vs. ≥ 75 years), baseline CVD risk category (ASCVD vs. no ASCVD and HeFH vs. no HeFH), baseline statin intensity (low or moderate vs. high), baseline non-statin lipid-lowering therapy (ezetimibe vs. non-ezetimibe and fibrate vs. non-fibrate); race (white vs. other), baseline LDL-C category (< 100 mg/dL vs. ≥ 100 mg/dL), history of diabetes (yes vs. no), BMI (< 25, 25 to < 30, ≥ 30 kg/m^2), region (North America, Europe).	Percentage change from baseline in LDL-C at week 12 was analysed within the following subgroups: sex (male vs. female), age (< 65 vs. ≥ 65 years and < 75 vs. ≥ 75 years), baseline CVD risk category (HeFH +/- ASCVD vs. ASCVD), baseline statin intensity (low or moderate vs. high), baseline LDL-C category (< 130 vs. ≥ 130 to < 160 vs. ≥ 160 mg/dL); race (white vs. other), history of diabetes (yes vs. no), BMI (< 25, 25 to < 30, ≥ 30 kg/m^2), region (North America, Europe).	Subgroup analyses were performed for the percentage change from baseline to week 12 in LDL-C in the following groups: CVD risk category (primary vs. secondary prevention), baseline LDL-C category (< 130 mg/dL, ≥ 130 and < 160 mg/dL, ≥ 160 mg/dL), history of DM, age (< 65, ≥ 65 to < 75, ≥ 75 years), race, sex, BMI category (< 25 kg/m^2, ≥ 25 and < 30 kg/m^2, ≥ 30 kg/m^2), and background LMT (statin, non-statin, none).	Subgroup analyses for the primary efficacy variable were performed for the following groups: baseline LDL-C category (< 130 mg/dL, ≥ 130 to < 160 mg/dL, ≥ 160 mg/dL); history of diabetes; age (< 65 years, ≥ 65 to < 75 years, ≥ 75 years); race (white vs. non-white); sex; region (North America vs. Europe); BMI category (< 25 kg/m^2, 25 to < 30 kg/m^2, ≥ 30 kg/m^2); and background LMT (statin vs. other).

AE = adverse event; apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; PCSK9 = Proprotein convertase subtilisin/kexin type 9; QD = once daily; TC = total cholesterol; TEAE = treatment-emergent adverse event; TG = triglycerides; UK = United Kingdom; US = United States.

[a] Defined as either diagnosis of HeFH or ASCVD (with established CHD or CHD risk equivalents).

[b] Average daily doses ≤ 40 mg prior to protocol amendment and < 40 mg after amendment.

[c] Defined as the inability to tolerate at least two statins, one at a low dose, owing to a prior adverse event that started or increased during statin therapy and resolved or improved when statin therapy was discontinued.

[c] Patients who required lipid-lowering therapy based on national guidelines.

[d] Patients with coronary artery disease, symptomatic peripheral arterial disease, and/or cerebrovascular atherosclerotic disease.

[e] Very low-dose statin therapy was defined as an average daily dose of rosuvastatin < 5 mg, atorvastatin < 10 mg, simvastatin < 10 mg, lovastatin < 20 mg, pravastatin < 40 mg, fluvastatin < 40 mg, or pitavastatin < 2 mg.

In summary, a pooled analyses of the four phase 3 trials including 3,623 patients, treatment with bempedoic acid lowered LDL-C significantly more than did placebo at week 12 (Banach et al., 2019). In particular:

- Absolute mean reduction from baseline to week 12 in LDL-C was greater in patients treated with bempedoic acid compared with placebo
- Reductions in LDL-C were observed at the first post-baseline study visit (week 4) and were maintained through the last measurement time point (52 weeks in the ASCVD/HeFH on statins pool and 24 weeks in the statin intolerant pool)
- Subgroup analyses demonstrated significantly greater LDL-C lowering with bempedoic acid compared with placebo for most demographic, disease-related, and background-therapy subgroups (P = < 0.01).

The high-sensitivity C-reactive protein (hsCRP) was included as a secondary endpoint in the phase 3 clinical trial programme, among other key secondary markers of CVD, including non–HDL-C, TC, and apo B. Numerous studies have demonstrated that an elevation of hsCRP, an important biomarker of inflammation, has been associated with increased cardiovascular risk (Bikdeli, 2011; Vidula et al., 2008), and lowering hsCRP with statin therapy, independent of the level of LDL-C achieved with the statin treatment, has been associated with reduced CV events in some cardiovascular outcomes trials (Ridker et al., 2008). Newer prospective interventional data using a direct treatment of inflammation, an IL-1 beta monoclonal antibody, demonstrated a significant reduction in ASCVD events and helped confirm the direct role of inflammation in ASCVD risk (Ridker et al., 2018; Ridker et al., 2017). The hsCRP data provide supporting scientific evidence of a biological effect.

Phase 2 bempedoic acid trials

The clinical effectiveness and safety evidence from two bempedoic acid trials identified as relevant to the NICE decision problem are summarised below and in Table 12 (Ballantyne et al., 2016; Thompson et al., 2016).

A phase 2b, randomised, double-blind, active comparator-controlled, parallel-group study was conducted to compare two doses of bempedoic acid, alone or combined with ezetimibe, versus. ezetimibe monotherapy for lowering LDL-C (Phase 2 study 1002-008; (Thompson et al., 2016). This trial consisted of a 5-week washout period and a 5-week single-blind, placebo run-in during the screening period. Selected patients were stratified (1:1) by history of statin intolerance and randomised at week 0 in a 4:4:4:1:1 ratio to QD treatment with capsules containing bempedoic acid 120 mg, bempedoic acid 180 mg, ezetimibe, bempedoic acid 120 mg plus ezetimibe, or bempedoic acid 180 mg plus ezetimibe for 12 weeks (Thompson et al., 2016).

A phase 2b, multicentre, double-blind, parallel-group, placebo-controlled, trial compared the lipid-lowering efficacy of bempedoic acid versus placebo as an add-on therapy to statins in patients with hypercholesterolaemia (Phase 2 study 1002-009; (Ballantyne et al., 2016). This trial consisted of a 6-

week screening and washout phase and a 12-week treatment phase. Patients were randomised in a 1:1:1 ratio to bempedoic acid 120 mg, bempedoic acid 180 mg, or placebo QD for 12 weeks in addition to ongoing low- or moderate-intensity statin therapy (atorvastatin 10 mg or 20 mg; simvastatin 5 mg, 10 mg, or 20 mg; rosuvastatin 5 mg or 10 mg; or pravastatin 10 mg, 20 mg, or 40 mg). Patients were stratified by history of statin intolerance, defined as discontinuation of ≥ 1 statins at any dose because of muscle-related symptoms (Ballantyne et al., 2016).

Table 12. Methodology of phase 2 trials reporting 12-week LDL-C data for bempedoic acid 180 mg

Trial number (acronym)	Phase 2 Study 1002-008 (Thompson et al., 2016)	Phase 2 Study 1002-009 (Ballantyne et al., 2016)
Location	70 clinical sites in US	41 clinical sites in the US
Trial design	Randomised, double-blind, active comparator-controlled, parallel-group consisting of a 6-week screening phase and a 12-week double-blind treatment period. The trial compared the efficacy and safety of bempedoic acid monotherapy and combination therapy with ezetimibe 10 mg vs. ezetimibe monotherapy among hypercholesterolemic patients with or without a history of statin-related muscle symptoms. Patients were stratified (1:1) by history of statin intolerance and randomised at week 0 in a 4:4:4:1:1 ratio to treatment with bempedoic acid or ezetimibe monotherapy or combination therapy.	Multicentre, double-blind, parallel-group, placebo-controlled trial consisting of a 6-week screening and washout phase and a 12-week treatment phase. The trial assessed the efficacy of bempedoic acid vs. PBO when added to ongoing statin therapy in patients with hypercholesterolaemia. Patients were randomised in a 1:1:1 ratio to bempedoic acid 120 mg, bempedoic acid 180 mg, or placebo QD for 12 weeks in addition to ongoing statin therapy. Patients were stratified by history of statin intolerance, defined as discontinuation of ≥ 1 statin at any dose because of muscle-related symptoms.
Eligibility criteria for participants	Inclusion criteria: • Medically stable, hypercholesterolemic patients aged 18-80 years with a BMI of 18-45 kg/m^2. • Fasting, calculated LDL-C values ≥ 130 and ≤ 220 mg/dL and a fasting TG level ≤ 400 mg/dL after washout of lipid-regulating drugs. • Statin-tolerant and statin-intolerant patients.[a] • Administration of 1 statin at the lowest approved daily dose.[b] Treatment with less than the lowest approved daily dose of a statin (i.e., skipping days) was considered	Inclusion criteria: • Hypercholesterolemic adult patients aged 18-80 years with a BMI of 18-45 kg/m^2 who were on stable statin therapy[c] • Fasting, calculated LDL-C levels from 115-220 mg/dL and a fasting TG level of ≤ 400 mg/dL after washout of lipid-regulating agents other than the statins listed previously Exclusion criteria: • Clinically significant CVD within 12 months of screening, including but not limited to ACS, stroke, TIA, carotid or peripheral artery disease, or cardiac arrhythmias • Current clinically significant CVD including decompensated heart failure, uncontrolled hypertension, or cardiac arrhythmias

Trial number (acronym)	Phase 2 Study 1002-008 (Thompson et al., 2016)	Phase 2 Study 1002-009 (Ballantyne et al., 2016)
	equivalent to not tolerating 1 statin at the lowest approved daily dose. Exclusion criteria: • Clinically significant CVD (including ACS, stroke, TIA, carotid or peripheral artery disease, decompensated heart failure, uncontrolled hypertension, or cardiac arrhythmias) • T1DM; uncontrolled T2DM • Non–statin-related musculoskeletal complaints or patients reporting new or worsening unexplained muscle-related AEs during the run-in period • Uncorrected hypothyroidism • Liver or renal dysfunction • Unexplained CK elevations off statin treatment > 3 times the ULN • Ingested < 80% of drug during single-blind run-in; or used anticoagulants, systemic corticosteroids, cyclosporine, metformin, or thiazolidinediones within 3 months of screening	• History of liver or muscle enzyme elevation that occurred during statin therapy and resolved after statin discontinuation • T1DM; uncontrolled T2DM • History of long-term muscle symptoms difficult to differentiate from myalgia or current muscle symptoms that may have been due to ongoing statin therapy • Uncontrolled hypothyroidism, liver or renal dysfunction; GIT disorders affecting drug absorption, unexplained CK; elevations • Use of anticoagulants, colchicine, systemic corticosteroids, digoxin, potent cytochrome P450 3A4 inhibitors or inducers, metformin, or thiazolidinediones within 4 weeks of screening
Settings and locations where the data were collected	See location	See location
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n = [x]) and comparator(s) (n = [x])**	Patients were stratified (1:1) by history of statin intolerance and randomised at week 0 in a 4:4:4:1:1 ratio to QD treatment for 2 weeks with: • Bempedoic acid 120 mg (n = 100) • Bempedoic acid 180 mg (n = 100)	Patients were randomised in a 1:1:1 ratio to: • Bempedoic acid 120 mg (n = 44) • Bempedoic acid 180 mg (n = 45) • Matching placebo (n = 45) Capsules were given QD for 12 weeks in addition to ongoing

Trial number (acronym)	Phase 2 Study 1002-008 (Thompson et al., 2016)	Phase 2 Study 1002-009 (Ballantyne et al., 2016)
	• Ezetimibe 10 mg (n = 90) • Bempedoic acid 120 mg plus ezetimibe 10 mg (n = 100), or • Bempedoic acid 180 mg plus ezetimibe 10 mg (n = 100)	statin therapy
Permitted and disallowed concomitant medication	**Disallowed medication:** Patients were required to washout all drugs or dietary supplements taken for lipid regulation during the 5 weeks before randomisation and abstained from these drugs and supplements throughout the study. This included, but was not limited to, monotherapies or combination therapies containing the following compounds: • Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin) • Selective cholesterol and/or bile acid absorption inhibitors (cholestyramine, colestipol, colesevelam hydrochloride) • Fibrates (gemfibrozil, fenofibrate, clofibrate) • Supplements (artichoke extract, psyllium, garlic extract, green tea extract, niacin, sitostanol, beta-sitosterol, red yeast rice, coenzyme Q10, pantethine, policosanol) • Other (niacin, ezetimibe, omega-3-acid ethyl esters) Patients were prohibited from using monotherapies or combination therapies containing the compounds listed below within 3 months before screening, and were prohibited from using them during the study:	**Permitted medication:** Patients had to be taking the following stable statin therapy daily for at least 3 months before screening: atorvastatin (10 mg or 20 mg), simvastatin (5 mg, 10 mg, or 20 mg), rosuvastatin (5 mg or 10 mg), and pravastatin (10 mg, 20 mg, or 40 mg). Use of the following medications had to be stable for a minimum of 5 weeks before randomisation and, if possible, was not to be adjusted during the study except for reasons of safety: postmenopausal hormone therapy; antihypertensive agents, and thyroid hormone supplements. Use of antiobesity agents was to be stable for a minimum of 6 months before randomisation and, if possible, was not to be adjusted during the study except for reasons of safety. **Disallowed medication:** • Statins (fluvastatin, lovastatin, and pitavastatin) • Selective cholesterol and/or bile acid absorption inhibitors (cholestyramine, colestipol, colesevelam hydrochloride) • Fibrates (gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate) • Supplements (artichoke extract, psyllium, garlic extract, green tea extract, niacin, sitostanol, beta-sitosterol, red yeast rice, coenzyme Q10, pantethine, policosanol) • Other (lomitapide, mipomersen, niacin, ezetimibe, omega-3-acid ethyl esters)

Trial number (acronym)	Phase 2 Study 1002-008 (Thompson et al., 2016)	Phase 2 Study 1002-009 (Ballantyne et al., 2016)
	• Anticoagulants, including warfarin and other vitamin K antagonists, factor Xa inhibitors, and direct thrombin inhibitors • Cyclosporine • Systemic corticosteroids • Metformin • Thiazolidinediones (pioglitazone and rosiglitazone)	• Anticoagulants, including warfarin and other vitamin K antagonists, factor Xa inhibitors, and direct thrombin inhibitors • Colchicine • Systemic corticosteroids • Digoxin or substances containing digitalis • Potent CYP3A4 inhibitors and CYP3A4 inducers • Metformin • Thiazolidinediones (pioglitazone and rosiglitazone)
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was percentage change in the LDL-C level from baseline to week 12 in patients treated with bempedoic acid vs. ezetimibe monotherapy.	The primary efficacy endpoint was the percentage change in calculated LDL-C from baseline to week 12.
Other outcomes used in the economic model/specified in the scope	Secondary endpoints included dose-response relationship between bempedoic acid and the percentage change in LDL-C from baseline to week 12, the percentage change in LDL-C from baseline to week 12 in patients treated with bempedoic acid plus ezetimibe vs. ezetimibe alone, and the percentage change from baseline to week 12 for all treatment groups in LDL particle number, apo B, TC, non–HDL-C, HDL-C, HDL particle number, TG, VLDL particle number, and high-sensitivity CRP. Safety assessments included TEAEs, clinical laboratory tests, physical examination findings, vital signs, ECG readings, weight, and ankle and waist circumference measurements.	Secondary endpoints included the percentage change from baseline to week 12 in apo B, non–HDL-C, TC, LDL particle number, HDL-C, HDL particle number, apo A-1, TG, VLDL particle number, and hsCRP. Safety assessments included TEAEs, clinical laboratory tests, physical examination findings, vital signs, ECG readings, weight, and ankle and waist circumference measurements.
Preplanned subgroups	NR	NR

ACS = acute coronary syndromes; AE = adverse event; Apo A-1; apolipoprotein A-I; Apo B = apolipoprotein B; BMI = body mass index; CK = creatine kinase; CVD = cardiovascular disease; ECG = electrocardiogram; GIT = gastrointestinal; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; NR = not reported; PBO = placebo; QD = once daily; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TC = total cholesterol; TEAE = treatment-emergent adverse events; TG = triglyceride; TIA = transient ischaemic attack; ULN = upper limit of normal; VLDL = very low-density lipoprotein.

[a] Statin intolerance was defined as the inability to tolerate ≥ 2 statins because of muscle-related symptoms such as pain, weakness, or cramping that began or increased during statin therapy and resolved on statin discontinuation.

[b] Defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg.

[c] Stable statin therapy was defined as use of atorvastatin (10 or 20 mg), simvastatin (5, 10, or 20 mg), rosuvastatin (5 or 10 mg), or pravastatin (10, 20, or 40 mg) for at least 3 months before screening.

B.2.3.2.2 Baseline characteristics

Phase 3 bempedoic acid trials

Table 13 presents baseline characteristics of the patients included in the phase 3 bempedoic acid trials.

In CLEAR Harmony, a total of 2,230 patients were included in the intention-to-treat (ITT) population and most patients were white (95.9%), had a history of ASCVD (97.6%), and were enrolled at European sites (65.6%). A greater proportion were male (73.0%), but patients were evenly distributed by sex across the treatment groups (bempedoic acid: 73.9%; placebo: 71.3%). The mean age of patients was 66.1 years (bempedoic acid: 65.8 years; placebo: 66.8 years). Baseline characteristics were similar between both populations, with no notable differences of distribution between treatment arms except for age (P = 0.02); the difference in age between the two groups was not considered to be clinically important. Overall, 6.6% used low-intensity therapy, 43.5% used moderate-intensity therapy, and 49.9% used high-intensity therapy. A total of 172 patients (7.7%) were receiving ezetimibe either alone or in combination with statins, and 80 patients (3.6%) were receiving fibrates. The mean (± standard deviation [SD]) LDL-C level at baseline was 103.2± 29.4 mg/dL (Ray et al., 2019b).

In CLEAR Wisdom, 779 patients were included in the ITT population. Demographic characteristics and efficacy parameters, including lipoproteins and hsCRP, were similar between treatment groups in the full analysis set (FAS) with no notable differences between groups. A greater percentage of men (63.7%) were included in the FAS but patients were evenly distributed by sex across the treatment groups (bempedoic acid: 65.4%; placebo: 62.8%). The mean age of the patients was 64.3 years and most patients were white (94.4%). Most patients (94.5%) had a diagnosis of ASCVD while a few patients (5.5%) had a diagnosis of HeFH (with or without ASCVD). Regarding background use of statin therapy, 15.1% were on low-intensity doses of statins or no statin, 31.8% were on moderate-intensity statins, and 53.0% of patients were on high-intensity statins. The mean (SD) LDL-C level at baseline was 119.4 (37.7) mg/dL in the bempedoic acid arm and 122.4 (38.3) in the placebo arm (Esperion Therapeutics data on file, 2019c.; Goldberg et al., 2019).

In CLEAR Serenity, of the 345 patients that were randomised, a higher proportion were white (89%), female (56.2%), and had a mean age of 65.2 years. A higher proportion of patients were enrolled for primary versus secondary prevention (61.2% and 38.8%, respectively). Few patients had HeFH (2%), and a history of diabetes mellitus and/or hypertension was common in both treatment arms. Patient demographics and baseline characteristics were generally balanced between treatment groups except for a significant difference in estimated glomerular filtration rate category (P = 0.044), with a greater proportion of patients with normal renal function in the bempedoic acid group and a greater proportion of patients with mild or moderate renal impairment in the placebo group. At baseline, mean (SD) LDL-C was 158.5 (40.4) in the bempedoic acid arm and 155.6 (38.8) in the placebo arm. Regarding background use of LMT, a greater proportion of patients were not on any LMT (bempedoic acid arm: 56.8%; placebo arm: 60.4%), 35.5% of patients in the bempedoic acid arm and 29.7% in placebo arm had non-statin while 7.7% of patients on bempedoic acid and 9.9% of those on placebo were on very low-dose statin (Laufs et al., 2019).

In CLEAR Tranquility a total of 269 patients met the study criteria and were randomised to receive treatment with bempedoic acid (n = 181) or placebo (n = 88). Demographics and baseline characteristics were similar between treatment groups in most respects. The mean age of the study population was 63.8 years, and most were white (89.2%), non-Hispanic or Latino (75.5%), and female (61.3%). Approximately 25.0% of patients had pre-existing cardiac disorder and most patients entered the study with a diagnosis of hypertension (60.2%). Mean baseline LDL-C, non–HDL-C, apo B, and TGs were slightly higher in the bempedoic acid treatment group (129.8, 162.4, 123.3, 153 mg/dL, respectively) compared with placebo (123, 151.6, 115.8, 135.5 mg/dL, respectively). Concomitant LMT (in addition to ezetimibe) was used by 44.8% of patients (47.5% bempedoic acid, 39.1% placebo). More patients in the bempedoic acid group (32.6%) were receiving concomitant statin therapy compared with those in the placebo group (27.6%) (Ballantyne et al., 2018).

Table 13. Patient characteristics in phase 3 bempedoic acid trials, by treatment arm

Trial number (acronym) Baseline characteristic	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)		CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)		CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018c; Laufs et al., 2019)		CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)	
	Bempedoic acid 180 mg	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid**	**Placebo**
Number randomised	1,488	742	522	257	234	111	181	88
Age, years, mean (SD)	65.8 (9.1)	66.8 (8.6)	64.1 (8.8)	64.7 (8.7)	65.2 (9.7)	65.1 (9.2)	63.8 (10.8)	63.7 (11.3)
Male, no. (%)	1,099 (73.9)	529 (71.3)	328 (62.8)	168 (65.4)	101 (43.2)	50 (45)	72 (39.78)	32 (36.4)
Race, no. (%)								
Black or African American	42 (2.8)	15 (2.0)	24 (4.6)	12 (4.7)	16 (6.8)	10 (9)	11 (6.1)	10 (11.4)
White	1,423 (95.6)	716 (96.5)	491 (94.1)	244 (94.9)	211 (90.2)	96 (86.5)	165 (91.2)	75 (85.2)
BMI, kg/m^2, mean (SD)	29.74 (4.919)	29.40 (4.935)	30.0 (5.2)	30.6 (5.0)	30.1 (5.8)	30.6 (5.2)	29.5 (4.7)	30.5 (5.8)
CV risk factor, no. (%)								
Primary prevention	NR	NR	NR	NR	144 (61.5)	67 (60.4)	NR	NR
Secondary prevention	NR	NR	NR	NR	90 (38.5)	44 (39.6)	NR	NR
ASCVD	1,449 (97.4)	727 (98.0)	NR	NR	NR	NR	NR	NR
ASCVD only	1,415 (95.1)	707 (95.3)	495 (94.8)	241 (93.8)	NR	NR	NR	NR
HeFH	56 (3.8)	23 (3.1)	NR	NR	4 (1.7)	3 (2.7)	NR	NR
HeFH with/without ASCVD	73 (4.9)	35 (4.7)	27 (5.2)	16 (6.2)	NR	NR	NR	NR
Cardiac disorder, n (%)	NR	NR	NR	NR	NR	NR	49 (27.1)	22 (25.0)
DM	425 (28.6)	212 (28.6)	155 (29.7)	81 (31.5)	63 (26.9)	26 (23.4)	35 (19.3)	17 (19.3)

Trial number (acronym) Baseline characteristic	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)		CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)		CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018c; Laufs et al., 2019)		CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)	
	Bempedoic acid 180 mg	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid**	**Placebo**
HTN	1,174 (78.9)	594 (80.1)	438 (83.9)	224 (87.2)	158 (67.5)	75 (67.6)	111 (61.3)	51 (58.0)
Impaired fasting glucose	NR	NR	9 (1.7)	5 (1.9)	NR	NR	NR	NR
Lipid measures at baseline, mg/dL, mean (SD)								
TC	179.7 (35.1)	178.6 (35.6)	202.1 (42.7)	204.8 (46.1)	245.7 (47.3)	241.1(44.3)	218.2 (35.9)	208.6 (35.7)
LDL-C	103.6 (29.1)	102.3 (30.0)	119.4 (37.7)	122.4 (38.3)	158.5 (40.4)	155.6 (38.8)	129.8 (30.9)	123.0 (27.2)
Non–HDL-C	130.9 (33.7)	129.4 (33.9)	150.7 (42.7)	153.7 (44.4)	193.5 (45.1)	190.7 (43.8)	162.4 (35.4)	151.6 (32.7)
HDL-C	48.7 (11.9)	49.3 (11.5)	51.4 (12.9)	51.1 (13.1)	52.2 (14.5)	50.4 (14.4)	55.8 (16.3)	57.1 (21.3)
Apo B	88.5 (21.6)	86.8 (21.8)	116.2 (29.6)	118.6 (30.5)	141.0 (31.6)	141.9 (30.4)	123.3 (26.5)	115.8 (23.5)
TG, median (IQR), mg/dL	126 (98-166)	123 (96-170)	139.3 (102.5-190.0)	143.0 (106.0-189.0)	156.5 (114.5-219)	164 (120-225.5)	153.0 (112.0-209.0)	135.5 (99.8-175.8)
hsCRP, median (IQR), mg/dL	1.49 (0.74-3.28)	1.51 (0.79-3.33)	1.61 (0.87-3.46)	1.88 (0.92-3.79)	2.92 (1.34-5.29)	2.78 (1.21-5.15)	2.21 (1.10-4.00)	2.26 (1.06-4.50)
LMT at Baseline, no. (%)								
Statins with or without other LMTs	1,485 (99.8)	742 (100)	470 (90.0)	228 (88.7)	NR	NR	NR	NR
Statins only	1,271 (85.4)	641 (86.4)	416 (79.7)	196 (76.3)	18 (7.7)	11 (9.9)	NR	NR
Statins with other	214 (14.4)	101 (13.6)	54 (10.3)	32 (12.5)	NR	NR	NR	NR

Trial number (acronym) Baseline characteristic	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)		CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)		CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018c; Laufs et al., 2019)		CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)	
	Bempedoic acid 180 mg	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid**	**Placebo**
LMT								
Very low-dose statin	NR	NR	NR	NR	18 (7.7)	11 (9.9)	NR	NR
No LMT	2 (0.1)	0	30 (5.7)	14 (5.4)	133 (56.8)	67 (60.4)	NR	NR
Other LMT only (non-statin)	1 (0.1)	0	22 (4.2)	15 (5.8)	83 (35.5)	33 (29.7)	NR	NR
Concomitant LMT, no. (%)								
Statin	1,485 (99.8)	742 (100)	470 (90.0)	228 (88.7)	NR	NR	59 (32.6)	25 (28.4)
Ezetimibe	116 (7.8)	56 (7.5)	38 (7.3)	24 (9.3)	1 (0.4)	1 (0.9)		
Fibrate	54 (3.6)	26 (3.5)	26 (5.0)	19 (7.4)	2 (0.9)	0	7 (3.9)	3 (3.4)
Nicotinic acid	NR	NR	NR	NR	NR	NR	3 (1.7)	4 (4.6)
Bile acid sequestrant	NR	NR	NR	NR	NR	NR	1 (0.6)	1 (1.1)
Other[b]	NR	NR	NR	NR	NR	NR	19 (10.5)	8 (9.2)
None	2 (0.1)	0	NR	NR	NR	NR	NR	NR
Statin therapy intensity, no. (%)								
Low	100 (6.7)	48 (6.5)	78 (14.9)	40 (15.6)	NR	NR	NR	NR
Moderate	646 (43.4)	324 (43.7)	166 (31.8)	82 (31.9)	NR	NR	NR	NR
High	742 (49.9)	370 (49.9)	278 (53.3)	135 (52.5)	NR	NR	NR	NR
eGFR category at baseline, no. (%)								
Normal: ≥ 90 mL/min/1.73 m^2	320 (21.5)	167 (22.5)	107 (20.5)	56 (21.8)	58 (24.8)	16 (14.4)	45 (24.9)	17 (19.3)
Mild renal impairment: 60 to < 90 mL/min/1.73 m^2	946 (63.6)	468 (63.1)	338 (64.8)	164 (63.8)	139 (59.4)	69 (62.2)	110 (60.8)	57 (64.8)

Trial number (acronym) Baseline characteristic	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019a; Ray et al., 2019b)		CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)		CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018c; Laufs et al., 2019)		CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)	
	Bempedoic acid 180 mg	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid 180 mg**	**Placebo**	**Bempedoic acid**	**Placebo**
Moderate renal impairment: 30 to < 60 mL/min/1.73 m^2	222 (14.9)	107 (14.4)	77 (14.8)	37 (14.4)	NR	NR	NR	NR
Severe renal impairment: 15 to < 30 mL/min/1.73 m^2	NR	NR	1 (0.2)	1 (0.4)	NR	NR	NR	NR
Renal impairment: < 60 mL/min/1.73 m^2	NR	NR	NR	NR	37 (15.8)	26 (23.4)	26 (14.4)	14 (15.9)
Reasons for statin intolerance, no. (%)								
Muscle symptoms	NR	NR	NR	NR	217 (92.7)	105 (94.6)	NR	NR
GIT symptoms	NR	NR	NR	NR	26 (11.1)	9 (8.1)	NR	NR
Elevated liver enzymes	NR	NR	NR	NR	15 (6.4)	7 (6.3)	NR	NR
Generalised fatigue	NR	NR	NR	NR	12 (5.1)	3 (2.7)	NR	NR
Cognitive decline	NR	NR	NR	NR	7 (3.0)	3 (2.7)	NR	NR
Elevated CK	NR	NR	NR	NR	2 (0.9)	1 (0.9)	NR	NR
Depression	NR	NR	NR	NR	1 (0.4)	0	NR	NR

apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; CK = creatine kinase; CVD = cardiovascular disease; CV = cardiovascular; DM = diabetes mellitus; ECG = echocardiogram; eGFR = estimated glomerular filtration rate; GIT = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; MI = myocardial infarction; NR = not reported; TC = total cholesterol; TG = triglycerides.

[a] Peripheral vascular disease.

[b] Includes fish oil, eicosapentaenoic acid ethyl ester, omega-3 fatty acids, salmon oil, and sitosterol.

Phase 2 bempedoic acid trials

Phase 2 study 1002-008

In total, 223 patients were included in the safety population of a phase 2b trial of bempedoic acid. Demographic and baseline characteristics were similar across treatment groups for all randomised patients with no notable differences of distribution between treatment arms. All treatment groups had a greater proportion of females (bempedoic acid: 51%; bempedoic acid+ezetimibe: 54%; ezetimibe 52%), white or Caucasians (bempedoic acid: 91%; bempedoic acid+ezetimibe: 92%; ezetimibe 88%) and non-Hispanic or Latinos (bempedoic acid: 85%; bempedoic acid+ezetimibe: 92%; ezetimibe: 90%). Age was similar across the treatment groups. The mean age of patients was 59 years in the bempedoic acid and bempedoic acid+ezetimibe groups and 60 years in the ezetimibe group. The mean LDL-C value at baseline was slightly similar in the bempedoic acid group (166 mg/dL), the bempedoic acid+ezetimibe group (162 mg/dL) and the ezetimibe group (165 mg/dL). Most patients across the treatment groups had a moderate or low National Cholesterol Education Program Adult Treatment Panel III risk category (Thompson et al., 2016). Table 14 presents baseline characteristics of the patients who received bempedoic acid 180 mg or control therapy in the phase 2 bempedoic acid trial.

Table 14. Patient characteristics in phase 2 study 1002-008 by treatment arm

Baseline characteristic	Bempedoic acid 180 mg	Bempedoic acid 180 mg + ezetimibe 10 mg	Ezetimibe 10 mg
Number randomised (statin intolerant)	100 (51)	24 (12)	99 (51)
Age	59 (9)	59 (9)	60 (10)
Male, no. (%)	49 (49)	11 (48)	45 (46)
Race, no. (%)			
White	91 (91)	22 (92)	87 (88)
Ethnicity, no. (%)			
Not Hispanic or Latino	85 (85.0)	22 (92)	89 (90)
Weight (kg)	89 (19)	83 (22)	85 (17)
BMI, kg/m^2	31 (5)	28 (5)	30 (5)
SBP (mmHg)	125 (12)	119 (12)	126 (12)
DBP (mmHg)	78 (7)	76 (9)	78 (7)
TC, mg/dL	253 (33)	246 (32)	248 (32)
LDL-C, mg/dL	166 (24)	162 (27)	165 (25)
HDL-C, mg/dL	52 (13)	52 (16)	49 (12)
TG, median (min.-max.), mg/dL	162 (38-371)	151 (50-343)	163 (64-434)
hsCRP, median (min.-max.) mg/L[a]	2.50 (0.1-20.3)	2.60 (0.3-31.7)	1.25 (0.2-4.7)

Baseline characteristic	Bempedoic acid 180 mg	Bempedoic acid 180 mg + ezetimibe 10 mg	Ezetimibe 10 mg
NCEP ATP-III risk category, no. (%)			
Very high	7 (7)	2 (8)	8 (8)
High	10 (10)	2 (8)	11 (11)
Moderate	49 (49)	11 (46)	48 (49)
Low	34 (34)	9 (38)	32 (32)

BMI = body mass index; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; NCEP ATP-III = National Cholesterol Education Program Adult Treatment Panel III; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; TG = triglycerides.

Note: the following additional arms were included in phase 2 study 1002-008, which are not relevant to the decision problem: bempedoic acid 120 mg and bempedoic acid 120 mg + ezetimibe 10 mg.

NCEP ATP-III Risk Category: Very high = CHD and two or more risk factors; High = CHD or CHD risk equivalents; Moderate = two or more risk factors; Low = 0-1 risk factors.

Values are mean (SD), unless otherwise indicated. Baseline defined as the mean of the values from weeks −1 and 0, unless otherwise indicated.

[a] Baseline defined as the last value before the first dose of study drug.

Source: Thompson et al. (2016).

Phase 2 study 1002-009

In total, 90 patients were included in the safety population of a phase 2b trial of bempedoic acid as an add-on therapy to statin in patients with hypercholesterolaemia. Baseline demographic and clinical characteristics were similar between the treatment groups. The mean age was similar between the treatment groups, 57 years and 56 years for patients in the bempedoic acid group and placebo group, respectively. Race and ethnicity were similar between the treatment groups. Most patients in the safety population were white or Caucasian (82% in both groups) and were non-Hispanic or Latino (bempedoic acid: 78%; placebo: 84%). Overall, 15% of the population reported a history of statin intolerance, defined as patient-reported discontinuation of at least one statin medication because of muscle-related symptoms (Ballantyne et al., 2016). Table 15 presents baseline characteristics of the patients who received bempedoic acid 180 mg in the phase 2 bempedoic acid add-on trial.

Table 15. Patient characteristics in Phase 2 study 1002-009 by treatment arm

Baseline characteristic	Bempedoic acid 180 mg	Placebo
Number randomised	45	45
Age, years	57 (10)	56 (10)
Male, no. (%)	14 (31)	23 (51)
Race, no. (%)		
White/Caucasian	37 (82)	37 (82)
Ethnicity, no. (%)		
Not Hispanic or Latino	35 (78)	38 (84)
Weight (kg)	83 (19)	90 (20)
BMI, kg/m^2	30 (6)	31 (6)
SBP (mmHg)	129 (14)	126 (12)
DBP (mmHg)	78 (9)	78 (7)
TC, mg/dL	229 (29)	212 (24)
LDL-C, mg/dL	142 (28)	131 (22)
HDL-C, mg/dL	55 (14)	54 (14)
TG, median (IQR), mg/dL	145 (122-196)	119 (82-159)
hsCRP, median (IQR), mg/L[a]	1.8 (1.20-4.00)	1.8 (1.10-4.60)
NCEP ATP-III risk category, no. (%)		
Very high	1 (2)	6 (13)
High	8 (18)	2 (4)
Moderate	22 (49)	13 (29)
Low	14 (31)	24 (53)

BMI = body mass index; CRP = C-reactive protein; DBP = diastolic blood pressure; hsCRP = high-sensitivity C-reactive protein; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; NCEP ATP-III = National Cholesterol Education Program Adult Treatment Panel III; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; TG = triglycerides.

NCEP ATP-III Risk Category: Very high = CHD and two or more risk factors; High = CHD or CHD risk equivalents; Moderate = two or more risk factors; Low = 0-1 risk factors.

Note: the following additional arm was included in phase 2 study 1002-009, which is not relevant to the decision problem: bempedoic acid 120 mg and bempedoic acid 120 mg + ezetimibe 10 mg.

Values are mean (SD), unless otherwise indicated. Baseline defined as the mean of the values from weeks −1 and 0, unless otherwise indicated.

[a] For CRP, baseline defined as the last value before the first dose of study drug.

Source: Ballantyne et al. (2016).

B.2.3.3 FDC trial: methodology and patient characteristics

The methodology of the phase 3 trial investigating FDC is presented in Table 16. The patient characteristics in this trial is presented in Table 17. Note that phase 2 study 1002-008 also investigated bempedoic acid+ezetimibe (24 patients were randomised to bempedoic acid 180 mg + ezetimibe 10 mg), as well as bempedoic acid (100 patients were randomised to bempedoic acid 180 mg), and

ezetimibe (99 patients). Details of phase 2 study 1002-008 are provided in Table 14 and Table 15.

B.2.3.3.1 Methodology

Study 1002FDC-053, a phase 3, multicentre, double-blind clinical trial, evaluated the efficacy and safety of FDC, bempedoic acid 180 mg, ezetimibe 10 mg or placebo in adult patients with hypercholesterolaemia and a high risk of CVD receiving maximally tolerated statin therapy. Patients were randomised 2:2:2:1 to oral, once-daily treatment with FDC, bempedoic acid 180 mg, ezetimibe 10 mg or placebo added to stable background statin therapy for 12 weeks. Randomisation was stratified by CVD risk category (ASCVD and/or HeFH vs. multiple CVD risk factors) and baseline statin intensity (high intensity vs. other). The Sponsor, patients, all clinical site personnel (e.g., investigator, pharmacist), and other vendor personnel were blinded to the treatment groups (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019d).

Table 16. Methodology of phase 3 FDC trial

Trial number (acronym)	**1002FDC-053 (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019d)**
Location	78 sites
Trial design	Phase 3, randomised, double-blind parallel-group study to evaluate the 12 week efficacy and safety of FDC compared with ezetimibe alone, bempedoic acid alone, and PBO in patients treated with maximally tolerated statin therapy, which could include statin regimens other than daily dosing or no statin at all (if not tolerated). Patients were randomised by IWRS on day 1 to receive either bempedoic acid+ezetimibe, bempedoic acid alone, ezetimibe alone or PBO in a 2:2:2:1 ratio. The randomisation was stratified by baseline statin intensity (high intensity vs. other) and disease characteristics (ASCVD and/or HeFH vs. multiple CV risk factors). The Sponsor, patients, all clinical site personnel (e.g., investigator, pharmacist), and other vendor personnel were blinded to the treatment groups.
Eligibility criteria for participants	Inclusion criteria: Age ≥ 18 years; treated with maximally tolerated statin therapy at stable dose for at least 4 weeks before screening; fasting LDL-C at week 2 while on maximally tolerated statin therapy as follows: • ASCVD and or HeFH: ≥ 100 mg/dL • Multiple CV risk factors: ≥ 130 mg/dL Meeting the definition for at least 1 of the following 3 categories: • ASCVD (including 1 or more of the following: acute MI, silent MI, unstable angina, coronary revascularisation procedure, clinically significant coronary heart disease, symptomatic peripheral arterial disease, cerebrovascular atherosclerotic disease) • HeFH, diagnosed by either genotyping or by clinical assessment • Multiple CV risk factors defined as diabetes + 1 other risk factor or 3 risk factors Exclusion criteria: Total fasting TG ≥ 500 mg/dL; renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR < 30 mL/min/1.73 m^2; BMI ≥ 40 kg/m^2; recent MI, unstable angina leading to hospitalisation, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, CVA, TIA, endovascular procedure or surgical intervention for peripheral vascular disease, or planned to undergo a major surgical or interventional procedure; uncontrolled hypertension; uncontrolled diabetes including HbA1c ≥ 10%; uncontrolled hypothyroidism; liver disease or dysfunction; GIT conditions or procedures that may have

Trial number (acronym)	**1002FDC-053 (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019d)**
	affected drug absorption; haematologic or coagulation disorders; active malignancy; unexplained CK elevation > 3 times the ULN any time before randomisation; history within the last 2 years of drug or alcohol abuse; blood donation, transfusion or loss within 30 days prior to randomisation; use of any experimental or investigational drugs within 30 days prior to screening; previous enrolment in a bempedoic acid clinical study; previous intolerance to ezetimibe.
Settings and locations where the data were collected	78 sites in US
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n = [x]) and comparator(s) (n = [x])**	Patients were randomly assigned in a 2:2:2:1 ratio to receive either oral FDC (n = 108), ezetimibe alone (n = 109), bempedoic acid alone (n = 110), or PBO (n = 55) for 12 weeks QD. Follow-up visits were conducted at weeks 4, 8, and 12.
Permitted and disallowed concomitant medication	**Permitted medications:** Topical and inhaled corticosteroids. The following drugs were allowed if stable at least 5 weeks prior to screening unless otherwise noted: hormone replacement; thyroid replacement; obesity medication (6 months before screening); omega 3 fatty acids; diabetes medications. **Disallowed medications:** Systemic corticosteroids Simvastatin ≥ 40 mg/day Non-statin LDL-C-modifying therapies: • Fibrates (including fenofibrate, gemfibrozil, clofibrate, ciprofibrate, bezafibrate) • Niacin and derivatives • Bile acid sequestrants (including cholestyramine, colestipol, colesevelam HCl) • Ezetimibe • Mipomersen or lomitapide (6 months before screening) • Apheresis

Trial number (acronym)	1002FDC-053 (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019d)
	• PCSK9 (4 months before screening except PCSK9 siRNA, which are prohibited if used at any time in the past) • CETP inhibitors (12 months before screening) • Red yeast rice extract-containing products (2 weeks before screening) Probenecid or cyclosporine Potent cytochrome *P* 3A4 inhibitors
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was percentage change from baseline to week 12 in LDL-C.
Other outcomes used in the economic model/specified in the scope	Secondary endpoints included percentage change from baseline to week 12 in hsCRP, non–HDL-C, TC, apo B, HDL-C, and TGs. Exploratory endpoints were percentage of patients attaining LDL-C < 70 mg/dL at week 12 and plasma trough concentrations at weeks 4, 8, and 12. Safety included incidence of AEs, clinical safety laboratory results, physical examination findings, vital sign measurements, and ECG readings.
Preplanned subgroups	The co-primary endpoints for LDL-C were analysed in the following subgroups: sex; age (< 65 years vs. ≥ 65 years); baseline CVD risk category (ASCVD and/or HeFH vs. multiple CV risk factors); baseline statin intensity (high intensity vs. other); race (white vs. other); baseline LDL category (< 130 mg/dL vs. ≥ 130 to < 160 mg/dL vs. ≥ 160 mg/dL) (efficacy only); history of diabetes (yes vs. no); BMI (< 25 kg/m^2, 25 to < 30 kg/m^2, ≥ 30 kg/m^2).

AE = adverse event; Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CABG = coronary artery bypass graft; CETP-I = cholesteryl ester transfer protein inhibitor; CK = creatine kinase; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; ECG = electrocardiograph; eGFR = estimated glomerular filtration rate; FDC = bempedoic acid and ezetimibe fixed-dose combination; GIT = gastrointestinal; HbA1c = glycosylated haemoglobin; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; IV = intravenous; IWRS = interactive web-response system; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; MI = myocardial infarction; PBO = placebo; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/ kexin type 9; QD = once daily; siRNA = small interfering RNA; TEAE = treatment-emergent adverse event; TC = total cholesterol; TG = triglycerides; TIA = transient ischaemic attack; ULN = upper limit of normal; US = United States.

[a] Low-dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg, which represents the lowest approved dose for each of these statins in the US. Average daily doses less than these were considered very low-dose statin therapy.

B.2.3.3.2 Baseline characteristics

In study 1002FDC-053, 382 patients were randomly assigned to treatment with FDC (n = 108), bempedoic acid (n = 110), ezetimibe (n = 109), or placebo (n = 55). The exclusion of three study sites because of data integrity concerns affected 81 patients, therefore, the post-hoc efficacy population comprised 301 patients. Demographic and baseline characteristics were generally similar across treatment groups, except for a lower percentage of males in the active treatment groups (45.5%-50.0%) compared with the placebo group (58.5%). The mean age of the study population was 64.3 years, and most patients were white (80.7%) and non-Hispanic (88.0%). A slightly higher proportion of patients entered the study with a diagnosis of ASCVD and/or HeFH (62.5%) than those who entered with multiple CV risk factors (37.5%). Most patients had a history of hypertension (> 80%) and diabetes (> 40%) and the proportion was similar across the groups. Most patients had a baseline mean LDL-C of 3.4 mmol/L or greater despite treatment with maximally tolerated statin therapy, which consisted of a high-intensity statin (34.6%), other-intensity statin (30.2%), or no statin (35.2%) (Ballantyne et al., 2019a).

Table 17. Patient characteristics in the FDC trial by treatment group

Trial number (acronym)	1002FDC-053 (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d)			
Baseline characteristic	**FDC**	**Bempedoic acid**	**Ezetimibe**	**Placebo**
Number randomised	86	88	86	41
Age, year	62.2 (9.5)	65.0 (9.8)	65.1 (8.9)	65.6 (8.4)
Male, n (%)	42 (48.8)	40 (45.5)	43 (50.0)	24 (58.5)
Race, n (%)				
Black or African American	16 (18.6)	17 (19.3)	12 (14.0)	7 (17.1)
White	67 (77.9)	70 (79.5)	72 (83.7)	34 (82.9)
Other	NR	NR	NR	NR
Ethnicity, n (%)				
Hispanic or Latino	10 (11.6)	11 (12.5)	9 (10.5)	6 (14.6)
Not Hispanic or Latino	76 (88.4)	77 (87.5)	77 (89.5)	35 (85.4)
BMI, kg/m^2	31.1 (6.3)	30.6 (5.5)	29.9 (4.4)	30.7 (4.2)
TC, mmol/L	6.14 (1.26)	5.83 (1.12)	5.98 (1.31)	5.98 (1.30)
Non–HDL-C, mmol/L	4.87 (1.21)	4.54 (1.05)	4.66 (1.22)	4.68 (1.29)
LDL-C, mmol/L	3.93 (1.05)	3.75 (0.99)	3.85 (1.08)	3.95 (1.21)
LDL-C category, n (%)				
< 3.4 mmol/L	30 (34.9)	40 (45.5)	31 (36.0)	13 (31.7)
≥ 3.4 to< 4.1 mmol/L	24 (27.9)	23 (26.1)	30 (34.9)	10 (24.4)
≥ 4.1 mmol/L	32 (37.2)	25 (28.4)	25 (29.1)	18 (43.9)
< 130 mg/dL	NR	NR	NR	NR
130 to < 160 mg/dL	NR	NR	NR	NR
≥ 160 mg/dL	NR	NR	NR	NR
HDL-C, mmol/L	1.27 (0.38)	1.29 (0.32)	1.33 (0.41)	1.30 (0.36)
TGs, mmol/L[a]	1.77 (1.20-2.36)	1.59 (1.22-2.15)	1.62 (1.24-2.40)	1.57 (1.18-1.90)

Trial number (acronym)	1002FDC-053 (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d)			
Apo B, mg/dL	121.1 (30.9)	113.4 (26.4)	115.5 (31.3)	115.1 (32.5)
hsCRP, mg/L[a]	3.1 (1.7-6.2)	2.9 (1.4-5.0)	2.8 (1.3-5.9)	3.0 (1.3-5.5)
CV risk category, n (%)				
ASCVD and/or HeFH	53 (61.6)	55 (62.5)	54 (62.8)	26 (63.4)
Multiple CV risk factors	33 (38.4)	33 (37.5)	32 (37.2)	15 (36.6)
Cardiac disorder, n (%)	NR	NR	NR	NR
History of diabetes, n (%)	35 (40.7)	45 (51.1)	43 (50.0)	17 (41.5)
History of hypertension, n (%)	74 (86.0)	77 (87.5)	71 (82.6)	35 (85.4)
SBP, mmHg	NR	NR	NR	NR
DBP, mmHg	NR	NR	NR	NR
Background LMT, n (%)				
Statin	NR	NR	NR	NR
Fibrate	NR	NR	NR	NR
Nicotinic acid	NR	NR	NR	NR
Bile acid sequestrant	NR	NR	NR	NR
Other[c]	NR	NR	NR	NR
eGFR category, n (%)				
≥ 90 mL/min/1.73 m^2	30 (34.9)	27 (30.7)	29 (33.7)	19 (46.3)
60-90 mL/min/1.73 m^2	40 (46.5)	41 (46.6)	43 (50.0)	14 (34.1)
< 60 mL/min/1.73 m^2	16 (18.6)	20 (22.7)	14 (16.3)	8 (19.5)
Baseline statin intensity, n (%)				
High statin intensity	31 (36.0)	29 (33.0)	28 (32.6)	16 (39.0)
Other statin intensity	22 (25.6)	32 (36.4)	26 (30.2)	11 (26.8)
No statin	33 (38.4)	27 (30.7)	32 (37.2)	14 (34.1)

ASCVD = atherosclerotic cardiovascular disease; apo B = apolipoprotein B; BMI = body mass index; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; NR = not reported; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

Note: Data are means (standard deviations) unless otherwise specified.

In 1002FDC-053 the baseline for LDL-C, non–HDL-C, HDL-C, TC, and TG was defined as the mean of the last two non-missing values from week −2 (Visit S1) and predose day 1/week 0 (Visit T1), while baseline for apo B and hsCRP was defined as the predose day 1/week 0 (Visit T1) value.

[a] Data are medians (interquartile ranges).

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

B.2.4.1 Bempedoic acid trials

Table 18 presents a summary of the statistical analyses and definition of study groups for the bempedoic acid trials.

Table 18. Summary of statistical analyses of bempedoic acid trials

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018b; Ray et al., 2019b)	That addition of bempedoic acid to other LMTs (including statins) resulted in higher reductions in lipid values compared with LMT alone.	All the patients who received at least one dose of bempedoic acid or placebo were included in the safety analysis (safety population). All the safety data were analysed with the use of descriptive statistics and were reported as observed, with no imputation of missing data. Efficacy analyses for the principal secondary endpoint were performed in the ITT population, which included all the patients who underwent randomisation. Key efficacy endpoints were included in a stepdown testing procedure to control the overall type 1 error. Percentage change in LDL-C, non–HDL-C, TC, and apo B at week 12 or week 24 were analysed using the ANCOVA method (with treatment and randomisation stratum as factors, and baseline value as a covariate). For hsCRP, a nonparametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and CI was performed.[a]	A total sample size of 1,950 (1,300 on bempedoic acid and 650 on placebo) was chosen a priori, with 52-week follow-up, so the trial would provide sufficient long-term exposure to bempedoic acid. This sample size would allow the trial to identify an excess relative risk of 2.0 regarding AEs occurring at rates between 1.6% and 13.6% in the placebo group (the 95% CI excludes 1). This sample size would also allow the trial to detect rare events at an incidence as low as 0.5% in the bempedoic acid group.	Missing data for efficacy endpoints included in the stepdown procedure were imputed using a pattern-mixture model to specify different imputation strategies depending on whether the patient was still on study treatment. Patients with missing lipid data at week 12 who were no longer taking study treatment were assumed to no longer be benefitting from study drug, and their missing value(s) were assumed to be similar to those of placebo patients who had data. Patients with missing lipid data at week 12 who were still taking study treatment were assumed to continue to benefit from study drug, and their missing value(s) were assumed to be similar to those who remained on study treatment and had data.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c)	To demonstrate the higher long-term efficacy and safety of bempedoic acid as an add-on therapy to LMT, including maximally tolerated statin therapy, in comparison with placebo.	The FAS, also known as the ITT set, was used for all efficacy analyses. LDL-C, non–HDL-C, TC, and apo B were analysed using an ANCOVA with treatment group and randomisation stratification factors (CV risk and baseline statin intensity) as factors and baseline LDL-C as a covariate. Descriptive statistics were also produced for LDL-C at each visit and for change from baseline by treatment group for overall population and for each stratification factor. A stepdown approach was used to test the primary and secondary efficacy endpoints, at a 0.05 significance level. For hsCRP, Wilcoxon rank-sum test analysis with Hodges-Lehmann estimates and CI was performed. The safety analysis set included all randomised patients who received at least 1 dose of bempedoic acid or placebo. Change from baseline values were provided for ECG, vital signs, laboratory and physical examinations. Descriptive statistics were provided for AEs, vital signs, CV endpoints, and laboratory examinations.	The total sample size of 750 (500 on bempedoic acid and 250 on placebo) was expected to provide > 95% power to detect a difference of 15% in the percentage change from baseline to week 12 in LDL-C between bempedoic acid and placebo. This calculation was based on a 2-sided t-test at the 5% level of significance ($\alpha = 0.05$) and a common SD of 15%. The larger sample size was selected to obtain additional long-term safety data (52 weeks duration) from a second randomised, controlled clinical study in order to propose a sufficiently large safety database for an approval of an LDL-C–lowering indication.	Missing values for any of the laboratory evaluations were not imputed; that is, only observed case data were used. Study day for adverse events with missing or partial adverse event start and end dates were imputed to calculate study day values only. For sensitivity analysis, missing data were imputed using a PMM, which accounts for treatment adherence. This approach provided a “de facto” estimate of the treatment effect and assumed missing not at random for the missing data.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CLEAR Serenity (1002-046) (Laufs et al., 2019)	That bempedoic acid plus LMT offers a safer and more effective oral therapeutic option vs. LMT alone for lipid lowering in patients with statin intolerance.	Primary efficacy analyses were performed using the ITT population. The primary and key secondary efficacy endpoints were analysed using ANCOVA model, with treatment group as the main effect adjusting for patient type (primary vs. secondary prevention/HeFH) and baseline values. Means, LS means, and SE were calculated for individual treatment groups, and 95% CIs and *P* values were determined for the placebo-corrected change from baseline. For hsCRP, nonparametric analyses (Wilcoxon rank-sum test) with Hodges-Lehmann estimates and CIs were performed. A stepdown approach was used to test the primary endpoint followed sequentially by specific secondary endpoints. Using this hierarchical testing structure, each hypothesis was tested at a significance level of 0.05, 2-sided.	A sample size of 300 randomised patients (200 to bempedoic acid and 100 to placebo) was chosen to provide > 95% power to detect a 15% difference between the bempedoic acid and placebo treatment groups in LDL-C percentage change from baseline to week 12. The calculation was based on a 2-sided t-test at 5% significance level and a common SD of 15%.	Missing data were imputed using a PMM. For patients with missing data who had already discontinued the study drug (bempedoic acid or placebo), the missing values were imputed using data from placebo group patients only (i.e., their responses were assumed to be similar to patients in the placebo group once they were off treatment). For patients who had missing data and were adherent to study treatment, their missing data were imputed using patient data from their respective treatment group. Predefined sensitivity analyses for all primary and secondary efficacy endpoints were performed without imputation for missing data.
CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)	That addition of bempedoic acid to background therapy with ezetimibe resulted in higher reductions in lipid values compared with background therapy with ezetimibe alone.	Efficacy analyses were performed using the ITT population. The primary and secondary efficacy endpoints were analysed using ANCOVA, with treatment group as a factor and baseline value as a covariate. If non-normality of the data was detected at any time point	A sample size of 150 in the bempedoic acid group and 75 in the placebo group has 95% power to detect a difference of 15% in the percentage change from baseline to week 12 in calculated LDL-C between	Missing values at week 12 were imputed using the multiple imputation method taking into account ongoing treatment. Patients who had missing values and were off treatment were imputed with placebo patient data only.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		for any parameter, a nonparametric test was used. For each lipid parameter, the LS mean, and SE were calculated for both treatment groups, as well as the placebo-corrected LS mean, 95% CI, and *P* value. A stepdown approach was used to test the primary efficacy endpoint and specific secondary efficacy endpoints in the following sequence: LDL-C, non–HDL-C, TC, apo B, and hsCRP. In this hierarchical testing structure, each hypothesis is tested at a significance level of 0.05, 2-sided. For the remaining secondary and tertiary efficacy endpoints, a significance level of 0.05 was used; given the large number of remaining endpoints, the *P* values for those endpoints were considered descriptive. The safety analysis population included all randomised patients who received at least one dose of study medication. Safety parameters, including AEs, clinical safety laboratory results, physical examination findings, vital sign measurements, ECG readings, and weight were summarised using descriptive statistics for each treatment group and time point.	treatment groups. This calculation is based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15%. A total of 269 patients (181 to bempedoic acid and 88 to placebo) were randomised.	There was no imputation for missing data in the sensitivity analyses.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Phase 2 study 1002-008 (Thompson et al., 2016)	To demonstrate the superior lipid-regulating effect of bempedoic acid (120 or 180 mg) or bempedoic acid+ezetimibe vs. ezetimibe alone in patients with hypercholesterolaemia +/- a history of statin intolerance.	ANCOVA was performed to compare each dose of bempedoic acid monotherapy with ezetimibe monotherapy for the primary efficacy endpoint in the mITT population. The primary model included the effect of treatment and statin intolerance, and the baseline value as a covariate. LS means and SEs were obtained for each treatment group; and differences in LS means, corresponding 2-sided 95% CI, and *P* value were obtained for the treatment comparisons. Secondary efficacy endpoints were analysed in a similar manner as the primary endpoint. Where significant departures from normality were observed, a nonparametric analysis was performed with median values presented for some secondary parameters (e.g., TG, hsCRP, and VLDL particle number). Statistical testing of primary and secondary efficacy endpoints was 2-sided and conducted at the 5% level of significance with no adjustment for multiple comparisons. All randomised patients who received at least 1 dose of study drug (safety population), safety data including AEs, clinical laboratory values, vital signs, ECGs, weight, and ankle and waist circumferences were	The planned sample size of 92 patients per monotherapy treatment group was expected to provide 90% power to detect a difference of 10% in the absolute percentage change from baseline to week 12 endpoint in calculated LDL-C between at least 1 bempedoic acid treatment group and the ezetimibe monotherapy group. This calculation was based on a 2-sided t-test at the 5% level of significance and assumed a common SD of 15% in the statin-tolerant patients and 22% in the statin-intolerant patients and a dropout rate of 15%. With 92 patients per monotherapy treatment group and 23 patients in each of the combination therapy treatment groups, the overall planned study sample size was 322 patients.	For week 12 endpoint, missing values at week 12 were imputed using the last observation carried forward procedure.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		summarised using descriptive statistics. ANCOVA model was used to assess the dose-response relationship for bempedoic acid.		
Phase 2 study 1002-009 (Ballantyne et al., 2016)	That addition of bempedoic acid to ongoing statin therapy resulted in higher reductions in lipid values compared with statin alone.	An ANCOVA was performed to compare each dose of bempedoic acid with placebo for the primary efficacy endpoint in the mITT population. The primary model included the effects of treatment and history of statin intolerance and the baseline value as a covariate. LS means and SEs were provided for each treatment group; and differences in LS means, corresponding 2-sided 95% CI, and *P* value were obtained for the treatment comparisons. If significant departures from the model assumptions or outliers were identified (based on statistical judgement), a nonparametric analysis (e.g., *P* values obtained from the Wilcoxon rank-sum test and estimates based on medians) or analysis excluding outliers may have been conducted. Actual values, changes from baseline, and percentage changes from baseline in LDL-C were summarised using descriptive statistics by treatment group and post-baseline time point. Secondary efficacy endpoints were	The planned sample size of 44 patients per treatment group was expected to provide 90% power to detect a difference of 15% in the percentage change in calculated LDL-C from baseline to week 12 endpoint between at least 1 bempedoic acid treatment group and the placebo group. This calculation was based on a 2-sided t-test at the 5% level of significance and assumed a common SD of 20% and a dropout rate of 10%. With 44 patients per treatment group, the overall planned study sample size was 132 patients. In total, 134 patients were randomised (45 each to placebo and bempedoic acid 180 mg groups and 44 to bempedoic acid 120 mg group).	For week 12 endpoint, missing values at week 12 were imputed using the last observation carried forward procedure (only post-baseline values were carried forward).

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		analysed in a manner similar to the primary efficacy endpoint. All patients included in the safety population were evaluated in the safety analyses. Changes from baseline were summarised using descriptive statistics by treatment group and post-baseline time point. ANCOVA model was used to assess the dose-response relationship for bempedoic acid. PK plasma concentrations of bempedoic acid and ESP15228 were summarised using descriptive statistics by treatment group and nominal time point.		

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; FAS = full analysis set; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; mITT = modified intention to treat; PK = pharmacokinetic; PMM = pattern-mixture model; SD = standard deviation; SE = standard errors; TC = total cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein.

[a] This was done because hsCRP is known to be skewed by extreme values and to have a non-normal distribution.

B.2.4.2 FDC trial: analyses

Table 19 presents a summary of the statistical analyses and definition of study groups for the FDC trial.

Table 19. Summary of statistical analyses of the FDC trial

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
1002FDC-053 (Ballantyne et al., 2019a; Ballantyne et al., 2019b)	To demonstrate that addition of FDC to background maximally tolerated statin therapy was better at lowering LDL-C compared with statin therapy, ezetimibe, and bempedoic acid monotherapy.	Percentage change from baseline in LDL-C was analysed using ANCOVA, with treatment group and randomisation stratification as factors and baseline LDL-C as a covariate. Baseline was defined as the mean of the values from week −2 and predose on day 1. Co-primary endpoint comparisons were conducted at a significance level of 0.05. LS means, SEs, 95% Cis, and associated *P* values were calculated for each treatment group as well as for each treatment group comparison. Key secondary efficacy endpoints (percentage change from baseline to week 12 in hsCRP, non–HDL-C, TC, and apo B) were analysed in a manner similar to the primary efficacy endpoint. Percentage change from baseline in hsCRP was analysed using a nonparametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and CIs. Changes in HDL-C	A total sample size of 350 patients (100 each to FDC, bempedoic acid, ezetimibe and 50 to placebo) would provide an overall power of at least 92% to detect the estimated treatment differences at an alpha level of 0.05 using a 2-sided t-test.	Missing values were imputed using a multiple imputation method, taking into account adherence to treatment. No imputation was performed for missing data in subgroup analyses. Following database lock and review, it was found that 51 patients on active drug had no detectable study drug in blood samples taken at week 12. Most (34 of 51) of these patients were from three study sites in the same metropolitan area. A root cause analysis ruled out issues with the production or distribution of study drug and the handling or analysis of pharmacokinetic samples. Owing to concerns about the integrity of any of the data from these three sites, and that data from these three sites would not accurately reflect either the safety or efficacy of experimental therapy, data from these three sites were excluded from the additional post-hoc efficacy and safety analyses but not the initial ITT

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		and TGs were summarised using descriptive statistics. For subgroup analysis, percentage change from baseline was analysed using ANCOVA, with treatment group, subgroup, and treatment by subgroup interaction as factors and baseline LDL-C as a covariate. Safety data were summarised using descriptive statistics.		and safety populations.

AE = adverse events; ANCOVA = analysis of covariance; apo B = apolipoprotein B; CI = confidence interval; ECG = electrocardiograph; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LS = least squares; SE = standard errors; TC = total cholesterol; TG = triglycerides.

Note that phase 2 study 1002-008 also investigated bempedoic acid+ezetimibe (24 patients were randomised to bempedoic acid 180 mg + ezetimibe 10 mg), as well as bempedoic acid (100 patients were randomised to bempedoic acid 180 mg) and ezetimibe (99 patients). Details of phase 2 study 1002-008 are provided in Table 18.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 20 to Table 21 summarise the quality assessments carried out for the bempedoic acid trials of interest.

B.2.5.1 Bempedoic acid trials: quality assessments

Table 20. Quality assessment of phase 2 study 1002-008

Study question	How Is the question addressed in the study?	Grade (yes/no/not clear/NA
Was randomisation carried out appropriately?	Patients were randomly assigned (4:4:4:1:1) to receive one of the following: • Bempedoic acid 120 mg • Bempedoic acid 180 mg • Ezetimibe 10 mg • Bempedoic acid 120 mg + ezetimibe 10 mg • Bempedoic acid 180 mg + ezetimibe 10 mg The randomisation sequence was generated with permuted blocks stratified by history of statin intolerance.	Yes
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive voice and web-response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics were well balanced across treatment groups.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided, and all the reasons for discontinuations were accounted for.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods were reported.	No

Study question	How Is the question addressed in the study?	Grade (yes/no/not clear/NA
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percent change from baseline to week 12 in calculated LDL-C, was performed on the modified ITT population, defined as all randomised patients who had a baseline assessment, received at least 1 dose of study medication, and had at least 1 on-treatment assessment (excluding any assessment taken more than 2 days after a dose of study drug). Furthermore, the secondary endpoints (percentage change from baseline to week 12 in additional lipid and cardiometabolic biomarkers) were analysed in the same manner. The level of missing data was low (9%) and balanced across arms: missing values were imputed using the last observation carried forward procedure.	Yes
Did the authors of the study publication declare any conflicts of interest?	1002-008 was funded by Esperion. Four authors were employees of Esperion; two authors received grants from Esperion during the conduct of the study.	Yes
Does the trial reflect routine clinical practice in England?	1002-008 included 349 patients at 70 sites in the US where bempedoic acid was used in a research setting. Subgroup analyses by region in the bempedoic acid trials showed similar efficacy results in patients treated in North America and in Europe (Section B.2.7).	Yes

ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; UK = United Kingdom; US = United States.

Table 21. Quality assessment of phase 2 study 1002-009

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Patients were randomly assigned (1:1:1) to receive either bempedoic acid 120 mg, bempedoic acid 180 mg, or placebo. The randomisation sequence was generated with permuted blocks stratified by history of statin intolerance.	Yes
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive voice and web-response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were imbalances in gender, ethnicity, weight, height, TGs, hsCRP, NCEP ATP III risk category and alcohol history. There were more female and fewer Hispanic/Latino patients in the placebo arm and in patients with higher TC, LDL-C, and TGs in the bempedoic acid 180 mg arm. No adjustments were made or investigations reported regarding whether these differences had an effect on outcome.	No

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided, and all the reasons for discontinuations were accounted for.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods were reported.	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percentage change from baseline to week 12 in calculated LDL-C, was performed on the mITT population, defined as all randomised patients who had a baseline assessment, received at least 1 dose of study medication, and had at least 1 on-treatment assessment (excluding any assessment taken more than 2 days after a dose of study drug). Furthermore, the secondary endpoints (percentage change from baseline to week 12 in additional lipid and cardiometabolic biomarkers) were analysed in the same manner. Missing data were imputed using the last observation carried forward procedure. Only post-baseline values were carried forward, but missing data were imbalanced among treatment arms.	Unclear
Did the authors of the study publication declare any conflicts of interest?	1002-009 was funded by Esperion. Five authors were employees of Esperion; one author received grants from Esperion during the conduct of the study.	Yes
Does the trial reflect routine clinical practice in England?	1002-009 included 134 patients at 41 sites in the US where bempedoic acid was used in a research setting. Subgroup analyses by region in the bempedoic acid trials showed similar efficacy results in patients treated in North America and in Europe (Section B.2.7).	Yes

hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; mITT = modified intention to treat; NA = not applicable; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; TC = total cholesterol; TG = triglyceride; UK = United Kingdom; US = United States.

Table 22. Quality assessment of CLEAR Harmony (1002-040)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Was randomisation carried out appropriately?	Patients were randomly assigned (2:1) to receive either bempedoic acid 180 mg or placebo in the parent study to this long-term extension study. Randomisation was stratified by CV risk and baseline statin intensity.	Yes
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive web-response system, stratified by CV risk and baseline statin intensity.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics were balanced across treatment groups.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No patient flow diagram was provided as this is an ongoing study.	NA
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods will be reported.	NA
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percentage change from baseline to week 12 in calculated LDL-C was assessed in the ITT population, including all randomised patients. The secondary endpoints (percentage change from baseline to week 12 in additional lipid and cardiometabolic biomarkers) were analysed in the same manner. Missing data for the efficacy endpoints were imputed using a pattern-mixture model with a sensitivity analysis using complete cases.	Yes
Did the authors of the study publication declare any conflicts of interest?	CLEAR Harmony was funded by Esperion. Four authors were employees of Esperion; three authors received grants from Esperion during the conduct of the study.	Yes

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Does the trial reflect routine clinical practice in England?	CLEAR Harmony included 2,230 patients at 114 sites in the 5 countries, including the UK, where bempedoic acid was used in a research setting; therefore, results may be generalisable to UK clinical practice depending on the number of UK patients within the study.	Yes

CV = cardiovascular; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; UK = United Kingdom.

Table 23. Quality assessment of CLEAR Serenity (1002-046)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Was randomisation carried out appropriately?	Patients were randomly assigned (2:1) to receive either bempedoic acid 180 mg or placebo. Randomisation was stratified by primary prevention vs. secondary prevention and/or heterozygous familial hypercholesterolaemia.	Yes
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive web-response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics were balanced across treatment groups.	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided, and all the reasons for discontinuations were accounted for.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods were reported.	No

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percentage change from baseline to week 12 in calculated LDL-C, was performed on the ITT population, defined as all patients randomised. Furthermore, the secondary endpoints (percentage change from baseline to week 12 in additional lipid and cardiometabolic biomarkers and percentage change from baseline to week 24 in LDL-C) were analysed in the same manner. A pattern-mixture modelling approach was used in which missing data were multiply imputed. However, different imputation strategies were employed dependent on whether patients were still taking the investigational medicine product.	Yes
Did the authors of the study publication declare any conflicts of interest?	CLEAR Serenity was funded by Esperion. Two authors were employees of Esperion; four authors received grants from Esperion during the conduct of the study.	Yes
Does the trial reflect routine clinical practice in England?	CLEAR Serenity included 345 patients at 67 sites in the US and Canada where bempedoic acid was used in a research setting. Subgroup analyses by region in the bempedoic acid trials showed similar efficacy results in patients treated in North America and in Europe (Section B.2.7).	Yes

ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; UK = United Kingdom; US = United States.

Table 24. Quality assessment of CLEAR Wisdom (1002-047)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Was randomisation carried out appropriately?	Patients were randomly assigned (2:1) to receive either bempedoic acid 180 mg or placebo. Randomisation was stratified based on the patient's cardiovascular risk and baseline statin intensity.	Yes
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive web-response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics were balanced across treatment groups.	Yes

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided, and all the reasons for discontinuations were accounted for.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods were reported.	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percentage change from baseline to week 12 in calculated LDL-C, was performed on the ITT population, defined as all patients randomised. Furthermore, the secondary endpoints (percentage change from baseline to week 12 in additional lipid and cardiometabolic biomarkers and percentage change from baseline to week 24 in LDL-C) were analysed in the same manner. A pattern-mixture model approach was used to specify different imputation strategies.	Yes
Did the authors of the study publication declare any conflicts of interest?	All authors have disclosed any conflicts of interest in the publication	Yes
Does the trial reflect routine clinical practice in England?	CLEAR Wisdom included 779 patients at 91 sites in Canada, Germany, Poland, Ukraine, the UK, and the US where bempedoic acid was used in a research setting; therefore, results may be generalisable to UK clinical practice depending on the number of UK patients within the study.	Yes

ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; UK = United Kingdom; US = United States.

Table 25. Quality assessment of CLEAR Tranquility (1002-048)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Was randomisation carried out appropriately?	Patients were randomly assigned (2:1) to receive either bempedoic acid 180 mg or placebo. No stratification was mentioned.	Yes

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive web-response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The author stated that demographics and baseline characteristics were well matched between treatment groups in most respects. Mean baseline LDL-C, non-HDL-C, apoB, and triglycerides were marginally higher in the bempedoic acid treatment group compared with placebo.	Not clear
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided, and all the reasons for discontinuations were accounted for.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods were reported.	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percent change from baseline to week 12 in calculated LDL-C, was performed on the ITT population, defined as all patients randomised. Furthermore, the secondary endpoints (percent change from baseline to week 12 in additional lipid and cardiometabolic biomarkers) were analysed in the same manner. A pattern-mixture modelling approach was used, in which missing data were multiply imputed. However, different imputation strategies were employed dependent on whether patients were still taking the investigational medicine product.	Yes
Did the authors of the study publication declare any conflicts of interest?	CLEAR Tranquility was funded by Esperion. All authors have disclosed any conflict of interest in the publication	Unclear
Does the trial reflect routine clinical practice in England?	CLEAR Tranquility included 269 patients at 90 sites in North America and Europe where bempedoic acid was used in a research setting. Subgroup analyses by region in the bempedoic acid trials showed similar efficacy results in patients treated in North America and in Europe (Section B.2.7).	Unclear

ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; UK = United Kingdom.

B.2.5.2 FDC trial: quality assessment

Table 26. Quality assessment of 1002FDC-053

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Was randomisation carried out appropriately?	Patients were randomly assigned (2:2:2:1) to receive one of the following: • Bempedoic acid 180 mg + ezetimibe 10 mg • Bempedoic acid 180 mg • Ezetimibe 10 mg • Placebo Randomisation was stratified by baseline statin intensity and disease characteristics (ASCVD and/or HeFH vs. multiple CV risk factors).	Yes
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive web-response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics were largely balanced across treatment groups; there were slight imbalances which were recognised by the authors. A higher percentage of women (52.9% overall) were included in the FAS, but a higher percentage of men were enrolled in the placebo group (60.0% men) compared with the other groups (46.3% FDC, 40.9% bempedoic acid, 47.7% ezetimibe). Other patient demographic and baseline characteristics were similar between treatment groups and baseline disease characteristics were consistent with the inclusion and exclusion criteria of the study population. In the post-hoc sensitivity analysis, patient characteristics generally are similar except that the percentage of randomised patients of Hispanic and Latino ethnicity decreased from 30.6% to 12.0% of the randomised population (FAS). There was a slight imbalance in age and the proportion of Hispanic/Latino patients among treatment arms. A post-hoc sensitivity analysis was made for the Hispanic/Latino difference only.	No
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided, and all the reasons for discontinuations were accounted for.	No

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in the methods were reported.	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, percentage change from baseline to week 12 in calculated LDL-C, was performed on the ITT population, defined as all patients randomised. Furthermore, the secondary endpoints (percentage change from baseline to week 12 in additional lipid and cardiometabolic biomarkers) were analysed in the same manner. Patients who had a missing value not taking IMP any longer were assumed to no longer be benefitting from IMP; thus their missing value was assumed to be the same as their baseline score. Patients with a missing value still taking IMP were assumed to be similar to those who continued with IMP: lipid values were imputed based on the observed values (multiple imputation).	Yes
Did the authors of the study publication declare any conflicts of interest?	1002FDC-053 was funded by Esperion. Two authors were employees of Esperion; one author received grants from Esperion during the conduct of the study.	Not clear
Does the trial reflect routine clinical practice in England?	1002FDC-053 included 382 patients at 125 sites in North America where bempedoic acid was used in a research setting. Subgroup analyses by region in the bempedoic acid trials showed similar efficacy results in patients treated in North America and in Europe (Section B.2.7).	No

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolaemia; IMP = Investigational medicine product; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; UK = United Kingdom; US = United States.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Bempedoic acid efficacy results

B.2.6.1.1 Analysis of Phase 3 bempedoic acid trials

Table 27 presents a summary of the efficacy results for phase 3 bempedoic acid trials. The primary, secondary, and some of the tertiary endpoints are described in detail in the sections below. The efficacy data presented in this section include results of analyses from the ITT, post-hoc, and FAS populations that are relevant to the NICE decision problem.

Table 27. Summary of the efficacy results for Phase 3 bempedoic acid trials

Efficacy parameter	CLEAR Harmony (1002-040) (Ray et al., 2019a; Ray et al., 2019b)			CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg et al., 2019)			CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018c; Laufs et al., 2019)			CLEAR Tranquility (1002-048) (Ballantyne et al., 2018) (Esperion Therapeutics data on file, 2018d)		
	LS mean % change from baseline to week 12		Difference of LS means (95% CI; *P* value)	LS mean % change from baseline to week 12		Difference of LS means (95% CI; *P* value)	Mean % change from baseline		Difference of LS means (95% CI; *P* value)	LS mean % change from baseline to week 12		
	Bempedoic acid (n = 1,488)	Placebo (n = 742)		Bempedoic acid (n = 499)[d]	Placebo (n = 253)[d]		Bempedoic acid (n = 234)	Placebo (n = 111)		Bempedoic acid (n = 181)	Placebo (n = 88)	Difference of LS means (95% CI); *P* value
LDL-C, mg/dL	−16.5 (0.52)	1.6 (0.86)	−18.1 (−20.0 to −16.1; < 0.001)	−15.1 (1.073)	2.4 (1.446)	−17.4 (−21 to −13.9; < 0.001)	−23.6	−1.3%	-21.4 (−25.1 to −17.7; < 0.001)	−23.5	5	−28.5 (−34.4 to −22.5); < 0.001
Non–HDL-C, mg/dL	−11.9 (0.48)	1.5 (0.76)	−13.3 (−15.1 to −11.6; < 0.001)	−10.8 (1.0)	2.3 (1.4)	−13.0 (−16.3 to −9.8; < 0.001)	−19	−0.4	−17.9 (−21.1 to 14.8; < 0.001)	−18.4	5.2	−23.6 (−29.005 to −18.121); < 0.001
TC, mg/dL	−10.3 (0.37)	0.8 (0.57)	−11.1 (−12.5 to −9.8; < 0.001)	−9.9 (0.7)	1.3 (1.0)	−11.2 (−13.6 to −8.8; < 0.001)	−16.1	−0.6	−14.8 (−17.3 to −12.2; < 0.001)	−15.1	2.9	−18.0 (−21.940 to −14.030); < 0.001
Apo B, mg/dL	−8.6 (0.47)	3.3 (0.70)	−11.9 (−13.6 to −10.2; < 0.001)	−9.3 (0.9)	3.7 (1.3)	−13.0 (−16.1 to −9.9; < 0.001)	−15.5	−0.2	−15.0% (−18.1% to −11.9%; < 0.001)	−14.6	4.7	−19.3 (−23.908 to −14.732); < 0.001
hsCRP, mg/l	−22.4 (72.5)[a]	2.6 (91.9)[a]	−21.5 (−27.0 to −16.0; < 0.001)	−18.7 (−46.1 to 23.9)	−9.4 (−36.3 to 35.2)	−8.7 (−17.2 to −0.4; 0.04)	−25.4	2.7	−24.3% (asymptotic confidence limits, −35.9% to −12.7%; < 0.001)	−32.5	2.1	−31.0 (−44.761 to −17.401) < 0.001
HDL-C, mg/dL	−5.92 (13.5)[b, c]	−0.09 (11.2)[b, c]		−6.4 (0.7)	−0.2 (0.9)	−6.13 (−8.4, −3.9; < 0.001)	−5.0 (16.53)	−0.1 (11.15)	-4.52 (−7.475 to −1.575; 0.003)	−7.3	1.4	NR; 0.002
TG, mg/dL	2.90 (−15.8, 26.2)[b, c]	−0.33 (−16.9, 20.8)[b, c]		11.0 (2.3)	6.1 (2.3)	4.9 (−1.5, 11.3; 13)	7.6 (39.51)	6.7 (36.97)	0.43 (−8.166 to 9.027; 0.921)	NR	NR	NR

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LS = least squares; NR = not reported; SD = standard deviation; TC = total cholesterol; TG = triglyceride.

Data are means (SD) unless otherwise stated.

[a] Data are medians (interquartile ranges).

[b] N = 1,427 for bempedoic acid group, and N = 726 for placebo group.

[c] Data are medians (Q1, Q3).

[d] Sample sizes varied for some outcomes. LDL-C and non–HDL-C: 498 for bempedoic acid group, and 253 for placebo group; Apo B: 479 for bempedoic acid group and 245 for placebo group; hsCRP: 467 for bempedoic acid group and 240 for placebo group.

CLEAR Harmony (1002-040)

Principal secondary efficacy outcome (change in LDL-C)

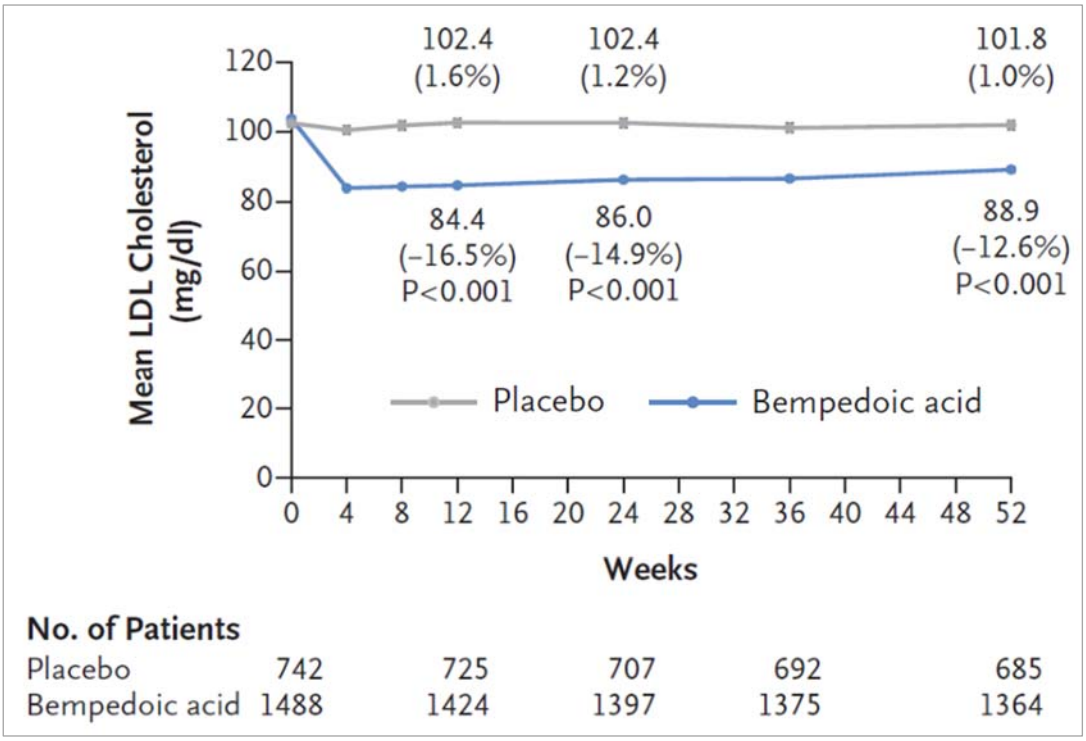
In the ITT analysis (all randomised patients regardless of treatment received) at week 12, treatment with bempedoic acid resulted in a significantly greater lowering of the LDL-C level than was observed in the placebo group (mean difference, −18.1; 95% CI, −20.0 to −16.1; $P < 0.001$) in patients on maximally tolerated statin therapy as part of their LMT. The percentage change in least squares (LS) mean from baseline to week 12 in LDL-C were −16.5% and 1.6% in the bempedoic acid and placebo groups, respectively. Treatment with bempedoic acid resulted in a greater absolute change in LDL-C (−19.23 mg/dL) compared with placebo (0.43 mg/dL). The significant treatment effects of bempedoic acid versus placebo were apparent from week 4 through week 52 (Figure 4) (Ray et al., 2019a; Ray et al., 2019b).

Other secondary and efficacy outcomes

Bempedoic acid demonstrated significantly greater treatment effects compared with placebo based on reductions from baseline to week 12 for non–HDL-C, TC, apo B, and high-sensitivity C-reactive protein (hsCRP) ($P < 0.001$ for all). The LS mean differences between bempedoic acid and placebo in percentage change from baseline at week 12, was −13.3% (95% CI, −15.1 to −11.6) for non–HDL-C, −11.1 % (95% CI, −12.5 to −9.8) for TC, −11.9 % (95% CI, −13.6 to −10.2) for apo B, and −21.5 % (95% CI, −27.0 to −16.0) for hsCRP.

In the ITT analysis, a significantly higher percentage of patients in the bempedoic acid group achieved LDL-C < 70 mg/dL compared with patients in the placebo group at weeks 12 (32.4% vs. 9%), 24 (32% vs. 10.2%), and 52 (28.2% vs. 9.5%) ($P < 0.001$ for all comparisons) (Ray et al., 2019a; Ray et al., 2019b).

Figure 4. Efficacy measures over the 52-week CLEAR Harmony trial (intention-to-treat population)



LDL = low-density lipoprotein.

Means with standard errors are shown.

Source: Ray et al. (2019b).

CLEAR Wisdom (1002-047)

Primary efficacy outcome (change in LDL-C)

The primary efficacy outcome was analysed using the FAS, which included all randomised patients regardless of whether they remained on treatment at the time of efficacy assessment. Treatment with bempedoic acid resulted in significantly greater reductions in LDL-C compared with placebo in patients with hypercholesterolaemia on maximally tolerated statins (LS mean percentage change from baseline to week 12: −15.1% vs. 2.4%). The LS mean difference between bempedoic acid and placebo in percentage change from baseline was −17.4 (95% CI, −21.0 to −13.9; P < 0.001) at week 12. Mean LDL-C levels at week 12 were 97.6 and 122.8 mg/dL in the bempedoic acid and placebo groups, respectively (Goldberg et al., 2019).

Secondary and other efficacy outcomes

Bempedoic acid also resulted in significant treatment effects compared with placebo in other lipid parameters and biomarkers (*P* < 0.001 for non–HDL-C, TC, and apo B endpoints).The LS mean difference between bempedoic acid and placebo in percentage change from baseline was −13.0% for non–HDL-C, −11.2% for TC, and −13.0% for apo B at week 12. Patients treated with bempedoic acid also experienced a significantly greater reduction in hsCRP compared with placebo, with a location shift

of −8.7% at week 12 (*P* = 0.04). The median percentage change in hsCRP was −18.7% and −9.4% for bempedoic acid and placebo.

Treatment with bempedoic acid resulted in significant reduction in HDL-C compared with placebo at week 12. The differences from placebo of LS means percentage change from baseline in HDL-C was −6.1% at week 12, −5.2% at week 24, and −4.0% at week 52 (*P* < 0.001 for all time points). Median percentage changes from baseline in triglyceride (TG) ranged from 6.0% to 11.0% for bempedoic acid and 4.8% to 6.1% for placebo (*P* value not stated).

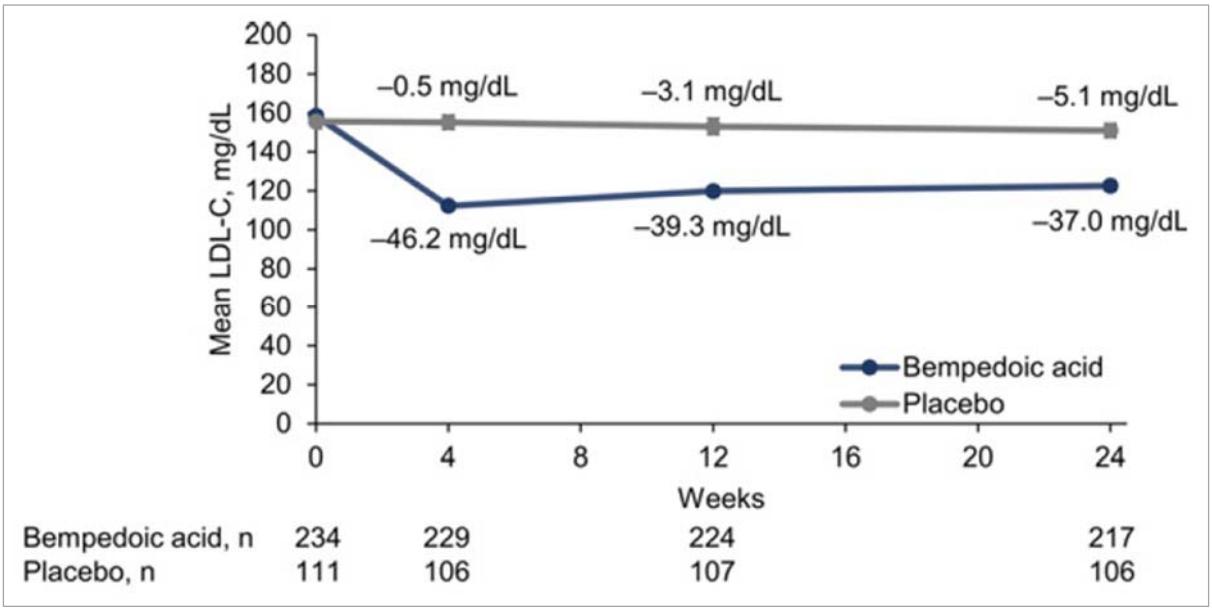
Over time greater reductions from baseline in LDL-C were observed in the bempedoic acid group compared with placebo for all reported time points. The LS mean difference between bempedoic acid and placebo in percentage change from baseline was [redacted] Greater reductions from baseline in other lipid parameters and biomarkers, including non–HDL-C, TC, apo B, and hsCRP were also sustained through week 52 in the bempedoic acid group compared with placebo. The *P* value was < 0.001 across all time points for all parameters except for hsCRP at week 12 (0.04) and week 52 (0.10) (Goldberg et al., 2019).

CLEAR Serenity (1002-046)

Primary efficacy outcome (change in LDL-C)

In the FAS at week 12, LDL-C lowering with bempedoic acid was significantly greater than that for placebo, (*P* < 0.001), with bempedoic acid providing a reduction of 21.4% (95% CI, −25.1% to −17.7%) compared with placebo. The LS mean change from baseline to week 12 in LDL-C were −21.2 mg/dL and −2.3 mg/dL for the bempedoic acid and placebo groups, respectively. Reductions in LDL-C were observed at the first post-baseline study visit (week 4) and were maintained throughout the study (Figure 5) (Laufs et al., 2019).

Figure 5. Effect of bempedoic acid on LDL-C in patients with statin intolerance: CLEAR Serenity



LDL-C = low-density lipoprotein cholesterol.

Data are means (SE).

Source: Laufs et al. (2019).

Secondary and other efficacy outcomes

Bempedoic acid resulted in significant reductions in all other lipid parameters and biomarkers at week 12 compared with placebo ($P < 0.001$). Changes from baseline were −17.9% (95% CI, −21.1% to −14.8%) for non–HDL-C, −14.8% (95% CI, −17.3% to −12.2%) for TC, and −15.0% (95% CI, −18.1% to −11.9%) for apo B, respectively. Bempedoic acid reduced hsCRP by 25.4% compared with an increase of 2.7% in the placebo group. The location shift from baseline to week 12 for hsCRP was −24.3% (asymptotic confidence limits, −35.9% to −12.7%; $P < 0.001$). Improvements in these parameters were maintained at week 24 (Laufs et al., 2019).

Changes in TGs were minimal and similar with bempedoic acid and placebo. Effects on HDL-C were negligible (< 6% change from baseline in both treatment groups) (Laufs et al., 2019).

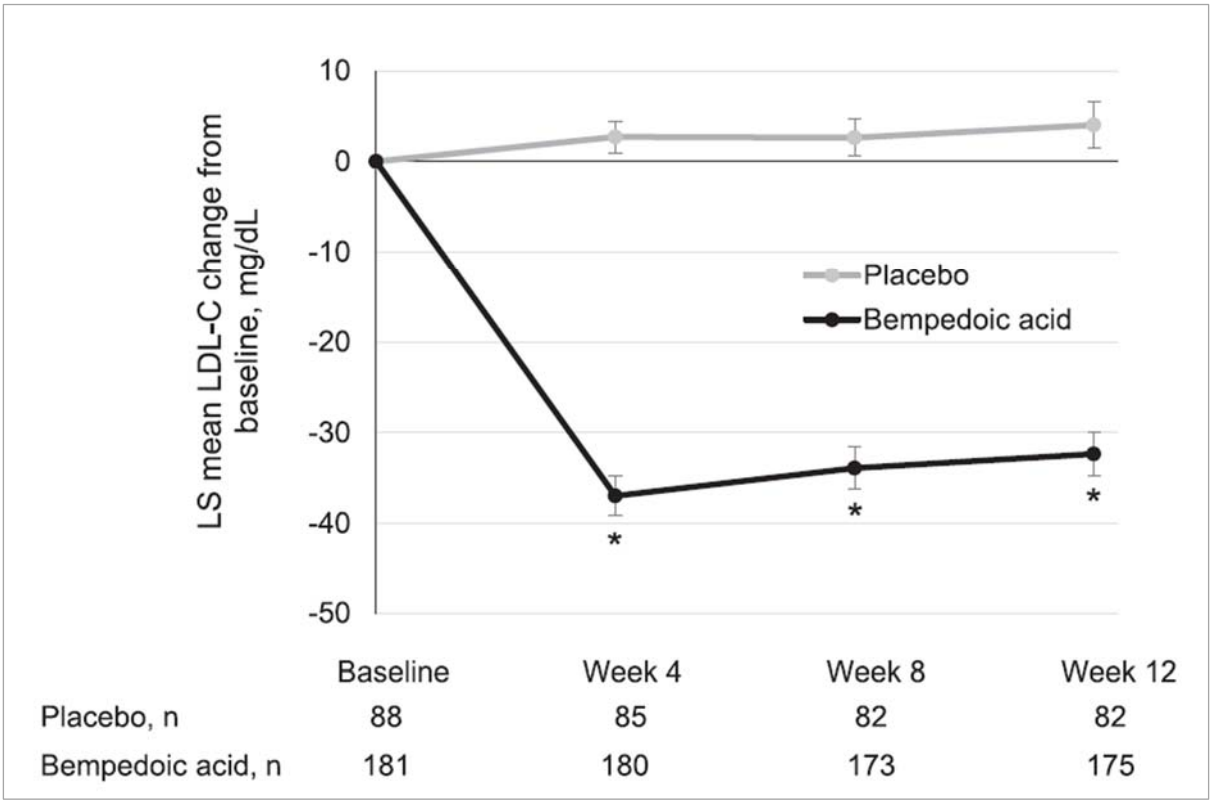
CLEAR Tranquility (1002-048)

Primary efficacy outcome (LDL-C reduction)

In the ITT analysis, bempedoic acid added to background LMT that included ezetimibe resulted in a placebo-corrected LS mean change in LDL-C of −28.5% (95% CI, −34.4% to −22.5%; $P < 0.001$) from baseline to week 12. While the mean LDL-C decreased to < 100 mg/dL among patients in the bempedoic acid treatment group (from 129.8 mg/dL at baseline to 96.2 mg/dL at week 12), patients who received placebo experienced a modest net increase in LDL-C from baseline (from 123.0 mg/dL at baseline to 128.8 mg/dL at week 12). Significant reductions in LDL-C with bempedoic acid were

observed at the first post-baseline study visit (week 4) and were maintained throughout the 12-week study (Figure 6) (Ballantyne et al., 2018).

Figure 6. CLEAR Tranquility: absolute change in low-density lipoprotein cholesterol over time (ITT analysis)



ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LS = least squares.

Source: Ballantyne et al. (2018).

Secondary efficacy outcomes

Bempedoic acid added to background LMT that included ezetimibe also improved other lipid and lipoprotein parameters, including non–HDL-C, TC, and apo B. Least squares mean non–HDL-C, TC, and apo B decreased significantly from baseline to week 12 in the bempedoic acid treatment group but increased slightly among those who received placebo ($P < 0.001$) (Table 18). Placebo-corrected changes from baseline were −23.6% ± 2.8%, −18.0% ± 2.0%, and −19.3% ± 2.3% for non–HDL-C, TC, and apo B, respectively. Significant differences between treatment groups for non–HDL-C and TC were observed at the first post-baseline assessment (week 4) and were maintained throughout the study (apo B was only measured at baseline and week 12). Marked reductions from baseline in median hsCRP were also observed in the bempedoic acid treatment group, with a placebo-corrected decrease of 31.0% ($P < 0.001$) (Ballantyne et al., 2019a; Ballantyne et al., 2019b). Elevated C-reactive protein levels are associated with increased risk for CHD and adverse CV outcomes, both in the general population and among patients receiving lipid-modifying therapy, including maximally tolerated statin treatment (Buckley et al., 2009; Li et al., 2017; Puri et al., 2013; Ridker et al., 2010).

High-density lipoprotein cholesterol decreased from baseline to week 12 in both the bempedoic acid and placebo treatment groups, although to a significantly larger extent in the former (−7.3% ± 1.2 and −1.4% ± 1.4, respectively; *P* = 0.002). Changes in TG levels were modest and comparable between treatment groups (median change: bempedoic acid, −1.4%; placebo, +7.8%) (Ballantyne et al., 2019a; Ballantyne et al., 2019b).

B.2.6.1.2 Analysis of Phase 2 bempedoic acid trials

Table 28 presents a summary of the efficacy results for two phase 2 bempedoic acid trials, Study 1002-008 and 1002-009 in patients who received bempedoic acid 180 mg. These are described in detail in the sections below. The efficacy data presented in this section include results from the modified ITT population, which consisted of randomised patients who had a baseline assessment, received at least one dose of study medication, and had at least one on-treatment assessment, excluding assessments taken 2 days after a dose of study drug.

Table 28. Summary of the efficacy results for Phase 2 bempedoic acid trials

Efficacy parameter	Study 1002-008 (Thompson et al., 2016)			Study 1002-009 (Ballantyne et al., 2016)		
LS mean percentage change from baseline to week 12	**Bempedoic acid (n = 99)**	**Ezetimibe (n = 98)**	***P* value**	**Bempedoic acid (n = 43)**	**Placebo (n = 43)**	***P* value**
LDL-C, mg/dL	−30.1 (1.3)	−21.2 (1.3)	< 0.0001	−24.3 (4.2)	−4.2 −(4.2)	< 0.0001
LDL particle number, nmol/L	−24.6 (1.8)	−12.7 (1.7)	< 0.0001	−2.3 (4.3)	−21.3 (4.3)	< 0.01
Non–HDL-C, mg/dL	−25.3 (1.1)	−18.7 (1.2)	< 0.0001	−10.75 (0.952)	−1.8 (3.9)	< 0.01
TC, mg/dL	−20.7 (0.9)	−14.3 (0.9)	< 0.0001	−15.3 (2.9)	−3.2 (2.9)	< 0.01
Apo B, mg/dL	−21.3 (1.3)	−15.2 (0.70)	NR	−17.2 (3.4)	−5.5 (3.4)	< 0.01
hsCRP, mg/l	−40.2 (53.3)[a]	−10.5 (59.0)[a]	≤ 0.01	−29.8 (50)	0 (89)	NR
HDL-C, mg/dL	−4.8 (13.5)	5.0 (1.4)	< 0.0001	−4.0 (2.7)	−2.0 (2.7)	NR
TG, mg/dL	−2.70 (46.2)[a]	7.0 (34.9)[a]	NR	−9.1 (47)	−3.0 (37)	NR
HDL particle number, mmol/L	6.2 (1.4)	6.7 (1.3)	NR	10.1 (2.8)	−1.6 (2.8)	< 0.01
Apo A-1, mg/dL	0.1 (1.2)	2.0 (1.1)	NR	−0.1 (2.2)	−3.7 (2.2)	NR
VLDL particle number, nmol/L*	15.3 (80.5)	−12.6 (63.4)	NR	−8.3 (91)	10.9 (76)	NR

Apo A-1 = apolipoprotein A-1; Apo B = apolipoprotein B; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LS = least squares; NR = not reported; SE = standard error; TC = total cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein.

Note: the following additional arm was included in phase 2 trials (study 1002-008 and study 1002-009), which is not relevant to the decision problem: bempedoic acid 120 mg and bempedoic acid 120 mg + ezetimibe 10 mg.

Data are LS means (SE), unless otherwise indicated.

[a] Median (interquartile range) values.

Study 1002-008

Primary efficacy outcome (LDL-C reduction)

In the modified ITT analysis, bempedoic acid monotherapy reduced LDL-C from baseline to week 12 more than ezetimibe monotherapy. The percentage reduction in LDL-C was 31% for those in the bempedoic acid group compared with 21% for those in the ezetimibe group (Thompson et al., 2016).

Secondary and exploratory efficacy outcomes

Treatment with bempedoic acid reduced other lipid parameters, including LDL particle number, apo B, TC, and non–HDL-C greater than ezetimibe therapy. Median values for hsCRP decreased significantly from baseline to week 12 by 40% with bempedoic acid compared with 10% with ezetimibe ($P < 0.01$). High-density lipoprotein cholesterol decreased with bempedoic acid treatment 4.8% and increased with ezetimibe alone by 5% ($P < 0.0001$) (Thompson et al., 2016).

Study 1002-009

Primary efficacy outcome (LDL-C reduction)

Bempedoic acid added to stable statin therapy reduced mean LDL-C significantly more than placebo. The LS mean (standard error [SE]) percentage changes from baseline in LDL-C were −4.2 (4.2%) with placebo and −24.3 (4.2%) with bempedoic acid ($P < 0.0001$). LDL-C reductions in the bempedoic acid monotherapy group was significantly greater than in the placebo group by week 2 and remained significantly greater through week 12 (Ballantyne et al., 2016).

Secondary and exploratory efficacy outcomes

Compared with placebo, treatment with bempedoic acid added to statin therapy also significantly reduced other lipid parameters, including apo B, non–HDL-C, TC, and LDL particle number. Median hsCRP values were reduced by 30% with bempedoic acid ($P = 0.08$ vs. placebo). Although slight decreases in HDL-C and apolipoprotein A-1 (apo A-1) levels were observed, the results were not significantly different between bempedoic acid and placebo groups. Treatment with bempedoic acid resulted in a small increase in HDL particle number; the difference in LS mean percentage change in HDL particle number was significant between bempedoic acid and placebo (10.1% increase vs. 1.6% decrease; $P = 0.0004$) (Ballantyne et al., 2016).

B.2.6.2 Bempedoic acid and ezetimibe FDC efficacy results

Results from the FDC arm and bempedoic acid arm of Study1002FDC-053 are presented in this section. Study 1002FDC-053 provides the primary evidence for FDC.

Of note, it may be expected that the efficacy and safety of bempedoic acid added to background therapy with ezetimibe in CLEAR Tranquility (presented in Section B.2.6.1.1) is very similar to FDC, because pharmacokinetic studies have shown the two presentations to be equivalent (Esperion Therapeutics data on file, 2019e; Esperion Therapeutics data on file, 2019f); see Appendix M for details of the pharmacokinetic studies).

Table 29 presents a summary of the efficacy results for FDC compared with placebo, bempedoic acid monotherapy, and ezetimibe monotherapy. These are described in detail in Section B.2.6.2.1.

Table 29. Summary of the efficacy results for FDC

Efficacy parameter	1002FDC-053 (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d)						
LS mean % change from baseline to week 12	**FDC (n = 86)**	**Placebo (n = 41)**	***Difference of LS means FDC vs. placebo (95% CI); P* value**	**Bempedoic acid (n = 88)**	***Difference of LS means FDC vs. bempedoic acid (95% CI); P* value**	**Ezetimibe (n = 86)**	***Difference of LS means FDC vs. bempedoic acid (95% CI); P* value**
LDL-C	−36.2	1.8	−38.0 (−46.5, −29.6); < 0.001	−17.2	−19.0 (−26.1, −11.9); < 0.001	−23.2	−13.1 (−19.7, −6.5); < 0.001
Non-HDL-C	−31.9	+1.8	−33.7 (−43.9, −23.4); < 0.001	−14.1	−17.8 (−25.1, −10.5); < 0.001	−19.9	−12.1 (−19.1, −5.0); < 0.001
TC	−26.4	−1.9	−27.1 (−35.1, −19.1); < 0.001	−12.1	−14.2 (−20.4, −8.1); < 0.001	−16.0	−10.4 (−16.1, −4.6); < 0.001
Apo B	−24.6	5.5	−30.1 (−39.9, −20.3); < 0.001	−11.8	−12.8 (−20.3, −5.3); < 0.001	−15.3	−9.3 (−16.5, −2.1); < 0.003
hsCRP[a]	−35.1	21.6	−46.1 (−78.8, −15.8); < 0.001	−31.9[a]	Not significant	-8.2[a]	−25.6 (−45.0, −7.2) 0.002
HDL-C	NR	NR	NR	NR	NR	NR	NR

Apo B = apolipoprotein B; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = non-high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LS = least squares; NR = not reported; TC = total cholesterol.

[a] Median percentage change from baseline.

B.2.6.2.1 Study 1002FDC-053

Primary efficacy outcome (LDL-C reduction)

Following database lock and review, it was determined that 51 patients on active drug had no detectable study drug in blood samples taken at week 12 for use in population pharmacokinetic modelling. Most (34 of 51) of these patients were from three study sites in the same metropolitan area. Owing to concerns about the integrity of any of the data from these three sites, data from these three sites were excluded from the additional post-hoc efficacy and safety analyses but not the initial ITT analysis.

In the post-hoc analysis (all randomised patients except the 81 patients from the three sites with data integrity issues) at week 12, LDL-C lowering with FDC was significantly greater than that for the placebo group ($P < 0.001$), with FDC providing a reduction of 38.0% compared with placebo. The mean absolute changes from baseline to week 12 in LDL-C were −36.2 mg/dL and 1.8 mg/dL for the FDC and placebo groups, respectively. Bempedoic acid monotherapy and ezetimibe monotherapy reduced LDL-C by 17.2% and 23.2%, respectively, compared with an increase of 1.8% with placebo at week 12. The FDC lowered LDL-C significantly more than ezetimibe alone (−23.2%; $P < 0.001$) or bempedoic acid alone (−17.2%; $P < 0.001$).

In the ITT analysis, the percentage reduction in LDL-C from baseline to week 12 was 31.5%, 21.0%, 17.7%, and 2.5% for FDC, ezetimibe monotherapy, bempedoic acid monotherapy, and placebo, respectively. Treatment with FDC resulted in a significantly greater reduction in mean LDL-C of 29.0% compared with placebo (95% CI, −36.8 to −21.3; $P < 0.001$) (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d).

Secondary and exploratory efficacy outcomes

In the post-hoc analysis, FDC reduced hsCRP by 35.1% compared with an increase of 21.6% with placebo ($P < 0.001$). FDC also reduced non–HDL-C, TC, and apo B while these lipid parameters increased with placebo ($P < 0.001$). Changes from baseline in HDL-C were modest (< 10.0%) in both groups. Treatment with bempedoic acid monotherapy or ezetimibe monotherapy also led to reductions in non–HDL-C, TC, apo B, and hsCRP compared with placebo. Minimal changes from baseline to week 12 for HDL-C and TGs were observed and were less than 10.0% in all treatment groups. There was a higher mean percentage change from baseline to week 12 in HDL-C for bempedoic acid [redacted] compared with ezetimibe [redacted] and placebo [redacted] The mean percentage change from baseline to week 12 in TG was [redacted] for bempedoic acid, 5.63% for ezetimibe, and [redacted] for placebo.

The ITT analysis showed that FDC compared with placebo resulted in a significant reduction in mean hsCRP of 37.2% (95% CI, −64.5 to −13.3; $P < 0.001$). FDC also significantly reduced non–HDL-C, TC, and apo B compared with placebo ($P < 0.001$) (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d). Treatment with bempedoic acid and ezetimibe led to a reduction in non–HDL-C, TC, apo B, and hsCRP, whereas treatment with placebo led to an increase in apo B and hsCRP but a minimal reduction in non–HDL-C and TC. At week 12, ezetimibe, bempedoic acid, and placebo reduced non–HDL-C by [redacted] respectively. At week 12, bempedoic

acid and ezetimibe reduced hsCRP by [redacted], respectively, compared with an increase of [redacted] with placebo (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d).

Exploratory analyses showed that a significantly greater proportion of patients had achieved LDL-C less than 1.8 mmol/L (70 mg/dL) at week 12 in the FDC treatment group compared with placebo (31.3% vs. 0.0%, respectively; $P < 0.001$).

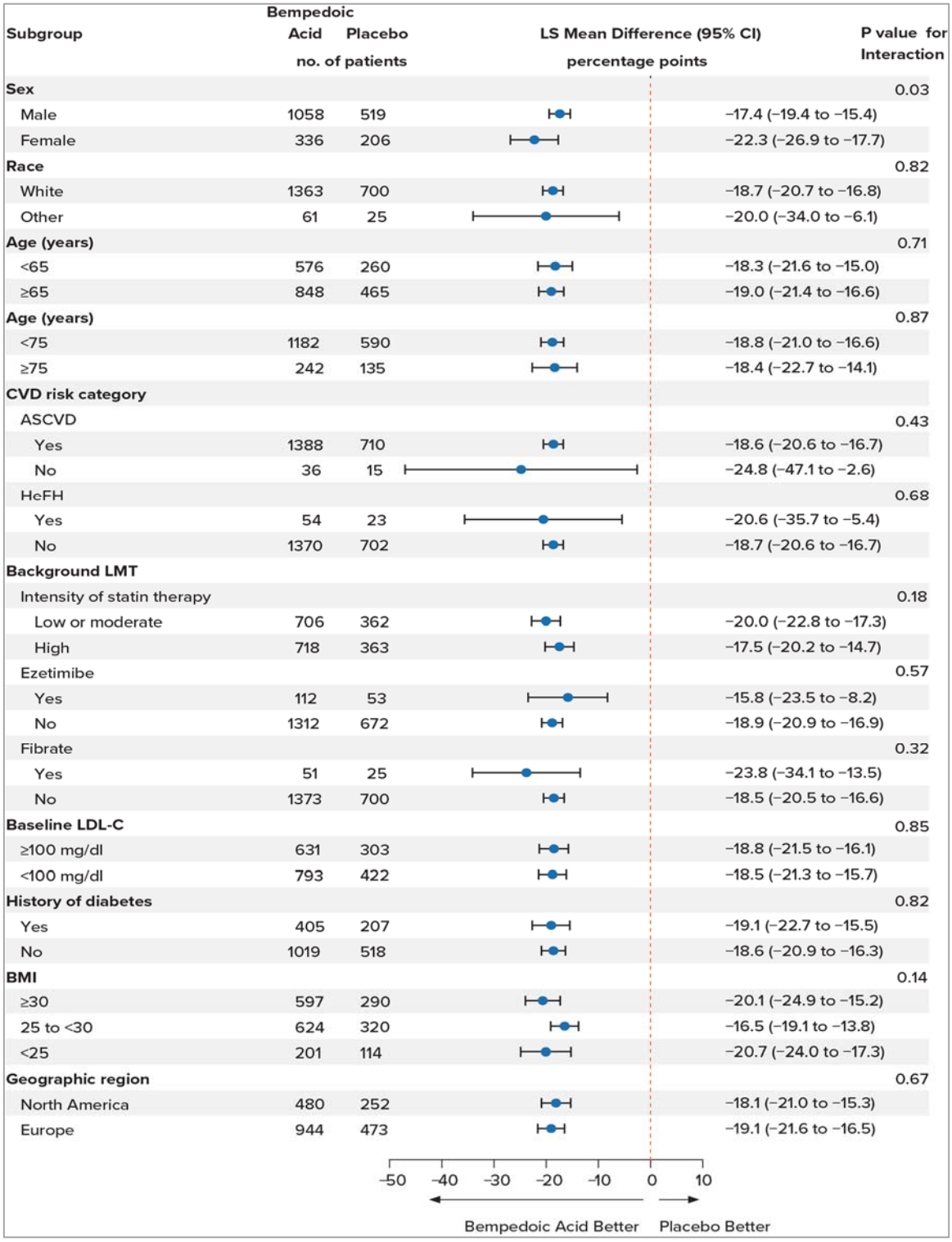
B.2.7 Subgroup analysis

B.2.7.1 Bempedoic acid efficacy in subgroup analyses

B.2.7.1.1 CLEAR Harmony

In the CLEAR Harmony trial, the principal efficacy endpoint (percentage change in LDL-C from baseline to week 12) was evaluated across pre-specified subgroups, including gender, age, baseline CV risk category, baseline statin intensity, race, baseline LDL-C category, history of diabetes, body mass index (BMI), and region. Efficacy did not vary cross subgroups, with the exception of there being a greater magnitude of effect with bempedoic acid therapy than with placebo among women (−22.3% difference in LS mean) than among men (−17.4% difference in LS mean; $P = 0.03$) (Figure 7) (Ray et al., 2019b).

Figure 7. CLEAR Harmony subgroup analysis: change from baseline LDL-C to week 12 (ITT population)



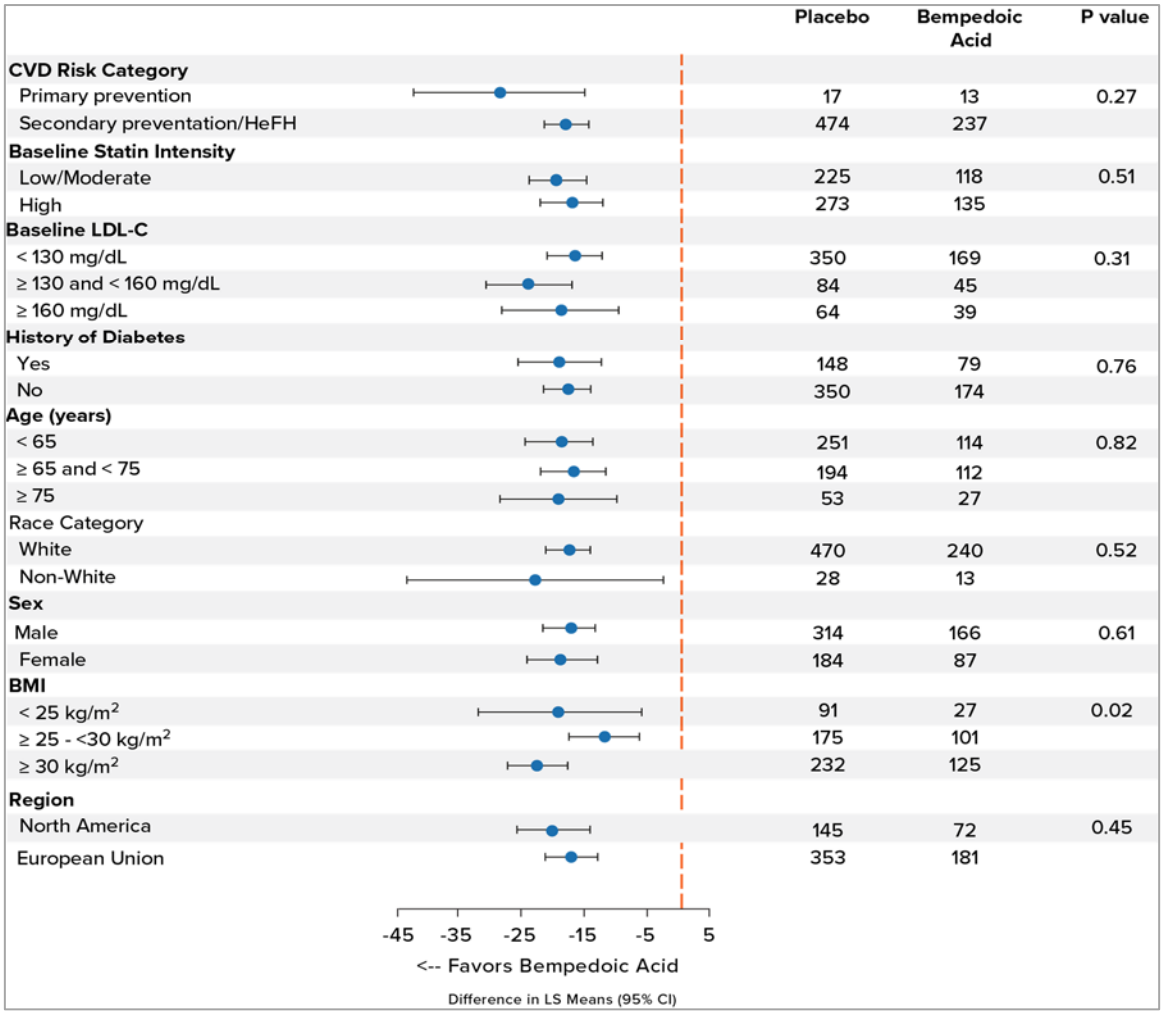
ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolaemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares.

Source: Ray et al. (2019b).

B.2.7.1.2 CLEAR Wisdom

In the CLEAR Wisdom trial, the primary endpoint (percentage change in LDL-C from baseline to week 12) was evaluated across pre-specified subgroups, including sex, age, race, baseline CV risk category, baseline statin intensity, baseline LDL-C category, history of diabetes, BMI, and region. As shown in Figure 8, the LDL-C–lowering effect of bempedoic acid versus placebo was consistent across all subgroups; however, a significant interaction between subgroup and treatment was observed for BMI ($P = 0.02$). The study reported similar LDL-C lowering in patients receiving a low-/moderate-intensity or high-intensity statin and placebo-corrected decreases from baseline of 22.0% (95% CI, −33.4% to −10.6%; $P < 0.001$) in patients receiving no statin and 26.8% (95% CI, −40.2% to −13.3%; $P < 0.001$) in patients receiving no lipid-lowering therapy (Goldberg et al., 2019).

Figure 8. CLEAR Wisdom subgroup analysis: change from baseline LDL-C to week 12 (ITT population)



BMI = body mass index; CVD = cardiovascular disease; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol.

Source: Goldberg et al. (2019).

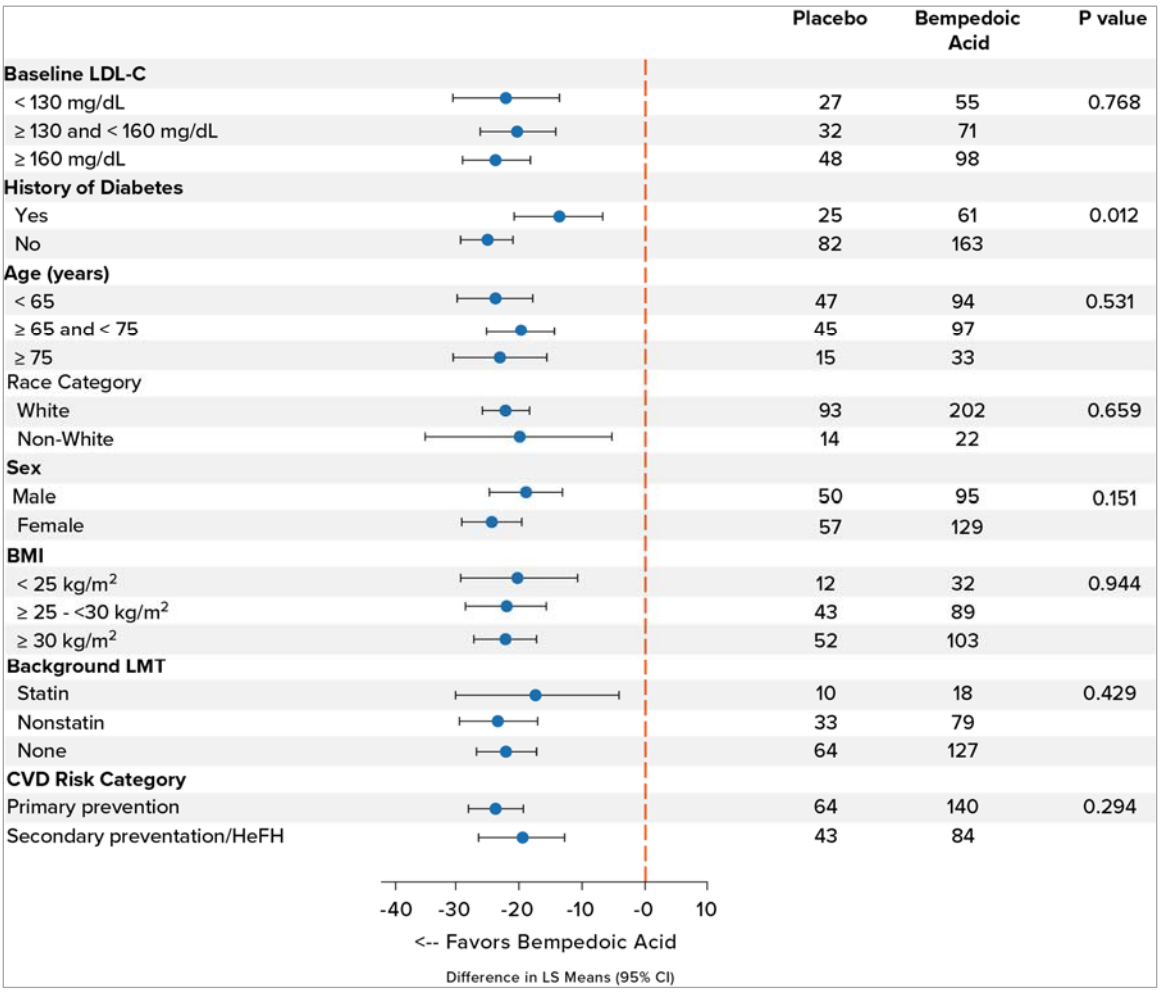
B.2.7.1.3 CLEAR Serenity

Subgroup analyses were performed for the primary endpoint (percentage change in LDL-C at week 12) based on the following groups: CVD risk category, baseline LDL category, history of diabetes, age, race, sex, and BMI category.

Lipid lowering was consistent across patient subgroups and was observed when bempedoic acid was administered as monotherapy or when added to stable background lipid-modifying therapy. Significant reductions in LDL-C at week 12 with bempedoic acid versus placebo were observed in all subgroups ($P \leq 0.01$) (Figure 9) (Laufs et al., 2019).

A difference in LDL-C reduction was observed among patients with a history of diabetes versus those with no history of diabetes (*P* value for interaction, 0.012) (Laufs et al., 2019). However, this was likely attributable to chance given the limited sample size, as LDL-C reduction with bempedoic acid was comparable in patients with and without diabetes in CLEAR Harmony (Section B.2.7.1.1 and CLEAR Tranquility (Section B.2.7.1.4) phase 3 clinical trials.

Figure 9. CLEAR Serenity subgroup analysis: change from baseline LDL-C to week 12 (ITT population)



BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolaemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares.

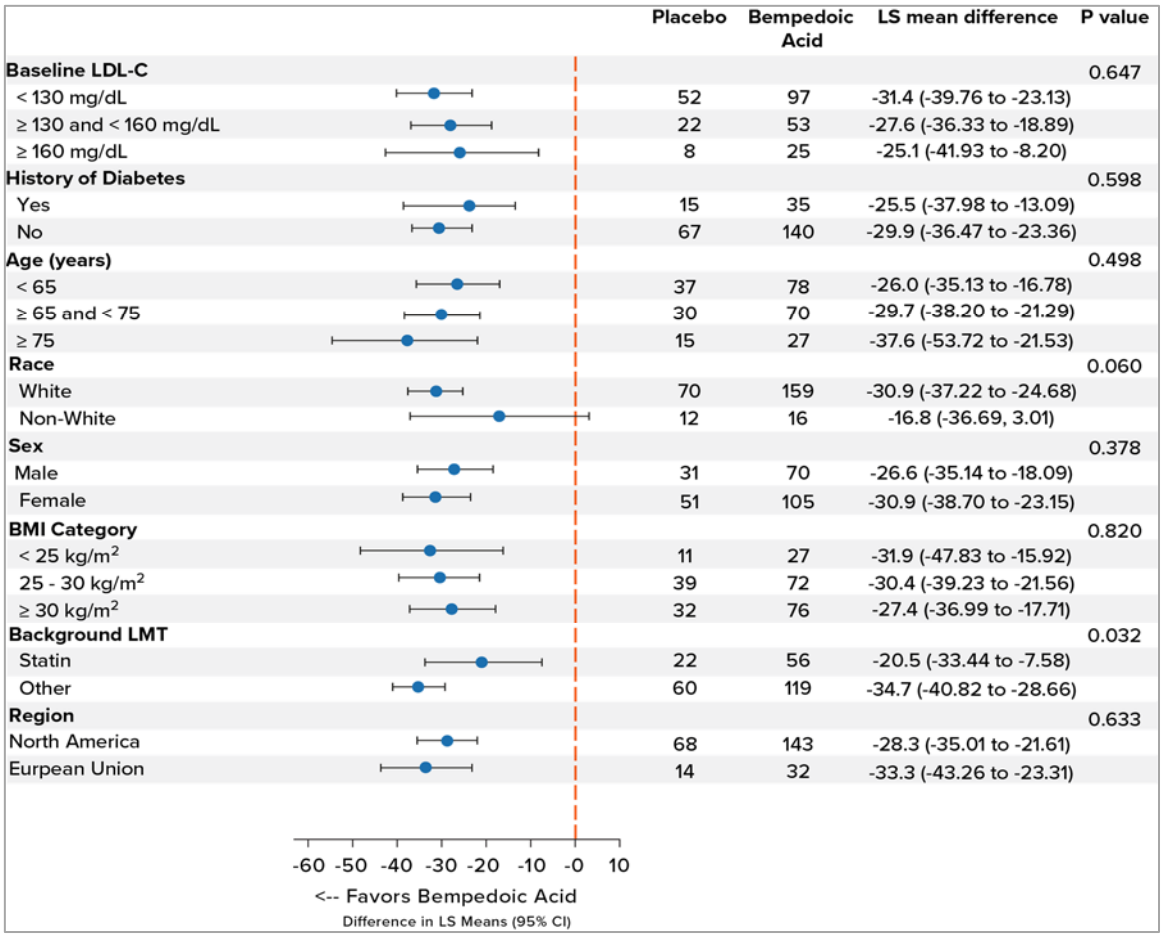
Source: Laufs et al. (2019).

B.2.7.1.4 CLEAR Tranquility (bempedoic acid+ezetimibe)

Exploratory analyses were performed to evaluate LDL-C lowering across subgroups, and although some numerical differences were observed, there were no clinically significant differences based on baseline LDL-C, history of diabetes, age, race, sex, BMI, or region (Figure 10).

Heterogeneity in LDL-C reduction was observed in the background statin use subgroups (*P* = 0.032 for treatment and subgroup interaction). The difference in LDL-C reduction between the bempedoic acid+ezetimibe and placebo+ezetimibe treatment groups was statistically significant in both subgroups; however, the LDL-C–lowering effect was greater among those who received no background statin therapy (−34.7%) compared with those on a low-dose or VLD statin (−20.5%) (Ballantyne et al., 2018).

Figure 10. Clear Tranquility (bempedoic acid+ezetimibe) exploratory subgroup analysis: change from baseline LDL-C to week 12



CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; LS = least squares.

Source: Ballantyne et al. (2018).

B.2.7.2 FDC efficacy in subgroup analyses

B.2.7.2.1 Study 1002FDC-053 (FDC vs. placebo)

Subgroup analyses of the percentage change from baseline to week 12 in LDL-C were performed for subgroups based on sex, age group, CVD risk category, statin intensity, race, baseline LDL-C category, history of diabetes, BMI, and calculated statin intensity.

Results indicated a consistent trend for LDL-C lowering in the FDC treatment group relative to placebo (Figure 11). Although the study was not powered to assess between-group differences in the subgroup analyses, LDL-C lowering with FDC was greater than placebo in all subgroups ($P \leq 0.001$). Moreover, FDC was statistically significantly superior to placebo in all statin intensity subgroups (Figure 11; Table 30) (Esperion Therapeutics data on file, 2019d).

Figure 11. Study 1002FDC-053 subgroup analysis: change from baseline LDL-C to week 12, FDC vs. placebo

Table 30. 1002FDC-053: subgroup analyses – percentage change from baseline in LDL-C at week 12, by calculated baseline statin intensity (full analysis set)

Calculated baseline statin intensity treatment	N	Least-square mean (SE)	Difference (SE)	95% CI of the difference	*P* value
No statin					
FDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]			
Other statin intensity					
FDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]			
High-intensity statin					
FDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]			

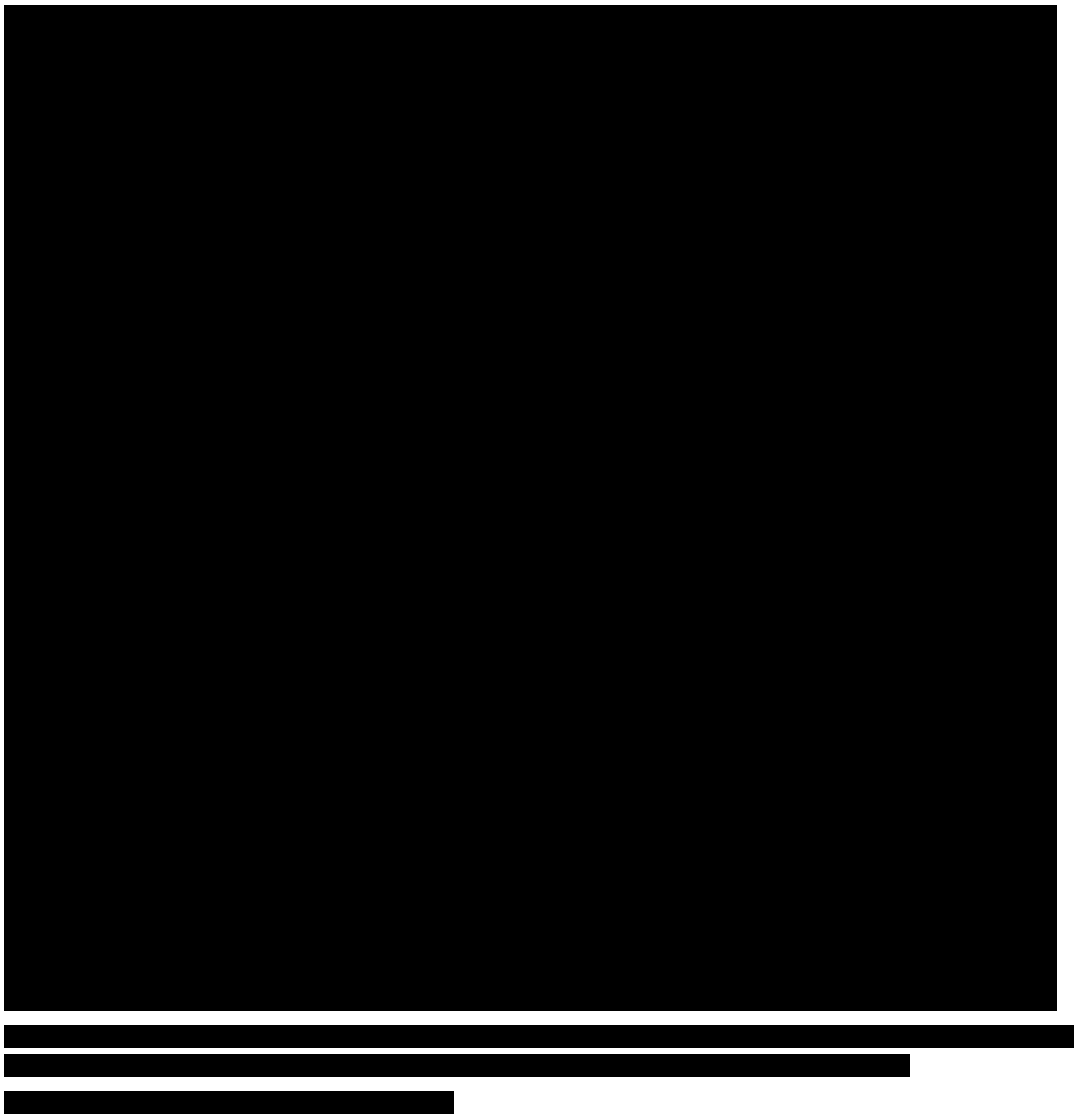
CI = confidence interval; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; SE = standard error.

Source: Esperion Therapeutics data on file (2019d).

B.2.7.2.2 Study 1002FDC-053 (FDC vs. bempedoic acid)

Subgroup analyses of the percentage change from baseline to week 12 in LDL-C were performed for subgroups based on sex, age group, CVD risk category, statin intensity, race, baseline LDL-C category, history of diabetes, BMI, and calculated statin intensity (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d). As shown in Figure 12, although LDL-C lowering with FDC was generally consistent in subgroup analyses, the differences between the FDC and bempedoic acid groups for some subgroups were either not statistically significant or were marginally significant (CVD risk category of "multiple CV risk factors" [*P* = 0.391]; statin intensity, "other-intensity statin" [*P* = 0.322]; and BMI 25 to ≤ 30 kg/m^2 [*P* = 0.775]) (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019d). Small sample sizes for some of these subgroups may account for this lack of statistical significance, as the trial was not powered to show statistical differences among patient subgroups. The small sample could also have led to the wide confidence intervals, thereby creating uncertainties about the true effect of the treatment.

Figure 12. Study 1002FDC-053 subgroup analysis: change from baseline LDL-C to week 12, FDC vs. bempedoic acid



B.2.8Meta-analysis

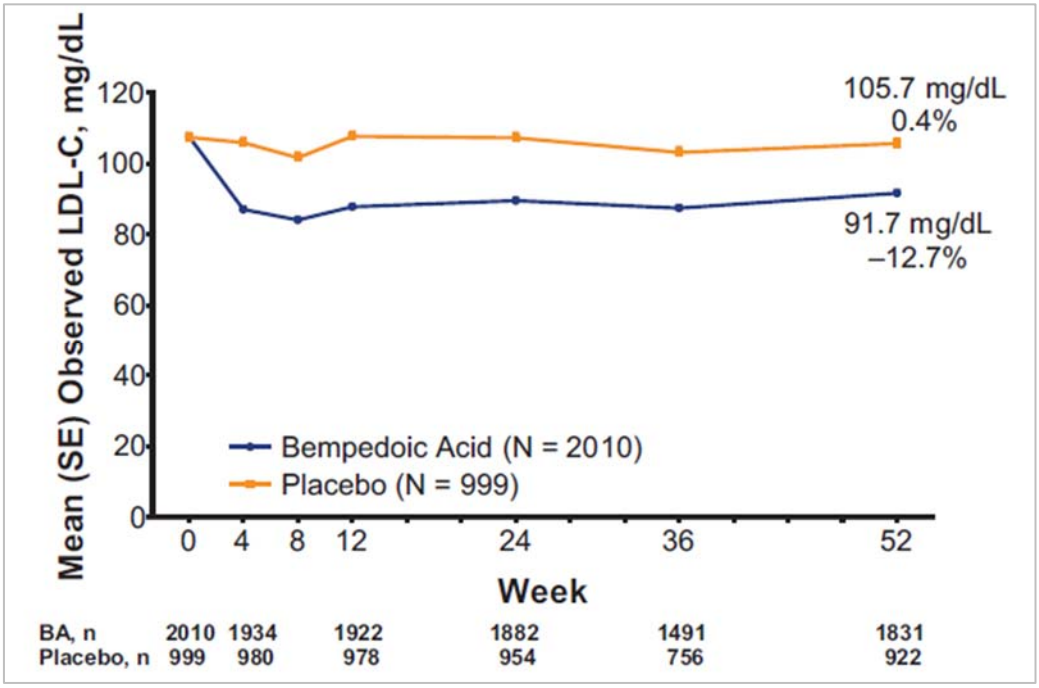
- Data from a large pooled analysis encompassing 3,623 adults with hypercholesterolemia enrolled in phase 3 clinical trials showed that treatment with bempedoic acid significantly lowered LDL-C compared with placebo.
- LDL-C lowering was maintained throughout the treatment period and was observed on a background of stable lipid-lowering therapy, which included statins and/or other non-statin agents.

B.2.8.1 Bempedoic acid trials: meta-analysis

A pooled analysis was performed of the two trials which compared bempedoic acid with placebo in patients with ASCVD or high risk for ASCVD receiving stable maximally tolerated statin therapy with or without additional lipid-lowering therapy (CLEAR Harmony and CLEAR Wisdom). The phase 2 trials 1002-008 and 1002-009 were not included in the meta-analysis because patients in these trials received no statin (phase 2 study 1002-008) or low-to-moderate-intensity statin (phase 2 study 1002-009). Bempedoic acid has greater efficacy in patients receiving no/low-dose statin than in patients receiving moderate to high background statin therapy (see Section B.2.6.1). Therefore, the treatment effect for bempedoic acid in the phase 2 trials is expected to be heterogeneous with that in the phase 3 trials.

The results of the pooled analysis are presented in Figure 13. Reductions in LDL-C were observed at the first post-baseline study visit (week 4) and were maintained through the last measurement time point (52 weeks). Treatment with bempedoic acid lowered LDL-C significantly more than did placebo at week 12: the LS mean percentage change in LDL-C from baseline to week 12 was −16.0 in the bempedoic acid group and 1.8 in the placebo group (between-group difference [95% CI], –17.8 [–19.5, –16.0]; $P < 0.001$). Absolute mean reduction from baseline to week 12 in LDL-C was greater in patients treated with bempedoic acid compared with placebo (bempedoic acid, –19.8 mg/dL; placebo, 0.3 mg/dL). A significantly greater percentage of patients in the bempedoic acid group achieved LDL-C < 70 mg/dL at week 12 compared with placebo (28.9% vs 8.0%; $P < 0.001$).

Figure 13. Pooled analysis of RCTs (CLEAR Harmony and CLEAR Wisdom) comparing bempedoic acid with placebo in patients with ASCVD/HeFH receiving stable maximally tolerated statin therapy with or without additional lipid-lowering therapy

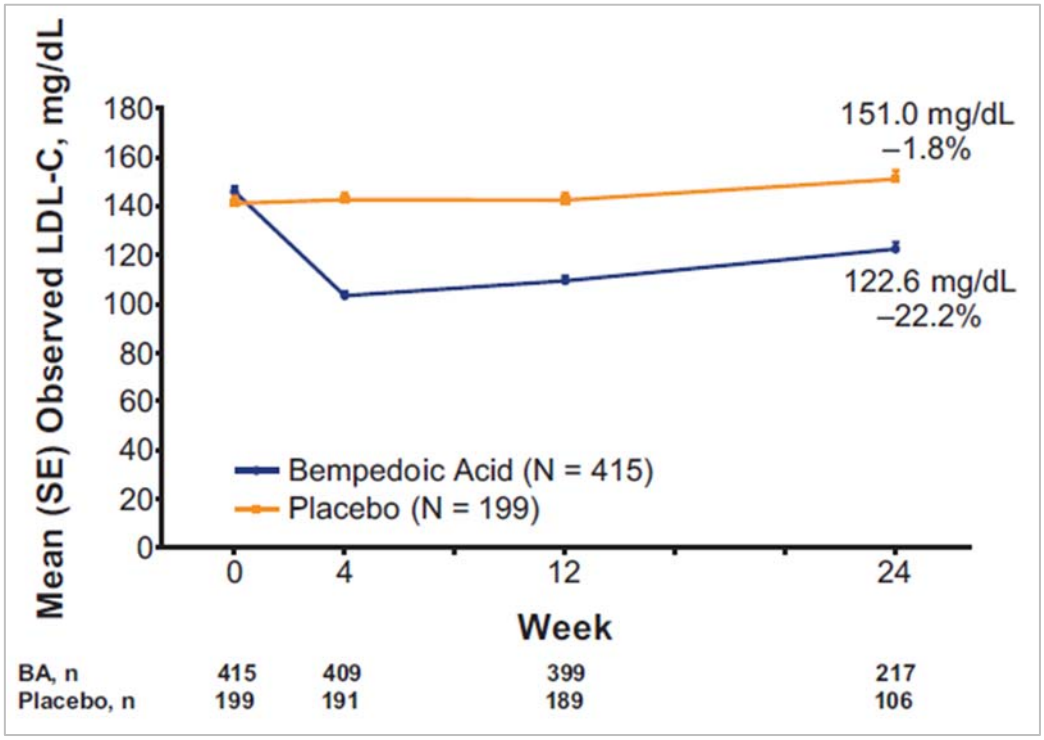


LDL-C = low-density lipoprotein cholesterol; RCT = randomised controlled trial; SE = standard error.

Source: Banach et al. (2019).

A pooled analysis was performed of the two trials which compared bempedoic acid with placebo in patients with ASCVD or high risk for ASCVD receiving no/low-dose statin therapy (i.e., statin-intolerant patients) (CLEAR Serenity and CLEAR Tranquility). The results of this pooled analysis are presented in Figure 14. Reductions in LDL-C were observed at the first post-baseline study visit (week 4) and were maintained through the last measurement time point (24 weeks). Treatment with bempedoic acid lowered LDL-C significantly more than did placebo at week 12: the LS mean percentage change in LDL-C from baseline to week 12 was −23.0 in the bempedoic acid group and 1.5 in the placebo group (between-group difference [95% CI], –24.5 [–27.8, –21.1]; $P < 0.001$). Absolute mean reduction from baseline to week 12 in LDL-C was greater in patients treated with bempedoic acid compared with placebo (bempedoic acid, –36.5 mg/dL; placebo, 0.6 mg/dL).

Figure 14. Pooled analysis of RCTs comparing bempedoic acid with placebo in patients with statin intolerance (CLEAR Serenity and CLEAR Tranquility)



ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid, LDL-C = low-density lipoprotein, RCT = randomised controlled trial; SE = standard error; VLD = very low dose.

Source: Banach et al. (2019).

B.2.8.2 Pooled subgroup analysis of bempedoic acid added to ezetimibe background therapy

In post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use.

In patients where the background dose of statin equalled no or low-dose statin therapy (studies 1002-046 and 1002-048), 415 patients were randomised to bempedoic acid and 199 were randomised to placebo. Of these, [redacted] bempedoic acid patients and [redacted] placebo patients were treated with background ezetimibe at the time of randomisation. In post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use. The LS mean reduction from baseline to week 12 in LDL-C for bempedoic acid compared with placebo was [redacted] versus [redacted], respectively, with a difference from placebo for the LS means of [redacted] in patients taking ezetimibe. In the subgroup of patients not taking ezetimibe, the percentage change from baseline was [redacted] for bempedoic acid versus [redacted] for placebo, with a difference from placebo for the LS means of [redacted].

In the two Phase 3, 52-week studies (1002-040 and 1002-047), patients treated with maximally tolerated statin could continue their other LMTs, including ezetimibe. Of the 2,010 patients randomised

to bempedoic acid in these studies, [redacted] patients reported ezetimibe background therapy; of the 999 patients randomised to placebo, [redacted] patients were also treated with ezetimibe background therapy. In post-hoc subgroup analyses by ezetimibe use at baseline, the LS mean reduction from baseline to week 12 in LDL-C for bempedoic acid compared with placebo was [redacted] versus [redacted], respectively, with a difference from placebo for the LS means of [redacted] in patients taking ezetimibe, and [redacted] versus [redacted], respectively, with a difference from placebo for the LS means of [redacted] in patients not taking ezetimibe.

B.2.8.3 FDC and bempedoic acid+ezetimibe trials: qualitative synthesis

No meta-analysis was performed for the trials investigating FDC (1002FDC-053) and bempedoic acid+ezetimibe (CLEAR Tranquility) because patients in 1002FDC-053 received background statin therapy, while in CLEAR Tranquility patients received no/low-dose statin therapy, and in the phase 2 study 1002-008 patients received no background statin. Therefore, the treatment effect for bempedoic acid in combination with ezetimibe among these three trials is expected to be heterogeneous (see Sections B.2.6.1 and B.2.6.2 for results of these studies).

B.2.9 Indirect and mixed-treatment comparisons

A network meta-analysis was performed to provide estimates of the efficacy of bempedoic acid and FDC versus ezetimibe, alirocumab and evolocumab in the two situations of interest:

- When statins are contraindicated or not tolerated
- When maximally tolerated statin dose does not appropriately control LDL-C

Consistent with previous meta-analyses of lipid-modifying therapy (LMT), the endpoint was the percentage change in LDL-C from baseline. The percentage change in LDL-C has been used as the measure of treatment effect in previous meta-analyses (e.g., Pandor et al. (2009); Toth et al. (2017b) as it is empirically more exchangeable between studies than the absolute change in LDL-C.

Randomised controlled trials of LMTs were identified by a systematic review (described in Section B.2.1.1 and Appendix D). Only studies of 12 weeks or greater were included, consistent with the trial endpoint of interest and previous technology assessments and guidelines addressing the efficacy of LMT (e.g., TA385) (NICE, 2016d). Trial arms investigating the interventions of interest were included in the evidence network, along with comparator arms in studies of these interventions which add connections within the evidence network. Quality assessments of the included studies are presented in Appendix D.

LDL-C data were analysed at baseline and week 12, the primary endpoint for the bempedoic acid and FDC studies and many comparator studies. If data were not available at week 12 for a given trial, the nearest time point was analysed if it fell between week 10 and 24 (inclusive) and the actual time point was noted. This time window was selected in order to include data from key comparator trials while avoiding longer-term data for comparators which could bias the analysis in favour of bempedoic acid

and FDC (recognising the slight decrease in efficacy in terms of LDL-C reduction observed over time for ezetimibe, alirocumab and evolocumab therapy, e.g., in the COMBO II study) (El Shahawy et al., 2017).

The alternative dosing schedules for alirocumab 75 mg, and 150 mg (150 mg at 12 weeks or 24 week data for 75 mg with possible uptitration to 150 mg at 12 weeks) were considered separate treatments in the network. The alternative dosing schedules for evolocumab (140 mg Q2W and 420 mg QM) have been shown to have very similar efficacy in reducing LDL-C, and meta-analyses combining both doses have been performed (e.g., Toth et al., 2017). Evolocumab 420 mg QM is not recommended by NICE (TA394) (NICE, 2016c) and is therefore not a comparator of interest. However, due to the similarity in efficacy with the 140 mg Q2W dose (e.g., Toth et al. (2017b)), efficacy data for the 420 mg QM dose may be considered relevant to that of the 140 mg Q2W dose. In order to include all relevant evidence, both doses have been combined in the analysis and treated as a single intervention.

The evidence network for statin-intolerant studies is presented in Figure 15; the network for maximally tolerated statin studies is presented in Figure 16.

Figure 15. Evidence network for statin-intolerant studies

Note: studies typically enrolled patients considered to be statin intolerant, often described as due to statin-related muscle symptoms (typically no patients received statin therapy in these studies). In studies of mixed populations where a subgroup analysis was performed and reported in statin-intolerant patients, the statin-intolerant subgroup has been included in the network. The numbers represent the number of trials (or trial subgroups) providing information for that comparison.

Figure 16. Evidence network for maximally tolerated statin studies

Note: studies typically enrolled patients who were not able to achieve their LDL-C target despite maximally tolerated statin therapy (maximally tolerated statin therapy may include no statin or low-, moderate-, or high-intensity statin therapy). For some patients included in these studies, maximally tolerated statin may be no or very low-dose statin; i.e., patients were statin intolerant. Where subgroup data were available for statin-intolerant and statin-tolerant patients, the subgroup data have been included in the statin-intolerant network and the maximally tolerated statin network, respectively. Where no separate analyses were presented, studies were included in the maximally tolerated statin network since this was the specified study design. Studies in statin-tolerant patients not receiving statin also were included. Maximally tolerated statin trials included those enrolling patients on background statins, and also those in which patients were randomised to statins. The numbers represent the number of trials (or trial subgroups) providing information for that comparison.

Frequentist and Bayesian random-effects analyses were performed for the percentage change in LDL-C, with baseline LDL-C as a covariate. Statistical methods were consistent with the NICE Decision Support Unit Technical Support Document (Dias et al., 2011); random-effects models were fitted as recommended by Jansen et al. (2014). Details of the methodology for the network meta-analysis (NMA) is presented in Appendix D.3.

B.2.9.1 NMA results for bempedoic acid

Estimates of the percentage change in LDL-C from baseline compared with ezetimibe from the Bayesian NMA of statin-intolerant studies are presented in Table 31. The corresponding estimates from the NMA for maximally tolerated statin studies are presented in Table 32.

Table 31. NMA results for bempedoic acid in statin-intolerant studies

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value
Bempedoic acid	[redacted]	[redacted]	[redacted]
Bempedoic acid+ezetimibe	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]
EvoMab+ezetimibe[a]	[redacted]	[redacted]	[redacted]
Alirocumab (75 mg)	[redacted]	[redacted]	[redacted]
Alirocumab (150 mg)	[redacted]	[redacted]	[redacted]

CrI = credible interval; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

Note: other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe. No trial data were identified for alirocumab+ezetimibe.

[a] Evolocumab+ezetimibe estimates are based on data for 30 patients in GAUSS (Sullivan et al., 2012).

Table 32. NMA results for bempedoic acid+statin in maximally tolerated statin studies

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value
Bempedoic acid+statin	[redacted]	[redacted]	[redacted]
FDC+ statin[a]	[redacted]	[redacted]	[redacted]
EvoMab+statin	[redacted]	[redacted]	[redacted]
AliMab (75 mg)+statin	[redacted]	[redacted]	[redacted]
AliMab (150 mg)+statin	[redacted]	[redacted]	[redacted]
AliMab (75 mg)+statin+ezetimibe	[redacted]	[redacted]	[redacted]
AliMab (150 mg)+statin+ezetimibe	[redacted]	[redacted]	[redacted]

AliMab = Alirocumab; EvoMab = evolocumab; CrI = Credible interval; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

[a] These data are used in the economic model to represent the efficacy of bempedoic acid+ezetimibe separate tablets in patients receiving maximally tolerated statin. Pharmacokinetic studies have shown the two presentations to be equivalent (see Appendix M).

Note: other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe.

B.2.9.2 NMA results for FDC

Estimates of the percentage change in LDL-C from baseline compared with ezetimibe from the statin-intolerant NMA are presented in Table 33. The corresponding estimates from the maximally tolerated statin NMA are presented in Table 34. Note that these data are the same as those presented in Table 31 and Table 32 but are repeated here to present evidence for FDC separately from the evidence for bempedoic acid single-agent tablet.

FDC has not been investigated in statin-intolerant patients or patients receiving no/VLD statin; supporting evidence for FDC in this population is provided based on trials investigating bempedoic acid+ezetimibe.

Table 33. NMA results for FDC in statin-intolerant studies

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value
Bempedoic acid+ezetimibe[a]	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]
EvoMab+ezetimibe[b]	[redacted]	[redacted]	[redacted]
Alirocumab (75 mg)	[redacted]	[redacted]	[redacted]
Alirocumab (150 mg)	[redacted]	[redacted]	[redacted]

CrI = credible interval; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

[a] These data are used in the economic model to represent the efficacy of FDC in statin-intolerant patients. Pharmacokinetic studies have shown the two presentations to be equivalent (see Appendix M).

[b] Evolocumab+ezetimibe estimates are based on data for 30 patients in GAUSS (Sullivan et al., 2012).

Note: other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe. No trial data were identified for alirocumab+ezetimibe.

Table 34. NMA results for FDC+statin in maximally tolerated statin studies

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value
FDC+ statin	[redacted]	[redacted]	[redacted]
EvoMab+statin	[redacted]	[redacted]	[redacted]
AliMab (75 mg)+statin	[redacted]	[redacted]	[redacted]
AliMab (150 mg)+statin	[redacted]	[redacted]	[redacted]
AliMab (75 mg)+statin+ezetimibe	[redacted]	[redacted]	[redacted]
AliMab (150 mg)+statin+ezetimibe	[redacted]	[redacted]	[redacted]

AliMab = Alirocumab; CrI = credible interval; EvoMab = evolocumab; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

Note: Other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe.

B.2.9.3 Uncertainties in the indirect and mixed-treatment comparisons

Results from the Bayesian random-effects models for both the statin-intolerant and maximally tolerated network had a high degree of heterogeneity; this was not resolved through the addition of baseline LDL-C as a covariate. The level of heterogeneity observed is not in line with the assumptions underlying NMA, hence caution should be taken when interpreting the results and credible intervals. For some

treatment comparisons, a difference was observed between the direct and indirect evidence. It may be possible that an explanatory variable which has not been included in the analysis may account for some of the underlying heterogeneity, such as the level of background statin or ezetimibe use. However, the extent of heterogeneity/inconsistency was considerable in both networks and we believe it is unlikely that there is a simple explanation for the degree of heterogeneity/inconsistency that was observed. Therefore, the variability estimated for relative comparisons may be underestimated. It was assumed that evolocumab 140 mg and evolocumab 420 mg have comparable efficacy and these treatments were pooled within the analysis. Estimates for evolocumab+ezetimibe were based on data for the 420 mg dose investigated in only 30 statin-intolerant patients (GAUSS) (Sullivan et al., 2012) and therefore should be treated with particular caution. An assumption was also made that the relative difference in percentage change at 24 weeks for alirocumab 75 mg uptitrated to alirocumab 150 mg and 12-week alirocumab 150 mg were equivalent. In the maximally tolerated statin network, it has been assumed that the relative efficacy of ezetimibe, evolocumab, and alirocumab are not impacted by differing background statin, or randomised statins when administered in both the comparator and reference arm within the trial.

Table 35 compares the NMA results with those from a published NMA of evolocumab, alirocumab, and ezetimibe trials in patients requiring further LDL-C reduction while on maximally tolerated medium- or high-intensity statin (Toth et al., 2017b). Toth et al. (2017a) also observed high statistical heterogeneity for some comparisons; the authors reported that sensitivity analyses investigating heterogeneity did not substantially change the results.

Table 35. Comparison of the NMA results in maximally tolerated statin studies with those reported by Toth et al. (2017a)

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe			
	Submission NMA		Toth et al. (2017a)	
	Mean	95% CrIs	Mean	95% CrIs
EvoMab+statin	[redacted]	[redacted]	−45.3[a]	−50.9, −39.8
AliMab (75 mg)+statin	[redacted]	[redacted]	−26.1	−31.2, −20.8
AliMab (150 mg)+statin	[redacted]	[redacted]	−32.5	−40.8, −23.9
AliMab (75 mg)+statin+ezetimibe	[redacted]	[redacted]	NR	NR
AliMab (150 mg)+statin+ezetimibe	[redacted]	[redacted]	NR	NR

AliMab = Alirocumab; CrI = credible interval; EvoMab = evolocumab; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; NR = not reported.

[a] Post-hoc analysis combining evolocumab 140 mg and evolocumab 420 mg. The estimate for evolocumab 140 mg was −46.1% (−53.3% to −39.1%).

B.2.10 Adverse reactions

- More than 3,600 patients have received bempedoic acid, with approximately 2,400 patients receiving doses of 180 mg daily in phase 3 studies (the majority for 52 weeks duration)
- Most adverse events have been mild to moderate in severity and generally balanced in occurrence with adverse events in patients receiving placebo
- The combination of bempedoic acid with ezetimibe was considered to be well tolerated
- Myopathy with concomitant use of simvastatin doses ≥ 40 mg is an important identified risk of bempedoic acid. As the risk of myopathy with simvastatin monotherapy is dose related, with specific risks noted for the 80 mg dose, the bempedoic acid product information will limit simvastatin dosage to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and high risk for CV complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks)
- Increases in serum uric acid were observed in clinical trials, and gout is considered a potential risk of treatment with bempedoic acid, but his could be reversed.
- Among the pooled phase 3 studies with treatment duration of 52 weeks, an assessment of adjudicated major adverse cardiovascular event (MACE) composite endpoints usually showed hazard ratios < 1.0 (ranging from 0.80 for 3-component MACE in the high-risk/long-term pool to 0.95 for 4-component MACE in the overall phase 3 pool), though there were too few events to make a definitive assessment.

B.2.10.1 Adverse reactions for bempedoic acid

An integrated overview analysis of safety was performed. Studies were pooled to include all relevant data from controlled trials that were similar in design and target population. The High-Risk/Long-Term pool included CLEAR Harmony and CLEAR Wisdom and the No- or Low-Dose Statin pool included CLEAR Serenity and CLEAR Tranquility. The overall phase 3 pool included all four of these studies, and the overall phase 2 pool included all 10 phase 2 studies (Esperion Therapeutics data on file, 2019b).

It should be noted that the overall phase 3 pool did not include Study 1002FDC-053, and safety results for this study are reported separately in Section B.2.10.2.

The safety endpoints for the integrated analyses were treatment-emergent adverse event incidences (including adverse events of special interest), positively adjudicated clinical endpoints, clinical laboratory test abnormalities and changes, vital signs and changes, and concomitant medication use. The safety population included all randomised patients who received at least one dose of study drug and patients were summarised according to the treatment that they actually received, regardless of their randomised treatment (Esperion Therapeutics data on file, 2019b).

More than 3,600 patients received bempedoic acid, with approximately 2,400 patients receiving doses of 180 mg daily in phase 3 studies (most for 52 weeks' duration). The total extent of clinical exposure from the phase 3 randomised controlled trial safety database is presented in Table 36 (Esperion Therapeutics data on file, 2019b).

Table 36. Number of patients exposed to bempedoic acid at time of marketing application submission

Duration	Estimated number of patients exposed to bempedoic acid from double-blinded phase 3 studies
≥ 12 weeks (80 days)	2,158
≥ 24 weeks (165 days)	1,811
≥ 36 weeks (265 days)	1,608
≥ 48 weeks (336 days)	1,558

Source: Esperion Therapeutics data on file (2019b).

B.2.10.1.1 Exposure

The safety population in the high-risk/long-term pool consisted of [redacted] patients who received bempedoic acid and [redacted] patients who received placebo in 52-week studies. All patients in the FAS (except 1 patient who did not receive bempedoic acid) were included in the safety population. The median number of days of investigational medicinal product (IMP) exposure was the same for both placebo and bempedoic acid groups [redacted].

In the no- or low-dose statin pool, the safety population comprised [redacted] patients who received bempedoic acid and [redacted] patients who received placebo. All patients in the FAS (except 1 patient who did not receive placebo) were included in the safety population. The median number of days of IMP exposure was lower for the bempedoic acid group [redacted] compared with the placebo group [redacted]. Most patients in the no- or low-dose statin pool received IMP for [redacted] bempedoic acid, [redacted] placebo) (Esperion Therapeutics data on file, 2019b).

The safety population in the overall phase 3 pool consisted of [redacted] patients who received bempedoic acid and [redacted] patients who received placebo. The median number of days of IMP exposure was similar for both bempedoic acid and placebo groups [redacted] for bempedoic acid, [redacted] for placebo). The safety population in ongoing extension CLEAR-OLE included [redacted] patients. Mean exposure to IMP during the open-label study was [redacted] days based on last patient visit of [redacted]. Most patients [redacted] had received IMP for [redacted] as of the cutoff date. Additionally, in phase 2 studies [redacted] patients received bempedoic acid, [redacted] patients received placebo, and [redacted] patients received ezetimibe alone. These trials ranged in duration from [redacted] In phase 1 studies, [redacted] patients received bempedoic acid (Esperion Therapeutics data on file, 2019b).

B.2.10.1.2 Overall adverse events

Bempedoic acid was well tolerated in clinical studies; adverse event rates and types of adverse events reported in patients treated with bempedoic acid were generally similar to those treated with placebo. Overall in phase 3 studies, the adverse events reported most frequently in patients who received bempedoic acid were generally reported at similar rates in patients who received placebo. Frequent adverse events that were reported at slightly higher [redacted] rates with bempedoic acid than

with placebo in one or more data pools were [redacted]

(Esperion Therapeutics data on file, 2019b).

Small changes in laboratory parameters (creatinine increases, uric acid increases, haemoglobin decreases, and liver function test elevations) were observed, and some of the preferred terms that occurred more frequently with bempedoic acid were driven by adverse events associated with laboratory results. These laboratory changes are well characterised.

Increased creatinine, hepatic enzyme elevations, decreased haemoglobin, and anaemia are considered to represent adverse reactions; however, as these changes did not appear to put patients at risk, they are not considered important potential or identified risks. The incidence of elevated liver transaminases was low and within the range reported for statins and ezetimibe. There were no elevations of total bilirubin > 2 × the upper limit of normal (ULN) in patients who received bempedoic acid and there were no cases of Hy's law. [redacted]

Uric acid increased is also considered to represent an adverse reaction. Because the overall incidence of gout was [redacted] in the bempedoic acid group versus [redacted] in the placebo group, [redacted] (Esperion Therapeutics data on file, 2019b).

B.2.10.1.3 Common adverse events

In all three phase 3 pools (the High-Risk/Long-Term pool, the No- or Low-Dose Statin pool, and the overall phase 3 pool), the adverse event preferred terms reported most frequently in bempedoic acid - treated patients occurred at similar rates in patients receiving placebo. No preferred term was reported at an incidence > 2% higher in the bempedoic acid group compared with the placebo group in the High-Risk/Long-Term pool or overall phase 3 pool. Blood uric acid increased was the only preferred term with an incidence in the bempedoic acid group > 2% higher than in placebo group in the No- or Low-Dose Statin pool. In the overall phase 2 pool, no adverse event had an incidence in bempedoic acid group > 2% higher than that in overall control. Common adverse events are presented in Table 37.

Table 37. Adverse reactions occurring in greater than or equal to 2.0% of patients receiving bempedoic acid and more frequently than with placebo

Adverse reaction	**Bempedoic acid [redacted] %**	**Placebo [redacted] %**
Upper respiratory tract infection	[redacted]	[redacted]
Hyperuricemia [a]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Back pain	[redacted]	[redacted]

Pain in extremity	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]

[a]Hyperuricemia includes hyperuricemia [redacted] and blood uric acid increased [redacted]

Source: Esperion Therapeutics data on file (2019b).

B.2.10.1.4 Serious adverse events

Similar percentages of patients in the bempedoic acid group and placebo group had a serious adverse event in the high-risk/long-term [redacted] low- or no-dose statin pool [redacted] and overall phase 3 pool [redacted] In general, the type and frequency of serious adverse events by system organ class (SOC) were similar between groups in all pools [redacted] (Esperion Therapeutics data on file, 2019b):

[redacted] Infections and infestations [redacted] and vascular disorders [redacted] in the high-risk/long-term pool and cardiac disorders [redacted]

[redacted] Injury, poisoning, and procedural complications [redacted]

The most common serious adverse event in all three pools was unstable angina (High-Risk/Long-Term pool [redacted] bempedoic acid, [redacted] placebo; No- or Low-Dose Statin pool [redacted] bempedoic acid, [redacted] placebo; overall phase 3 pool [redacted] bempedoic acid, [redacted] placebo). Serious adverse events were considered related to IMP in [redacted] in bempedoic acid treatment group [redacted] patients in the placebo treatment group [redacted] in the overall phase 3 pool; no preferred term was reported in more than 1 patient.

In the overall phase 2 pool, serious adverse events occurred in [redacted] in the bempedoic acid group and [redacted] in the overall control group. No notable differences in SOC were observed between treatment groups (Esperion Therapeutics data on file, 2019b).

B.2.10.1.5 Cardiovascular events

The phase 3 studies were not powered to detect treatment differences between groups in terms of CV events. Potential CV events and all fatal events were adjudicated in all phase 3 studies by a blinded independent clinical endpoints committee that reviewed all studies as an overall examination of CV safety. Events adjudicated included MACE events such as CV death, non-fatal MI, non-fatal stroke, HUA, and coronary revascularisation and non-MACE events such as non-CV death, non-coronary arterial revascularisation, and hospitalisation for heart failure. This analysis was descriptive only.

Analyses of these events did not indicate any trend towards CV harm. Most CV events occurred in the large 52-week studies. In both the individual long-term studies and the overall phase 3 pool and Long-Term/High-Risk pool, there were trends to lower rates of MACE in the bempedoic acid group (Table 38).

MACE component analysis was neutral when heart failure events were included (Table 39) (Esperion Therapeutics data on file, 2019b).

Table 38. Adjudicated MACE and non-MACE events by event type in the overall phase 3 pool (safety analysis set)

	High-risk/long-term pool (pool 1)		Overall phase 3 pool (pool 3)		CLEAR-OLE
	Bempedoic acid [redacted]	PBO [redacted]	Bempedoic acid [redacted]	PBO [redacted]	Bempedoic acid [redacted]
Any positively adjudicated event (MACE or non-MACE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated MACE					
CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for unstable angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary revascularisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other adjudicated non-MACE events					
Non-CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-coronary arterial Revascularisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CV = cardiovascular; MACE = major adverse cardiovascular event; PBO = placebo.

Source: Esperion Therapeutics data on file (2019b).

Table 39. MACE composite with hazard ratio for cox-regression model for time-to-first adjudicated MACE composite (safety analysis set)

	High-risk/long-term pool (pool 1)			Overall phase 3 pool (pool 3)		
	Bempedoic acid [redacted]	PBO [redacted]	Hazard ratio (95% CI)	Bempedoic acid [redacted]	PBO [redacted]	Hazard ratio (95% CI)
5-component MACE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-component MACE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-component MACE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-component MACE + hospitalisation for heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-component MACE + hospitalisation for heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-component MACE + hospitalisation for heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LDL = low-density lipoprotein; MACE = major adverse cardiac event; PBO = placebo.

Notes:

3-component MACE is defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

4 component MACE is defined as 3-component MACE events plus coronary revascularisation.

5-component MACE is defined as 4-component MACE events plus hospitalisation for unstable angina.

Percentages are based on N, number of patients treated within each treatment group in the pooled safety population.

Patients that experienced more than one of an individual MACE (for example, two non-fatal MI) are counted once for that individual MACE, regardless of how many times they experienced the event.

Cox-regression model includes treatment group and baseline LDL as covariates.

Source Esperion Therapeutics data on file (2019b).

A significant difference in MACE would not be expected to be observed without a greater number of accumulated events, as in a cardiovascular outcomes trial. Additionally, the shorter follow-up time can diminish the ability to detect significant positive effect on MACE as well. The hazard ratio for a 1 mmol/L reduction in LDL-C was [redacted] of therapy in the pooled statin cardiovascular outcomes trials and [redacted] overall in statin MACE trials where the mean length of follow-up if 5 years (Cholesterol Treatment Trialists et al., 2010; Ference et al., 2018) as cited in (Esperion Therapeutics data on file,

2019b) The effects of bempedoic acid on cardiovascular outcomes will be formally evaluated further in the ongoing phase 3 cardiovascular outcomes trial (Esperion Therapeutics data on file, 2019b).

B.2.10.1.6 Adverse events leading to discontinuation of IMP

Adverse events that led to discontinuation of IMP occurred in [redacted] of patients in the bempedoic acid group and [redacted] patients in the placebo group in the High-Risk/Long-Term pool, in [redacted] of patients in the bempedoic acid group and [redacted] of patients in the placebo group in the Low- or No-Dose Statin pool, and in [redacted] of patients in the bempedoic acid group and [redacted] of patients in the placebo group in the Overall Phase 3 pool.

A difference in the incidence of adverse events leading to discontinuations of IMP was driven by slightly increased rates of discontinuation owing to preferred terms in the investigations, Gastrointestinal, and Musculoskeletal Disorders SOCs. In the overall phase 3 pool, the most frequent preferred terms that led to discontinuation of IMP more often in the bempedoic acid treatment groups were [redacted] none of which differed by [redacted] between treatment groups (Esperion Therapeutics data on file, 2019b).

B.2.10.1.7 Adverse events of special interest

As the adverse events of special interest categories in the phase 2 studies were not identical to the categories evaluated in the phase 3 studies, the discussion in this section focuses on the adverse events of special interest from the phase 3 programme. In studies of bempedoic acid in combination with maximally tolerated statin or a PCSK9 inhibitor or as part of triplet therapy with ezetimibe and atorvastatin, safety results were consistent with the safety profile observed in the phase 3 studies.

Table 40. Summary of adverse events of special interest (overall phase 3 pool)

Adverse reaction	**Bempedoic acid** [redacted]	**Placebo** [redacted]
Hypoglycaemia	[redacted]	[redacted]
Metabolic acidosis	[redacted]	[redacted]
New onset diabetes/hyperglycaemia	[redacted]	[redacted]
Hepatic enzyme elevation		
ALT and/or AST elevation > 3 x ULN	[redacted]	[redacted]
ALT and/or AST elevation > 5 x ULN	[redacted]	[redacted]
Muscular disorders	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Neurocognitive disorders	[redacted]	[redacted]
Renal disorders	[redacted]	[redacted]
Increased uric acid/gout	[redacted]	[redacted]

Adverse reaction	Bempedoic acid [redacted]	Placebo [redacted]
Decreased haemoglobin $	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LLN = lower limit of normal; ULN = upper limit of normal.

$ decrease in haemoglobin from baseline of ≥ 2 g/dL and less than the LLN.

Source: Esperion Therapeutics data on file (2019b).

Results showed that there was [redacted] with bempedoic acid. There was no trend for a greater difference between the bempedoic acid and placebo groups in rates of [redacted], but as they do not appear to be a risk to patients, elevated hepatic enzymes are not considered an important potential or important identified risk for bempedoic acid.

There was no increased risk of neurocognitive adverse events with bempedoic acid. [redacted] was identified as an adverse reaction, but the changes were not considered clinically meaningful. No renal-related change is considered to represent an adverse reaction to bempedoic acid. Uric acid increased is considered an adverse reaction of bempedoic acid; however, it is unclear whether the increased uric acid puts patients at increased risk for gout; thus, gout is considered a potential risk. While decreased haemoglobin and anaemia are considered adverse reactions potentially associated with bempedoic acid, [redacted].

[redacted], such as myalgia and muscle weakness. The incidence of muscle spasms was [redacted] and pain in extremity was [redacted] with bempedoic acid and placebo, respectively; other muscle-related events are reported at similar rates between treatment groups. [redacted] (Esperion Therapeutics data on file, 2019b). In CLEAR Tranquility, treatment-emergent adverse events (TEAEs) were reported by 127 (47.0%) patients overall, slightly more frequently in the bempedoic acid+ezetimibe group than in the ezetimibe+placebo group (48.6% vs. 44.8%) (Ballantyne et al., 2018).

Table 41. Overview of TEAEs and AEs with a ≥ 1% difference between treatment groups

	CLEAR Harmony (1002-040)		CLEAR Wisdom (1002-047)		CLEAR Serenity (1002-046)		CLEAR Tranquility (1002-048)	
	Placebo (N = 742) n (%)	Bempedoic acid (N = 1,487) n (%)	Placebo (N = 257) n (%)	Bempedoic acid (N = 522) n (%)	Placebo (N = 111) n (%)	Bempedoic acid (N = 234) n (%)	Placebo+ ezetimibe (N = 87) n (%)	Bempedoic acid+ ezetimibe N = 181) n (%)
Patients with ≥ 1 TEAE	[redacted]	[redacted]	182 (70.8)	366 (70.1)	63 (56.8)	150 (64.1)	39 (44.8)	88 (48.6)
Patients with ≥ 1 serious TEAE	[redacted]	[redacted]	48 (18.7)	106 (20.3)	4 (3.6)	14 (6.0)	3 (3.4)	5 (2.8)
Patients with ≥ 1 TEAE with a fatal outcome	[redacted]	[redacted]	2 (0.8)	6 (1.1)	0	0	[redacted]	[redacted]
Patients with ≥ 1 TEAE leading to discontinuation of IMP	[redacted]	[redacted]	22 (8.6)	57 (10.9)	13 (11.7)	43 (18.4)	5 (5.7)	11 (6.1)
Patients with any positively adjudicated CV or fatal clinical event	42 (5.7)	68 (4.6)	26 (10.1)	43 (8.2)	0	3.8 (9)	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	13 (5.1)	27 (5.2)	[redacted]	[redacted]	1 (1.1)	4 (2.2)
Urinary tract infection	[redacted]	[redacted]	5 (1.9)	26 (5.0)	9 (8.1)	8 (3.4)	5 (5.7)	5 (2.8)
Arthralgia	[redacted]	[redacted]	8 (3.1)	18 (3.4)	5 (4.5)	14 (6.0)		
Muscle spasms	[redacted]	[redacted]	3 (1.2)	11 (2.1)	5 (4.5)	10 (4.3)	3 (3.4)	6 (3.3)
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	6 (5.4)	6 (2.6)		
Pain in extremity	[redacted]	[redacted]	1 (0.4)	11 (2.1)	4 (3.6)	13 (5.6)	0	1 (0.6)
Angina pectoris	[redacted]	[redacted]	5 (1.9)	16 (3.1)	[redacted]	[redacted]		

	CLEAR Harmony (1002-040)		CLEAR Wisdom (1002-047)		CLEAR Serenity (1002-046)		CLEAR Tranquility (1002-048)	
	Placebo (N = 742) n (%)	**Bempedoic acid (N = 1,487) n (%)**	**Placebo (N = 257) n (%)**	**Bempedoic acid (N = 522) n (%)**	**Placebo (N = 111) n (%)**	**Bempedoic acid (N = 234) n (%)**	**Placebo+ ezetimibe (N = 87) n (%)**	**Bempedoic acid+ ezetimibe N = 181) n (%)**
Osteoarthritis	[redacted]	[redacted]	5 (1.9)	16 (3.1)	[redacted]	[redacted]		
AAT increased	1 (0.1)	7 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAT = Aspartate aminotransferase; AE = adverse event; CV = cardiovascular; FDC = bempedoic acid and ezetimibe fixed-dose combination; IMP = investigational medical product; NR = not reported; TEAE = treatment-emergent adverse event.

Note that study 2001FDC-053 also investigated FDC; the results for this arm are presented in Table 42.

Sources: Ballantyne et al. (2019a); Esperion Therapeutics data on file (2017b); Esperion Therapeutics data on file (2018c); Esperion Therapeutics data on file (2019c); Esperion Therapeutics data on file (2019d); Laufs et al. (2019); Ray et al. (2019b).

B.2.10.2 Adverse reactions for FDC

Adverse event information for bempedoic acid in combination with ezetimibe is taken from study 1002FDC-053 (Ballantyne et al., 2018; Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2018d; Esperion Therapeutics data on file, 2019d).

It should be noted that information from the FDC Study 1002FDC-053 was not included in the overall summary of safety, and information on the frequency of adverse events from Study 1002FDC-053 is presented in Table 41 and Table 42.

In Study 1002FDC-053 TEAEs were reported by 176 (58.7%) patients overall and were slightly more frequent in the FDC and bempedoic acid groups than in the ezetimibe or placebo groups (62.4% vs. 54.7% vs. 43.9%) (Ballantyne et al., 2019a). Bempedoic acid in combination with ezetimibe was well tolerated; most TEAEs were mild or moderate in intensity and were judged to be not related or not likely to be related to the investigational study drug (Ballantyne et al., 2018; Ballantyne et al., 2019a). Moreover, rates of discontinuation because of an adverse event were similar across treatment arms and no TEAEs or fatal adverse events occurred during either study. This study considered that bempedoic acid in combination with ezetimibe has a favourable safety profile (Ballantyne et al., 2018; Ballantyne et al., 2019a).

Table 42. Overview of TEAEs and AEs with a ≥ 1% difference between treatment groups (safety population)

	1002FDC-053			
	Placebo (N = 41) n (%)	**Ezetimibe (N = 86) n (%)**	**Bempedoic acid (N = 88) n (%)**	**FDC (N = 85) n (%)**
Patients with ≥ 1 TEAE	18 (43.9)	47 (54.7)	58 (65.9)	53 (62.4)
Patients with ≥ 1 serious TEAE	1 (2.4)	9 (10.5)	7 (8.0)	8 (9.4)
Patients with ≥ 1 TEAE with a fatal outcome	0	0	0	0
Patients with ≥ 1 TEAE leading to discontinuation of IMP	2 (4.9)	10 (11.6)	9 (10.2)	7 (8.2)
Patients with any positively adjudicated CV or fatal clinical event	Not performed	Not performed	Not performed	Not performed
Nasopharyngitis	0	4 (4.7)	6 (6.8)	4 (4.7)
Urinary tract infection	1 (2.4)	2 (2.3)	3 (3.4)	5 (5.9)
Arthralgia	1 (2.4)	3 (3.5)	4 (4.5)	1 (1.2)
Muscle spasms	0	4 (4.7)	1 (1.1)	2 (2.4)
Back pain	2 (4.9)	2 (2.3)	3 (3.4)	3 (3.5)
Bronchitis	0	3 (3.5)	0	3 (3.5)
Pain in extremity	1 (2.4)	1 (1.2)	2 (2.3)	2 (2.4)
Angina pectoris	NR	NR	NR	NR
Osteoarthritis	NR	NR	NR	NR
AAT increased	0	0	0	1 (1.2)

AAT = aspartate aminotransferase; CV = cardiovascular; FDC = bempedoic acid and ezetimibe fixed-dose combination; IMP = investigational medical product; NR = not reported; TEAE = treatment-emergent adverse event.

Note that study 1002FDC-053 also investigated bempedoic acid; results for this arm are presented in Table 41.

Sources: Ballantyne et al. (2018); (Ballantyne et al., 2019a); Esperion Therapeutics data on file (2018d); Esperion Therapeutics data on file (2019d).

B.2.11 Deaths

In the bempedoic acid placebo-controlled phase 3 studies, there were [redacted] fatal adverse events among the [redacted] total high-risk patients with CVD; fatal events occurred in [redacted] of patients treated with bempedoic acid and [redacted] of patients treated with placebo. [redacted] fatal adverse events in placebo-controlled phase 3 studies were determined [redacted] by the investigator or the Sponsor Medical Monitor. Individual cases of adverse events with a fatal outcome were medically reviewed to determine whether any pattern across cases could be identified relating to bempedoic acid use.

In the high-risk/long-term pool, TEAEs with a fatal outcome were reported for [redacted] patients in the bempedoic acid group an[redacted] patients in the placebo group. No patient had a fatal adverse event in the no- or low-dose statin pool. In the long-term safety data set of patients who were at a very high risk for CVD and on a background of maximally tolerated statins (high-risk/long-term pool), TEAEs with a fatal outcome were reported for [redacted] patients in the bempedoic acid group and [redacted] patients in the placebo group. In CLEAR Harmony, the incidence of fatal adverse events was [redacted] patients) in the bempedoic acid group and [redacted] patients) in the placebo group. In CLEAR Wisdom, the incidence of adverse events with a fatal outcome was [redacted] patients) in the bempedoic acid group an[redacted] patients) in the placebo group (Esperion Therapeutics data on file, 2019b).

The [redacted] difference in frequency between the treatment groups in the largest and longest study, CLEAR Harmony, was driven primarily by an increased frequency of events in the cardiac disorders [redacted] and neoplasms benign, malignant and unspecified (including cysts and polyps) [redacted] SOCs. By comparison, in the other 52-week study, CLEAR Wisdom, the rate of fatal events in the cardiac disorders SOC was [redacted] Additionally, there were no fatal neoplasms in CLEAR Wisdom. Other fatal events in CLEAR Wisdom in the bempedoic acid group fell in the general disorders and administration site conditions [redacted] infections and infestations [redacted] and injury, poisoning and procedural complications [redacted] SOCs (Esperion Therapeutics data on file, 2019b).

B.2.11.1.1 Fatal cardiovascular events

The frequency of deaths due to cardiac disorders in the bempedoic acid group of the high-risk/long-term pool was [redacted] compared with [redacted] Consistent with the study entry criteria and the overall population, these patients had an extensive prior history of CVD and significant medical histories of CV events and other risk factors and comorbidities, such as smoking, obesity, hypertension, and/or diabetes that likely contributed to the fatalities.

While there was a numerically higher frequency of deaths in the high-risk/long-term pool because of CV disorders with bempedoic acid compared with placebo [redacted] bempedoic acid [redacted] placebo), the frequency of serious adverse events in the cardiac disorders SOC [redacted] respectively) and events that led to discontinuation of IMP in the cardiac disorders SOC [redacted] respectively), were comparable between treatment groups. All suspected CV events and all fatal events were adjudicated by an independent and blinded clinical endpoints committee. In the high-risk/long-term pool, a total of [redacted] had a positively adjudicated clinical event, the patient incidence of any positively adjudicated CV clinical endpoint was lower in the bempedoic acid group [redacted] compared with the placebo group [redacted] Notably, the incidences of 5-component, 4-component, and 3-component MACE did not indicate any trend towards cardiovascular harm and the hazard ratios for these composite endpoints were all [redacted] A large cardiovascular outcome trial is currently ongoing to assess the CV risk reduction potential of bempedoic acid in [redacted] who need additional LDL-C lowering. This ongoing study is monitored by a data-monitoring committee in an ongoing and unblinded fashion. No safety signals of concern have

been raised by the data-monitoring committee (Esperion Therapeutics data on file, 2019b).

B.2.11.1.2 Fatal neoplasms

The rate of fatal events in the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC in the high-risk/long-term pool was [redacted] in the bempedoic acid arm and [redacted] in the placebo arm. All fatal neoplasm cases occurred in CLEAR Harmony, and there were no fatal neoplasms in CLEAR Wisdom. For the [redacted] in the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC, [redacted] fatal neoplasm events were associated with lung cancers. All patients had baseline characteristics and medical history that put them at elevated risk for cancer: all were current or former tobacco users, 2 had chronic obstructive pulmonary disease, 1 had prior pleural effusion, 1 had prior mass, and 1 had prior cancer (hepatic metastases). [redacted] the onset of the fatal adverse event was within [redacted] of the first dose of bempedoic acid. The overall rate of serious adverse events in the high-risk/long-term pool for the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC was [redacted] for bempedoic acid and [redacted] for placebo, and the overall incidence of TEAEs in this SOC was [redacted] for bempedoic acid and [redacted] for placebo. Similarly, treatment-emergent non-fatal neoplasm adverse events in CLEAR Harmony occurred in [redacted] receiving bempedoic acid and [redacted] receiving placebo. There were two preferred terms with a numerical difference greater than [redacted] between treatment groups (seborrheic keratosis, bempedoic acid [redacted] placebo [redacted] and melanocytic naevus, bempedoic acid [redacted] placebo [redacted]

There was no relationship between the tumours observed in the clinical study and the nonclinical findings. The Sponsor has completed the evaluation of bempedoic acid in a series of studies to assess genotoxic potential. The results of these studies indicate that bempedoic acid is not genotoxic. Nonclinical studies confirm that bempedoic acid is not genotoxic (Esperion Therapeutics data on file, 2019b).

B.2.11.1.3 Other fatal events

[redacted] deaths were due to sepsis [redacted] bempedoic acid group), or septic shock [redacted] bempedoic acid group [redacted] placebo group). All [redacted] were attributed to complications from abdominal surgeries. Other fatal adverse events that occurred within the high-risk/long-term pool included pancreatic pseudocyst and gas poisoning (Esperion Therapeutics data on file, 2019b).

B.2.12 Ongoing studies

There are two ongoing studies: CLEAR Harmony open-label extension [OLE] and CLEAR Outcomes. CLEAR Harmony-OLE is expected to report in December 2019, and the CLEAR Outcomes study is expected to report in [redacted].

CLEAR Harmony-OLE (ClinicalTrials.gov Identifier: NCT03067441) is aimed at assessing the long-term safety of bempedoic acid in patients with high CV risk and elevated LDL-C that is not adequately controlled by their current therapy. A total of 1,452 patients have been enrolled in the study. The primary

endpoint is incidence of adverse events.

CLEAR Outcomes (ClinicalTrials.gov Identifier: NCT02993406) is an event-driven CV outcomes trial to assess the effects of bempedoic acid on the occurrence of major CV events in patients with, or at high risk for, CVD who are statin intolerant.

CLEAR Outcomes is a global, randomised, double-blind, placebo-controlled study expected to enrol approximately 12,600 patients with hypercholesterolaemia and high CVD risk at more than 600 sites in approximately 30 countries. The expected average treatment duration will be 3.5 years with a minimum treatment duration of approximately 2.25 years. Patients enrolling in the study will be required to have a history of, or be at high-risk for, CVD with LDL-C levels between 100 mg/dL and 190 mg/dL despite background lipid-lowering therapy, resulting in an expected average baseline LDL-C level in all patients of approximately 135 mg/dL.

The primary efficacy endpoint of the study is the effect of bempedoic acid versus placebo on the risk of major adverse CV events (CV death, non-fatal MI, non-fatal stroke, HUA, or coronary revascularisation; also referred to as "5-component MACE"). Similar to other CV outcome studies, CLEAR Outcomes is designed to provide greater than 85% power to detect an approximately 14% relative risk reduction in the primary endpoint in the bempedoic acid treatment group compared with the placebo group, and is expected to complete with a minimum of 1,437 patients experiencing the primary endpoint (Esperion Therapeutics, 2017).

Table 43 presents an overview of the ongoing bempedoic acid studies.

Table 43. Ongoing bempedoic acid studies: CLEAR Harmony-OLE and CLEAR Outcomes

	CLEAR Harmony-OLE	**CLEAR Outcomes study**
ClinicalTrials.gov identifier	**NCT03067441**	**NCT02993406**
Study title	A multicentre, open-label extension study to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg	A randomised, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant
Study design	Open-label, single-arm study	Randomised, double-blind, parallel-group, placebo-controlled phase 3 study
Intervention	Bempedoic acid 180 mg	Bempedoic acid 180 mg
Comparator	None (single-arm study)	Matching placebo
Enrolment	Actual enrolment: 1,452	Estimated enrolment: 12,600 patients

	CLEAR Harmony-OLE	CLEAR Outcomes study
Population	Successfully completed CLEAR Harmony (1002-040) parent study	Patients aged 18-85 years History of, or at high risk for, CVD including coronary artery disease, symptomatic peripheral arterial disease, cerebrovascular atherosclerotic disease, or at high risk for a CV event Patient-reported history of statin intolerance Fasting blood LDL-C ≥ 100 (2.6 mmol/L) at screening
Expected completion	December 2019	[redacted]

CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Source: ClinicalTrials.gov (NCT02993406).

B.2.13 Innovation

Bempedoic acid is a non-statin, first-in-class, adenosine triphosphate citrate lyase (ACL) inhibitor with a targeted mechanism of action. It is a small-molecule pro-drug with bioavailability when taken orally. Upon activation in the liver, bempedoic acid acts in the same cholesterol biosynthesis pathway as statins and upregulates LDL receptors by suppression of cholesterol synthesis (Pinkosky et al., 2016). Bempedoic acid increases LDL receptor-mediated clearance of LDL-C by inhibition of an enzyme distinct from, but also complimentary to, those targeted by existing lipid-modifying therapies. Unlike statins, bempedoic acid does not inhibit cholesterol synthesis in skeletal muscle cells because the enzyme needed for its activation is not present in skeletal muscle cells (Pinkosky et al., 2016; Saeed and Ballantyne, 2018). In phase 3 clinical trials, the incidence of muscle-related side effects is similar between bempedoic acid and placebo. The target of bempedoic acid, ACL, is a different enzyme on the cholesterol biosynthesis pathway than the primary target of statins, HMG-CoA reductase; the activity of these two enzymes occurs at different steps on the pathway, and they are independently regulated.

Once absorbed and transported to the liver, bempedoic acid is rapidly converted to its active metabolite, a bempedoic acid–coenzyme A thioester (Bilen and Ballantyne, 2016; Pinkosky et al., 2013; Saeed and Ballantyne, 2018). Bempedoic acid is absorbed through the small intestine and transported to the liver by a mechanism distinct from statins (Bilen and Ballantyne, 2016; Saeed and Ballantyne, 2018). Bempedoic acid may also provide additional benefits by reducing cardiovascular inflammation markers, as evidenced by consistent reductions in the inflammatory biomarker hsCRP (Bilen and Ballantyne, 2016; Ford et al., 2016; Gutierrez et al., 2014).

B.2.14 Interpretation of clinical effectiveness and safety evidence

B.2.14.1 Clinical efficacy and safety of bempedoic acid

B.2.14.1.1 Efficacy

The lowering of LDL-C is associated with a reduction in the incidence of major coronary events, ischaemic strokes, and revascularisations (Baigent et al., 2011). The overall goal of the clinical development programme for bempedoic acid was to evaluate the efficacy of bempedoic acid in reducing LDL-C as an add-on therapy to other LMTs, including maximally tolerated statins (which may also mean no statin at all) or ezetimibe, for the treatment of adults with primary hyperlipidaemia who require additional lowering of LDL-C. The results from the bempedoic acid trials consistently demonstrated the efficacy of bempedoic acid for the treatment of hypercholesterolaemia. Across the four CLEAR phase 3 trials (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, and CLEAR Tranquility) conducted in over 3,000 patients, bempedoic acid demonstrated substantial and statistically significant reductions in LDL-C in the target patient populations compared with placebo. Similar reductions in LDL-C were also observed in the two phase 2 trials (Study 1002-008 and 1002-009) While bempedoic acid produced clinically meaningful reductions in LDL-C on the background of a statin, LDL-C lowering was slightly greater in the absence of background statin therapy than in the presence of background statin therapy. A rapid onset of efficacy and persistence of treatment effect was observed from week 4 through to week 52.

In the phase 3 trials, LS mean difference from placebo in percentage change from baseline to week 12 in LDL-C ranged from −15.7% to −38.0% ($P < 0.001$) (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019c; Laufs et al., 2019; Ray et al., 2019b). In patients receiving maximally tolerated statin therapy as part of their LMT, LS mean reduction from baseline in LDL-C for bempedoic acid compared with placebo was −15.1% versus 2.4%, respectively, in CLEAR Wisdom (Study 1002-047); −16.5% versus −1.6%, respectively, in CLEAR Harmony (Study 1002-040); and −17.2% versus +1.8%, respectively, in Study 1002FDC-053(Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019c; Laufs et al., 2019; Ray et al., 2019b). In CLEAR Serenity (Study 1002-046) and CLEAR Tranquility (Study 1002-048), where the maximum tolerated dose of statin equalled no statin or low-dose statin, larger treatment effects were seen (Ballantyne et al., 2018; Laufs et al., 2019). In CLEAR Serenity (Study 1002-046), the LS mean reduction from baseline in LDL-C for bempedoic acid compared with placebo was −23.6% versus −1.3%, respectively. The difference from placebo for the LS means was statistically significant ($P < 0.001$), with bempedoic acid providing a reduction of 18.1% compared with placebo (Laufs et al., 2019). In CLEAR Tranquility (Study 1002-048), bempedoic acid added to background lipid-lowering therapy that included ezetimibe resulted in a placebo-corrected LS mean change in LDL-C of −28.5% ($P < 0.001$). The LS mean reduction from baseline in LDL-C for bempedoic acid compared with placebo was −23.5% versus +5%, respectively. (Ballantyne et al., 2018).

The treatment effect of bempedoic acid was similar in patients with and without ezetimibe use, based on post-hoc subgroup analyses by ezetimibe use at baseline. In the two trials where the background dose of statin equalled no or low-dose statin therapy (studies 1002-046 [CLEAR Serenity] and 1002-048 [CLEAR Tranquility), the difference from placebo for the LS means was [redacted] in patients taking ezetimibe and [redacted] in patients not taking ezetimibe. In patients on maximally tolerated statin (studies 1002-040 and 1002-047) the difference from placebo for the LS means was [redacted] in patients taking ezetimibe, and [redacted] in patients not taking ezetimibe.

Treatment with bempedoic acid also had a positive impact across a spectrum of lipid parameters that would be expected to be associated with a reduction in CVD. Compared with placebo, treatment with bempedoic acid added to statin therapy significantly reduced apo B, non–HDL C, and TC (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019c; Laufs et al., 2019; Ray et al., 2019b).

The primary endpoint (percentage change in LDL-C from baseline to week 12) was evaluated across pre-specified subgroups, including sex, age, race, baseline CV risk category, baseline statin intensity, baseline LDL-C category, history of diabetes, and BMI. Treatment effect was highly consistent across a range of different patient subgroups and demographics (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019c; Laufs et al., 2019; Ray et al., 2019b).

In the phase 2 trials, the LS mean percentage change from baseline to week 12 in LDL-C ranged from −24.3% to −30.1% ($P < 0.0001$). In Study 1002-008, treatment with bempedoic acid monotherapy resulted in significantly greater decrease in mean LDL-C compared with treatment with ezetimibe monotherapy. The LS mean change in LDL-C from baseline to week 12 was −30.1% in the bempedoic acid group and −21.2 in the ezetimibe group (Thompson et al., 2016). In the phase 2 study of bempedoic acid in combination with background statin therapy (Study 1002-009), treatment with bempedoic acid resulted in significantly greater reduction for LS means in LDL-C compared with placebo, −24.3% versus −4.2% in the in the bempedoic acid and placebo group, respectively ($P < 0.0001$) (Ballantyne et al., 2016).

B.2.14.1.2 Safety

Across trials, the majority of adverse events have been mild to moderate in severity and have been balanced in occurrence with adverse events in patients receiving placebo. Overall, in the phase 3 studies the adverse events reported most frequently in patients who received bempedoic acid were generally reported at similar rates in the patients who received placebo. Small changes in laboratory parameters (creatinine increases, haemoglobin decreases, and liver function test elevations) are well characterised, reversible, and result in little clinical impact to patients. Two randomised, placebo-controlled, long-term clinical trials, CLEAR Harmony and CLEAR Wisdom, of 52 weeks of treatment involving > 3000 patients with 2,000 patients in the bempedoic acid treatment arms as part of a large and robust data set, demonstrate the long-term safety of bempedoic acid. These long-term data are consistent with data from the ongoing OLE study (Esperion Therapeutics data on file, 2019b).

Myopathy has been identified as a risk with concomitant use of simvastatin doses ≥ 40 mg, and the

bempedoic acid product information limits simvastatin dosage to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and at high risk for CV complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks).In addition, gout was reported in more patients receiving bempedoic acid than placebo [redacted] and has been considered an identified risk with bempedoic acid treatment) (Esperion Therapeutics data on file, 2019b).

B.2.14.2 Clinical efficacy and safety of FDC

B.2.14.2.1 Efficacy

In Study 1002FDC-053, treatment with FDC resulted in greater reductions in LDL-C at week 12 compared with placebo in patients receiving maximally tolerated statin therapy as part of their LMT. The LS mean reduction from baseline in LDL-C was −36.2% for FDC versus an increase of 1.8% for placebo. The difference versus placebo for LS means was −38% (Ballantyne et al., 2019a; Ballantyne et al., 2019b). Significant reductions in LDL-C with FDC versus placebo were observed at the first post-baseline study visit (week 4) and were maintained throughout the 12-week duration of the study ($P < 0.001$). The statistical significance of the overall treatment benefit of FDC at week 12 was observed across all key secondary endpoints, including non–HDL-C, TC, apo B, and hsCRP at week 12 ($P < 0.001$ for all) (Ballantyne et al., 2018; Ballantyne et al., 2019a; Ballantyne et al., 2019b). Evidence from CLEAR Tranquility also showed that bempedoic acid added to background lipid-lowering therapy that included ezetimibe resulted in significant reduction in LDL-C compared with placebo in statin-intolerant patients (Ballantyne et al., 2018). Pharmacokinetic studies have shown the FDC and separate pill presentations of bempedoic acid+ezetimibe to be equivalent (Esperion Therapeutics data on file, 2019e; Esperion Therapeutics data on file, 2019f).

Although Study 1002FDC-053 was not powered to assess between-group differences in subgroup analyses, results indicated a consistent trend for LDL-C lowering in the FDC treatment group relative to placebo (Ballantyne et al., 2019a).

B.2.14.2.2 Safety

FDC was shown to be well tolerated. Adverse events were reported slightly more frequently in the FDC study arms versus placebo, but most adverse events were mild or moderate in intensity and were judged to be not related or unlikely to be related to the investigational study drug (Ballantyne et al., 2018; Ballantyne et al., 2019a). Furthermore, rates of discontinuation because of an adverse event were similar across treatment arms and no TEAEs or fatal adverse events occurred during the study; FDC was considered to have a favourable safety profile (Ballantyne et al., 2018; Ballantyne et al., 2019a).

B.3 Cost-effectiveness

- A de novo Markov model was developed to assess the incremental cost-effectiveness of bempedoic acid and FDC.
- The main patient populations included in the model are as follows:
  - When statins are contraindicated or not tolerated (position 1)
  - When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C (position 2)
  - When maximally tolerated statin dose does not appropriately control LDL-C (position 3)
  - When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C (position 4)
- Cost-effectiveness results are presented for the target positions (position 2 and 4).
- The model allows evaluation of patient groups with different baseline LDL-C levels, based on differing thresholds for eligibility for treatment.
- The baseline risk of cardiovascular events and transition probabilities were obtained from real-world data from the UK THIN database.
- Data on LDL-C–lowering efficacy came from the CLEAR trial programme and an NMA. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C, treatment with bempedoic acid resulted in a positive net monetary benefit (£52) compared with no additional treatment on background ezetimibe using a threshold value of £30,000/QALY. Further, in patients for whom alirocumab and evolocumab are appropriate, bempedoic acid was cost-effective, as alirocumab and evolocumab provided a negative net monetary benefit compared with bempedoic acid.
- When maximally tolerated statin dose and ezetimibe do not appropriately control LDL-C, treatment with bempedoic acid resulted in an increase of QALYs compared with no additional treatment on background ezetimibe but a negative net monetary benefit (£−3,123) using a threshold value of £30,000/QALY. However, in patients for whom alirocumab and evolocumab are appropriate, bempedoic acid was cost-effective, as alirocumab and evolocumab provided a negative net monetary benefit compared with bempedoic acid.
- The cost-effectiveness results for FDC were the same as for bempedoic acid with background ezetimibe, as the price and efficacy were equivalent.
- The conclusions were consistent across a range of scenario and sensitivity analyses.

B.3.1.1 Published cost-effectiveness studies

An SLR was undertaken to identify all cost-effectiveness studies relevant to the decision problem from the published literature. Details of the search strategy, study selection process, and results are presented in Appendix H. A total of 26 economic evaluation studies were identified, including 4 health technology assessment (HTA) submissions. A total of 22 studies conducted cost-utility analysis and 4 studies conducted cost-effectiveness analysis. The results of this SLR provided insight and guidance on model development and structure. However, as no studies evaluating bempedoic acid were identified from the review they are not considered directly relevant to the decision problem. Economic evaluations identified in the SLR that assisted in the model development and structure are described in further detail in Section B.3.1.2.

B.3.1.2 Economic analysis

The de novo economic model developed for the submission and the rationale for the model development are described below.

B.3.1.3 Patient population

The model was developed to assess the incremental cost-effectiveness of bempedoic acid alone versus current standard of care and (separately) FDC versus current standard of care in adult patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed dyslipidaemia in the following circumstances:

- When statins are contraindicated or not tolerated
- When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C
- When maximally tolerated statin dose does not appropriately control LDL-C
- When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C

In view of the target positioning for bempedoic acid and FDC (Figure 3), cost-effectiveness estimates are presented for situations when ezetimibe does not appropriately control LDL-C, such as in the following situations:

- When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C (positions 2a and 2b in Figure 3)
- When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C (positions 4a and 4b in Figure 3)

The population characteristics that are modelled include the following:

- Presence or risk of CVD (secondary prevention and primary prevention, respectively)
- Patients with HeFH
- Severity of hypercholesterolaemia (defined by baseline LDL-C level)

All these populations were included in the bempedoic acid and FDC trials.

B.3.1.4 Model structure

Table 44 summarises the key features of the economic analysis and previous appraisals (a detailed table of features in previous appraisals is provided in Section B.6.1.4).

Table 44. Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA385	TA393	TA394	Chosen values	Justification
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Reference case
Were health effects measured in QALYs; if not, what was used?	QALYs	QALYs	QALYs	QALYs	Reference case
Cycle length	1-year	1-year	1-year	1-year	Cycle length chosen to fit available data and in line with earlier Tas
Half-cycle correction	Yes	Yes	Yes	Yes	Mitigate bias due to cycle length
Discounting	3.5% for costs and outcomes	3.5% for costs and outcomes	3.5% for costs and outcomes	3.5% for costs and outcomes	Reference case
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	Reference case

NHS = National Health Service; PSS = Personal and Social Services; QALY = quality-adjusted life year.

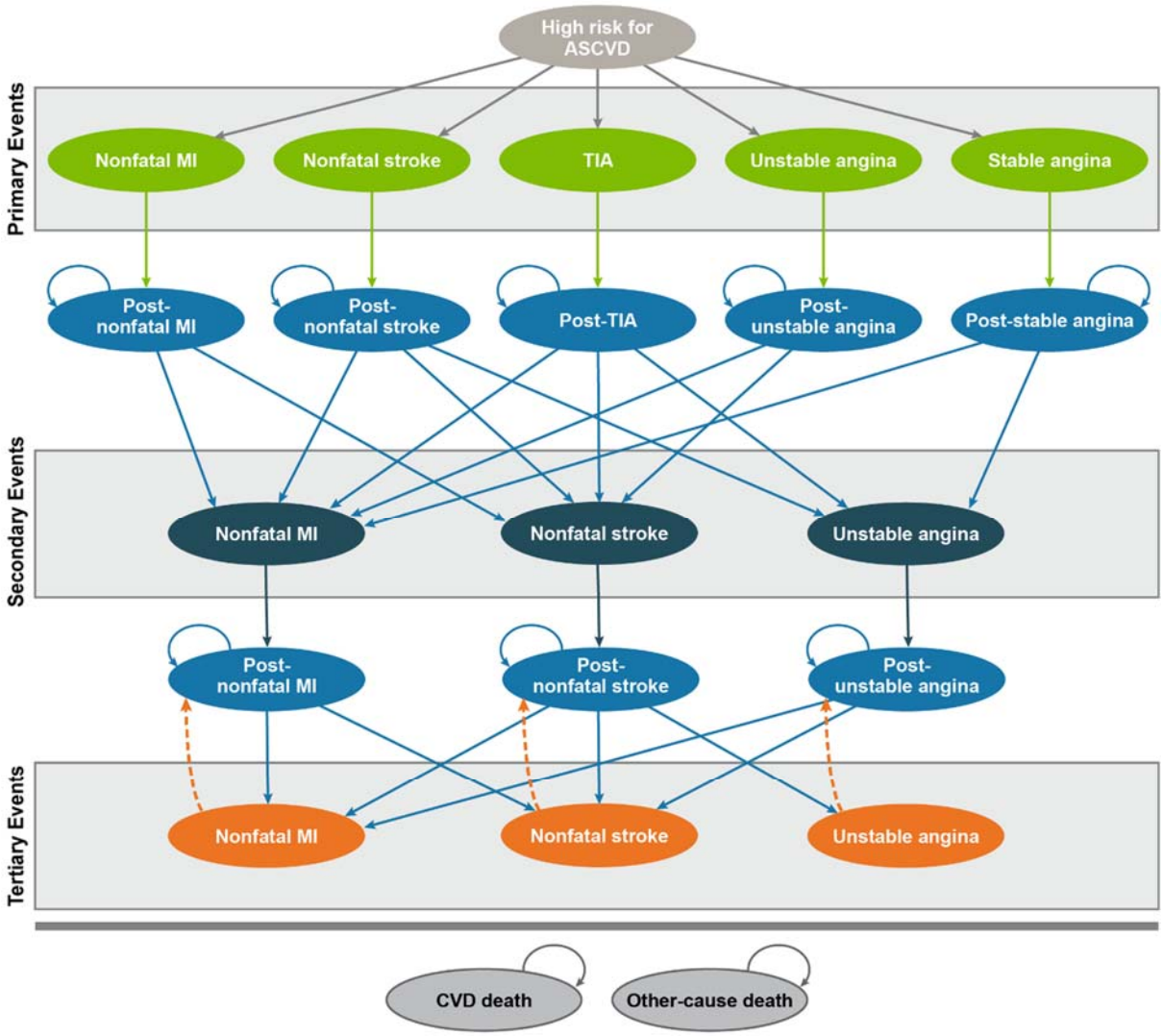
A Markov model structure with a lifetime time horizon and 1-year cycle length was developed (Figure 17). The model structure was informed by a review of existing models developed for primary hypercholesterolaemia or mixed dyslipidaemia, and by the SLR of cost-effectiveness studies (Section B.3.1.1). A review of NICE HTA submissions and guidelines associated with modelling CV conditions (NICE, 2016a; NICE, 2016b; NICE, 2016c; NICE, 2016d), along with the output of the economic SLR on cost-effectiveness studies, indicated that this is an appropriate model structure to address the decision problem adequately.

The model includes the following core health states: MI, unstable angina (UA), stable angina (SA), ischaemic stroke (IS), and transient ischaemic attack (TIA). Revascularisations are modelled as events which may occur for patients in any relevant health state. Such an approach captures the key clinical endpoints in CVD and is consistent with other published cost-effectiveness models in the therapy area. Updates to previous model structures were made to address the critique of previous models submitted to NICE. The model structure allows utilities and costs for multiple events to be modelled with sufficient flexibility to enable variation in these parameters from time since an event, to reflect adequately patient quality of life and clinical practice. Heart failure health states, included in CG181 and TA394, were considered for inclusion in the model but, as highlighted by the Evidence Review Group (ERG) in TA394, there is a paucity of data on the impact of cholesterol-lowering therapies for this type of event or the impact of CV death following heart failure. Hence, this health state was not included. Although the base case assumes no relationship between LDL-C lowering and the risk for SA and TIA, these

were included in the model to avoid the risk for overestimation of some risks due to exclusion of competing risks.

The model development incorporated feedback from individual experts and information from the clinical and economic SLRs. Expert opinion included recommendations on the model structure, inclusion and sources of inputs, and major assumptions from clinical and health economic perspectives.

Figure 17. Structure of the cost-effectiveness model



ASCVD = arteriosclerotic cardiovascular disease; CVD = cardiovascular disease; MI = myocardial infarction; TIA = transient ischaemic attack.

Note: while unstable and stable angina are chronic conditions, health states for "Post-unstable angina" and "Post-stable angina" are included in order to differentiate costs and quality of life in the second and subsequent years from those in the first year after developing the condition. Revascularisations are included as events in the model and may occur in patients in any relevant health state.

Events in the model are treated as instantaneous; patient transitions between health states which occur between two cycles and patients remain in the destination health state for the remainder of the model

cycle (1 year). In order to avoid over or underestimation of results, a half-cycle correction is applied in the model.

Owing to the memoryless nature of Markov models and to allow for changing risks, costs and, quality of life in the few years after CV events, the model includes post-event health states. Post-event health states include 0 to 1-year post-CV events, 1 to 2-year post-CV events, and > 2 years post-events (by which time the risk is expected to be approximately stable). The model health states are presented in Table 45. This approach is used in the model to reflect risks over time more accurately and provide more flexibility for scenario analyses. In any of the post-MI, post-UA, post-SA, post-TIA, or post-IS event states, patients are able to transition to another event of the same type or to a different type of event, or they can remain in their current post-event state. Patients are able to transition from any state to death.

Table 45. Summary of core model health states

Core health state	Description of health state
High risk for ASCVD	Patients with no prior ASCVD events but at a high risk of events
Non-fatal MI	Patients with MI less than a year ago
Post-non-fatal MI 1-2 years	Patients with MI between 1 and 2 years ago
Post-non-fatal MI 2+ years	Patients with MI more than 2 years ago
UA	Patients with UA during the last year
Post-UA 1-2 years	Patients with UA between 1 and 2 years ago
Post-UA 2+ years	Patients with UA more than 2 years ago
SA	Patients with SA less than a year ago
Post-SA 1-2 years	Patients with SA between 1 and 2 years ago
Post-SA 2+ years	Patients with SA more than 2 years ago
Non-fatal IS	Patients with IS during the last year
Post-non-fatal IS 1-2 years	Patients with IS between 1 and 2 years ago
Post-non-fatal IS 2+ years	Patients with IS more than 2 years ago
TIA	Patients with TIA during the last year
Post-TIA 1-2 years	Patients with TIA between 1 and 2 years ago
Post-TIA 2+ years	Patients with TIA more than 2 years ago

ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; UA, unstable angina; IS, Ischaemic Stroke; SA = stable angina; TIA, transient ischaemic attack.

Note: revascularisations are included as events in the model and may occur in patients in any relevant health state.

The initial starting states are populated with patients to reflect the selected analysis. For example, in the analyses for statin-intolerant patients with ASCVD or with a high risk for ASCVD, patients are distributed among the “High risk for ASCVD” and the initial CVD health states (according to the CVD history) at the start of model time, and risks are determined based on, for example, the baseline LDL-C level, prevalence of diabetes, prevalence of HeFH (baseline risks are described in Section B.3.1.5.1).

Patients starting in one of the initial health states can experience events and transition to post-event health states, or can stay in the initial state. In terms of events, patients can, as listed in Table 46, experience an Mi, a TIA, development of UA, development of SA, an IS, or an elective revascularisation. Additional events that have been considered include heart failure, diabetes onset, and peripheral artery disease; however, the relationship between these events and LDL-C reduction is currently uncertain (Karatasakis et al., 2017; NICE, 2016c; NICE, 2016d) and an inclusion would make the model unnecessarily complex.

Table 46. Model event definitions

Event	Definition
MI	Non-fatal myocardial infarction
UA	Episode of angina that occurs randomly or unpredictably and is unrelated to any obvious trigger
SA	Angina that occurs when the heart must work harder, for instance due to physical exertion
Revascularisation	An elective revascularisation that did not occur as a result of a CV event
IS	Ischaemic stroke
TIA	Transient ischaemic attack
CV death	Death due to any CV event
Non-CV death	Death due to any non-CV cause

CV = cardiovascular; IS, Ischaemic stroke; MI, myocardial infarction; SA = stable angina; TIA = transient ischaemic attack; UA, unstable angina.

Transitions from MI, UA, TIA, or SA health states to IS health states are allowed, but the reverse is not permitted in the model. This is because post-stroke health states are usually associated with lower health utility than the same health state with no prior stroke. Transition to an MI, UA, TIA, or SA health state after a stroke would result in an increase in a patient's quality of life and therefore is not permitted in the model. However, the event itself is modelled to calculate accurately the cost of managing the event and the overall number of events in each treatment cohort. An alternative approach would be to use composite health states for patients experiencing more than one type of event. However, as also discussed by the ERG in the TA393 appraisal, this makes the model complex and there are limited data available for these health states.

Revascularisation procedures are included within the model events. These are modelled as separate events because, as noted in previous NICE assessments (NICE, 2016a), elective revascularisation has a different pattern of risk, costs, and utilities than urgent revascularisation occurring as part of an episode of care for an MI or UA event. A proportion of patients in the MI and UA health states will receive a non-elective revascularisation and this is expected to be included already in the cost and utility data for those health states.

The model simulates identical entry cohorts for bempedoic acid (with or without ezetimibe and/or statin) and comparators over a specified time horizon (lifetime horizon as base case), and compares the costs

and outcomes between the treatment groups. The cohort characteristics are defined based on multiple criteria, including starting age, proportion of males, prevalence of diabetes, baseline LDL-C, and CV risk category. The background therapy is identical for all treatment cohorts.

B.3.1.4.1 Justification for the chosen model structure

The model structure captures the expected patient pathway from treatment initiation to death and reflects the expected clinically important differences in costs and outcomes between the group of patients receiving bempedoic acid and the group of patients receiving the comparator treatments. The structure is also similar to previous NICE submissions (Carroll et al., 2017; NICE, 2016a; NICE, 2016d). The structure (including separate states for years 1, 2, and ≥ 3 following a CV event) allows for variation in the risk of subsequent events and death over the time horizon. The model cycle length of 1 year has been selected to provide precision in the tracking of the number of patients in each health state over time without making it unnecessarily complex. UK clinical experts confirmed that the model structure and functionality is relevant to address the decision problem.

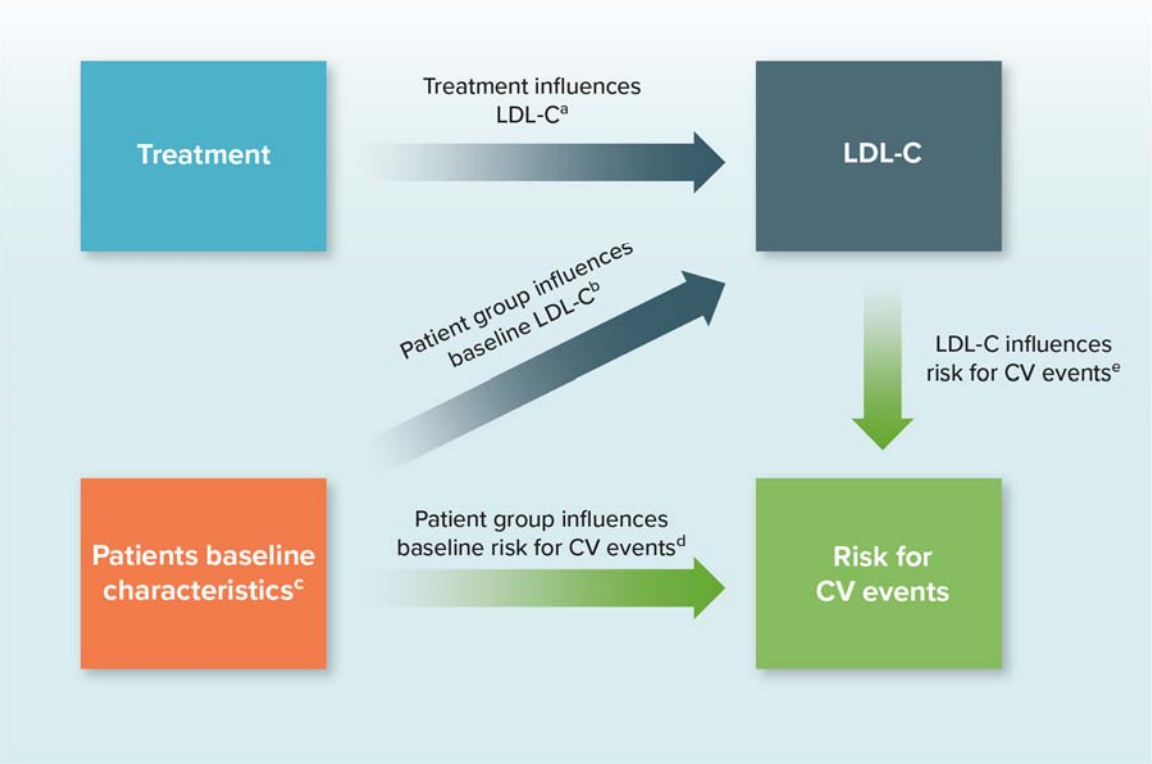
B.3.1.5 Data inputs

The primary source of data for the efficacy and safety of bempedoic acid are the five phase 3, randomised trials that directly compare bempedoic acid with placebo, supplemented by two phase 2 trials also reporting LDL-C data at 12 weeks for the anticipated licensed dose of bempedoic acid (1002-008 and 1002-009) in populations relevant for the scope. Efficacy data used in the model were taken from the NMA (Section B.2.9). These data are supplemented with data for other parameters from the literature to allow for estimation of long-term costs and outcomes.

B.3.1.5.1 Risk of CV events

The primary endpoint of the completed trials investigating bempedoic acid is reduction in LDL-C; the trials were not designed to evaluate the effect of treatment on the risk for CV events. Large studies with several years of follow-up have been found necessary to capture the full effect of lipid-lowering drugs. As CV outcomes data are not yet available for bempedoic acid, the well-recognised relationship between LDL-C lowering and CV risk were combined with baseline risks for the UK population to estimate the number of events in the model. Figure 18 presents an influence diagram, providing a schematic presentation of how the CV risk is estimated in the model in the absence of CV outcomes data for bempedoic acid. Details of the risk equations and estimation methods are provided in the following sections and tables, as indicated in the footnote to Figure 18.

Figure 18. Influence diagram



LDL-C = low-density lipoprotein cholesterol; CV = cardiovascular.

[a] LDL-C is reduced according to the efficacy of the treatment option (see Section B.3.2.1).

[b] Baseline mean LDL-C depends on the selected patient group and the selected threshold for treatment (see Table 50).

[c] The selected patient group (see Section B.3.1.3) influences the modelled baseline patient characteristics (Table 47).

[d] The patient baseline characteristics (age, diabetes, prior CV events) influence the baseline risks of CV events (Table 49).

[e] The LDL-C level (baseline level adjusted for the treatment effect for each intervention) influences the risk for CV events (see Section B.3.2.2).

Each component influencing long-term outcomes depicted in the figure is considered in turn in the following sections.

Patient baseline characteristics

The model allows specification of key baseline characteristics for patients entering the model that have an impact on CV risk and other parameters: mean age, sex, CVD history, prevalence of diabetes, prevalence of FH, recurrent CV event, and mean LDL-C (dependent on the LDL-C threshold for treatment or subgroup). These characteristics are presented for each of the potential positionings of bempedoic acid in Table 63.

In the base-case analyses for both the statin-intolerant and maximally tolerated statin analyses, the simulated overall cohort includes both primary and secondary prevention patients based on the proportions in the bempedoic acid trials. Further, for all cohorts, mean age, the prevalence of diabetes, and proportion of males by risk category were taken from the bempedoic acid trial data. THIN data

presented in TA393 (NICE, 2016a) were included in the model for potential scenario analyses and were in general well-aligned with the data from the bempedoic acid studies.

For the patients that already have experienced a CV event (the secondary prevention population), the distribution of CV event history at the start of model time was taken from Ward et al. (2007). The estimates have been previously used in NICE guidelines (NICE, 2016b) and appraisals (NICE, 2016d) and are presented in Table 47.

Table 47. Distribution of the secondary prevention patients at the start of model time by age, sex, and type of prior CV event

Gender	Age (Years)	Post-UA	Post-MI	Post-IS
Male	40-54	16%	58%	26%
	55-64	14%	62%	24%
	65-74	20%	52%	28%
	75+	19%	46%	35%
Female	40-54	19%	43%	38%
	55-64	18%	43%	39%
	65-74	21%	42%	38%
	75+	25%	32%	43%

IS = ischaemic stroke; MI = myocardial infarction; SA = stable angina; TIA = transient ischaemic attack; unstable angina.

Source: Ward et al. (2007).

Background cardiovascular risks: secondary prevention

As with the NICE appraisal of alirocumab, the real-world UK data from THIN was deemed most appropriate to inform CV event probabilities (Table 48) (NICE, 2016a) of the identified sources to model CV risk in a secondary prevention population. Risk estimators such as QRISK3 are not suitable for high-risk groups, including for patients who have experienced a CV event (NICE, 2016a). Annual CV event probabilities are assigned to health states based on the characteristics of patients in that health state (Table 48).

Table 48. Background cardiovascular risks: annual probabilities

Diabetic patients	CV death	IS	MI	UA	SA	Elective revascularisation	TIA
MI < 12 months prior	6.0%	1.7%	5.2%	3.3%	0.0%	4.9%	0.9%
MI 12-24 months	4.1%	1.2%	2.8%	2.1%	0.0%	0.8%	0.6%
MI > 36 months	2.8%	0.9%	1.6%	1.1%	0.0%	0.9%	0.5%
SA[b] < 12 months prior	2.7%	0.9%	1.5%	0.8%	0.0%	0.93%	0.5%
SA[b] 12-24 months	2.7%	0.9%	1.5%	0.8%	0.0%	0.93%	0.5%
SA[b] > 36 months	2.7%	0.9%	1.5%	0.8%	0.0%	0.93%	0.5%
UA < 12 months prior	6.0%	1.7%	5.2%	3.3%	0.0%	4.9%	0.9%
UA 12-24 months	4.1%	1.2%	2.8%	2.1%	0.0%	0.8%	0.6%

Diabetic patients	CV death	IS	MI	UA	SA	Elective revascularisation	TIA
UA > 36 months	2.8%	0.9%	1.6%	1.1%	0.0%	0.9%	0.5%
IS < 12 months prior	4.2%	2.8%	1.5%	0.7%	0.0%	0.5%	1.4%
IS 12 - 24months prior	4.2%	2.8%	1.5%	0.7%	0.0%	0.5%	1.4%
IS > 36 months prior	4.2%	2.8%	1.5%	0.7%	0.0%	0.5%	1.4%
TIA < 12 months prior	3.5%	4.2%	0.6%	0.0%	0.0%	0.0%	0.0%
TIA 12-24 months prior	3.5%	4.2%	0.6%	0.0%	0.0%	0.0%	0.0%
TIA > 36 months prior	3.5%	4.2%	0.6%	0.0%	0.0%	0.0%	0.0%
Non-diabetic patients	**CV death**	**IS**	**MI**	**UA**	**SA**	**Elective revascularisation**	**TIA**
MI < 12 months prior	2.9%	0.8%	4.1%	2.4%	0.0%	3.6%	0.4%
MI 12-24 months	2.2%	0.5%	2.4%	1.3%	0.0%	0.8%	0.3%
MI > 36 months	2.2%	0.7%	1.5%	0.7%	0.0%	0.7%	0.3%
SA[b] < 12 months prior	2.0%	0.8%	1.1%	0.5%	0.0%	0.7%	0.4%
SA[b] 12-24 months	2.0%	0.8%	1.1%	0.5%	0.0%	0.7%	0.4%
SA[b] > 36 months	2.0%	0.8%	1.1%	0.5%	0.0%	0.7%	0.4%
UA < 12 months prior	2.9%	0.8%	4.1%	2.4%	0.0%	3.6%	0.4%
UA 12-24 months	2.2%	0.5%	2.4%	1.3%	0.0%	0.8%	0.3%
UA > 36 months	2.2%	0.7%	1.5%	0.7%	0.0%	0.7%	0.3%
IS < 12 months prior	3.8%	2.4%	1.1%	0.4%	0.0%	0.3%	1.2%
IS 12 - 24months prior	3.8%	2.4%	1.1%	0.4%	0.0%	0.3%	1.2%
IS > 36 months prior	3.8%	2.4%	1.1%	0.4%	0.0%	0.3%	1.2%
TIA < 12 months prior	3.5%	4.2%	0.6%	0.0%	0.0%	0.0%	0.0%
TIA 12-24 months prior	3.5%	4.2%	0.6%	0.0%	0.0%	0.0%	0.0%
TIA > 36 months prior	3.5%	4.2%	0.6%	0.0%	0.0%	0.0%	0.0%

CV = cardiovascular; IS = ischaemic stroke; MI = myocardial infarction; SA = stable angina; THIN = The Health Improvement Network; TIA = transient ischaemic attack; UA = unstable angina; UK = United Kingdom.

[a] The prevalence of diabetes by CV risk category (based on the UK THIN data) (NICE, 2016a) is used in conjunction with the risks for patients with and without diabetes to generate risks which are generalisable to the total model population.

[b] SA assumed to be the same as "Other CHD," and transitions to SA were blocked for prior event health states.

Source: Appendix 11 in the alirocumab submission (NICE, 2016a).

In line with the approach in the alirocumab submission, the data from THIN was adjusted for expected undercoding in registry data; risks for all non-fatal events were therefore adjusted upwards by 25%, based on Herrett et al. (2013).

In line with CG181, event risks in patients with a history of TIA were obtained from Ward et al. (2007). as these data were not available from THIN in TA393 (NICE, 2016a). Limited evidence was available for the risk for TIA in the different secondary prevention subgroups, the ratio of TIA versus IS patients with a previous event in the Clinical Practice Research Database was therefore used to estimate the risk for TIA (Danese et al., 2016). The risks in the secondary prevention cohort were also adjusted for

prevalence of HeFH in the cohort. In line with the appraisal of evolocumab (NICE, 2016c) a 6.1 hazard ratio adapted based on Benn et al. (2012) was applied for patients with HeFH and previous events.

Background cardiovascular risks: primary prevention

For the base-case analysis (in contraindicated or not tolerated population), a 30.3% 10-year risk of MI, stroke or CV death was applied for high-risk primary prevention patients, estimated using the QRISK3 risk assessment tool recommended in the recent Lipid Modification guideline (NICE, 2016b). The QRISK3 algorithm calculates a person's risk of developing a heart attack or stroke over the next 10 years. The base-case risk in the model was calculated using the definition of high risk in the ESC guidelines (SCORE 5-10, 5%-10% risk of fatal event) and dividing the midpoint (7.5%) by the relative rate for CV death in Ward et al. (2007) (7.5/0.2473 = 30.13). The distributions between the different types of events in Ward et al. (2007) are shown in Table 49.

Table 49. Relative rates of first events in primary prevention patients – QRISK3

	SA	UA	MI	TIA	IS	CV death
Men						
40-54	0.5848	0.2038	0.5619	0.1143	0.2457	0.1924
55-64	0.6406	0.1387	0.3359	0.1738	0.4023	0.2617
65-74	0.3549	0.1376	0.2869	0.1658	0.4478	0.2653
75-84	0.2952	0.1252	0.2488	0.1236	0.5301	0.2210
85+	0.3175	0.1424	0.2760	0.0237	0.5208	0.2033
Women						
40-54	0.813	0.293	0.200	0.400	0.573	0.228
55-64	0.712	0.150	0.189	0.195	0.593	0.218
65-74	0.300	0.077	0.180	0.108	0.567	0.254
75-84	0.208	0.047	0.142	0.136	0.646	0.212
85+	0.182	0.039	0.134	0.116	0.670	0.197

CV = cardiovascular; IS = ischaemic stroke; MI = myocardial infarction; SA = stable angina; TIA = transient ischaemic attack; UA = unstable angina.

Note: the distribution of MI, IS, and CV death sum to 1.00 as these are the events included in QRISK3. The other events (SA, UA, and TIA) have been calculated proportionately.

In Ward et al. (2007), the annual incidence rates for CV events were divided by the total incidence of those events (Table 49). The relative rates in Table 49 were then multiplied by the annual CV risk to get the annual baseline risk of each event. The annual CV risk was calculated by converting the 10-year risk (probability) into a rate and then converting this rate into a 1-year probability. Thus, for example, a 10-year risk of 20% corresponds to a 1-year risk (annual probability) of 2.207%, so for a QRISK3 risk score of 20% (10-year risk), the values in Table 49 were all multiplied by 0.02207 to give the baseline transition probabilities from high risk for ASCVD to each CV event each year. As in CG181, it should be observed that the distribution of the events sum to more than 1. The reason for this is that not all events are included in QRISK3 (SA, UA, and TIA are not included), so when estimating the risk for all

the CV events (and not only those included in QRISK3) these rates need to be calculated. In line with CG181, this calculation was performed by assuming the risk of events is proportional to the number of events in Ward et al. (2007). For instance, if there are twice as many IS compared with TIA in Ward et al. (2007), then the risk of TIA is 50% of the risk of IS. This is consistent with the approach adopted in the CG181 cost-effectiveness analysis (NICE, 2016b).

Other risk algorithms such as Framingham were considered, but as QRISK3 and QRISK2 are validated for a UK population (while the Framingham equations are based on US data) the QRISK estimates were deemed most relevant for this submission. Furthermore, QRISK is used in the NICE guideline (CG181) for predicting CV risk.

Background cardiovascular risk adjustment by age and LDL-C

In addition to specifying the CV risk category, the age, percentage of females, prevalence of diabetes, and baseline LDL-C are factors that are used to define the starting cohort. These are key factors known to have an impact on CV risk.

For age, the risk for non-fatal CV events is increased by 3% and the risk for CV death is increased by 5% with each year of age, in line with the alirocumab NICE submission (NICE, 2016a) and input from clinical experts. The Wilson reference in NICE (2016a) was used because it is based on a high-risk patient group which should align well to the high-risk groups simulated in our model. This source was also preferred as it splits the age adjustment into fatal and non-fatal CV events. Previous models in CV disease have used varied sources and varied rates for these parameters (from as low as 0.008% in Ward et al. (2007) to up to 10.7% in the Rivaroxaban NICE submission (NICE, 2015).

For sex, as the data by CV risk category (Table 48) are taken from UK THIN data (2015) or Ward et al. (2007), this is assumed to be representative of the UK population as a whole and, therefore, the data are expected to be generalisable without any adjustment of CV risk by sex.

To explore the cost-effectiveness of bempedoic acid by severity of hypercholesterolaemia it is important to take account of the influence of baseline LDL-C on background CV risk. To do this, the model takes account of the average LDL-C value found for the different CV risk categories in the CLEAR studies.

In the base-case the latest CTT meta-analyses is used to estimate the relationship between LDL-C and CV risk. The analysis estimates the rate ratio per unit reduction in LDL-C ($\propto$) for various CV events. The RR reduction per unit reduction in LDL-C is thus $1 - \propto$. The CTT papers report a log-linear relationship (Cholesterol Treatment Trialists et al., 2015). On the basis of this information, the relationship between event probability and LDL-C change can, as in the alirocumab NICE submission (NICE, 2016a), be represented as follows:

$$1) \quad \frac{E_{0i}-E_i}{E_{0i}} = 1 - \propto_i^{(L_0-Li)}$$

$$2) \quad E_i = E_{0i}[\propto_i^{(L_0-Li)}]$$

$$3) \quad \ln(E_i) = \ln(E_{0i}) + (L_0 - Li)\ln(\propto_i),$$

where:

- L_0 is the baseline LDL-C level in mmol/L
- Li is the new LDL-C level in mmol/L
- E_{0i} is the 1-year probability for experiencing event i at the baseline LDL-C level of L_0
- E_i is the 1-year probability for experiencing event i at the LDL-C level of Li
- $\propto_i$ is the rate ratio per unit change in LDL-C for event i

These equations are used to adjust the CV risk based on the baseline LDL-C, i.e., if the patient cohort overall had a baseline LDL-C of L_0, and an event rate of E_{0i}, when considering a cohort with a baseline LDL-C of L_i, equation 2 is used to estimate the event rate E_i. The rate ratios in the CTT analysis are presented in Table 55. The de novo meta-regressions of the relationship between LDL-C and CV events are available in the economic model and used for scenario analyses.

Mean LDL-C levels at baseline by different "starting" thresholds

Different mean baseline LDL-C levels are applied in the model depending on which patient group is selected for the analysis. The model also allows the user to set a minimum starting LDL-C threshold, the model then applies the average LDL-C value for patients with an LDL-C above this threshold value, based on data taken from the relevant CLEAR studies (Table 50). Baseline LDL-C was collected for all the phase 3 bempedoic acid studies presented in Table 9. Data for these trials were analysed additionally to obtain the baseline LDL-C for the patient populations relevant in the NICE scope. Hence, for the base-case analyses, the threshold selected for the model depends on whether the patients are receiving background statin or no/very low-dose statin and whether the patients would be eligible for PCSK9i treatment according to the NICE guidelines (NICE, 2019).

Table 50. Average Baseline LDL-C values by LDL-C threshold in the CLEAR studies

LDL-C threshold	CLEAR Wisdom		CLEAR Harmony		CLEAR Tranquility		CLEAR Serenity		No or low-dose statin[a]	Max dose statin[b]
	Patients	Mean (SD)	Patients	Mean (SD)	Patients	Mean (SD)	Patients	Mean (SD)	Mean (SD)	Mean (SD)
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1.81 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 2.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 2.5 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 2.59 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3.36 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3.5 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4.14 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4.5 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 5.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LDL-C threshold	CLEAR Wisdom		CLEAR Harmony		CLEAR Tranquility		CLEAR Serenity		No or low-dose statin[a]	Max dose statin[b]
	Patients	Mean (SD)	Patients	Mean (SD)	Patients	Mean (SD)	Patients	Mean (SD)	Mean (SD)	Mean (SD)
PCSK9i eligible[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-PCSK9i eligible[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CV = cardiovascular; HeFH = heterozygous familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation.

[a] Weighted average for CLEAR Tranquility and CLEAR Serenity.

[b] Weighted average for CLEAR Harmony and CLEAR Wisdom. The FDC-053 trial was not included in the analysis of the baseline LDL-C as the inclusion criteria in that trial implied a very high proportion of patients with diabetes which was expected to have a negative effect on the generalizability of the baseline LDL-C to a UK general population of patients with maximal tolerated dose of statins. As the efficacy of bempedoic acid is expected not to differ between subgroups the trial is relevant in other parts of this submission but is expected to create results that are not representative of a UK population if included for the analysis of baseline LDL-C.

[c] Based on NICE recommendations (Table 5).

Source: (Esperion Therapeutics data on file, 2019a).

The model also allows selection of the average values corresponding to different LDL-C cutoffs based on THIN data (Table 51). The rationale for using the trial data rather than the THIN data is that the level of detail in the presented THIN data is not sufficient to divide patients into PCSK9i-eligible and PCSK9i–non-eligible groups.

Table 51. Average LDL-C values by LDL-C cutoff in the THIN database

Cutoff threshold	No cutoff	> 1.81 mmol/L	> 2.59 mmol/L	> 3.36 mmol/L	> 4.14 mmol/L
MI < 1 year	2.50	2.60	3.31	4.11	4.83
MI 1-2 year	2.60	2.62	3.31	4.07	4.93
UA < 1 year	2.50	2.60	3.31	4.11	4.83
UA 1-2 year	2.60	2.62	3.31	4.07	4.93
IS	2.50	2.65	3.27	4.00	4.67

IS = ischaemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; SA = stable angina; THIN = The Health Improvement Network; UA = unstable angina.

Source: NICE (2016a).

B.3.1.6 Intervention technology and comparators

The interventions included in the model are presented in Table 52, along with their route of administration and recommended dosing schedule. These agents may be used in conjunction with background statin and/or ezetimibe, and/or other lipid-lowering agents (e.g., nicotinic acid, bile acid sequestrants, and fibrates).

Table 52. Interventions and comparators in the model

Intervention	Route of administration	Dosing schedule
Bempedoic acid[a]	Oral	180 mg once daily
FDC	Oral	Bempedoic acid 180 mg + ezetimibe 10 mg FDC, once daily
Comparators		
No additional treatment (placebo)[a]	NA	NA
Ezetimibe	Oral	10 mg once daily
Alirocumab	Subcutaneous injection	75 mg or 150 mg every 2 weeks
Evolocumab	Subcutaneous injection	140 mg every 2 weeks

FDC = bempedoic acid and ezetimibe fixed-dose combination; NA = not applicable.

[a] In positions 2 and 4, given with background ezetimibe, 10 mg once daily.

B.3.2 Clinical parameters and variables

B.3.2.1 LDL-C reduction efficacy

The main result driver in the model for both cost and effects is the reduction in LDL-C. This is the primary efficacy outcome in the five phase 3 bempedoic acid trials and two phase 2 trials that inform the model. The percentage reduction in LDL-C from baseline to week 12 in the phase 3 trials is presented in Table 53.

Table 53. Phase 3 bempedoic acid randomised controlled trials: primary efficacy results

Study	LDL-C reduction from baseline to week 12, placebo corrected
CLEAR Harmony (Ray et al., 2019b) (N = 2,230)	−18.1% (−20.0 to - 6.1; *P* < 0.001)
CLEAR Wisdom (Esperion Therapeutics data on file, 2019c) (N = 779)	−17.4% (−20.95 to −13.90; *P* < 0.001)
CLEAR Serenity (Laufs et al., 2019) (N = 345)	−21.4% (−25.1 to −17.7; *P* < 0.001)
CLEAR Tranquility (Ballantyne et al., 2018) (N = 269)	−28.5% (−34.4 to −22.5; *P* < 0.001)
1002FDC-053 (Ballantyne et al., 2019a) (N = 382) (for FDC vs. placebo)	−29.0% (−36.8, −21.3); p< 0.001
1002FDC-053 (Ballantyne et al., 2019a) (N = 382) (for bempedoic acid vs. placebo)	−15.2% (Bempedoic acid: −17.7% (SE, 2.28), Placebo: −2.5% (SE, 3.07))

FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; SE = standard error.

The NMA (presented in Section B.2.9), provides the LDL-C reduction parameters used in the model. The data from the NMA that are used in the model is outlined in Table 54.

Table 54. Network meta-analysis data used in the model

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe			
	When statin is contraindicated or not tolerated		When maximally tolerated statin dose does not appropriately control LDL-C	
	Mean	95% CrIs	Mean	95% CrIs
FDC; Bempedoic acid on background ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe			
	When statin is contraindicated or not tolerated		When maximally tolerated statin dose does not appropriately control LDL-C	
	Mean	95% CrIs	Mean	95% CrIs
AliMab+ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]

CrI = credible interval; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NA = not available.

The mean percentage change in LDL-C is multiplied by the baseline LDL-C level (adjusted for background ezetimibe treatment in positions 2 and 4) to derive absolute reductions in LDL-C for each of the treatments. As pharmacokinetic studies have shown the two presentations to be equivalent (Esperion Therapeutics data on file, 2019e; Esperion Therapeutics data on file, 2019f), the mean percentage reduction for bempedoic acid in patients on background ezetimibe was assumed to be the same as the reduction for the FDC.

The treatment effect observed for LDL-C reduction at 12 weeks is assumed to remain constant for the duration of the model's time horizon or until the treatment is discontinued.

B.3.2.1.1 LDL-C return after treatment discontinuation

The model allows for treatment discontinuation and non-compliance. LDL-C lowering and consequently any CV risk benefits are assumed to stop immediately on treatment discontinuation. The assumption that CV benefit stops immediately on treatment cessation is the most conservative and appropriate if no other data are available. If this assumption is not used, a higher discontinuation rate may result paradoxically in improved incremental cost-effectiveness ratios. This assumption has a been previously used in NICE appraisals (NICE, 2016a).

B.3.2.2 Modelling the relationship between LDL-C lowering and CV risk reduction

The CLEAR OUTCOMES trial, which investigates major adverse CV events as the primary outcome, is ongoing at this time and is not due to report until [redacted]. However, there is evidence from numerous studies indicating that treatments which reduce LDL-C levels also reduce the incidence of CV events—for example, Cholesterol Treatment Trialists et al. (2010); Cholesterol Treatment Trialists et al. (2015); Navarese et al. (2015); Navarese et al. (2018)—and this assumption has been accepted previously in NICE appraisals (NICE, 2016a; NICE, 2016c; NICE, 2016d). Therefore, LDL-C reduction has been used as a surrogate outcome to model the benefit of bempedoic acid on CV outcomes. LDL-C was the only surrogate considered for CVD risk in the economic evaluation given that the body of evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes is overwhelming. The relationship between other lipid markers and CV event rates, and whether changing these markers through therapeutic intervention has an effect on CVD risk, is less well-established and understood than the relationship between LDL-C and CV events. Therefore, other markers were not considered.

Two analyses have been used in previous NICE appraisals in hypercholesterolaemia (NICE, 2016a; NICE, 2016c). Since these appraisals, additional CV outcomes studies have been completed for lipid-lowering therapies, and several further analyses have been published exploring the relationship between LDL-C reduction and CV risk. For example, Silverman et al. (2016) reported an analysis of 49 trials (involving 312,175 patients with 39,645 major vascular events) investigating statins, ezetimibe, PCSK9 inhibitors, and a variety of other lipid-lowering therapies. The authors concluded that statin and non-statin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar rate ratios of major vascular events per unit change in LDL-C (Silverman et al., 2016). Bempedoic acid acts in the same cholesterol biosynthesis pathway as statins and upregulates LDL receptors by suppression of cholesterol synthesis (Section B.2.13). More recently, based on a systematic review, meta-analyses, and meta-regressions of 34 trials investigating statins, ezetimibe, and PCSK9 inhibitors (in more than 270,000 patients), Navarese et al. (2018) concluded that more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in the risk of total and CV mortality in trials of patients with higher baseline LDL-C levels. This association was not present when the baseline LDL-C level was less than 100 mg/dL (Navarese et al., 2018). Similar findings also were reported for PCSK9 inhibitor trials by Karatasakis et al. (2017).

Navarese et al. (2018) investigated the association between baseline LDL-C level and CV outcomes after adjustment for magnitude of LDL-C reduction; however, results were not reported which allow estimation of the rate ratio per unit reduction in LDL-C at specified baseline LDL-C concentrations. Furthermore, additional CV outcomes studies have been reported since the Navarese et al. (2018) analysis was performed which are expected to add relevant evidence. A de novo meta-regression has therefore been performed to include recently published evidence, and to allow estimation of the rate ratio per unit reduction in LDL-C at specified baseline LDL-C concentrations. Details of this analysis are presented in Appendix E.

The model includes two options to model the relationship between LDL-C reduction and CV risk, based on the following studies:

- The Cholesterol Treatment Trialists Collaboration (CTTC) meta-analyses of statin studies (base case) (Cholesterol Treatment Trialists et al., 2015)
- A de novo meta-regression that updates the analysis reported by Navarese et al. (2018) to include studies reported since the closing date of their systematic review (scenario)

Details of the de novo meta-analysis are presented in Appendix E.

The CTTC meta-analysis was selected for the base-case analysis because it was based on patient-level data rather than aggregated published data, and for consistency of decision making, as this analysis was used (and preferred over the Navarese et al. (2018) analysis) in previous NICE appraisals (TA385, TA393, TA394). The de novo meta-regression is explored in sensitivity analyses. The analysis by Navarese et al. (2018) was not used because the authors observed that the association between LDL-C reduction and CV risk was not present when baseline LDL-C levels were less than 100 mg/dL, while the rate ratio per unit reduction in LDL-C reported in the study included many large trials with

mean baseline LDL-C less than 100 mg/dL (notably TNT, SEARCH, IMPROVE-IT, FOURIER, and SPIRE-1, contributing a total of 84,590 patients to the analysis). Therefore, the RRs reported by Navarese et al. (2018) may not be generalisable to the patient populations in positions 2 and 4, where the mean baseline LDL-C was estimated to range from 2.91 to 4.39 mg/dL (112 to 170 mmol/L) (Table 63).

For both sources, hazard ratios are normalised to apply a rate ratio per 1 mmol/L reduction in LDL-C using the following formula:

- Rate ratio per 1 mmol/L reduction in LDL-C = EXP(LN(hazard ratio)/absolute reduction).

The rate ratios applied in the model are presented in Table 55. The rate ratios for SA and TIA were conservatively assumed to be 1, as there is not strong evidence supporting a relationship between these events/health states and LDL-C lowering.

Table 55. Rate Ratio for CV events per 1 mmol/L reduction in LDL-C

	Mean (CI)	**Mean (CI)**	**Mean (CI)**	**Mean (CI)[a]**
MI	0.64 (0.43- 0.96)	0.76 (0.73-0.79)	0.85 (0.78-0.96)	[redacted]
UA	0.64 (0.43- 0.96)	0.76 (0.73-0.79)	0.85 (0.78-0.96)	[redacted]
SA	1	1	1	1
Revascularisation	0.64 (0.43- 0.96)	0.76 (0.73-0.78)	0.89 (0.82-0.96)	[redacted]
IS	0.64 (0.43- 0.96)	0.85 (0.80-0.89)	0.99 (0.86-1.08)	[redacted]
TIA	1	1	1	1
CV death	0.64 (0.40-1.04)	0.88 (0.84-0.91)	0.89 (0.73-1.01)	[redacted]
Source	Navarese et al. (2015)	(Cholesterol Treatment Trialists et al., 2015)	Navarese et al. (2018)	De novo meta-regression

CI = confidence interval; CV = cardiovascular; IS = ischaemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; SA = stable angina; TIA = transient ischaemic attack; UA = unstable angina.

[a] Assuming an LDL-C level of [redacted] mmol/L.

B.3.2.3 Increased risk with multiple events

Patients with a prior CV event have a higher risk of future events. Consistent with this, an increase in event probabilities is modelled as further events are experienced in the model. This assumption in the model is informed by a publication by Smolina et al. (2012). This study of over 387,000 MIs in England found that the risk of death in survivors of a recurrent MI is 1.5 times higher than that for survivors of a first MI. Thus, the model increases the baseline probability of CV death in all post-event health states for the CV-populations by a factor of 1.5. This increase is also applied to the probability of recurrent CV events in all post-CV health states. In the base case, a recurrent cardiac event (MI, UA and SA) only affects the risk for cardiac events (MI, UA, SA and CV death) while a recurrent IS only affects the risk of IS and CV death.

B.3.2.4 Non-cardiovascular death

The probabilities of non-CV death for various age ranges and sex are based on UK Life Tables (ONS, 2018). By default, the model analyses a cohort over its remaining lifetime, which is assumed to be a maximum of 99 years of age. In the base case the risk of CV death (due to MI, aortic aneurysm and dissection, cardiac arrest, heart failure, ill-defined heart disease, and cerebrovascular events [selection of CV death was based on ESC guidelines of study endpoints] (Hicks et al., 2018)) was subtracted from the general population mortality data to derive the risk of death from other causes in the general population (to avoid double-counting of CV death as this is predicted from CV events in the model).

B.3.3 Measurement and valuation of health effects

B.3.3.1 Health-related quality-of-life data from clinical trials

No health-related quality of life (HRQOL) data were collected in the bempedoic acid or FDC trials.

B.3.3.2 Mapping

No mapping was performed.

B.3.3.3 Health-related quality-of-life studies

An SLR was undertaken to identify HRQOL studies relevant to the decision problem from the published literature. Detailed methods and results in the SLR are provided in Appendix H.

The SLR identified 18 studies reporting health-state utility estimates in a UK population with hypercholesterolaemia and mixed dyslipidaemia. Details of these studies and the health-state utility estimates are presented in Appendix I.

B.3.3.4 Adverse reactions

As detailed in Section B.2.10, in all three phase 3 pools (the High-Risk/Long-Term Pool, the No- or Low-Dose Statin Pool, and the Overall Phase 3 Pool), the adverse event preferred terms reported most frequently in bempedoic acid-treated patients occurred at similar rates in patients receiving placebo. No preferred term was reported at an incidence > 2% higher in the bempedoic acid group compared with the placebo group in the High-Risk/Long-Term Pool or Overall Phase 3 Pool. In line with the previous appraisals of alirocumab, evolocumab, and ezetimibe, no adverse events were modelled because no relevant economic or utility differences in the safety profiles of the drugs were identified.

B.3.3.5 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.3.5.1 Health-state utility estimates

HRQOL is not constant over time but varies according to CV events experienced in the model and age. We model utility by first applying an age-adjusted baseline utility weight with multiplicative CV disutilities based primarily on Health Survey for England data.

Acute and chronic disutilities are applied to reflect the greater disutility immediately after an event (i.e., during the first year after the CV event) and the stabilisation afterward (> 1 year after the CV event). Utilities are applied in a multiplicative manner. This is in line with recent International Society for Pharmacoeconomics and Outcomes Research Guidelines (Brazier et al., 2019) and the Technical Support Document (Ara and Wailoo, 2011) produced by NICE's Decision Support Unit, which states that when health-state utility values from cohorts with combined health conditions are not available, based on the current evidence, the multiplicative method should be used to combine the data derived from subgroups with the single health conditions. The multiplier used to combine these data should be estimated using age-adjusted data, rather than an assumption of perfect health, to increase accuracy in the estimated values.

To follow this methodology we mainly used a study by Ara and Brazier (2010). We selected this study as it was the most complete and coherent source of utility values for all the health states in the model. This study used data from the 2003 and 2006 Health Survey for England, which included questions about history of CVD and asked a random sample to complete the EQ-5D questionnaire. Preference-based health-state utility values for a range of CVD health states were estimated using the weights obtained using time trade-off valuations from the UK general public. The study included a regression by age for both patients without a history of a CV event, and for the general population, which allowed estimation of multipliers based on age-adjusted data, in line with Decision Support Unit guidance.

We apply the regression equation for individuals reporting no history of CVD derived from the analysis of Health Survey for England data:

- EQ-5D utility = $0.9454933 + 0.0256466 \times \text{male} - 0.0002213 \times \text{age} - 0.0000294 \times \text{age}^2$

Cardiovascular multipliers are then applied in the model to the age-adjusted baseline. Acute disutilities applied to the 0 to 1 years post-event state are based on the values in Ara and Brazier (2010) for patients with an event < 12 months ago. Chronic disutilities are based on the values in Ara and Brazier (for patients with an event > 12 months ago). For TIA health states we applied utility values based on Luengo-Fernandez et al. (2013a).

Table 56. Age-adjusted cardiovascular multipliers

Health state	Utility multiplier	N	SE	Reference	Age	Age-adjusted multipliers
SA < 1 year[a]	0.615	271	0.019	Ara and Brazier (2010)	68.8	0.765
SA > 1 year[a]	0.775	246	0.015		68.0	0.960
UA < 1 year[a]	0.615	271	0.019		68.8	0.765
UA > 1 year[a]	0.775	246	0.015		68.0	0.960
MI < 1 year[b]	0.615	271	0.019		68.8	0.765
MI > 1 year	0.742	206	0.019		65.1	0.906
IS < 1 year	0.626	76	0.038		67.9	0.775
IS > 1 year	0.668	291	0.018		66.8	0.822

Health state	Utility multiplier	N	SE	Reference	Age	Age-adjusted multipliers
TIA < 1 year	0.760	NR	0. 0.015	Luengo-Fernandez et al. (2013a)	73.0	0.968
TIA > 1 year	0.760	NR	0.020		73.0	0.968

CV = cardiovascular; IS = ischaemic stroke; MI = myocardial infarction; NR = not reported; SA = stable angina; SE = standard error; TIA, Transient ischaemic attack; UA = unstable angina.

[a] Angina was used for both SA and UA.

[b] Small sample size for acute MI (N=31), health state utility multiplier assumed to be the same as acute UA.

Source: NICE (2016d).

Ara and Brazier (2010) was used for the base-case scenario, as this is the most commonly used data source for these health states and precedent exists from a previous NICE appraisal (NICE, 2016a; NICE, 2016c). However, alternative utility weights were tested in the model using both the more recent utility data from (Pockett et al., 2018) for recent MI, history of MI, recent UA, history of UA, recent stroke, and history of stroke and the utilities used in previous NICE appraisals of the area (NICE, 2016b).

As described in section B.3.1.4 we blocked transitions from the IS health state to other health states to not allow for an increased utility because of events. This correction implies that we do not fully capture the negative utility effect of first year MI (0.765) compared with long-term IS (0.822). However, this is expected to have a limited effect on the results.

Table 57. Alternative source for utility estimates

Health state	Utility multiplier	N	SE	Reference	Age (years)	Male	Age- and sex-adjusted multipliers
MI < 1 year	0.702	733	0.290	Pockett et al. (2018)	67.4	0.704	0.86127
UA < 1 year	0.637	522	0.311		69.1	0.644	0.789991
IS < 1 year	0.496	13	0.362		75.9	0.759	0.636882
MI > 1 year	0.706	888	0.336		68.9	0.704	0.87297
UA > 1 year	0.611	635	0.352		70.6	0.644	0.763897
IS > 1 year	0.527	16	0.403		77.4	0.759	0.682906

IS = ischaemic stroke; MI = myocardial infarction; SE = standard error; UA = unstable angina.

B.3.4 Cost and health care resource use identification, measurement and valuation

The types of costs considered in the economic model included drug costs related to the intervention, monitoring and management of the disease, management of cardiovascular events, and costs associated with management of adverse events associated with treatments.

An SLR was conducted to identify costs and resource use in the treatment and ongoing management

of patients with hypercholesterolaemia and mixed dyslipidaemia from a UK perspective as described in Appendix J.

B.3.4.1 Intervention and comparators' costs and resource use

B.3.4.1.1 Drugs and administration

The drug costs are calculated, assuming that any unused drug (due to dose reductions or treatment pauses) is carried over to the next treatment cycle and any unused drug in dispensed packs on treatment discontinuation is wasted. Treatment costs are not linked to events in the model but are calculated independently from the model health states using treatment discontinuation data from the trials.

The model includes the option to administer bempedoic acid as:

1. Bempedoic acid single agent
2. FDC

The cost of comparators and background therapies is listed in Table 58. On the basis of data availability, acquisition costs were sourced from lowest cost in the drug and pharmaceutical electronic market information tool (Department of Health), the NICE British National Formulary (British Medical Association RPS, 2019) or (MIMS, 2019). Costs are calculated as an annual cost and are applied throughout the model until death or discontinuation.

Table 58. Drug cost Bempedoic acid, background therapies, and comparators

Treatment	Dose	Annual Cost (£)
Bempedoic acid	180 mg daily	[redacted]
FDC	180 mg with 10 mg daily	[redacted]
Ezetimibe	10 mg daily	24.26
Atorvastatin	10 mg daily	8.87
	20 mg daily	12.65
	40 mg daily	15.91
	80 mg daily	23.74
Rosuvastatin	5 mg daily	17.48
	10 mg daily	19.05
	20 mg daily	24.39
	40 mg daily	30.26
Simvastatin	40 mg daily	13.44
	80 mg daily	21.13
Alirocumab	75 mg per 2 weeks	4,383.00
	150 mg per 2 weeks	4,383.00

Treatment	Dose	Annual Cost (£)
Evolocumab	140 mg per 2 weeks	4,437.79

FDC = bempedoic acid and ezetimibe fixed-dose combination.

Source: British Medical Association RPS (2019); MIMS (2019).

For simplicity, and as the background treatment with statins was not expected to differ between the treatment arms, atorvastatin was assumed to be used in all patients with background statin treatment. Other options are available in the model but have a minimal impact on the result.

The cost for administration of oral drugs is assumed to be zero. Bempedoic acid and FDC are anticipated to be prescribed in both primary and secondary care settings in England whilst alirocumab and evolocumab are prescribed by specialists in a hospital setting only and are self-administered as subcutaneous injection, with assistance provided during regular check-ups. Those requiring help with administration would almost certainly be needing help for other reasons, so administration is unlikely to place a significant extra burden on the health care systems. One-off cost of 1 hour of training with a nurse was assumed for all patients treated with subcutaneous administration. The model includes an option to add administration cost for the various treatments.

The model includes the option to explore independently the discounts from the listed price for alirocumab and evolocumab as they currently have patient access scheme discounts in the UK (NICE, 2019).

Discontinuation and compliance

No study has assessed the long-term discontinuation rate of bempedoic acid and the rates for the comparators vary depending on study, definition, and setting. The possibility to adjust the dose for statin treatments makes long-term evidence from statin trials less accurate to estimate the adherence to bempedoic acid. Long-term data of evolocumab showing an annualised rate of 6.7% was therefore used in the base case (Koren et al., 2019). This is similar to the ERG treatment discontinuation of 8% in the alirocumab NICE submission (NICE, 2016a).

It is likely that the discontinuation rates in a real-world setting differs from the rates in the studies. The absolute rates are not expected to be an important parameter for the cost-effective analysis, but the relative rates between the compared interventions are important. Hence, a conservative approach was to consider the same discontinuation rates for all treatments. When patients discontinue bempedoic acid or comparator treatment, it is assumed that they no longer receive the benefits of treatment or incur the costs of treatment. After patients discontinue bempedoic acid or comparator treatment, it is assumed that they return to the baseline CV risk associated with that cohort. It is worth noting that patients who discontinue bempedoic acid or comparator treatment are still on background therapy.

The discontinuation rates applied in the model are presented in Table 59.

Table 59. Annual discontinuation rates

Treatment	Mean (CI)	Source
FDC	6.7% (6.0%-7.4%)	Assumed the same as evolocumab
Bempedoic acid with ezetimibe as background treatment	6.7% (6.0%-7.4%)	Assumed the same as evolocumab
Ezetimibe	6.7% (6.0%-7.4%)	Assumed the same as evolocumab
Alirocumab	6.7% (6.0%-7.4%)	Assumed the same as evolocumab
Evolocumab	6.7% (6.0%-7.4%)	Koren et al. (2019)

CI = confidence interval; FDC = bempedoic acid and ezetimibe fixed-dose combination.

Subsequent treatment

The model includes an option to allow for the cost of subsequent treatment but no subsequent treatment was assumed in the base case.

B.3.4.1.2 Cost of monitoring

Monitoring for patients receiving bempedoic acid may not differ from patients receiving comparator therapies, particularly as bempedoic acid is mainly given on top of other therapies. However, as patients receiving more effective therapies are expected to live longer, the monitoring cost and resource use presented in Table 60 have been applied (consistent with previous NICE appraisals).

Resource use associated with monitoring of treatment was obtained from CG181 since it was used in previous NICE assessments (NICE, 2016a; NICE, 2016b; NICE, 2016c; NICE, 2016d).

Table 60. Monitoring cost and resource use

Resource use	1st year	Subsequent years	Source	Cost	Source
Routine appointments:					
Appointment to take blood sample (with health care assistant)	2	1	CG181 (NICE)	£6.66	PSSRU (2018) (Curtis and Burns)
GP appointment	2	2		£37.40	
Blood tests:					
Total cholesterol	2	1	CG181 (NICE)	£1.03	Assumption (NICE, 2016d)
HDL cholesterol	2	1		£1.03	
Liver transaminase (ALT or AST)	2	1		£1.03	
Total annual monitoring costs, first year				**£94.29**	
Total annual monitoring costs, subsequent years				**£84.55**	

ALT = alanine amino transferase; AST = aspartate aminotransferase; HDL = high-density lipid; GP = general practitioner; PSSRU = Personal Social Services Research Unit.

B.3.4.2 Health-state unit costs and resource use

There is limited published literature that explores in detail the resource use associated with adults with hypercholesterolaemia and mixed dyslipidaemia. However, data of unit costs and resource use from a large UK study of patients treated with lipid-modifying therapy (Danese et al., 2016) is applicable for this population and therefore used in the base case. For SA and death events, these data were complemented with data from a UK registry study (Walker et al., 2016) and data from CG181 (NICE, 2016b).

As in the study by Danese et al. (2016), the model separates the costs for the first 3 years post-CV event and the cost for the third year is applied for the rest of the patient's life or until another event. If the patient has a subsequent CV event, the model stops incurring costs for the first event once the second event occurs. For example, if a patient has an IS 1 year after an MI, the patient only incurs the event and first-year costs of the MI and then starts to incur the costs of the IS, without ever incurring the second- or third-year costs of the MI.

Table 61 presents details for the yearly health-state costs used in the model.

Table 61. Health-state costs

Health state	Event and first-year cost (£) (SE)	Incremental second-year costs (£) (SE)	Incremental third-year costs* (£) (SE)	Source[a]
SA	£7,907.06	£245.31	£245.31	CG181 (NICE, 2016b)
UA	£2,469.42 (50.81)	£381.40 (74.47)	£381.40 (74.47)	Danese et al. (2016)
MI	£4,861.80 (95.51)	£979.98 (134.53)	£979.98 (134.53)	Danese et al. (2016)
Revascularisation	£5,682.03 (85.13)			Danese et al. (2016)
CV death	236.11	—	—	Walker et al. (2016)
IS	£4,205.58 (103.05)	£974.56 (261.93)	£974.56 (261.93)	Danese et al. (2016)
TIA	£2,011.49 (68.74)	£810.38 (146.55)	£810.38 (146.55)	Danese et al. (2016)

CV = cardiovascular; IS = ischaemic stroke; MI = myocardial infarction; SA = stable angina; SE = standard error; TIA = transient ischaemic attack; UA = unstable angina.

* Applied for the rest of the patient's life in the base-case.

[a] The costs are inflated to 2019 values using the hospital & community health services index (Curtis and Burns, 2018).

The negative value for CV death is due to the lower cost of CV deaths than non-CV deaths in the study published by Walker et al. (2016). As the cost-effectiveness is calculated using a lifelong time horizon it is reasonable to apply this negative cost for CV death.

Additional scenario analyses were performed using data from previous NICE appraisals (NICE, 2016a;

NICE, 2016c) for MI, UA, TIA, CV death, non-CV death, and IS health states, as these have been frequently used for cost-effectiveness models, but these data are not as recent and do not include as relevant patients as Danese et al. (2016). Danese et al. (2016) include only patients with lipid-lowering therapy and therefore is especially relevant for this analysis. Further, additional data (Luengo-Fernandez et al., 2012; Luengo-Fernandez et al., 2013b; Luengo-Fernandez et al., 2013c) were also considered for the IS health states because the data for IS in the previous models were criticised by the ERGs (NICE, 2016a; NICE, 2016c). However, compared with Danese et al. (2016), these studies included a less relevant patient population. No unique resource use or cost data were identified for the models developed for HTA submission; hence, these were not considered.

B.3.4.3 Adverse reaction unit costs and resource use

As described in Section B.3.3.4, no adverse events are modelled in line with previous NICE appraisals in the disease area (NICE, 2016a; NICE, 2016c; NICE, 2016d).

B.3.4.4 Miscellaneous unit costs and resource use

No societal cost was included in the base case. However, several studies have showed high costs and disutilities for informal care of stroke survivors (Joo et al., 2017; Persson et al., 2017a; Persson et al., 2017b). A scenario analyses are available in the model using costs and resource use from Persson et al. (2017b) as this study of Swedish patients was considered most relevant to a UK setting of the identified studies.

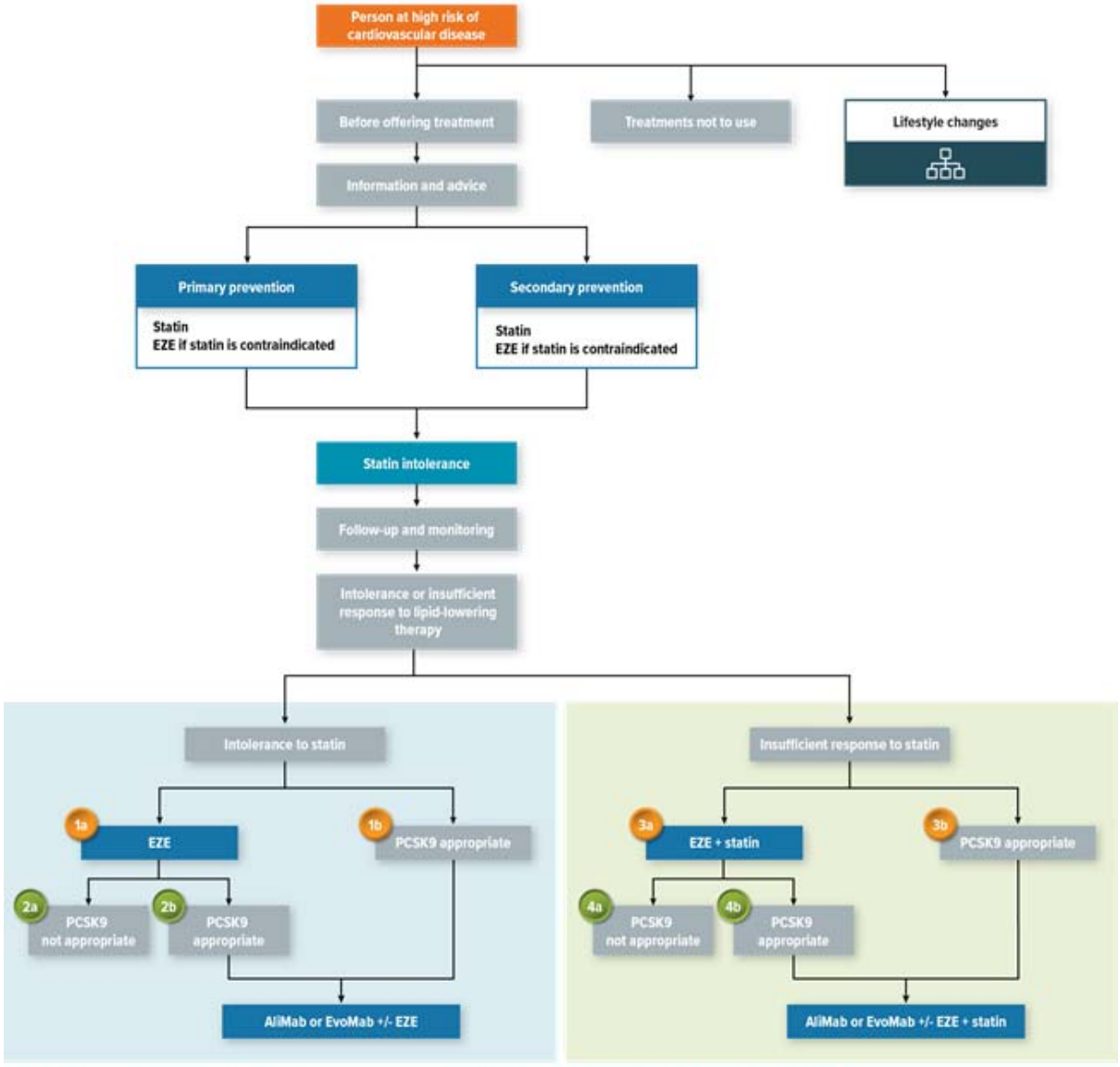
There are no other miscellaneous resource use items.

B.3.4.5 Summary of base-case analysis inputs and assumptions

B.3.4.6 Summary of base-case analysis inputs

We present cost-effectiveness results for the comparisons presented in Table 62. Analyses are presented for each of the target positions in the pathway (positions 2a, 2b, 4a, and 4b in Figure 19). The base-case population characteristics and source of treatment effect estimates for each of these comparisons are presented in Table 63.

Figure 19. NICE pathway and proposed placement of bempedoic acid and FDC



Position	Background therapy	Intervention	Phase 3 trial evidence for BA / FDC
1	None	BA	CLEAR Serenity (1002-046)
		FDC	Position not clinically relevant
2	Ezetimibe	BA	CLEAR Tranquility (1002-048)
		FDC[a]	CLEAR Tranquility (1002-048) [SE]
3	Maximally tolerated stain	BA	CLEAR Harmony (1002-040); CLEAR Wisdom (1002-047)
		FDC	Position not clinically relevant
4	Maximally tolerated stain and ezetimibe	BA	CLEAR Harmony (1002-040); CLEAR Wisdom (1002-047); 1002FDC-053
		FDC[a]	1002FDC-053

BA = bempedoic acid 180 mg oral once daily; EZE = ezetimibe 10 mg once daily; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NICE = National Institute for Health and Care Excellence; PCSK9 = proprotein convertase subtilisin/ kexin type 9.

Table 62. Comparative analyses presented

Situation	Position (Figure 3)[a]	Comparator	Section in which results are presented	
			Bempedoic acid[b]	FDC
When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C	2a	No additional treatment, on background ezetimibe (when evolocumab and alirocumab are not appropriate)	Section B.4	Section B.5
	2b	Evolocumab (with or without another lipid-lowering therapy)		
		Alirocumab (with or without another lipid-lowering therapy)		
When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C	4a	No additional treatment, on background ezetimibe with a statin (when evolocumab and alirocumab are not appropriate)		
	4b	Evolocumab with a statin (with or without another lipid-lowering therapy)		
		Alirocumab with a statin (with or without another lipid-lowering therapy)		

LDL-C = low-density lipoprotein cholesterol.

[a] Positions ending “a” relate to when alirocumab or evolocumab are not appropriate. Positions ending “b” relate to when alirocumab or evolocumab are appropriate.

[b] Bempedoic acid on background ezetimibe.

Table 63. Baseline population characteristics for the potential positions of bempedoic acid and FDC

Position	2a	2b	4a	4b
Description	**When statins are contraindicated or not tolerated and alirocumab and evolocumab are not appropriate**	**When statins are contraindicated or not tolerated and alirocumab and evolocumab are appropriate**	**When maximally tolerated statin dose does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate**	**When maximally tolerated statin dose does not appropriately control LDL-C and alirocumab and evolocumab are appropriate**
Mean age	65.0	65.0	66.0	66.0
Female (%)	59.1%	59.1%	29.4%	29.4%
Diabetes (%)	[redacted]	[redacted]	[redacted]	[redacted]
No prior CV event (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior UA (%)	4.2%	20.0%	19.3%	19.5%
Prior MI (%)	9.5%	45.2%	47.5%	48.1%
Prior IS (%)	7.0%	33.2%	29.8%	30.2%
Recurrent CV (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean LDL-C[a]	[redacted]	[redacted]	[redacted]	[redacted]

CV = cardiovascular; FDC = bempedoic acid and ezetimibe fixed-dose combination; IS = ischaemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NA = not applicable; NMA_{BS} = network meta-analysis for patients on maximally tolerated statin (based on trials in patients receiving medium-to-high-intensity statin therapy); NMA_{SI} = network meta-analysis for statin-intolerant patients (based on trials in statin-intolerant patients or receiving no/VLD statin); SA = stable angina; TIA = transient ischaemic attack; UA = unstable angina; VLD – very low dose.

[a] Estimates are based on patient-level data from the CLEAR studies (Esperion Therapeutics data on file, 2019a) (see Table 50), Daiichi Sankyo Europe data on file (2019a), and Ward et al. (2007) via (NICE, 2016b).

Other base-case variables are summarised in Table 64.

Table 64. Summary of variables applied in the economic model in the base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Discount rate: outcomes	3.5%	Fixed	B.3.1.4
Discount rate: costs	3.5%	Fixed	B.3.1.4
Time horizon	55 years	Fixed	B.3.1.4
Efficacy			
LDL-C reductions in the statin-intolerant population (vs. ezetimibe)	Bempedoic acid[a] and FDC: [redacted] Alirocumab: [redacted] Evolocumab: [redacted]	Posterior distribution from the Bayesian NMA	B.3.2.1, Appendix D
LDL-C reductions in the background statins population (vs. ezetimibe)	Bempedoic acid[a] and FDC: [redacted] Alirocumab: [redacted] AliMab+ezetimibe: [redacted] Evolocumab: [redacted]	Posterior distribution from the Bayesian NMA	B.3.2.1, Appendix D
Risks			
CV risk reduction per 1 mmol/L reduction in LDL-C	CV death: 0.88 IS: 0.85 MI: 0.76 UA: 0.76 SA: 1.00 Revascularisation: 0.76 TIA: 1.00	LogNormal (−0.27464,0.02014) LogNormal (−0.27464,0.02014) LogNormal (−0.00012,0.01531) LogNormal (−0.27458,0.01678) Fixed LogNormal (−0.00026,0.02296) Fixed)	B.3.2.2
Risk for CV death (secondary prevention - diabetes)	MI < 12 months prior:6.0% MI 12-24 months: 4.1% MI > 36 months: 2.8% SA < 12 months prior: 2.7% SA 12-24 months: 2.7% SA > 36 months: 2.7% UA < 12 months prior: 6.0% UA 12-24 months: 4.1% UA > 36 months: 2.8% IS < 12 months prior: 4.2% IS 12-24months prior: 4.2%	Beta(59,924) Beta(37,865) Beta(302,10484) Beta(689,24830) Beta(689,24830) Beta(689,24830) Beta(59,924) Beta(37,865) Beta(302,10484) Beta(182,4151) Beta(182,4151)	B.3.1.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	IS > 36 months prior: 4.2% TIA < 12 months prior: 3.5% TIA 12-24 months prior: 3.5% TIA > 36 months prior: 3.5%	Beta(182,4151) Beta(24,668) Beta(24,668) Beta(24,668)	
Risk for CV death (secondary prevention – no diabetes)	MI < 12 months prior:2.9% MI 12-24 months: 2.2% MI > 36 months: 2.2% SA < 12 months prior: 2.0% SA 12-24 months: 2.0% SA > 36 months: 2.0% UA < 12 months prior: 2.9% UA 12-24 months: 2.2% UA > 36 months: 2.2% IS < 12 months prior: 3.8% IS 12-24months prior: 3.8% IS > 36 months prior: 3.8% TIA < 12 months prior: 3.5% TIA 12-24 months prior: 3.5% TIA > 36 months prior: 3.5%	Beta(99,3315) Beta(68,3023) Beta(732,32541) Beta(1709,83741) Beta(1709,83741) Beta(1709,83741) Beta(99,3315) Beta(68,3023) Beta(732,32541) Beta(490,12405) Beta(490,12405) Beta(490,12405) Beta(24,668) Beta(24,668) Beta(24,668)	B.3.1.5.1
Risk for IS (secondary prevention - diabetes)	MI < 12 months prior: 0.0173 MI 12-24 months: 0.012 MI > 36 months: 0.0093 SA < 12 months prior: 0.0093 SA 12-24 months: 0.0093 SA > 36 months: 0.0093 UA < 12 months prior: 0.0173 UA 12-24 months: 0.012 UA > 36 months: 0.0093 IS < 12 months prior: 0.028 IS 12 - 24months prior: 0.028 IS > 36 months prior: 0.028 TIA < 12 months prior: 0.0423 TIA 12-24 months prior: 0.0423 TIA > 36 months prior: 0.0423	Beta(12,680) Beta(8,659) Beta(78,8279) Beta(192,20379) Beta(192,20379) Beta(192,20379) Beta(12,680) Beta(8,659) Beta(78,8279) Beta(87,3020) Beta(87,3020) Beta(87,3020) Beta(24,541) Beta(24,541) Beta(24,541)	B.3.1.5.1
Risk for IS (secondary prevention – no diabetes)	MI < 12 months prior: 0.008 MI 12-24 months: 0.0053 MI > 36 months: 0.0067 SA < 12 months prior: 0.008 SA 12-24 months: 0.008 SA > 36 months: 0.008 UA < 12 months prior: 0.008	Beta(20,2480) Beta(12,2238) Beta(167,24883) Beta(466,57784) Beta(466,57784) Beta(466,57784) Beta(20,2480)	B.3.1.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	UA 12-24 months: 0.0053 UA > 36 months: 0.0067 IS < 12 months prior: 0.024 IS 12 - 24months prior: 0.024 IS > 36 months prior: 0.024 TIA < 12 months prior: 0.0423 TIA 12-24 months prior: 0.0423 TIA > 36 months prior: 0.0423	Beta(12,2238) Beta(167,24883) Beta(226,9191) Beta(226,9191) Beta(226,9191) Beta(24,541) Beta(24,541) Beta(24,541)	
Risk for MI (secondary prevention - diabetes)	MI < 12 months prior: 0.052 MI 12-24 months: 0.028 MI > 36 months: 0.016 SA < 12 months prior: 0.0147 SA 12-24 months: 0.0147 SA > 36 months: 0.0147 UA < 12 months prior: 0.052 UA 12-24 months: 0.028 UA > 36 months: 0.016 IS < 12 months prior: 0.0147 IS 12 - 24months prior: 0.0147 IS > 36 months prior: 0.0147 TIA < 12 months prior: 0.0055 TIA 12-24 months prior: 0.0055 TIA > 36 months prior: 0.0055	Beta(37,675) Beta(19,660) Beta(125,7688) Beta(272,18273) Beta(272,18273) Beta(272,18273) Beta(37,675) Beta(19,660) Beta(125,7688) Beta(47,3158) Beta(47,3158) Beta(47,3158) Beta(25,4495) Beta(25,4495) Beta(25,4495)	B.3.1.5.1
Risk for MI (secondary prevention – no diabetes)	MI < 12 months prior: 0.0413 MI 12-24 months: 0.024 MI > 36 months: 0.0147 SA < 12 months prior: 0.0107 SA 12-24 months: 0.0107 SA > 36 months: 0.0107 UA < 12 months prior: 0.0413 UA 12-24 months: 0.024 UA > 36 months: 0.0147 IS < 12 months prior: 0.0107 IS 12 - 24months prior: 0.0107 IS > 36 months prior: 0.0107 TIA < 12 months prior: 0.0055	Beta(105,2435) Beta(53,2155) Beta(350,23514) Beta(671,62235) Beta(671,62235) Beta(671,62235) Beta(105,2435) Beta(53,2155) Beta(350,23514) Beta(103,9553) Beta(103,9553) Beta(103,9553) Beta(25,4495) Beta(25,4495) Beta(25,4495)	B.3.1.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	TIA 12-24 months prior: 0.0055 TIA > 36 months prior: 0.0055		
Risk for UA (secondary prevention - diabetes)	MI < 12 months prior: 0.0333 MI 12-24 months: 0.0213 MI > 36 months: 0.0107 SA < 12 months prior: 0.008 SA 12-24 months: 0.008 SA > 36 months: 0.008 UA < 12 months prior: 0.0333 UA 12-24 months: 0.0213 UA > 36 months: 0.0107 IS < 12 months prior: 0.0067 IS 12 - 24months prior: 0.0067 IS > 36 months prior: 0.0067 TIA < 12 months prior: 0 TIA 12-24 months prior: 0 TIA > 36 months prior: 0	Beta(25,725) Beta(14,642) Beta(90,8348) Beta(159,19716) Beta(159,19716) Beta(159,19716) Beta(25,725) Beta(14,642) Beta(90,8348) Beta(22,3278) Beta(22,3278) Beta(22,3278)	B.3.1.5.1
Risk for UA (secondary prevention – no diabetes)	MI < 12 months prior: 0.024 MI 12-24 months: 0.0133 MI > 36 months: 0.0067 SA < 12 months prior: 0.0053 SA 12-24 months: 0.0053 SA > 36 months: 0.0053 UA < 12 months prior: 0.024 UA 12-24 months: 0.0133 UA > 36 months: 0.0067 IS < 12 months prior: 0.004 IS 12 - 24months prior: 0.004 IS > 36 months prior: 0.004 TIA < 12 months prior: 0 TIA 12-24 months prior: 0 TIA > 36 months prior: 0	Beta(60,2440) Beta(29,2146) Beta(169,25181) Beta(349,65089) Beta(349,65089) Beta(349,65089) Beta(60,2440) Beta(29,2146) Beta(169,25181) Beta(38,9462) Beta(38,9462) Beta(38,9462)	B.3.1.5.1
Risk for elective revascularisation (secondary prevention - diabetes)	MI < 12 months prior: 0.0493 MI 12-24 months: 0.008 MI > 36 months: 0.0093 SA < 12 months prior: 0.0093 SA 12-24 months: 0.0093 SA > 36 months: 0.0093 UA < 12 months prior: 0.0493 UA 12-24 months: 0.008 UA > 36 months: 0.0093	Beta(37,713) Beta(5,620) Beta(69,7324) Beta(178,18893) Beta(178,18893) Beta(178,18893) Beta(37,713) Beta(5,620) Beta(69,7324)	B.3.1.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	IS < 12 months prior: 0.0053 IS 12 - 24months prior: 0.0053 IS > 36 months prior: 0.0053 TIA < 12 months prior: 0 TIA 12-24 months prior: 0 TIA > 36 months prior: 0	Beta(17,3171) Beta(17,3171) Beta(17,3171)	
Risk for elective revascularisation (secondary prevention – no diabetes)	MI < 12 months prior: 0.036 MI 12-24 months: 0.008 MI > 36 months: 0.0067 SA < 12 months prior: 0.0067 SA 12-24 months: 0.0067 SA > 36 months: 0.0067 UA < 12 months prior: 0.036 UA 12-24 months: 0.008 UA > 36 months: 0.0067 IS < 12 months prior: 0.0027 IS 12 - 24months prior: 0.0027 IS > 36 months prior: 0.0027 TIA < 12 months prior: 0 TIA 12-24 months prior: 0 TIA > 36 months prior: 0	Beta(94,2517) Beta(18,2232) Beta(147,21903) Beta(438,65262) Beta(438,65262) Beta(438,65262) Beta(94,2517) Beta(18,2232) Beta(147,21903) Beta(31,11594) Beta(31,11594) Beta(31,11594)	B.3.1.5.1
Risk for TIA (secondary prevention - diabetes)	MI < 12 months prior: 0.0087 MI 12-24 months: 0.006 MI > 36 months: 0.0047 SA < 12 months prior: 0.0047 SA 12-24 months: 0.0047 SA > 36 months: 0.0047 UA < 12 months prior: 0.0087 UA 12-24 months: 0.006 UA > 36 months: 0.0047 IS < 12 months prior: 0.014 IS 12 - 24months prior: 0.014 IS > 36 months prior: 0.014 TIA < 12 months prior: 0 TIA 12-24 months prior: 0 TIA > 36 months prior: 0	Beta(25,2834) Beta(25,4116) Beta(25,5306) Beta(25,5306) Beta(25,5306) Beta(25,5306) Beta(25,2834) Beta(25,4116) Beta(25,5306) Beta(25,1735) Beta(25,1735) Beta(25,1735)	B.3.1.5.1
Risk for TIA (secondary prevention – no diabetes)	MI < 12 months prior: 0.004 MI 12-24 months: 0.0027 MI > 36 months: 0.0033 SA < 12 months prior: 0.004 SA 12-24 months: 0.004 SA > 36 months: 0.004	Beta(25,6199) Beta(25,9324) Beta(25,7449) Beta(25,6199) Beta(25,6199) Beta(25,6199)	B.3.1.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	UA < 12 months prior: 0.004 UA 12-24 months: 0.0027 UA > 36 months: 0.0033 IS < 12 months prior: 0.012 IS 12 - 24months prior: 0.012 IS > 36 months prior: 0.012 TIA < 12 months prior: 0 TIA 12-24 months prior: 0 TIA > 36 months prior: 0	Beta(25,6199) Beta(25,9324) Beta(25,7449) Beta(25,2033) Beta(25,2033) Beta(25,2033)	
QRISK3 score (10 year risk of MI, IS, and CV death)	30.3%	20% SE assumed	B.3.1.5.1
Relative rates of events	CV Death: 25% IS: 52% MI: 24% UA: 12% SA: 50% TIA: 16%	20% SE assumed	B.3.1.5.1
Recurrent event multiplier	1.5	20% SE assumed	B.3.2.3
Age adjustments	Non-fatal events per year: 3% Fatal events per year: 5%	20% SE assumed	B.3.1.5.1
Costs			
Monitoring costs	First year: £94.29 Subsequent years: £84.55 Additional cost for PSCK9i first year: £42.00	20% SE assumed	B.3.4.1.2
Drug costs (pack prices)	BA : [redacted] (per 28 days) FDC: [redacted] (per 28 days) Alirocumab (Bi-weekly): £168.00 Evolocumab (Bi-weekly): £170.10 Ezetimibe: £1.86 Atorvastatin: £0.69 Atorvastatin: £0.81 Atorvastatin: £0.98 Atorvastatin: £1.65 Rosuvastatin: £1.44 Rosuvastatin: £1.41 Rosuvastatin: £2.01 Rosuvastatin: £2.40	Fixed	B.3.4.1.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Simvastatin: £0.87 Simvastatin: £1.49		
Health state costs	MI < 1 year: 4862 MI 1-2 years: 980 MI > 2 years: 980 SA < 1 year: 7907 SA 1-2 years: 245 SA > 2 years: 245 UA < 1 year: 2469 UA 1-2 years: 381 UA > 2 years: 381 Revascularisation: 5682 IS < 1 year: 4206 IS 1-2 years: 975 IS > 2 years: 975 TIA < 1 year: 2011 TIA 1-2 years: 810 TIA > 2 years: 810 CV death: −236	Gamma(2591,2) Gamma(53,18) Gamma(53,18) Gamma(25,316) Gamma(25,10) Gamma(25,10) Gamma(2362,1) Gamma(26,15) Gamma(26,15) Gamma(4455,1) Gamma(1666,3) Gamma(14,70) Gamma(14,70) Gamma(856,2) Gamma(31,27) Gamma(31,27) Gamma(123,-2)	B.3.4.2
Utility			
Health-state multipliers	No CVD: 1 SA < 1 year: 0.765 SA > 1 year: 0.96 UA < 1 year: 0.765 UA > 1 year: 0.96 MI < 1 year: 0.765 MI > 1 year: 0.906 TIA < 1 year: 0.968 TIA > 1 year: 0.968 IS < 1 year: 0.775 IS > 1 year: 0.822	Fixed Beta(380,117) Beta(163,7) Beta(380,117) Beta(163,7) Beta(380,117) Beta(216,23) Beta(129,4) Beta(76,3) Beta(93,27) Beta(370,80)	B.3.3.5.1
General population utility	Baseline: 0.9454933 Sex: 0.0256466 Age: 0.0002213 Age^2: 0.0000294	Normal SE: 0.01090134 Normal SE: 0.00512932 Normal SE: 0.00004426 Normal SE: 0.00000588	B.3.3.5
Discontinuation rate	BA: 6.7% Placebo: 6.7% Alirocumab: 6.7% Evolocumab: 6.7% EZE: 6.7%	Beta(328,4572) Beta(328,4572) Beta(328,4572) Beta(328,4572) Beta(328,4572) Beta(328,4572)	B.3.4.1.1

BA = bempedoic acid; CI = confidence interval; CV = cardiovascular; EZE = Ezetimibe; IS = ischaemic stroke; MI = myocardial infarction; PCSK9 = proprotein convertase subtilisin / kexin type 9; SA = stable angina; SE = standard error; TIA = transient ischaemic attack; UA = unstable angina.

[a] Efficacy of bempedoic acid added to background ezetimibe, versus ezetimibe background therapy.

B.3.4.7 Assumptions

Table 65 summarises the key assumptions made in the model.

Table 65. Key model assumptions

Assumption	Justification and/or Comments
LDL-C is a surrogate outcome for CV events	There is strong evidence that reducing LDL-C levels reduces CV events, (CTTC et al., 2015; Navarese et al., 2018) and this assumption has been accepted previously in NICE submissions (NICE, 2016a; NICE, 2016b; NICE, 2016c; NICE, 2016d)
THIN data are representative of UK general population CV risk in secondary prevention populations	THIN is a general practice medical records database containing medical records from over 12 million patients, of which over 3.6 million are actively registered. It has been used previously in UK research, for example, in development of the QRISK score. This assumption has also been used in earlier NICE appraisals (NICE, 2016a).
Distribution of risks in (Ward et al., 2007) is relevant for a primary prevention population	It is likely that this is reflective of the UK as (Ward et al., 2007) used UK registry data to calculate the distribution of different CV events. This assumption has also been used in earlier NICE appraisals and guidelines (NICE, 2016b; NICE, 2016d).
Patients no longer benefit from any continuation of treatment effects after treatment discontinuation	The most conservative assumption that has been previously used in NICE appraisals (NICE, 2016a).
No additional cost of monitoring and administration is associated with bempedoic acid treatment	Accepted in previous NICE submissions as the patients treated with bempedoic acid are likely to receive other treatments and, therefore, no additional visits would be needed.

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; NICE = National Institute for Health and Care Excellence.

B.4 Cost-effectiveness results for bempedoic acid

B.4.1.1 Bempedoic acid base-case results

The results of the model with base-case assumptions are presented below. Total costs, LYs, QALYs, and incremental costs per QALY for bempedoic acid in positions 2 and 4 are presented in Table 66. As shown in the table, bempedoic acid implied a positive net monetary benefit versus no further treatment with background ezetimibe in position 2a. Further, alirocumab and evolocumab implied a negative net monetary benefit versus bempedoic acid in positions 2b and 4b.

Table 66. Bempedoic acid base-case fully incremental cost effectiveness results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)	
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate										
No further treatment/placebo with background ezetimibe	8,202.62	11.58	8.57							
Bempedoic acid with background ezetimibe	14,084.75	11.82	8.76	5,882.13	0.24	0.20	−1,926.02	−1,926.02	52.04	52.04
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate										
Bempedoic acid with background ezetimibe	18,672.47	10.07	6.94							
Alirocumab	41,516.34	10.15	7.00	22,843.87	0.09	0.06	−21,614.94	−21,614.94	−21,000.47	−21,000.47
Evolocumab	41,949.52	10.19	7.03	23,277.05	0.13	0.09	−21,486.24	128.70	−20,590.83	409.64
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate										
No further treatment/placebo with background ezetimibe	12,689.77	9.80	6.81							
Bempedoic acid with background ezetimibe	18,110.56	9.91	6.89	5,420.79	0.11	0.08	−3,888.70	−3,888.70	−3,122.66	−3,122.66
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate										
Bempedoic acid with background ezetimibe	18,089.59	9.35	6.48							
Alirocumab	40,210.11	9.63	6.69	22,120.52	0.28	0.20	−18,029.66	−18,029.66	−15,984.23	−15,984.23
AliMab+ezetimibe	40,430.00	9.67	6.71	22,340.41	0.32	0.23	−17,755.36	274.30	−15,462.83	521.40
Evolocumab	40,919.10	9.81	6.82	22,829.52	0.46	0.34	−16,124.95	1,630.41	−12,772.66	2,690.17

AliMab = alirocumab; NMB = net monetary benefit; LY = life-year; QALY = quality-adjusted life year.

B.4.2 Bempedoic acid sensitivity analyses

B.4.2.1 Bempedoic acid probabilistic sensitivity analysis

A second-order Monte Carlo simulation was run for 5,000 iterations. Results of the probabilistic sensitivity analysis are shown in Table 67, which also shows results from the deterministic analysis for comparison. The probabilistic mean NMB results were similar to the deterministic results.

Table 67. Results of the probabilistic sensitivity analysis for bempedoic acid

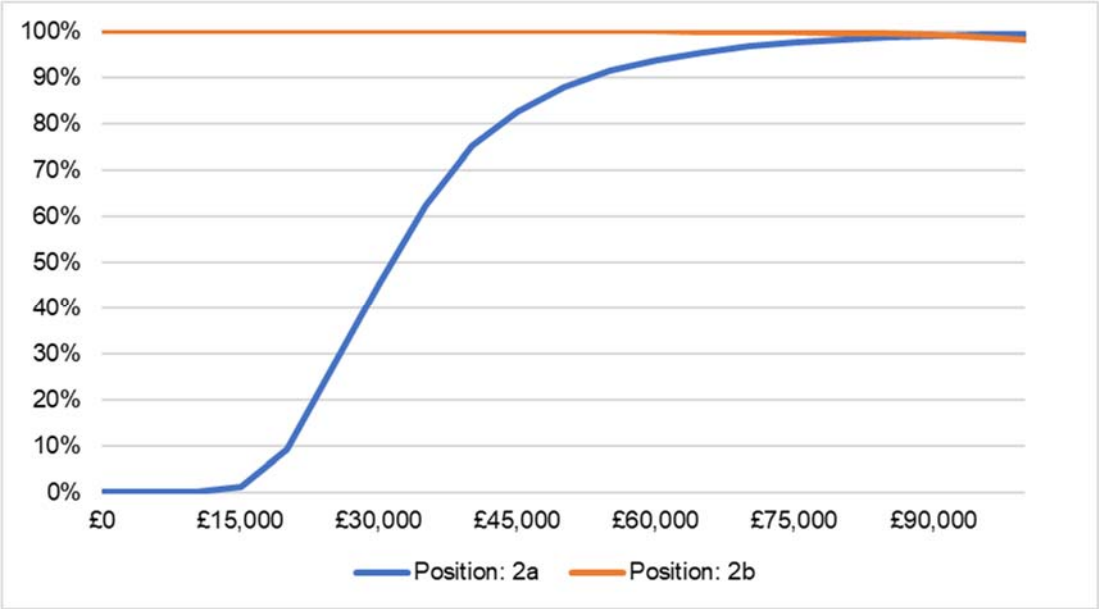
Position (Figure 3)	Comparator	Deterministic NMB	Probabilistic mean NMB	95% CrIs for NMB	Probability of cost-effectiveness	
					£20,000/QALY	£30,000/QALY
2a	No further treatment/placebo with background ezetimibe	−£1,926	−£1,985	(1157, -4499)	9.3%	45.5%
2b	Evolocumab	£21,615	£21,831	(18770,24420)	100.0%	100.0%
	Alirocumab	£21,486	£21,688	(18554, 24327)		
4a	No further treatment/placebo with background ezetimibe + statin	−£3,889	−£3,997	(-914, -5940)	0.8%	6.4%
4b	AliMab + statin	£18,030	£18,027	(11729,22194)	100.0%	98.6%
	AliMab + ezetimibe +statin	£17,755	£17,752	(11054, 22244)		
	EvoMab +statin	£16,125	£16,120	(8809, 21060)		

AliMab = alirocumab; CrI = credible interval; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NMB = net monetary benefit.

Note: the NMB is presented at £20,000 per QALY.

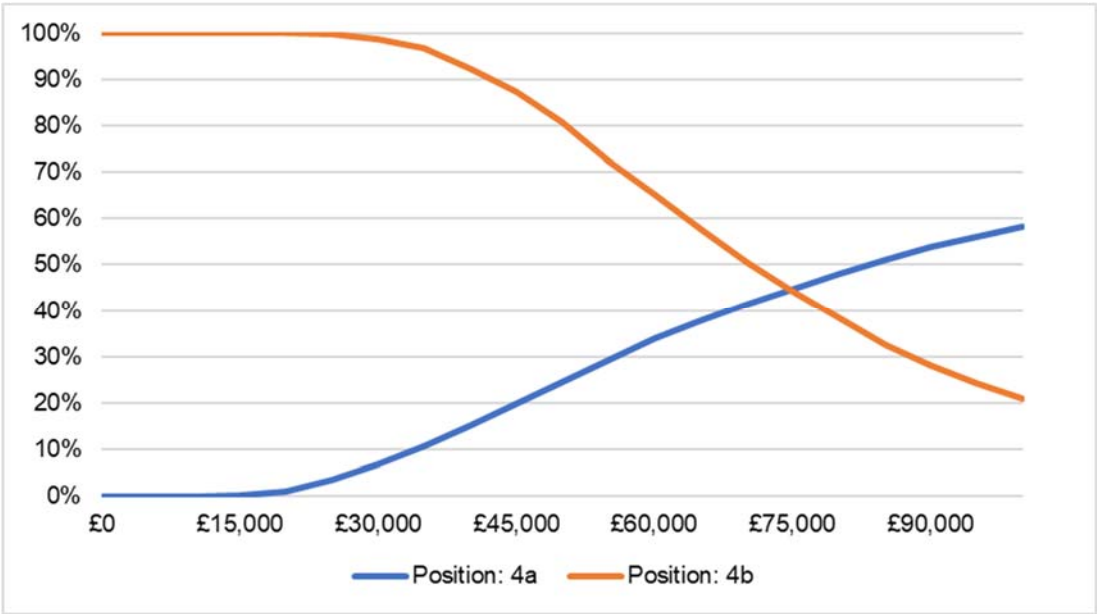
Figure 20 presents the cost-effectiveness acceptability curves for bempedoic acid in positions 2a and 2b. Figure 21 presents the cost-effectiveness acceptability curves for bempedoic acid in positions 4a and 4b. The probability of cost-effectiveness in each of the positions is presented in Table 67.

Figure 20. Cost-effectiveness acceptability curve: bempedoic acid when statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C



QALY = quality-adjusted life year.

Figure 21. Cost-effectiveness acceptability curve: bempedoic acid when maximally tolerated statin dose and ezetimibe does not appropriately control LDL-C

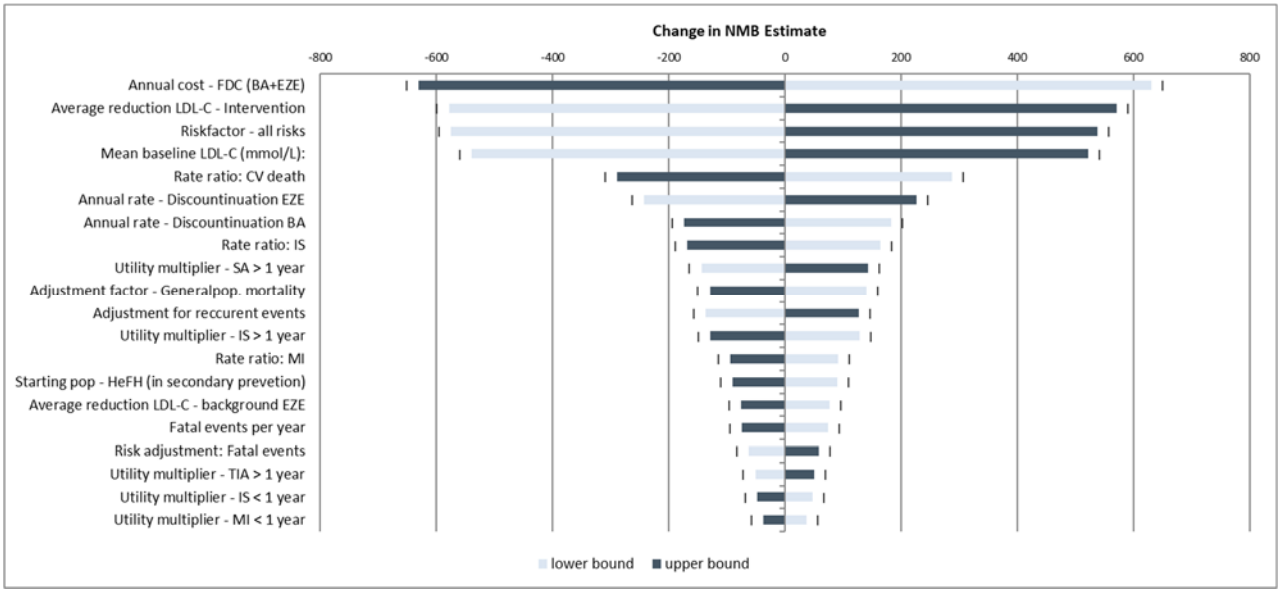


LDL-C = lower density lipoprotein cholesterol; QALY = quality-adjusted life year.

B.4.2.2 Bempedoic acid deterministic sensitivity analysis

Figure 22 presents the tornado diagram for position 2a. The largest impact on the NMB is driven by cost of bempedoic acid, average reduction in LDL-C by bempedoic acid, and the risk for CV events. Tornado diagrams for the other positions are presented in the Appendix K3, and the results are summarised in Table 68.

Figure 22. Tornado diagram for bempedoic acid in position 2a



AE = adverse event; NMB = incremental cost-effectiveness ratio.

Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). NMB calculated using £30,000 per QALY.

Table 68. Summary of bempedoic acid deterministic sensitivity analyses

Position	Most influential parameters	Lower Bound NMB	Upper Bound NMB
2a	[redacted]	[redacted]	[redacted]
	Average reduction LDL-C - Intervention	−578	571
	Risk factor - all risks	−575	538
	Mean baseline LDL-C (mmol/L):	−539	522
2b	Average reduction LDL-C - AliMab	946	−934
	Average reduction LDL-C - Intervention	−769	761
	Annual rate - Discontinuation AliMab	−636	598
	[redacted]	[redacted]	[redacted]
4a	[redacted]	[redacted]	[redacted]
	Risk factor - all risks	−281	264
	Average reduction LDL-C - Intervention	−223	222

Position	Most influential parameters	Lower Bound NMB	Upper Bound NMB
	Mean baseline LDL-C (mmol/L):	−207	204
4b	Average reduction LDL-C - AliMab	945	−933
	[redacted]	[redacted]	[redacted]
	Mean baseline LDL-C (mmol/L):	532	−515
	Annual rate - Discontinuation AliMab	−534	504

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein-cholesterol; NMB = net monetary benefit at £30,000/QALY.

B.4.2.3 Bempedoic acid scenario analysis

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. All undertaken scenario analyses are presented in Table 69 to Table 72. Using a different meta-regression for the relationship between LDL-C reductions and CV events had the largest impact on the NMB. For all other scenarios, the impact on the NMB was marginal.

Table 69. Bempedoic acid scenario analyses – position 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate

Scenario	Alternative input	Base-case value	Comparator	Incremental costs (£)	Incremental QALYs	NMB: £20,000/QALY (£)	NMB: £30,000/QALY (£)
Base case			No further treatment	5,882	0.20	−1,926	52
1	Discount rate benefits 1.5%	Discount rate benefits 3.5%	No further treatment	5,882	0.26	−729	1,847
2	De novo meta regression for relationship between LDL-C and CV events	CTTC meta regression for relationship between LDL-C and CV events	No further treatment	6,062	0.25	−1,012	1,513
3	CG181 utility estimates	Ara and Brazier (2010) Luengo-Fernandez et al. (2013)	No further treatment	5,882	0.20	−1,834	190
4	TA393 health state costs	Danese et al. (2016) Walker et al. (2016)	No further treatment	5,693	0.20	−1,737	241

NMB = net monetary benefit; QALY = quality-adjusted life year.

Table 70. Scenario analyses – position 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate

Scenario	Alternative input	Base-case value	Comparator	Incremental costs (£)	Incremental QALYs	NMB: £20,000/QALY (£)	NMB: £30,000/QALY (£)
Base case			Alirocumab	−22,844	−0.06	21,615	21,000
			Evolocumab	−23,277	−0.09	21,486	20,591
1	Discount rate benefits 1.5%	Discount rate benefits 3.5%	Alirocumab	−22,844	−0.08	21,290	20,513
			Evolocumab	−23,277	−0.11	21,012	19,879
2	De novo meta regression for relationship between LDL-C and CV events	CTTC meta regression for relationship between LDL-C and CV events	Alirocumab	−24,123	−0.10	22,053	21,018
			Evolocumab	−24,660	−0.15	21,656	20,155
3	CG181 utility estimates	Ara and Brazier (2010) Luengo-Fernandez et al. (2013)	Alirocumab	−22,844	−0.06	21,717	21,154
			Evolocumab	−23,277	−0.08	21,636	20,815
4	TA393 health state costs	Danese et al. (2016) Walker et al. (2016)	Alirocumab	−22,829	−0.06	21,600	20,986
			Evolocumab	−23,255	−0.09	21,465	20,569

CTTC = Cholesterol Treatment Trialists Collaboration; NMB = net monetary benefit; QALY = quality-adjusted life year.

Table 71. Scenario analyses – position 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate

Scenario	Alternative input	Base-case value	Comparator	Incremental costs (£)	Incremental QALYs	NMB: £20,000/QALY (£)	NMB: £30,000/QALY (£)
Base case			No further treatment	5,421	0.08	−3,889	−3,123
1	Discount rate benefits 1.5%	Discount rate benefits 3.5%	No further treatment	5,421	0.10	−3,499	−2,538
2	De novo meta regression for relationship between LDL-C and CV events	CTTC meta regression for relationship between LDL-C and CV events	No further treatment	5,410	0.07	−4,064	−3,391
3	CG181 utility estimates	Ara and Brazier (2010) Luengo-Fernandez et al. (2013)	No further treatment	5,421	0.07	−4,000	−3,289
4	TA393 health state costs	Danese et al. (2016) Walker et al. (2016)	No further treatment	5,396	0.08	−3,864	−3,098

CTTC = Cholesterol Treatment Trialists; NMB = net monetary benefit; QALY = quality-adjusted life year.

Table 72. Scenario analyses – position 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate

Scenario	Alternative input	Base-case value	Comparator	Incremental costs (£)	Incremental QALYs	NMB: £20,000/QALY (£)	NMB: £30,000/QALY (£)
Base case			Alirocumab	−22,121	−0.20	18,030	15,984
			Alirocumab+ezetimibe	−22,340	−0.23	17,755	15,463
			Evolocumab	−22,830	−0.34	16,125	12,773
1	Discount rate benefits 1.5%	Discount rate benefits 3.5%	Alirocumab	−22,121	−0.26	17,019	14,468
			Alirocumab+ezetimibe	−22,340	−0.29	16,620	13,760
			Evolocumab	−22,830	−0.42	14,453	10,265
2	De novo meta regression for relationship between LDL-C and CV events	CTTC meta regression for relationship between LDL-C and CV events	Alirocumab	−23,542	−0.35	16,449	12,902
			Alirocumab+ezetimibe	−23,848	−0.40	15,924	11,962
			Evolocumab	−24,665	−0.57	13,249	7,541
3	CG181 utility estimates	Ara and Brazier (2010) Luengo-Fernandez et al. (2013)	Alirocumab	−22,121	−0.19	18,338	16,447
			Alirocumab+ezetimibe	−22,340	−0.21	18,101	15,981
			Evolocumab	−22,830	−0.31	16,631	13,532
4	CG181/TA393 cost estimates	Danese et al. (2016) Walker et al. (2016)	Alirocumab	−22,060	−0.20	17,969	15,924
			Alirocumab+ezetimibe	−22,273	−0.23	17,688	15,395
			Evolocumab	−22,730	−0.34	16,026	12,673

CTTC = Cholesterol Treatment Trialists; NMB = net monetary benefit; QALY = quality-adjusted life year.

B.4.2.4 Bempedoic acid summary of sensitivity analyses results

As shown in this Section B.4.2.2, the results of the sensitivity analyses are robust and not sensitive to changes in important parameters. The scenario analyses show that the presented base-case incremental cost-effectiveness ratio is conservative in relation to many parameters.

B.4.3 Bempedoic acid subgroup analysis

We have explored in section B.4.1.1, as per the scope, the cost-effectiveness of bempedoic acid in clinically relevant patient subgroups, including patients with statin intolerance, on maximally tolerated statin dose, with various levels of severity of hypercholesterolaemia (varying baseline LDL-C), and varying CVD risk (primary prevention, and secondary prevention or HeFH). No further subgroup analyses are presented in this section.

B.5 Cost-effectiveness results for FDC

B.5.1 FDC base-case results

The results of the model with base-case assumptions are presented below. Total costs, LYs, QALYs, and incremental costs per QALY for bempedoic acid in positions 2 and 4 are presented in Table 73. As shown in the table, bempedoic acid implied a positive net monetary benefit versus no further treatment with background ezetimibe in position 2a. Further, alirocumab and evolocumab implied a negative net monetary benefit versus bempedoic acid in positions 2b and 4b.

Note that the results are the same as those presented in Section B.4.1.1 because the FDC price is equivalent to that for bempedoic acid with background ezetimibe.

Table 73. FDC base-case fully incremental cost effectiveness results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)	
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate										
No further treatment/placebo with background ezetimibe	8,202.62	11.58	8.57							
FDC	14,084.75	11.82	8.76	5,882.13	0.24	0.20	−1,926.02	−1,926.02	52.04	52.04
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate										
FDC	18,672.47	10.07	6.94							
Alirocumab	41,516.34	10.15	7.00	22,843.87	0.09	0.06	−21,614.94	−21,614.94	−21,000.47	−21,000.47
Evolocumab	41,949.52	10.19	7.03	23,277.05	0.13	0.09	−21,486.24	128.70	−20,590.83	409.64
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate										
No further treatment/placebo with background ezetimibe	12,689.77	9.80	6.81							
FDC	18,110.56	9.91	6.89	5,420.79	0.11	0.08	−3,888.70	−3,888.70	−3,122.66	−3,122.66
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate										
FDC	18,089.59	9.35	6.48							
Alirocumab	40,210.11	9.63	6.69	22,120.52	0.28	0.20	−18,029.66	−18,029.66	−15,984.23	−15,984.23
AliMab+ezetimibe	40,430.00	9.67	6.71	22,340.41	0.32	0.23	−17,755.36	274.30	−15,462.83	521.40
Evolocumab	40,919.10	9.81	6.82	22,829.52	0.46	0.34	−16,124.95	1,630.41	−12,772.66	2,690.17

AliMab = alirocumab; NMB = net monetary benefit; LY = life-year; QALY = quality-adjusted life year.

B.5.2 FDC sensitivity analyses

The cost of FDC is equivalent to bempedoic acid with background ezetimibe. Therefore, the sensitivity analysis results are the same as those already presented for bempedoic acid with background ezetimibe in section B.4.2. Please refer to section B.4.2 for FDC sensitivity and scenario analyses.

B.5.3 FDC subgroup analysis

We have explored in section B.5.1, as per the scope, the cost-effectiveness of FDC in clinically relevant patient subgroups, including patients with statin intolerance, on maximally tolerated statin dose, with various levels of severity of hypercholesterolaemia (varying baseline LDL-C), and varying CVD risk (primary prevention, and secondary prevention or HeFH). No further subgroup analyses are presented in this section.

B.6 Validation

B.6.1.1 Validation of cost-effectiveness analysis

The completed phase 3 studies investigating bempedoic acid and FDC provide LDL-C data for up to 52 weeks. Therefore, validation of long-term model predictions for cardiovascular events by comparison with the trial data has not been possible. Further, no data of the comparator arms was identified for the specific patient populations modelled in this submission.

B.6.1.2 Face validity

Throughout the development of the economic model and submission, clinical and economic expert advice was sought to ensure both clinical and economic validity.

A UK advisory board was held on 11 November 2019, attended by 5 clinical and HTA experts. The discussions focused on the following:

- Model structure
- Comparators and position in the treatment pathway
- Methodology of the NMA and de novo meta-regression
- Selection of the meta-analysis for the association between LDL-C lowering and cardiovascular risk for the base-case analysis
- Validation of resource use and costs included in the economic model

B.6.1.3 Internal validity

- Quality-control procedures for verification of input data and coding was performed by health economists working for a vendor not involved in the model development and in accordance with a pre-specified test plan. Procedures included verification of all input data with original sources and programming validation.
- Verification of all input data was documented (by the health economist performing the quality-control procedure and the date the quality-control procedure was performed) in the relevant worksheets of the model. Any discrepancies was discussed, and the model input data was updated where required.
- Programming validation included checks of the model results, calculations (including the testing extreme values), data references, model interface, and Visual Basic for Applications code.

B.6.1.4 Cross validity

No economic evaluations of bempedoic acid or FDC were identified by the SLR. A comparison of the model inputs with those for other relevant models used in previous NICE appraisals evaluating ezetimibe, alirocumab and evolocumab are presented in Table 74. As shown in the table, the inputs and assumptions used in the current model is similar to what has been previously used. When other sources or assumptions has been used this has been justified in earlier sections. Cost-effectiveness results from previous TAs could not be directly compared with the results from the de novo model, as

different populations were modelled.

Table 74. Summary of models inputs in NICE submissions for dyslipidemia

Model/ analysis	De novo model	CG181 (NICE, 2016b)	TA385 (NICE, 2016d)	TA393 (NICE, 2016a)	TA394 (NICE, 2016c)
Baseline risk primary prevention	QRISK2/3	QRISK2/ UKPDS	QRISK2	Not applicable (THIN data in HeFH patients)	Framingham (updated to QRISK2)
Source of baseline risk secondary prevention	THIN data and the South London Stroke Register for TIA (via NICE [2016b])	Nottingham Heart Attack Register And the South London Stroke Register	Nottingham Heart Attack Register And the South London Stroke Register	THIN data	REACH registry
LDL-C and CV event relationship	(Cholesterol Treatment Trialists et al., 2015)	Not applicable	(Cholesterol Treatment Trialists et al., 2010)	Navarese et al. (2015)— updated to (Cholesterol Treatment Trialists et al., 2015)	(Cholesterol Treatment Trialists et al., 2015)
Age adjustments	3% all non-fatal CV events. 5% all fatal CV events	0.03% for men, 0.008% for women	0.03% for male and 0.008% for female	3% all non-fatal CV events. 5% all fatal CV events	Unknown
Adjustment for recurrent events	1.5	Unknown	Unknown	1.5	Included in REACH equation
Utilities	SA < 1 year 0.765 SA > 1 year 0.960 UA < 1 year 0.765 UA > 1 year 0.960 MI < 1 year 0.765 MI > 1 year 0.906 TIA < 1 year: 0.968 TIA > 1 year: 0.968 IS < 1 year 0.775 IS	Stable angina 0.808 Post-stable angina 0.808 Unstable angina 0.770 Post-unstable angina 0.880 MI 0.760 Post-MI 0.880 TIA 0.900 Post-TIA 0.900	Unstable angina 0.770 Post-unstable angina 0.80 MI 0.760 Post-MI 0.80 Stroke 0.50 Post-stroke 0.628	NF MI 0.765 Post-MI 0.906 UA 0.765 Post-UA 0.960 ACS 0.765 Post-ACS 0.924 IS 0.775 Post-IS 0.822	ACS: 0.77 Post-ACS: 0.88 IS: 0.63 Post-IS: 0.63 HF: 0.68 Post-HF: 0.68

	> 1 year 0.822	Stroke 0.628 Post-stroke 0.628 Heart failure 0.683 Post-heart failure 0.683 PAD 0.808 Post-PAD 0.808			
Administration costs	Introduction of treatment has no effect on current administration costs	Introduction of treatment has no effect on current administration costs		Introduction of treatment has no effect on current administration costs	Training cost £84.00
Monitoring costs	CG181	First year: £120.17 Subsequent years: £100.71	CG181	CG181	CG181 and training with nurse for evolocumab treated patients
Health-state costs	High risk (no event) £0.00 MI < 1 year £4,861.80 MI 1-2 years £979.98 MI > 2 years £979.98 SA < 1 year £7,907.06 SA 1-2 years £245.31 SA > 2 years £245.31 UA < 1 year £2,469.42 UA 1-2 years £381.40 UA > 2 years £381.40 IS < 1 year £4,205.58 IS 1-2 years £974.56 IS > 2 years £974.56 TIA < 1 year £2,011.49 TIA 1-2 years £810.38	SA £7736 Post-SA £240 UA £3,313 Post-UA £385 MI £3,337 Post-MI £788 TIA £578 Post-TIA £124 Stroke £4,092 Post-stroke £155 Heart failure £2,297 Post-HF £2,597 PAD £952 Post-PAD £529	Unstable angina £575.21 Post-unstable angina £285.52 MI £6,154.50 Post-MI £625.27 Stroke £14,151.26 Post-stroke £3,927.73	NF MI first year 3337.00 NF MI second year+ 788.00 UA first year 3313.00 UA second year+385.00 ACS first year 3329.00 ACS second year+ 653.67 IS first year 4092.00 IS second year+ 155.00	No CVD (annual) £0.00 ECVD (annual) £522.34 ACS (annual) £3,263.63 Stroke (annual) £4,063.60 HF (annual) £3,178.32 Post-ACS (annual) £522.34 Post-stroke (annual) £887.33 Post-HF (annual) £1,078.26

	TIA > 2 years £810.38				
Event costs	CV death £2,116.79 Revascularisation £5,682.03	CV death £1,174	CV death £5,697.23	CV death 1174.00 Revascularisation 3802.32	CHD death (once only cost) £717.96 Stroke death (once only cost) £1,847.92 Revascularisation £5,648.60

ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; ECVD = Established CVD HeFH = heterozygous familial hypercholesterolaemia; HF = heart failure; IS = ischaemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NF = non-fatal; PAD = peripheral artery disease; SA = stable angina; THIN = The Health Improvement Network; TIA = transient ischaemic attack; UA = unstable angina; UKPDS = United Kingdom Prospective Diabetes Study.

B.6.1.5 External validity

Comparisons of model predictions with outcomes in the bempedoic acid and FDC studies used to build the model (i.e., dependent, external validity) is not possible as these studies provide LDL-C data for up to 52 weeks but no long-term CV event data. Compared with the general population the model predicts a shorter survival, which is expected as this is a high risk population. In the review of the literature we have not identified a study that match the populations simulated in the de novo model.

B.6.1.6 Quality check by an independent health economics research group

An independent health economics research group performed quality checks of the final model. The following checks were performed:

- Validation of the inputs and referencing in the model to ensure they have been traced and have been correctly transcribed from the original publications/sources
- Review of the model structure and data inputs in relation to previous hypercholesterolemia models
- Review of Visual Basic for Applications code
- Review of core engine calculations
- Logical tests
- Review of probabilistic and one-way sensitivity analysis

The reviewers concluded that, with a few minor corrections (which have been performed), the model is fit for purpose for a NICE HTA submission.

B.7 Interpretation and conclusions of economic evidence

B.7.1Consistency of the results from the economic evaluation with the published economic literature

This is, to our knowledge, the first economic evaluation undertaken for bempedoic acid or FDC in primary hypercholesterolaemia or mixed dyslipidaemia. Therefore, there are no published economic analyses with which to compare.

B.7.2 Generalisability of the results to clinical practice in England and relevance to all patients as identified in the decision problem

The analysis is likely to be directly applicable to clinical practice in England as follows:

- The CLEAR trials included [redacted] UK study sites and the patient population in the trials and the economic analysis are likely to be reflective of patients with primary hypercholesterolaemia or mixed dyslipidaemia in the UK in terms of baseline characteristics and the treatment pathway. Therefore, the clinical outcomes are likely to be applicable to the patient population in England.
- The economic model structure is in line with other hypercholesterolaemia models and previous submissions to NICE.
- Data sources for baseline risk of CV events and the relationship between LDL-C lowering and CV events have been validated by UK clinicians and have been accepted in previous NICE technology appraisals.
- The utility estimates have been validated by UK clinicians and were accepted in previous NICE technology appraisals.
- The resource use and costs in the analysis have been validated by UK clinicians and were sourced from UK-based publications (e.g., NHS Reference Costs and British National Formulary) and previous NICE technology appraisals.

B.7.3 Strengths and weaknesses of the evaluation

In terms of risk-equations, baseline risks, unit costs, resource utilisation, and utilities, inputs were validated and aligned with previous NICE technology appraisals and identified from UK sources when possible. A limitation with the results of the current analyses is that the cost of all treatments is based on list prices. This is aligned with NICE's request during the decision problem meeting, but results are likely to be subject to change because of the patient access schemes agreed for alirocumab and evolocumab.

B.7.4 Cost-effectiveness of bempedoic acid

When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C, treatment with bempedoic acid resulted in a positive net monetary benefit (£52) compared with no additional treatment on background ezetimibe using a threshold value of £30,000/QALY. Further, in patients where alirocumab and evolocumab are appropriate, bempedoic acid was cost-effective as

alirocumab and evolocumab provided a negative net monetary benefit compared with bempedoic acid.

When maximally tolerated statin dose and ezetimibe do not appropriately control LDL C, treatment with bempedoic acid resulted in an increase of QALYs compared with no additional treatment on background ezetimibe but a negative net monetary benefit (£-3,123) using a threshold value of £30,000/QALY. However, in patients where alirocumab and evolocumab are appropriate, bempedoic acid was cost-effective as alirocumab and evolocumab provided a negative net monetary benefit compared with bempedoic acid.

The conclusions were consistent across a range of scenario and sensitivity analyses.

B.7.4.1 Cost-effectiveness of FDC

The cost-effectiveness results for FDC were the same as for bempedoic acid with background ezetimibe, as the price and efficacy were equivalent.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Clarification questions

December 2019

File name	Version	Contains confidential information	Date
ID1515 Clarification questions	2.0	Yes	16 January, 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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[redacted]

Table 1. Anticipated indication for the FDC of bempedoic acid and ezetimibe as described in the draft SmPC

[redacted]	[redacted]

EMA = European Medicines Agency; FDC = bempedoic acid plus ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; SmPC = summary of product characteristics.

Section A: Clarification on effectiveness data

The ERG has concerns about the LDL-C treatment effects derived from the current network meta-analyses (NMAs) given the extent of statistical heterogeneity observed, which is likely related to the variation in doses, background treatments, and populations combined in the analysis. In addition, the ERG notes that TA393 (alirocumab) & TA394 (evoculumab) resulted in recommendations for different subgroups and is therefore concerned that these subgroups are not considered separately in the current NMAs.

The ERG considers that the current submission does not provide evidence suitable for assessing bempedoic acid or bempedoic acid plus ezetimibe fixed dose combination (FDC) in the four subpopulations specified in the comparators section of the NICE final scope (people in whom statins

are contraindicated or not tolerated; people in whom statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C; people in whom maximally tolerated statin dose does not appropriately control LDL-C; people in whom maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C).

The ERG suggest the company use the following steps to create more coherent networks of evidence in order to answer the decision problem:

Statin intolerant NMA

a. Exclude the 420 Q4W dose of evolocumab and the corresponding placebo arms (e.g. all arms of GAUSS and GAUSS-3, two arms of GAUSS-2);

b. Exclude the Krysiak 2011 (statin intolerant subgroup, n = 66) for which concomitant therapy is unknown;

c. Consider the appropriateness of including Study 1002-008 given the concomitant statin eligibility and mean doses listed in the Excel file provided; and

d. Exclude the alirocumab 300 mg Q4W arm in ODYSSEY CHOICE I.

Maximally tolerated statin NMA

a. Exclude the 420 Q4W dose of evolocumab (selected arms of YUKAWA and YUKAKA-2), the 300 Q4W dose of alirocumab (ODYSSEY CHOICE I), and the corresponding placebo arms;

b. Exclude studies that exclusively recruited populations with Type 1 diabetes or Type 2 diabetes (ODYSSEY-DM and DM-DYSLIPIDEMIA and DM-INSULIN, BANTING, ODYSSEY LONGTERM and BERSON);

c. Exclude studies that exclusively recruited populations with heterozygous familial hypercholesterolaemia (HeFH) (ODYSSEY FH I, ODYSSEY FH II, ODYSSEY HIGH FH, RUTHERFORD-2 and RUTHERFORD), and consider presenting these results separately to illustrate response to the PCSK9s in HeFH compared with the wider HC population; and

d. Include only the moderate/high dose background statin arms from LAPLACE-2 (atorvostatin 80 mg, rosuvastatin 40mg, simvastatin 40mg) DESCARTES (atorvastatin 80mg), and YUKAWA-2 (atorvastatin 20mg). Consider whether the low dose subgroups from these studies are eligible for inclusion in the statin-intolerant NMA.

Network meta-analyses in the company submission

A1. Priority question. Please conduct revised NMAs for the statin-intolerant studies and maximally tolerated statin studies based on the suggestions detailed above for the following outcomes, where possible, and justify the choice of studies:

a) % change in LDL-C at 12 weeks;

b) % change in LDL-C at 24 weeks;

c) % change in non-HDL-C at 12 weeks;

d) % change in non-HDL-C at 24 weeks.

Company response: As per the ERG suggestions on revising the NMAs for the statin intolerant and maximally tolerated statin studies described above in section A, we are performing these updates in the NMA for the % change in low-density lipoprotein cholesterol (LDL-C) at 12 weeks. As agreed with NICE, the results of these analysis will be provided on the 16th January 2020.

Bempedoic acid and FDC are anticipated to be approved for an LDL-C lowering indication and therefore the endpoint of LDL-C reduction is consistent with the intended indication. Besides, percent change in LDL-C was the primary endpoint for the pivotal trials of bempedoic acid, FDC, and indirect comparator trials of ezetimibe and proprotein convertase subtilisin / kexin type 9 (PCSK9) inhibitors (with the exception of the outcome trials with cardiovascular (CV) endpoints), reflecting the established consensus that LDL-C reduction (rather than non–high-density lipoprotein cholesterol [HDL-C] reduction) is the most important lipid endpoint from a clinical perspective.

The ERG has suggested that NMAs using the percentage change in non-HDL are performed, however the company will not be providing these for the following reasons:

- Whilst non-HDL-C provides useful additional clinical information (can be calculated as total cholesterol minus HDL-C and is a measure of the total cholesterol carried by all atherogenic ApoB-containing lipoproteins), LDL-C is the primary and widely acceptable lipid measure used in clinical guidelines to define thresholds for treatment and treatment goals, including the NICE Clinical Guideline (CG181) (NICE, 2016d), NICE technology appraisals (TA385, TA393, TA394) (NICE, 2016a; NICE, 2016b; NICE, 2016c), and the ESC/EAS guidelines (Mach et al., 2019).
- Lowering LDL-C has been accepted as a surrogate endpoint for the reduction of CV events by clinicians and regulatory authorities for many years (Cannon et al., 2017; Ference et al., 2016; Jacobson et al., 2014). To date, all cholesterol lipid-lowering drug approvals in the United States (US) and European Union (EU) have been initially based on LDL C lowering without confirmed CV outcomes benefits. Initial approvals of PCSK9 inhibitors, based on an LDL-C lowering mechanism through the LDL receptor and validation by human genetics, are the most recent evidence of the continued acceptance of LDL-C lowering as a validated surrogate (Ference et al., 2016; Repatha (evolocumab) injection PI, 2017; Repatha (evolocumab) SmPC, 2018; Silverman et al., 2016).
- In 2017, the European Atherosclerosis Society (EAS) confirmed with a consensus statement the LDL-C hypothesis i.e. that “there is a dose-dependent, log-linear association between absolute LDL cholesterol and CV risk, and this association is independent of other CV risk factors (Ference et al., 2017). Evidence for the direct correlation between LDL-C and cardiovascular disease (CVD) comes from preclinical, epidemiological, genetics, and interventional studies (Ference et al., 2017).
- Furthermore, despite the association between non-HDL-C and CV risk being known at the time of previous NICE appraisals (e.g.,Boekholdt et al. (2012), this was not used as a surrogate endpoint for assessment. Indeed, LDL-C reduction was used instead in previous NICE appraisals as the primary evidence for clinical effectiveness and surrogate outcome in the cost-effectiveness evaluation. We also took this approach in agreement with the rationale and to remain consistent in decision-making.

- Use of LDL-C rather than non–HDL-C is consistent with the mechanism of action for bempedoic acid which acts as an adenosine triphosphate citrate lyase (ACL) inhibitor that lowers LDL-C by inhibition of cholesterol synthesis in the liver.
- Our approach in using LDL-C lowering as the primary measure of clinical effectiveness and the surrogate outcome for prediction of CV risk has been verified with advisory boards and United Kingdom (UK) clinical expert opinion. Details of the UK Advisory Board were provided in the Company evidence submission (section B.6.1.2).

Furthermore, the ERG is requesting analyses for percentage change in LDL-C at 24 weeks; the company considers this additional analysis is not appropriate as the primary endpoint for the phase 3 trials of bempedoic acid and FDC was percentage change of LDL-C at 12 weeks. (Note that in trials where there was possible uptitration of the alirocumab dose at 12 weeks, with the primary measurement of the titrated dose at 24 weeks, the 24-week data were used in the NMA). As the rationale for these additional analyses at 24 weeks is unclear and has not been justified or discussed during the scoping phase, the company is recommending that these are not provided. The percentage LDL-C reduction has been shown to be consistent at 12 and 24 weeks with non-significant changes, this is shown in graphs also submitted to regulatory files and in Figure 1.

Figure 1. Percentage change of LDL-C from baseline with observed values (mean +/- SE) by visit in pool 1 (high-risk/long-term pool) (efficacy population)

Source: Esperion Therapeutics data on file (2018a).

The percentage change in non-HDL-C is available as part of the Integrated Summary of Efficacy analysis (Table 2).

Table 2. Percentage change from baseline to week 24 and week 52 in non–HDL-C in pool 1 (high-risk/long-term pool) (efficacy population)

Source: Esperion Therapeutics data on file (2018a).

A2. Priority question. Please conduct NMAs for the following subgroups for the outcomes as detailed in question A1. The ERG acknowledges there is likely to be low patient numbers and insufficient detail for some studies and so not all analyses may be feasible but please provide justification for any analyses not conducted:

a) Primary non-familial hypercholesterolaemia;

b) Mixed dyslipidaemia;

c) Heterozygous familial hypercholesterolaemia;

d) Prior CVD (based on the definition used in TA393 and TA394); and

e) No prior CVD (based on the definition used in TA393 and TA394).

Company response: [redacted] subgroup analyses presented are exploratory.

Primary non-familial hypercholesterolaemia (FH) and mixed dyslipidaemia are two lipid disorders which had not been planned for subgroup analyses in terms of efficacy in the pivotal trials of bempedoic acid

as there was no scientific rationale. They are both considered as the indication of bempedoic acid and FDC in the proposed label. These two have not been specified as subgroups of interest in the NICE scope and therefore cannot be considered for this appraisal. Both lipid disorders are related to high cholesterol levels although in mixed dyslipidemia there are high levels of triglycerides (TGs) in addition to high cholesterol or LDL-C. The phase 3 studies of bempedoic acid have shown that changes from baseline in TG levels were comparable between treatment groups and due to the mechanism of action of bempedoic acid, there is anticipated effect in the LDL levels but not in TGs. Overall, results of HDL-C and TGS in studies 1002-040, 1002-046, and 1002-047 were consistent with corresponding results from Study 1002-048. The impact of bempedoic acid on HDL-C and TGs was minimal; no consistent, clinically meaningful changes in TGs were identified. A difference in efficacy (in terms of percentage LDL-C reduction) for patients with primary non-FH compared with those with mixed dyslipidaemia is not anticipated from a clinical basis or in view of the consistency of treatment effect observed in other subgroup analyses conducted (see Company evidence submission, section B.2.7).

Heterozygous familial hypercholesterolaemia (HeFH) (subgroup c) represents only a small proportion of patients with hypercholesterolaemia and, since there are no dedicated FH trials conducted for bempedoic acid and FDC, the numbers of patients included in our global phase 3 trials are small (see Table 13 in the Company evidence submission; data are also presented below in Table 3 for convenience). CLEAR Harmony included the largest group of patients with HeFH, and subgroup analysis suggested that the treatment effect is consistent with the non-HeFH population (see Figure 7 in the Company evidence submission, excerpt presented in Figure 2 below for convenience). A subgroup analysis for the pooled data from CLEAR Harmony and CLEAR Wisdom provided similar findings (Figure 3); the *P*-value for the treatment 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]) and therefore the company considers that an updated NMA in this subgroup would not be informative.

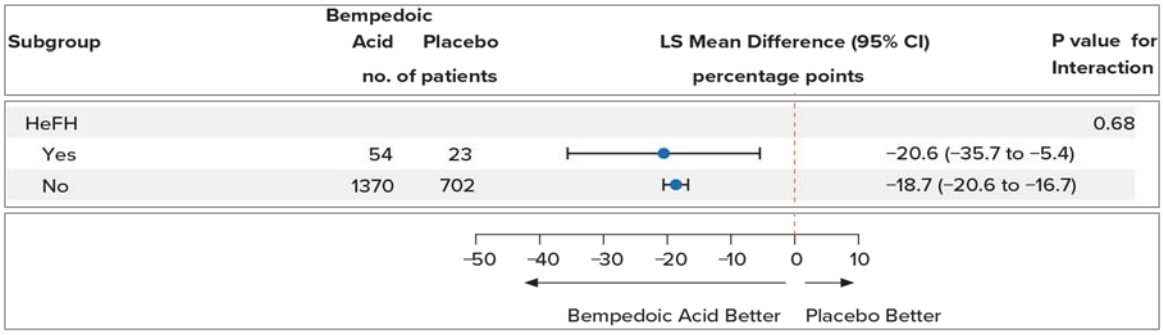
Table 3. Patients with HeFH in phase 3 bempedoic acid trials, by treatment arm

Trial number (acronym) Baseline characteristic	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018a; Ray et al., 2019a; Ray et al., 2019b)		CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019a; Goldberg et al., 2019)		CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018b; Laufs et al., 2019)		CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)	
	Bempedoic acid 180 mg	Placebo	Bempedoic acid 180 mg	Placebo	Bempedoic acid 180 mg	Placebo	Bempedoic acid	Placebo
Number randomised	1,488	742	522	257	234	111	181	88
HeFH	56 (3.8)	23 (3.1)	NR	NR	4 (1.7)	3 (2.7)	NR	NR
HeFH with/without ASCVD	[redacted]	[redacted]	27 (5.2)	16 (6.2)	NR	NR	NR	NR

ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolaemia.

Data are not available for CLEAR Tranquility or study 1002FDC-053

Figure 2. CLEAR Harmony HeFH subgroup analysis: change from baseline LDL-C to week 12 (ITT population)



CI = confidence interval; HeFH = heterozygous familial hypercholesterolaemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares.
Source: Ray et al. (2019b).

Figure 3. Pooled analysis of CLEAR Harmony and CLEAR Wisdom HeFH subgroup analysis: change from baseline LDL-C to week 12 (ITT population)

BA = bempedoic acid; CI = confidence interval; HeFH = heterozygous familial hypercholesterolaemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LS = least squares; Pbo = placebo.
Source: Esperion Therapeutics data on file (2019d).

NMAs for subgroups by prior CVD and no prior CVD based on the definition used in TA393 and TA394 (subgroups d and e above) are not feasible for the following reasons:

- The definitions of prior CVD in the bempedoic acid and FDC trials do not align precisely with the definitions in TA393 and TA394. A comparison of the definitions in the trials and in the NICE appraisals is presented in the response to question A16 (Table 14).
- The comparator studies also did do not use definitions which align with TA393/TA394 or the bempedoic acid studies. Therefore, consistent data across studies are not available.

The treatment effect for bempedoic acid and FDC was consistent for patients with and without prior atherosclerotic cardiovascular disease (ASCVD) (see Figure 7, Figure 8, Figure 9, and Figure 11 of the Company evidence submission; the *P*-values for the subgroup interaction were not significant). Note that CLEAR Tranquility only enrolled patients with no recent history of CVD (Table 14).

A3. Priority question. Please provide an assessment of the extent to which the populations assessed across the studies in the current NMAs is applicable to

the populations defined in the scope and provide the proportions of patients in each study with primary HC and mixed dyslipidemia.

Company response: The studies included in the NMAs were identified by a systematic literature review (SLR), in which the population inclusion criteria were aligned with the NICE final scope (details are provided in Appendix D of the Company evidence submission, Document C). The population characteristics for each study are presented in the systematic literature review data tables excel file (filename *ID1515_SLR Data Tables_20 Nov 2019*) provided on 13 December 2019. As noted in the Company evidence submission, we agree that there is heterogeneity among the patient populations included in the NMA, and this has been noted by other researchers performing similar NMAs–for example, Toth et al. (2017) (see section B.2.9.3 of the Company evidence submission, Document B). As noted in this same section, the NMA results are similar to those reported by other researchers (see Table 35 of the Company evidence submission, Document B). Exploration of the heterogeneity as suggested by the ERG on page 3 is being performed; the results will be provided on 16 January 2020, as agreed.

The proportion of patients with primary hyperlipidaemia (primary hypercholesterolaemia and mixed dyslipidaemia) in each study is presented in the systematic literature review data tables excel file (filename *ID1515_SLR Data Tables_20 Nov 2019*) provided on 13 December 2019. We understand that the ERG's clinical expert has indicated that background treatment and response to treatment can vary for patients with primary HC compared with patients with mixed dyslipidaemia. As these subgroups were not specified in the NICE final scope, they are not relevant to the appraisal. The data were not extracted from trials for these subgroups, and this subgroup analysis was not performed for the phase 3 bempedoic acid and FDC trials.

A4. Priority question. Please justify the selection of baseline LDL-C for inclusion as a covariate in the NMAs, explain the methods for how it has been implemented and justify why no other covariates were included in the NMAs.

Company response: The treatment effect for bempedoic acid (difference in percentage change in LDL-C from baseline compared with placebo) is consistent across the baseline LDL-C categories investigated in the phase 3 trials. However, the absolute percentage reduction in each treatment arm for lipid-modifying therapies (LMTs) has been previously found to be related to the baseline LDL-C, and baseline LDL-C has been used as proxy for disease severity.

In line with the meta-regression, baseline LDL-C was included as a covariate. Baseline LDL-C was a commonly reported variable in the underlying study publications. Other covariates that may have been of interest included percentage statin use along with the associated statin dose for the maximally tolerated statin network, however, this was not consistently reported across all studies. Similarly, for both networks, background ezetimibe may have been of interest, but was not consistently reported across all studies.

The model fit statistics for models including baseline LDL-C and not including baseline LDL-C are presented in Table 4 and Table 5 for the statin-intolerant and maximally tolerated NMAs, respectively.

Table 4. Fit statistics for the statin-intolerant NMA

Model	Baseline LDL-C	Total residual deviance	*pD*	DIC	Between study standard deviation (σ) (95% CrI)	Baseline LDL-C (95% CrI)
Fixed effects	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	✓	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	✓	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CrI = credible interval; DIC = deviance information criterion; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; pD = sum of leverage_arm (i.e. total leverage).

Table 5. Fit statistics for the maximally tolerated statin NMA

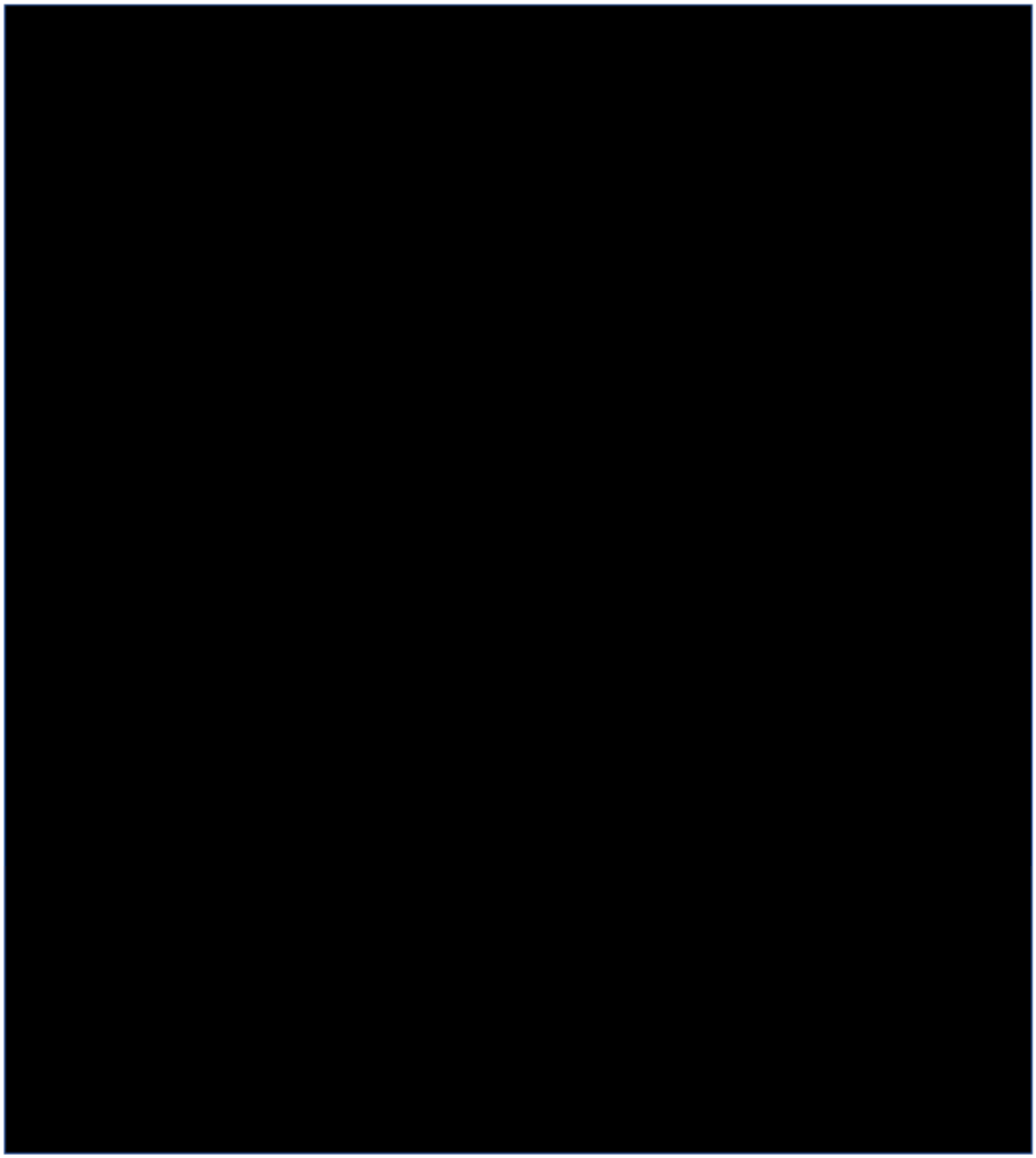
Model	Baseline LDL-C	Total residual deviance	*pD*	DIC	Between study standard deviation (σ) (95% CrI)	Baseline LDL-C (95% CrI)
Fixed effects	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	✓	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	✓	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CrI = credible interval; DIC = deviance information criterion; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; pD = sum of leverage_arm (i.e. total leverage).

The addition of baseline LDL-C improves the fit of the fixed-effects models, but has less impact on the random-effects models, although it did help reduce the heterogeneity in the statin-intolerant population.

The associated code for the inclusion of LDL-C is presented in Figure 4.

Figure 4. Code for the inclusion of LDL-C



LDL-C = low-density lipoprotein cholesterol.

Network meta-analyses in line with the NICE final scope

A5. Priority question. Please explore the possibility of conducting NMAs to assess bempedoic acid and bempedoic acid+ezetimibe against the relative comparators (listed in the NICE final scope) separately for each of the four subpopulations defined in the NICE final scope, including the two without ezetimibe at baseline (i.e. populations 1 and 3; people in whom statins are

contraindicated or not tolerated, and people in whom maximally tolerated statin dose does not appropriately control LDL-C, respectively) for the following outcomes and please provide justification if this is deemed inappropriate or infeasible:

a) % change in LDL-C at 12 weeks;

b) % change in LDL-C at 24 weeks;

c) % change in non-HDL-C at 12 weeks;

d) % change in non-HDL-C at 24 weeks.

Company response: The four subpopulations defined in the NICE final scope are as follows:

1. When statins are contraindicated or not tolerated
2. When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C
3. When maximally tolerated statin dose does not appropriately control LDL-C
4. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C

[redacted] Bempedoic acid also is not anticipated to be used prior to ezetimibe in the treatment pathway in the National Health Service (NHS) setting (see Section B.1.1.1 of the Company evidence Submission, Document B). Therefore, cost-effectiveness results for bempedoic acid or FDC are not presented in positions 1 or 3. Cost-effectiveness results are presented for positions 2 and 4 in the company submission, given this is the anticipated position in clinical practice and in the context of the NHS.

Separate NMAs were presented in the submission when statins are contraindicated or not tolerated (positions 1 and 2), and when maximally tolerated statin dose does not appropriately control LDL-C (positions 3 and 4). Insufficient data are available to support separate NMAs in each of these situations prior to ezetimibe therapy (positions 1 and 3) and when ezetimibe does not appropriately control LDL-C (positions 2 and 4); this was not the rationale of the clinical programme (which aimed to explore bempedoic acid efficacy across patients who were either statin intolerant or required additional LMT despite any oral optimised therapy) and is acknowledged by the company that patient numbers with prior ezetimibe usage are small. However, in post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use (see Section B.2.8.2 of the Company evidence submission, Document B). Therefore, the comparative effectiveness in positions 1 and 2 are expected to be similar, and the comparative effectiveness in positions 3 and 4 also are expected to be similar. Furthermore, the NMA results presented in the submission are similar to the results of the post-hoc subgroup analyses in patients with ezetimibe use

(Table 6).

Table 6. Estimated difference in % change in LDL-C from baseline for bempedoic acid on background ezetimibe compared with placebo on background ezetimibe

	Bempedoic acid trials, post-hoc subgroup analyses	NMA estimate
Statin intolerant	[redacted]	[redacted]
Maximally tolerated statin	[redacted]	[redacted]
Reference section in the Company evidence Submission, Document B	B.2.8.2	B.2.9.1

LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

A6. Priority question. Please conduct NMAs for LDL-C at 12 and 24 weeks for the following subgroups of the populations specified in question A5 (people in whom statins are contraindicated or not tolerated; people in whom statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C; people in whom maximally tolerated statin dose does not appropriately control LDL-C; people in whom maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C):

a) Primary non-familial hypercholesterolaemia;

b) Mixed dyslipidaemia;

c) Heterozygous familial hypercholesterolaemia;

d) Prior CVD (based on the definition used in TA393 and TA394); and

e) No prior CVD (based on the definition used in TA393 and TA394).

Company response: As detailed in the responses to questions A2 and A5, these analyses are not feasible or appropriate.

A7. Please conduct NMAs as described in question A6 for non-HDL-C at 12 and 24 weeks and provide data tables with the data used in the NMAs.

Company response: As detailed in the responses to questions A1, A2, and A5, these analyses are not feasible or appropriate.

General NMA questions

A8. Priority question. Please provide summary data tables for each of the studies included in the NMAs in response to questions A1, A2, A5 and A6 with details of the population or subgroup used, the intervention and dosage included in the NMAs, the mean baseline LDL-C and non-HDL-C for each study arm included and the data included in the NMA (mean percentage change and standard deviation; as provided in table).

Company response: Summary data tables for the revised NMAs will be provided along with the results on 16 January 2020.

A9. Please justify the following decisions in the current NMAs:

a) Combining studies with varying eligibility and proportions of primary and secondary hypercholesterolemia (HC), heterozygous familial HC (HeFH), and mixed dyslipidaemia, many of which are reported and are known to affect baseline severity and how patients respond to therapy.

b) Combining studies with a range of eligibility criteria and proportions of patients with and without CVD (i.e. primary and secondary prevention), and at varying risks of CV events.

c) Including studies focused on distinct subgroups of patients (e.g. those recruiting only patients with type 1 or type 2 diabetes, and those with HeFH).

Company response: The pivotal trials of bempedoic acid and FDC have demonstrated that the treatment effect (percentage LDL-C reduction from baseline to 12 weeks vs. placebo) is consistent across the subgroups listed in point (a), and a consistent treatment effect has been observed across baseline LDL-C levels (see section B.2.7 of the Company evidence submission, Document B and Table 16 in the response to question A20). Although the company is aware of the variability in eligibility and inclusion criteria across the studies of lipid lowering therapies, a realistic and practically feasible approach was decided since this was in agreement with expert opinion and prior HTAs to our knowledge. Often there were insufficient data from trials in which the patient populations were precisely aligned to provide separate NMAs within each subpopulation. Our approach to inclusion of trials with these varying inclusion criteria was consistent with previously published NMAs in hypercholesterolaemia and mixed dyslipidaemia (e.g. Toth et al., 2017).

The treatment effect for bempedoic acid and FDC (percentage reduction LDL-C from baseline to 12 weeks vs. placebo) has been demonstrated to be consistent in patients with or without prior CVD in four of the five phase 3 trials (see section B.2.7 of the Company evidence submission, Document B), and

with or without diabetes in four of the pivotal phase 3 CLEAR trials (see section B.2.7 of the Company evidence submission, Document B). As noted in the response to question A2, there is no evidence to suggest that the treatment effect for bempedoic acid and FDC differs for patients with HeFH, and subgroup analyses of CLEAR Harmony and a pooled analysis with CLEAR Wisdom suggest a consistent treatment effect in this group versus non-HeFH patients.

Assessment of inconsistency and heterogeneity

A10. Priority question. Please provide the I2 and Cochran's Q test (with associated p-value) for all pairwise comparisons in the NMAs presented in response to questions A1, A2, A5, A6 and A7.

Company response: These details for the revised NMAs will be provided along with the results on 16 January 2020.

A11. Priority question. Please provide a comparison of loops in the NMAs where there is more than one loop forming an indirect comparison for the same direct treatment effect for the NMAs presented in response to questions A1, A2, A5, A6 and A7.

Company response: These details for the revised NMAs will be provided along with the results on 16 January 2020.

A12. Please provide fit statistics as presented in Table 29 of the company submission (CS) for the NMAs presented in response to Questions A1, A2, A5, A6 and A7.

Company response: These details for the revised NMAs will be provided along with the results on 16 January 2020.

Bempedoic acid studies

A13. Priority question. Please provide details of the type of statin used at baseline, including a breakdown of the number of patients on each different statin along with the mean dose (with standard deviation) and median dose (with interquartile range) for each of the four CLEAR studies (Harmony, Wisdom, Serenity and Tranquility) and the FDC trial.

Company response: Details of the type of statin used at baseline are presented in Table 7 (pooled data for CLEAR Harmony and CLEAR Wisdom) and Table 8 to Table 10. The mean and median dose are not available; however, the proportions of patients receiving each dose are presented.

Table 7. Baseline statin medications in pool 1, high-risk/long-term pool (CLEAR Harmony and CLEAR Wisdom) by statin dose (safety population)

Source: Esperion Therapeutics data on file (2019e).

Table 8. Baseline statin medications for CLEAR Serenity by statin dose (safety population)

Source: Esperion Therapeutics data on file (2019e).

Table 9. Baseline statin medications for CLEAR Tranquility by statin dose (safety population)

Source:Esperion Therapeutics data on file (2019e).

Table 10. Statin at baseline by preferred term for Study 053 excluding sites 1028, 1058, and 1068 (full analysis set)

Source: Esperion Therapeutics data on file (2019e).

A14. In the company submission (CS), Table 13, please clarify what is meant by the following row headings:

a) ASCVD only;

b) HeFH with/without ASCVD;

c) Very low-dose statin;

d) Statin therapy intensity low;

e) Statin therapy intensity moderate; and

f) Statin therapy intensity high.

Company response: The row headings in Table 13 are defined below:

Baseline statin intensity (high intensity statin, moderate intensity statin, low intensity statin) was

determined for each patient based on the patient's average daily dose at baseline.

[redacted]

A15. Please clarify the baseline lipid-modifying therapies (LMTs) used in CLEAR Tranquility, in particular, the proportion of patients on statin, ezetimibe or other LMTs.

Company response: CLEAR Tranquility was a phase 3, randomised, double-blind, placebo-controlled, parallel-group study with a 1-week screening period, a 4-week single-blind placebo and ezetimibe run-in period, and a 12-week treatment period. Patients on low-dose or less than low-dose statin therapy (including patients unable to tolerate a statin at any dose) and who required additional LDL-C lowering were eligible for screening. Patients started screening at Week -5 (Visit S1), approximately 5 weeks prior to randomisation. Eligible patients returned to the clinical site at Week -4 (Visit S2) to begin treatment with study-supplied ezetimibe and single-blind placebo. Patients who met all enrolment criteria continued their background lipid-modifying therapies (LMTs) for lipid regulation and maintained consistent diet and exercise patterns throughout the study. Low-dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. Very low-dose statin therapy was defined as an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg.

Table 11 presents the baseline and concomitant LMT used in CLEAR Tranquility. Patients received ezetimibe during the 4-week run-in period, therefore all patients received ezetimibe at baseline. The table provides a summary of patients who reported the use of at least 1 concomitant LMT (47.5% for bempedoic acid patients and 39.1% for placebo patients). The most common LMT used concomitantly was HMG-CoA reductase inhibitors (32.6% for bempedoic acid patients and 27.6% placebo patients).

Table 11. LMTs used in CLEAR Tranquility

	Placebo (N = 88)	Bempedoic Acid (N = 181)
Baseline background LMT	n (%)	n (%)
Statins[a]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]
Number of patients with ≥ 1 concomitant LMT	[redacted]	[redacted]
HMG-CoA reductase inhibitors	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]
Simvastatin	[redacted]	[redacted]
Rosuvastatin	[redacted]	[redacted]
Pravastatin	[redacted]	[redacted]
Lovastatin	[redacted]	[redacted]
Other LMT	[redacted]	[redacted]
Fish oil	[redacted]	[redacted]
Eicosapentaenoic acid ethyl ester	[redacted]	[redacted]
Omega-3 fatty acid	[redacted]	[redacted]
Salmon oil	[redacted]	[redacted]
Sitosterol	[redacted]	[redacted]
Fibrates	[redacted]	[redacted]
Fenofibrate	[redacted]	[redacted]
Bezafibrate	[redacted]	[redacted]
Fenofibric acid	[redacted]	[redacted]
Nicotinic acid and derivatives	[redacted]	[redacted]
Nicotinic acid	[redacted]	[redacted]
Bile acid sequestrants	[redacted]	[redacted]
Colesevelam hydrochloride	[redacted]	[redacted]
Colestipol	[redacted]	[redacted]

CoA = coenzyme A; HMG = β-hydroxy-β-methylglutaryl; LMT= lipid- modifying therapy; N = number of patients; % = percentage of patients calculated relative to the total number of patients in the analysis set.

Note: All patients received ezetimibe 10mg/day as background therapy throughout the study.

[a] Statin use included those who started prior to randomization and taken continually during the study as background LMT.

[b] Includes patients who took a non-statin LMT or who took no LMT at time of randomisation.

Source: Esperion Therapeutics data on file (2018b).

A16. Please clarify the proportion of patients in each of the CLEAR studies and the FDC trial at baseline with the following and provide subgroup results for LDL-C and non-HDL-C:

a) Primary non-familial hypercholesterolaemia;

b) Mixed dyslipidaemia;

c) Heterozygous familial hypercholesterolaemia;

d) Prior CVD (based on the definition used in TA393 and TA394); and

e) No prior CVD (based on the definition used in TA393 and TA394).

Company response: Not all bempedoic acid trials reported data on the proportion of patients with primary non-FH, and those with mixed dyslipidaemia. Below are shown the proportions of patients reported with each of the disorders, however there is no rationale to expect that the effect of bempedoic acid on LDL-C lowering would be different in patients with primary non-FH or mixed dyslipidaemia.

- CSR Study 040 (CLEAR Harmony): By preferred term, hypertension was the most common medical history term overall [redacted] and also balanced across groups. Other preferred terms occurring in ≥20% of patients overall included hyperlipidemia [redacted] hypercholesterolemia [redacted] osteoarthritis [redacted] type 2 diabetes mellitus [redacted], and gastroesophageal reflux disease [redacted].
- CSR Study 047 (CLEAR Wisdom): Not reported; only familial HeFH (with or without ASCVD) was reported in [redacted] of patients on placebo, [redacted] of patients on bempedoic acid and in total [redacted] of patients.
- CSR Study 046 (CLEAR Serenity): Other concurrent illnesses occurring in ≥20% of patients overall were gastroesophageal reflux disease ([redacted] bempedoic acid, [redacted] placebo), type 2 diabetes mellitus ([redacted] bempedoic acid, [redacted] placebo), osteoarthritis ([redacted] bempedoic acid, [redacted] placebo), and dyslipidemia ([redacted] bempedoic acid, [redacted] placebo).
- CSR Study 048 (CLEAR Tranquility): Among concurrent illnesses occurring in ≥ 20 % of patients were hyperlipidemia [redacted] hypercholesterolemia [redacted] dyslipidemia [redacted] and gastroesophageal reflux disease [redacted]
- CSR Study 1002FDC-053: Not reported

Furthermore, primary non-FH or mixed dyslipidaemia were not specified as subgroups of interest in the NICE final scope and therefore are not relevant to the appraisal. For the remaining subgroups, the trial data were not collected in a way which aligns with the definition of prior CVD in TA393 and TA394. The patient numbers in subgroups with ASCVD (or secondary prevention) and HeFH as defined in the bempedoic acid and FDC trials were presented in Section B.2.3.2.2 and B.2.3.3.2 of the Company evidence submission, Document B, and are presented again in Table 12 and 0, respectively. A comparison of the definitions used in the bempedoic acid and FDC trials with the definitions used in TA393 and TA394 is presented in Table 14. The subgroup results for LDL-C are presented in Figures 7 to 12 in the Company evidence Submission, Document B, and are tabulated in the response to question A18. Note that subgroup analyses for HeFH are available only for CLEAR Harmony; the numbers of patients with HeFH in the other trials were very small (≤ 27 per arm). Note that subgroup results for CLEAR Tranquility are not presented, because patients with no recent history of CVD were excluded, and HeFH was not recorded. Therefore, the overall trial population represents patients with no recent history of CVD. Subgroup analyses for non-HDL-C have not been performed; LDL-C was the primary endpoint for the bempedoic acid, FDC, and comparator trials, and clinical guidelines recommend treating to target LDL-C goals and not non-HDL-C goals (as detailed in the response to

question A1).

Table 12. Patient characteristics in phase 3 bempedoic acid trials, by treatment arm

Trial number (acronym) Baseline characteristic	CLEAR Harmony (1002-040) (Esperion Therapeutics data on file, 2018a; Ray et al., 2019a; Ray et al., 2019b)		CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019a; Goldberg et al., 2019)		CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018b; Laufs et al., 2019)		CLEAR Tranquility (1002-048) (Ballantyne et al., 2018)[a]	
	Bempedoic acid 180 mg	Placebo	Bempedoic acid 180 mg	Placebo	Bempedoic acid 180 mg	Placebo	Bempedoic acid	Placebo
Number randomised	1,488	742	522	257	234	111	181	88
CV risk factor, no. (%)								
Primary prevention	NR	NR	NR	NR	144 (61.5)	67 (60.4)	NR	NR
Secondary prevention	NR	NR	NR	NR	90 (38.5)	44 (39.6)	NR	NR
ASCVD	1,449 (97.4)	727 (98.0)	NR	NR	NR	NR	NR	NR
ASCVD only	[redacted]	[redacted]	495 (94.8)	241 (93.8)	NR	NR	NR	NR
HeFH	56 (3.8)	23 (3.1)	NR	NR	4 (1.7)	3 (2.7)	NR	NR
HeFH with/without ASCVD	[redacted]	[redacted]	27 (5.2)	16 (6.2)	NR	NR	NR	NR

apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; CK = creatine kinase; CVD = cardiovascular disease; CV = cardiovascular; DM = diabetes mellitus; ECG = echocardiogram; eGFR = estimated glomerular filtration rate; GIT = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; MI = myocardial infarction; NR = not reported; TC = total cholesterol; TG = triglycerides.

[a] Patients with recent history of documented clinically significant cardiovascular disease were excluded from the study.

Table 13. Patient characteristics in the phase 3 FDC trial by treatment group

Trial number (acronym)	1002FDC-053 (Ballantyne et al., 2019a; Ballantyne et al., 2019b; Esperion Therapeutics data on file, 2019b)			
Baseline characteristic	**FDC**	**Bempedoic acid**	**Ezetimibe**	**Placebo**
Number randomised	86	88	86	41
CV risk category, n (%)				
ASCVD and/or HeFH	53 (61.6)	55 (62.5)	54 (62.8)	26 (63.4)
Multiple CV risk factors	33 (38.4)	33 (37.5)	32 (37.2)	15 (36.6)

ASCVD = atherosclerotic cardiovascular disease; apo B = apolipoprotein B; BMI = body mass index; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FDC = bempedoic acid and ezetimibe fixed-dose combination; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; NR = not reported; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

Table 14. Comparison of the definitions used in TA393 and TA394 and in the bempedoic acid and FDC trials

Source	Subgroup	Definition
TA393 and TA394	Prior CVD	[redacted]
	No prior CVD	[redacted]
CLEAR Harmony	ASCVD	[redacted]
	ASCVD only	[redacted]

Source	Subgroup	Definition
CLEAR Wisdom	ASCVD	[redacted]
	ASCVD only	[redacted]
CLEAR Serenity	Primary prevention	[redacted]

Source	Subgroup	Definition
	Secondary prevention	[redacted]

Source	Subgroup	Definition
CLEAR Tranquility	No recent history of CVD	[redacted]

Source	Subgroup	Definition
1002-FDC 053	ASCVD and/or HeFH	[redacted]

Source	Subgroup	Definition
	Multiple CV risk factors	[redacted]

ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; CHD = coronary heart disease; CTA = computed tomography angiography; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; ST = xxx; T2DM = type 2 diabetes mellitus; WHO = World Health Organization.

Source: Esperion Therapeutics data on file (2018b); Esperion Therapeutics data on file (2018c); Esperion Therapeutics data on file (2018d); Esperion Therapeutics data on file (2019b); Esperion Therapeutics data on file (2019c).

A17. Please clarify how well the full trial population of each of the CLEAR studies and the FDC trial assesses bempedoic acid and/or bempedoic acid+ezetimibe for each of the four subpopulations defined in the NICE final scope and detailed in Figure 3, including the two without ezetimibe at baseline (i.e. populations 1 and 3; people in whom statins are contraindicated or not tolerated, and people in whom maximally tolerated statin dose does not appropriately control LDL-C, respectively).

Company response: Table 15 presents an assessment of how well the full trial population of the phase 3 bempedoic acid and FDC trials align with the four subpopulations defined in the NICE final scope. For positions 2 and 4 (where ezetimibe does not appropriately control LDL-C), it is noteworthy that in post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use (detailed in Section B.2.8.2 of the Company evidence submission, Document B). As noted in the response to questions A5 and B1, and in the Company evidence submission (Section B.3.1.3, Document B), cost-effectiveness results have been presented for positions 2 and 4, given UK clinical experts have stated these would be the expected places in therapy for bempedoic acid and FDC. As noted in the Company evidence submission (Section B.2.14.1.1, Document B), the treatment effect of FDC in patients where maximally tolerated stain does not appropriately control LDL-C and in patients where statins are contraindicated or not tolerated is expected to be consistent, with supporting evidence presented from trials investigating bempedoic acid and ezetimibe for patients where statins are contraindicated or not tolerated.

Table 15. Assessment of how well the full trial population of the phase 3 bempedoic acid and FDC trials align with the subpopulations defined in the NICE final scope

Position	1	2	3	4
	When statins are contraindicated or not tolerated	When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C	When maximally tolerated statin dose does not appropriately control LDL-C	When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C
CLEAR Harmony (1002-040)	Not relevant[a]	Not relevant[a]	Close alignment[a]	Close alignment with regard to statin treatment[a] [redacted] of patients were treated with ezetimibe at baseline [redacted] in the placebo arm and [redacted] in the bempedoic acid arm; safety population)
CLEAR Wisdom (1002-047)	Not relevant[a]	Not relevant[a]	Close alignment[a]	Close alignment with regard to statin treatment[a] [redacted] of patients were treated with ezetimibe at baseline [redacted] in the placebo arm and [redacted] in the bempedoic acid arm; safety population)
CLEAR Serenity (1002-046)	Close alignment[b]	Close alignment with regard to statin intolerance[b] [redacted] of patients were treated with ezetimibe at baseline [redacted] in the placebo arm and [redacted] in the bempedoic acid arm; safety population)	Not relevant[b]	Not relevant[b]
CLEAR Tranquility (1002-048)	Close alignment[b]	Close alignment with regard to statin intolerance[b] and ezetimibe treatment. Patients received ezetimibe during the 4-week run-in period; baseline LDL-C data reflected levels on ezetimibe treatment. Patients had no recent history of CVD.	Not relevant[b]	Not relevant[b]
1002FDC-053	Not relevant[c]	Not relevant[c]	Close alignment[c]	Close alignment with regard to statin treatment[c] Patients treated with ezetimibe within 5 weeks prior to screening were excluded.

CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy

[a] Trial inclusion criteria specified that patients were on maximally tolerated LMT, defined as maximally tolerated statin either alone or in combination with other LMTs, at stable doses for at least 4 weeks before screening; fasting LDL C ≥ 70 mg/dL before screening visit.

[b] Trial inclusion criteria specified that patients had a history of statin intolerance.

- CLEAR Serenity: patient-reported statin intolerance defined as an inability to tolerate two or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued. Low-dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. Patients tolerating very low-dose statin therapy (an average daily dose of rosuvastatin < 5 mg, atorvastatin < 10 mg, simvastatin < 10 mg, lovastatin < 20 mg, pravastatin < 40 mg, fluvastatin < 40 mg, or pitavastatin < 2 mg) were considered intolerant to low-dose statin. Patients could continue taking very low-dose statin therapy throughout the study provided that it was stable (used for at least 4 weeks prior to screening, S1) and taken at a consistent time each day. Fasting (minimum of 10 hours) calculated LDL-C at Week 5 (Visit S1): primary prevention ≥ 130 mg/dL (3.4 mmol/L); secondary prevention and/or heterozygous HeFH ≥ 100 mg/dL (2.6 mmol/L); all patients must have had fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) at Week 1 (Visit S3).
- CLEAR Tranquility: received stable (≥ 4 weeks prior to screening) background statin dose that did not exceed low-dose statin therapy. Patients had to have reported attempting statin therapy and being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered. Low-dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. Very low-dose statin therapy was defined as an average daily dose of rosuvastatin < 5 mg, atorvastatin < 10 mg, simvastatin < 10 mg, lovastatin < 20 mg, pravastatin < 40 mg, fluvastatin < 40 mg, or pitavastatin < 2 mg. Patients on low- or very low-dose statin or unable to tolerate any statin at any dose were eligible. Patients could continue taking low- or very low-dose statin therapy throughout the study provided that it was stable (≥ 4 weeks prior to screening) and well tolerated. Patients unable to take any dose of statins were also eligible provided that statin therapy had been attempted as described above. Fasting (minimum of 10 hours) calculated LDL-C at Week 5 (Visit S1) as defined by ezetimibe use at screening. For patients who were taking ezetimibe 10 mg daily prior to Week 5 (Visit S1): fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) on stable background LMT (≥ 4 weeks prior to screening). For patients who were not taking ezetimibe Week 5 (Visit S1): fasting LDL-C ≥ 120 mg/dL (3.1 mmol/L) on stable background LMT (≥ 4 weeks prior to screening). All patients had to have had fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) at Week 1 (Visit S3).

[c] Trial inclusion criteria specified that patients were treated with maximally tolerated statin therapy at stable dose for at least 4 weeks before screening; fasting LDL-C at Week 2 while on maximally tolerated statin therapy as follows: ASCVD and/or HeFH: ≥ 100 mg/dL; multiple CV risk factors: ≥ 130 mg/dL.

Subgroups

A18. Please provide the least-squares (LS) mean difference and associated 95% confidence interval (CI) for all subgroups shown in Figures 8 and 9 of the submission (CLEAR Wisdom and CLEAR Serenity, respectively).

Company response: The least squares (LS) mean difference and associated 95% confidence interval (CI) for all subgroups shown in Figures 8 and 9 of the Company evidence submission are presented in Figure 5 and Figure 6 for CLEAR Wisdom and CLEAR Serenity, respectively.

Figure 5. CLEAR Wisdom forest plot of percentage change from baseline to week 12 in LDL-C by subgroups (full analysis set)

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LS = least square.

Source: Esperion Therapeutics data on file (2019b).

Figure 6. CLEAR Serenity forest plot of percentage change from baseline to week 12 in LDL-C by subgroups (full analysis set)

ANCOVA = analysis of variance; BMI = body mass index; CI = confidence interval; CVD = cardiovascular risk; LDL-C = low density lipoprotein- cholesterol; LS = least squares.

Note: baseline was defined as the mean of the LDL-C values from the last two non-missing values on or prior to Day 1. LS-means, 95% CIs, and *P*-values were based on an ANCOVA with percentage change from baseline as the dependent variable, treatment as a fixed effect, and baseline as a covariate.

Source: Esperion Therapeutics data on file (2018d).

A19. Please provide subgroup results by CV risk category for LDL-C in CLEAR Tranquility (primary prevention versus secondary prevention/HeFH, as is shown for CLEAR Serenity in Figure 9).

Company response: In CLEAR Tranquility, patients with recent history of CVD were excluded from the study. The definition of recent history of CVD is provided in Table 14. Other CVD history and HeFH were not recorded in the study.

A20. Please provide the p-values for the tests for subgroup differences in Figure 11 (Study 1002FDC-053), as for Figures 7 to 10.

Company response: The *P*-values for the tests for subgroup differences in Figure 11 of the Company evidence submission Document B (Study 1002FDC-053) are presented in Table 16.

Table 16. *P*-values for subgroup and treatment Interaction for percentage change in LDL-C at week 12 in Study 1002FDC-053

	Treatment interaction *P*-value
Sex (men, women)	0.648
Age group (<65, ≥65)	[redacted]
CVD risk category (ASCVD and/or HeFH, multiple CV factors)	
Baseline statin intensity (high, other)	
Race (white, other)	
Baseline LDL-C category (<130, ≥130 and <160, ≥160 mg/dL)	
History of diabetes (yes, no)	
BMI (<25, 25 to <30, ≥30 kg/m2)	
Calculated baseline statin intensity (high, other, none)	

BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Source: Esperion Therapeutics data on file (2019a).

A21. Priority question. Please populate the table to show the number of patients in each category at baseline in CLEAR Harmony, Wisdom, Serenity and Tranquility, and the FDC trial using the definition of high risk CVD used in TA393 and TA394:

	No prior CVD	With CVD
Primary non-familial HC		
Primary familial HC (HeFH)		
Mixed dyslipidemia		

Company response: Not all bempedoic acid trials reported data on the proportion of patients with primary non-FH, and mixed dyslipidaemia. Furthermore, these subgroups were not specified in the NICE final scope. For the “no prior CVD” and “with CVD” subgroups, the trial data were not collected in a way which aligns with the definition of prior CVD in TA393 and TA394. The patient numbers in subgroups with ASCVD (or secondary prevention) and HeFH as defined in the bempedoic acid and FDC trials were presented in Section B.2.3.2.2 and B.2.3.3.2 of the Company evidence Submission, Document B, and are presented again in Table 12 and 0 (in question A16), respectively. A comparison of the definitions used in the bempedoic acid and FDC trials with the definitions used in TA393 and

TA394 is presented in Table 14.

A22. Priority question. Please provide the results for each subgroup specified in Question A21 for CLEAR Harmony, Wisdom, Serenity and Tranquility, and the FDC trial for the following outcomes (as provided for the full trial populations for the CLEAR studies in Table 29):

a) LDL-C;

b) non-HDL-C.

Company response: The subgroup results for LDL-C are presented in Figures 7 to 12 in the Company evidence Submission, Document B, and are tabulated in the response to question A18. Note that subgroup analyses for HeFH are available only for CLEAR Harmony; the numbers of patients with HeFH in the other trials was very small (≤ 27 per arm). Note that subgroup results for CLEAR Tranquility are not presented, because patients with no recent history of CVD were excluded, and HeFH was not recorded. Therefore, the overall trial population represents patients with no recent history of CVD. Subgroup analyses for non–HDL-C have not been performed; LDL-C was the primary endpoint for the bempedoic acid, FDC, and comparator trials, and clinical guidelines recommend treating to target LDL-C goals and not non–HDL-C goals (as detailed in the response to question A1).

Ongoing studies

A23. Please provide details of the outcome data expected from the OLE study 1002-050.

Company response: The OLE study 1002-050 is a multicenter Open-Label Extension (OLE) study assessing the long-term safety and efficacy of bempedoic Acid 180 mg (ClinicalTrials.gov No. NCT03067441). The primary objective was to characterize the safety and tolerability of long-term administration of bempedoic acid 180 mg. Secondarily the study aimed to characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in LDL-C, HDL-C, non-HDL-C, apolipoprotein B (apo B), total cholesterol, TGs, and hsCRP.. In particular the below endpoints are being collected:

- Primary endpoint: [redacted]

[redacted]

- Secondary efficacy endpoints: [redacted]

[redacted]

A24. Please provide an update on the status of the OLE study 1002-050 and any results.

[redacted]

[redacted]

Safety results

[redacted]

[redacted]

[redacted]

[redacted]

Table 17. Treatment-emergent and positively adjudicated adverse cardiovascular events by event type, safety population

[redacted]

CV = cardiovascular; MACE = major adverse cardiovascular event

Source: Esperion Therapeutics data on file (2017).

Secondary efficacy results

[redacted]

[redacted]

[redacted]

Table 18. Summary of the efficacy results for Phase 3 OLE Study

	Mean (SD) % change from parent study baseline to week 12		Mean (SD) % change from parent study baseline to week 52	
	Former placebo patients (n = [redacted])	Former bempedoic acid patients (n = [redacted])	Former placebo patients (n = [redacted])	Former bempedoic acid patients (n = [redacted])
LDL-C, mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
Non–HDL-C, mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
TC, mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
Apo B, mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP, mg/l[d]	[redacted]	[redacted]	[redacted]	[redacted]
HDL-C, mg/d[d]	[redacted]	[redacted]	[redacted]	[redacted]
TG, mg/d[d]	[redacted]	[redacted]	[redacted]	[redacted]

Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; OLE = open-label extension; SD = standard deviation; TC = total cholesterol; TG = triglyceride.

[a]LDL-C: [redacted].

[b]Apo B: [redacted]

[c]Apo B: [redacted]

[d]Median (Q1, Q3).

Source: Esperion Therapeutics data on file (2017).

Section B: Clarification on cost-effectiveness data

Please note: if as a result of the responses to the cost-effectiveness clarification questions the company base case analyses are revised, please indicate what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the as an addendum to the company submission.

Please provide all requested scenario analyses as options in the economic model.

Please provide all cost-effectiveness results as ICER (cost per QALY) values. The net-monetary benefit at £20,000 per QALY may be presented in addition to ICER values.

B1. Please explain why cost-effectiveness results for populations 1 and 3 were omitted from the company's submission [redacted]. Please provide cost-effectiveness results for populations 1 and 3 using the clinical effectiveness analysis requested in clarification questions:

a) A5a (% change in LDL-C at 12 weeks); and

b) A5b (% change in LDL-C at 24 weeks).

Company response: As noted in the Company evidence submission (Section B.1.1) and the response to question A5, the proposed position for bempedoic acid is narrower than the anticipated marketing authorisation because it is not anticipated that bempedoic acid would be used prior to ezetimibe in the treatment pathway in the NHS.. In addition, [redacted]. Therefore, cost-effectiveness results for populations 1 and 3 (prior to ezetimibe treatment) are not included in the Company evidence submission.

B2. Priority question. Please provide cost-effectiveness results for populations 2 and 4 based on the clinical effectiveness analysis requested in clarification questions:

a) A1a (% change in LDL-C at 12 weeks);

b) A1b (% change in LDL-C at 24 weeks);

c) A5a (% change in LDL-C at 12 weeks); and

d) A5b (% change in LDL-C at 24 weeks).

Company response: Cost-effectiveness results based on the revised NMAs for % change in LDL-C at 12 weeks will be provided along with the NMA results on 16 January 2020.

B3. Priority question. Please explain why cost-effectiveness results were not provided separately for the subgroups outlined in the NICE final scope. Please provide separate cost-effectiveness results of bempedoic acid at 12

weeks and 24 weeks using the feasible subgroup analyses requested in clarification questions:

a) A2; and

b) A6.

Company response: As per the NICE final scope, the cost-effectiveness of bempedoic acid and FDC was explored in clinically relevant patient subgroups in the Company evidence submission (Sections B.4 and B.5, Document B), including patients with statin intolerance, on maximally tolerated statin dose, with various levels of severity of hypercholesterolaemia (varying baseline LDL-C), and varying CVD risk (primary prevention, and secondary prevention or HeFH). As presented in the Company evidence submission (Section B.2.7; Document B), the treatment effect for bempedoic acid and FDC is consistent for patients with or without ASCVD, patients with HeFH, and differing severity of hypercholesterolaemia (as indicated by baseline LDL-C category).

Non-HDL-C

B4. Priority question. Clinical experts advising the ERG have highlighted the importance of non-HDL-C on CV risk. Please explain why non-HDL-C was not used to predict CV risk? Please provide scenario analyses using evidence from the published literature on the relationship between non-HDL-C and CV risk:

a) Please provide cost-effectiveness results for populations 2 and 4 based on the clinical effectiveness analysis requested in clarification questions:

   I. A1c (% change in non-HDL-C at 12 weeks);

   II. A1d (% change in non-HDL-C at 24 weeks)

   III. A5c (% change in non-HDL-C at 12 weeks); and

   IV. A5d (% change in non-HDL-C at 24 weeks).

b) Please provide cost-effectiveness results for populations 1 and 3 based on the clinical effectiveness analysis requested in clarification questions:

   I. A5c (% change in non-HDL-C at 12 weeks); and

   II. A5d (% change in non-HDL-C at 24 weeks).

Company response: Although non-HDL-C is an important lipid marker, the company approach was to maintain consistency with previous NICE appraisals in this disease area and with widely accepted rationale in using LDL-C as the primary lipid endpoint of interest, and as the surrogate for CV risk. This approach was verified with expert opinions during two advisory boards in the UK and separate consultations and is aligned with the expected indication in LDL-C lowering as well as the mechanism of action of bempedoic acid. Therefore, and as detailed in the response to question A1, non–HDL-C was not used to predict CV risk in the cost-effectiveness model as part of this submission. No scenario analyses based on non–HDL-C as the surrogate outcome are presented.

B5. Please provide separate cost-effectiveness results of bempedoic acid at 12 weeks and 24 weeks using the feasible subgroup analyses requested in clarification question A7.

Company response: As detailed in the response to question A1, non–HDL-C was not used to predict CV risk in the cost-effectiveness model because LDL-C is well accepted as the primary lipid endpoint of interest, and as the surrogate for CV risk and has been used in previous NICE TAs in this therapeutic area. No subgroup analyses using non–HDL-C as the surrogate outcome are presented.

Patient baseline characteristics

B6. Priority question. Table 51 in Ward et al. 2007 reports the distribution of secondary prevention patients by prior CV event and these include post-stable angina, post-unstable angina, post-MI post-TIA and post-stroke.

a) Please clarify why TIA and stable angina were not included as prior CV events for secondary prevention patients;

b) As a scenario analysis, please include TIA and stable angina as prior CV events for secondary prevention patients, using the distributions of prior CV events recorded in Ward et al. 2007

Company response: Prior transient ischaemic attack (TIA) and stable angina were not included as starting prior events to better align with the definition of prior CV/high risk in TA393 and TA394. This is also aligned with starting cohorts in TA385 and, therefore, makes our results more comparable with the technology assessments of the relevant comparators.

0 presents the results for the four base-case positions (2a, 2b, 4a and 4b) if TIA and stable angina are included as starting populations. As can be seen in the table, this has a limited effect on the results.

Table 19. Scenario results populations if TIA and stable angina are included as starting populations

	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	NMB (£20,000)	NMB (£30,000)
Position 2a									
Bempedoic acid with background ezetimibe	13,907	11.87	8.84						
No further treatment/placebo with background ezetimibe	8,025	11.63	8.64	5,882	0.24	0.20	29,793	-1,933	41
Position 2b									
Bempedoic acid with background ezetimibe	17,888	10.32	7.28						
Alirocumab	41,085	10.40	7.34	-23,196	-0.08	-0.06	379,904	21,975	21,365
Evolocumab	41,507	10.44	7.37	-23,619	-0.12	-0.09	265,450	21,839	20,949
Position 4a									
Bempedoic acid with background ezetimibe	17,324	10.13	7.21						
No further treatment/placebo with background ezetimibe	11,847	10.03	7.14	5,478	0.10	0.08	72,450	-3,966	-3,210
Position 4b									
Bempedoic acid with background ezetimibe	17,446	9.59	6.81						
Alirocumab	39,853	9.86	7.01	-22,407	-0.27	-0.20	110,719	18,360	16,336
Alirocumab+EZE	40,061	9.89	7.03	-22,615	-0.30	-0.23	99,697	18,079	15,810
Evolocumab	40,492	10.03	7.14	-23,046	-0.44	-0.33	69,459	16,410	13,092

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit; TIA = transient ischaemic attack.

B7. Priority question. If data are available, please provide a scenario analysis using the distribution of secondary prevention patients by prior CV event recorded in the CLEAR trials.

Company response: These data are currently not available to us from the CLEAR trials. Further, due to the limited sample size in the CLEAR studies in some of the relevant positions and the number of health states, the data from Ward et al. (2007) is likely more accurate for the relevant populations in this submission.

B8. Priority question. The ERG has identified a discrepancy between the LDL-C baseline values reported in Table 50 of the CS with the chosen values in the 'Risks' worksheet of the economic model. Please clarify if the values in the CS or the 'Risks' worksheet are correct for the following:

a) No or low-dose statin, non-PCSK9i eligible, population 2a(Table 50 of the CS reports [redacted]; 'Risks'J13 reports [redacted]);

b) Max dose statin, non-PCSK9i eligible, population 4a (Table 50 of the CS reports [redacted]; 'Risks'J13 reports [redacted]);

c) Please clarify if 'Default Data'AA248 is erroneously calling from 'CLEAR data input'AE28 when it should be calling from CLEAR data input'AE52.

Company response: This is intended and not a discrepancy or error. Limited patients fulfilling the criteria for proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) treatment actually receive PCSK9i treatment based on clinical expert opinion from the Daiichi Sankyo Delphi panel (Daiichi Sankyo Europe data on file, 2019). Hence, it seemed reasonable to use the baseline LDL-C of all patients when presenting results for the non-PCSK9i population in position 2a/4a in the base case. The model and the results in the dossier reflect this and are correct.

Briefly, the current assumptions used in the model are the following:

- **For position 2b and 4b** (patients eligible for PCSK9i treatment), the mean baseline LDL-C data from patients eligible for PCSK9i treatments in the CLEAR trials were used.
- **For position 2a and 4a**, the mean baseline LDL-C data from all patients included in the CLEAR trials were used.

B9. Priority question. The ERG has identified a discrepancy in the model: 'Input summary general'J29 reflects "Starting pop - HeHF (secondary prevention)" and this calls from 'Analysis Settings'J104 which reflects "Prevention

(primary)'. Please clarify if 'Analysis Settings'J108 should be called instead and correct where necessary.

Company response: This is a labelling error in the model. 'Input summary general'J29 should be "="Starting pop - primary prevention" rather than "="Starting pop - "&'Analysis Settings'!B108". The value was correctly used in the model, but the labelling in the "Input summary general"- sheet has been updated.

Background cardiovascular (CV) risks: primary prevention

B10. Priority question. On page 160 of the CS it states, "For the base-case analysis (in contraindicated or not tolerated population), a 30.3% 10-year risk of MI, stroke or CV death was applied for high-risk primary prevention patients, estimated using the QRISK3 risk assessment tool recommended in the recent Lipid Modification guideline (NICE, 2016b)". According to Table 64 in the CS, this risk is also used to inform the economic model.

a) Please clarify where a risk of 30.3% can be found in the economic model as the ERG can only identify a risk of 7.5% from the European Society of Cardiology (ESC) guidelines ('Default Data'H146);

b) If a risk of 30.3% has not been used to inform the economic model, please explain why.

Company response: Bempedoic acid has been studied in patients at high to very-high risk of CV events. This value (30.3%) is calculated based on what according to the SCORE risk algorithm in the ESC guideline is considered high risk (7.5% 10-year risk of CV death, which is the mid-value of the range: 5%-10%) (Mach et al., 2019). The SCORE risk is converted to a QRISK3-score of 30.3% when using the distribution of CV events in Ward et al. (2007) (in line with the methodology in CG181 only events that were included in QRISK3 in Ward et al. (2007) were included when the relative rates were used). Using an aggregated estimate of the risk in the primary prevention cohort is in line with the accepted approach in CG181 and TA385 (NICE, 2016b; NICE, 2016d; Ward et al., 2007).

This value can, for instance, be found in "Analysis setting" K110, when position 2a/2b (in contraindicated or not tolerated population) is selected. If another position is selected the value changes slightly due to differences in sex distribution as this influences the relative rates of CV death. For example, the corresponding value for position 4a/4b is 29.4%.

B11. Priority question. Please explain why the characteristics of a UK primary prevention cohort were not entered into the QRISK3 tool

(https://qrisk.org/three/) to estimate the baseline risk of the patient cohort that might be considered for bempedoic acid.

Company response: Individual patient-level data covering all the required data points in a relevant UK primary prevention cohort was not easily available for us. Aggregated risk data have been previously accepted in TA385 and CG181 (NICE, 2016a; NICE, 2016d). The TA394 committee papers have been requested but are not publically available. Hence, the methodology proposed and acceptance of this in TA394 could not be assessed.

B12. Priority question. Please explain why primary prevention CV risks are not adjusted by age and/or gender.

a) As a scenario analysis, please apply rates each year of 0.03% for males and 0.008% for females, to reflect the methods employed in NICE CG181 and TA385, based on the evidence in Ward et al. 2007.

Company response: As the cohorts get older, the risk for the primary prevention cohort is adjusted for age and increased by each cycle in a similar way to the risk for subsequent CV events (secondary prevention).

But for the primary prevention cohort, the risk itself together with the LDL-C are the most important factors for deciding if a patient without prior CV event should receive treatment (defining the relevant cohort for the model), it is not appropriate to adjust the baseline risk for age/sex. Hence, the baseline CV risks in the primary prevention cohort are considered to be already representative of the cohort that should simulated to answer the decision problem.

A scenario with age-adjustments of 0.03% for males and 0.008% for females is presented in 0. However, for the primary prevention cohort, these adjustments are only applied for when the patients get older in the model and no adjustments to the baseline risks are performed as outlined in the paragraph above.

Table 20. Results using 0.03% for males and 0.008% for females for age adjustments.

Position 2a									
	Total cost (£)	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**	**NMB (£20,000)**	**NMB (£30,000)**
Bempedoic acid with background ezetimibe	13,816	12.37	9.18						
No further treatment/placebo with background ezetimibe	7,843	12.13	8.98	5,973	0.24	0.20	29,911	-1,979	18
Position 2b									
Bempedoic acid with background ezetimibe	18,605	10.17	7.00						
Alirocumab	41,187	10.27	7.07	-22,582	-0.10	-0.07	323,414	21,186	20,487
Evolocumab	41,632	10.31	7.10	-23,027	-0.14	-0.10	226,434	20,993	19,976
Position 4a									
Bempedoic acid with background ezetimibe	18,178	10.12	7.03						
No further treatment/placebo with background ezetimibe	12,767	10.00	6.95	5,411	0.12	0.08	64,331	-3,729	-2,888
Position 4b									
Bempedoic acid with background ezetimibe	18,132	9.54	6.61						
Alirocumab	40,222	9.85	6.84	-22,090	-0.32	-0.23	97,439	17,556	15,289
Alirocumab+EZE	40,453	9.89	6.86	-22,320	-0.35	-0.25	87,888	17,241	14,702
Evolocumab	40,987	10.05	6.98	-22,855	-0.52	-0.37	61,680	15,444	11,739

BA=bempedoic, EZE=ezetimibe; FDC = bempedoic acid plus ezetimibe fixed-dose combination; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B13. Priority question. On page 160 of the CS it states, "The distributions between the different types of events in Ward et al. (2007) are shown in Table 49". The ERG has several issues relating to this:

a) The ERG suspects Table 49 in the CS has been reproduced from Table 72 in Appendix L of CG181 and represents relative rates of first events in primary prevention using QRISK2, and not the distribution of first events in primary prevention patients as suggested in the text, please clarify;

b) Please clarify if Table 49 in the CS should match the distribution of patients given in Table 49 in Ward et al. 2007 and Table 26 (page 114 of 222) in the committee papers for TA385;

c) Please provide the distribution of the relative risks of first events in primary prevention patients (using QRISK3 if a QRISK tool is used) and make the necessary changes to the economic model in light of your responses.

Company response: The data are correct. The table using QRISK2 table from CG181 is based on the same source data and presents the same data as the table in TA385 and Ward et al. (2007) (NICE, 2016b; NICE, 2016d; Ward et al., 2007). The differences in our submission and CG181 (NICE, 2016d) compared with Ward et al. (2007) and TA385 (NICE, 2016a) is that the values have been proportionally reweighted so the event distribution (relative rates) for the events included in QRISK2 sums to 1. This conversion is made in CG181 to reflect what the QRISK2 score, we have followed this methodology in the company submission. If the relative rates in the Company submission (or the rates in CG181) are divided by the sum of all the relative rates, the values in Ward et al. (2007) are restored (see Table 21).

Table 21. Conversion of relative rates between CG181 (QRISK2) and Ward et al. (2007)/TA385

Men	Sum of relative rates in the CS	Restored distribution of events					
		SA	UA	MI	TIA	IS	CV death
40–54	190.3%	30.73%	10.71%	29.53%	6.01%	12.91%	10.11%
55–64	195.3%	32.80%	7.10%	17.20%	8.90%	20.60%	13.40%
65–74	165.8%	21.40%	8.30%	17.30%	10.00%	27.00%	16.00%
75–84	154.4%	19.12%	8.11%	16.12%	8.01%	34.34%	14.31%
85+	148.4%	21.40%	9.60%	18.60%	1.60%	35.10%	13.70%
Women							
40–54	250.7%	32.43%	11.69%	7.98%	15.96%	22.86%	9.09%
55–64	205.7%	34.61%	7.29%	9.19%	9.48%	28.83%	10.60%
65–74	148.6%	20.19%	5.18%	12.11%	7.27%	38.16%	17.09%
75–84	139.1%	14.95%	3.38%	10.21%	9.78%	46.44%	15.24%

Men	Sum of relative rates in the CS	Restored distribution of events					
		SA	UA	MI	TIA	IS	CV death
85+	133.8%	13.60%	2.91%	10.01%	8.67%	50.07%	14.72%

CS=Company submission, CV= cardiovascular; MI= myocardial infarction; SA=stable angina, TIA= transient ischemic attack; UA=unstable angina, .

Hence, the Company submission it is not supposed to match the table in TA385 as we followed the methodology in CG181 where relative rates are adjusted.

Further, as the QRISK3 score is calculated based on the relative rate of CV death, the use of rates directly from Ward et al. (2007) would have very limited impact on the cost-effectiveness result of but would change the QRISK3 score.

B14. Priority question. Page 160 of the CS states "*for example, a 10-year risk of 20% corresponds to a 1-year risk (annual probability) of 2.207%, so for a QRISK3 risk score of 20% (10-year risk), the values in Table 49 were all multiplied by 0.02207 to give the baseline transition probabilities from high risk for ASCVD to each CV event each year*" but this is not reflected in the model. Please explain this discrepancy and provide explicit details of how the transition probabilities were calculated and applied in the model.

a) Instead of adjusting a 10-year risk of 7.5% from the ESC guidelines, please provide a scenario analysis using a 10-year risk of 20% to reflect the methods in CG181 and TA385.

Company response: We see no discrepancy between what is stated in the dossier and how the risks are calculated in the model (Support_engine C61:T73). The methodology used in the model and described in the Company submission is in line with the approach in CG181 and TA393 (NICE, 2016c; NICE, 2016d). As stated in the dossier, the 20% is an example as the 10-year risk varies depending on the population that is selected in the model (see question B10). See question B16 for supporting details.

As described in the Company submission, the following approach is used to estimate baseline transition probabilities from high risk for ASCVD to each CV event each year:

- The 10-year risk of CV death in the high-risk population (7.5%) (Mach et al., 2019) was converted to a 10-year risk of CV events according to QRISK3 using the relative rate of death in Ward et al. (2007) via CG181 (NICE, 2016d). (See 'Default Data'!H146)
- The 10-year QRISK score was converted to yearly probabilities using
  - =1 – EXP(ln(1-"10-year probability (QRISK score)")/10)) (see Support_engine!D69)
  - The yearly probability of a QRISK event was multiplied with the relative rates in Table 49 to obtain probabilities from high risk for ASCVD to each CV event each year. (see Support_engine!F70:L70)

An exploratory scenario analysis with 20% 10-year risk for CV events is presented in Table 22. As ezetimibe is likely also to be used also in a populations with lower risk patients it is not unreasonable to assume that the patients relevant for bempedoic acid will have a higher mean 10-year risk for CV events than the patients considered in TA385.

Table 22. Scenario with 20% 10-year risk for CV events

Position 2a									
	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	NMB (£20,000)	NMB (£30,000)
Bempedoic acid with background ezetimibe	13,185	12.36	9.23						
No further treatment/placebo with background ezetimibe	7,105	12.15	9.07	6,080	0.21	0.17	36,540	-2,752	-1,088
Position 2b									
Bempedoic acid with background ezetimibe	18,653	10.08	6.95						
Alirocumab	41,511	10.16	7.01	-22,858	-0.09	-0.06	373,097	21,633	21,020
Evolocumab	41,945	10.20	7.04	-23,291	-0.13	-0.09	260,889	21,506	20,613
Position 4a									
Bempedoic acid with background ezetimibe	18,075	9.93	6.91						
No further treatment/placebo with background ezetimibe	12,647	9.82	6.83	5,428	0.11	0.08	71,270	-3,905	-3,143
Position 4b									
Bempedoic acid with background ezetimibe	18,067	9.36	6.50						
Alirocumab	40,205	9.64	6.70	-22,138	-0.28	-0.20	108,611	18,061	16,023
Alirocumab+EZE	40,425	9.68	6.73	-22,358	-0.32	-0.23	97,867	17,789	15,504
Evolocumab	40,914	9.82	6.83	-22,846	-0.46	-0.33	68,392	16,165	12,825

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B15. Please explain why the 10-year risk of MI, IS and CV death ('Default Data'H146) is based on the relative rate for CV death (0.2554) and not the relative rates for MI (0.2741) or IS (0.4706).

Company response: The proportion of CV death is used to convert the SCORE risk (10-year fatal CVD risk) to QRISK3 (risk of MI, ischaemic stroke [IS], and CV death). As the SCORE risk algorithm refers to CV death this should be used for this conversion rather than MI and IS. We used the proportion of CV death of all events included in QRISK3 (MI, IS, and CV death) from Ward et al. (2007) to make a more detailed calculation of 10-year risk of MI, IS, and CV death. This is described in more detail in Company submission Section B.3.1.5.

B16. Please explain why age categories of 55-64 and 65-74 (Support_engine'E63:L65) are used in the economic model to calculate background CV risks in primary prevention and not the age category of patients included in the CLEAR studies (65-74).

Company response: The mean starting age is ~65 in the model. Assuming approximately a normal distribution for age and the median age of ~65 in the CLEAR studies, patients should in reality be almost equally distributed in the two age groups rather than all being 65 to 74. Hence, both groups are used to achieve a more representative distribution of primary events in the model.

B17. Please explain why the prevalence of diabetes was considered when estimating the baseline CV risks in secondary prevention, but not primary prevention.

Company response: As discussed in questions B10 and B12, the risk itself together with LDL-C are the most important factors for establishing whether a patient without prior events receives treatment and in extension for defining a relevant primary prevention patient population. The risk in the primary prevention cohort (7.5%) is the "definition" of a high-risk population, (Mach et al., 2019) therefore, the baseline risk applied for the primary prevention cohort should be considered as covering all relevant patients (diabetic and non-diabetic). Adjusting the baseline risk in the primary prevention cohort when it is the most influential factor defining the population would therefore not be appropriate.

The most influential factors defining the secondary prevention cohort are prior events and LDL-C level. The data used for secondary prevention was separated for patients with and without diabetes. Hence, the proportion of diabetic patients was needed to estimate accurately the risk in secondary prevention patients.

B18. Please explain why the prevalence of HeFH was considered when estimating the baseline CV risks in secondary prevention, but not primary prevention.

Company response: We apply the same rationale as for diabetes and sex in question B17, question B10, and question B12.

Background cardiovascular (CV) risks: secondary prevention

B19. Priority question. In the economic model, the baseline risk of CV events in THIN are adjusted for differences in age and baseline LDL-C compared with the CLEAR studies.

a) Please explain this process as this adjustment has been omitted from the CS;

b) Please add row and column headings to the data in 'Support_engine'C35:S56.

Company response: This is described in the company submission section 5.3.1.5.1. Briefly, the baseline risk for events was adjusted to reflect the baseline LDL-C and age that is selected in the model. The selection of baseline LDL-C and age is in the base-case, as the ERG outlines, dependent on the age and baseline LDL-C in the CLEAR studies. Briefly, the baseline risks are adjusted for:

- Baseline LDL-C using the meta-regression from CTTC et al (2015) (Cholesterol Treatment Trialists et al., 2015)
- Baseline age using Wilson (2012) (Wilson et al., 2012)

Row and column headings have been added to the model in 'Support_engine'C35:S56.

B20. Priority question. Please explain why CV risk adjustments for age (increased risks for CV events) ('Support engine'C106:D112) are used to inform the transitions from a CV event that occurred less than a year ago to between 1 and 2 years ago and to more than 2 years ago.

Company response: The patients in the health states of events 'less than a year ago', 'between 1 and 2 years ago' and 'more than 2 years ago' all have a risk to experience additional/new CV events. As the CV risk for new events increases with age in all health states, the probability of no new events (for instance patients move from "MI 0-1 year ago" to "MI 1-2 years ago") also needs to be adjusted for the increased age to capture that fewer patients should stay in the health state when older patients. The total population cohort (dead+alive) in the model would otherwise increase >1.

B21. Instead of adjusting for age alone, please provide a scenario analysis where the annual increase in CV risk is adjusted for age and gender, using the evidence in Wilson et al. 2012.

Company response: The THIN data was deemed to be reflective of a UK general population by clinical experts and adjusting for gender for this data could be problematic (NICE, 2016c). From a technical perspective, the core of the model does not allow for a changing distribution of sex over time. Hence, we are not able to perform this scenario analysis. See question B12 for a scenario where different adjustments are used for male and female patients.

Recurrent events

B22. Priority question. Please clarify the difference between a recurrent CV event ([redacted] in 'Analysis Settings'J112) and a prior CV event ('Analysis Settings'J104). In 'CLEAR data input'C23, a recurrent CV event is also defined as a polyvascular event and therefore the ERG questions using this outcome to inform the proportion of recurrent CV events, please explain.

Company response: Recurrent events imply more than one prior event, while prior event implies more than zero prior events. Detailed data of recurrent/polyvascular events are sparse in the literature, however the [redacted] is in line with the estimates from the Alirocumab studies in TA393 (7% - 27%). It is correct that this estimate includes also patients with polyvascular disease as it was difficult to easily track recurrent events in the CLEAR data. Further, we did not identify reliable data of the increase risk of recurrent vs. polyvascular events. This parameter could, therefore, be overestimated but is included in the OWSA and is not identified as a major result driver.

B23. Priority question. Please explain why recurrent events (two or more events) in the economic model are not capped or split into secondary events and tertiary events as inferred by Figure 17 of the CS.

Company response: We did not identify reliable data that would support a more detailed split of recurrent events. The model structure diagram is presented in this way as we believe it better describes the flow. The third level in the figure is necessary to describe the changing risk after a recurrent event (2+ events). Capping the model to just 3 events would underestimate the risk for CV events as some patients experience more than 3 events over a lifetime.

B24. Priority question. On page 169 of the CS it states "a recurrent cardiac event (MI, UA and SA) only affects the risk for cardiac events (MI, UA, SA and CV death) while a recurrent IS only affects the risk of IS and CV death" but the ERG's clinical experts have advised that recurrent cardiac events also affect the risk for IS events, and that recurrent IS events also affect the risk for cardiac events. Please provide a scenario analysis where recurrent cardiac events also affect the risk for IS events.

Company response: This assumption was used as it was deemed most conservative and also in line with our understanding of TA393. A scenario where the recurrent cardiac events also affect the risk for IS events is presented in Table 23.

Table 23. Cost-effectiveness results when recurrent cardiac events also affect the risk for IS events

	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	NMB (£20,000)	NMB (£30,000)
Position 2a									
Bempedoic acid with background ezetimibe	14,086	11.81	8.76						
No further treatment/placebo with background ezetimibe	8,208	11.56	8.56	5,878	0.24	0.20	29,503	-1,893	99
Position 2b									
Bempedoic acid with background ezetimibe	18,680	10.03	6.91						
Alirocumab	41,481	10.12	6.97	-22,801	-0.09	-0.06	365,827	21,554	20,931
Evolocumab	41,914	10.16	7.00	-23,234	-0.13	-0.09	255,817	21,417	20,509
Position 4a									
Bempedoic acid with background ezetimibe	18,119	9.87	6.87						
No further treatment/placebo with background ezetimibe	12,709	9.77	6.79	5,410	0.11	0.08	69,555	-3,854	-3,076
Position 4b									
Bempedoic acid with background ezetimibe	18,099	9.31	6.45						
Alirocumab	40,173	9.59	6.66	-22,074	-0.29	-0.21	106,380	17,924	15,849
Alirocumab+EZE	40,393	9.63	6.69	-22,294	-0.32	-0.23	95,860	17,643	15,317
Evolocumab	40,885	9.78	6.79	-22,786	-0.47	-0.34	66,999	15,984	12,583

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B25. Please explain why patients cannot have a recurrent TIA in the economic model.

Company response: The current modelling approach in the base-case used this as a conservative assumption. We identified limited data on this in the literature and no previous TAs has applied recurrent TIA, so this was left out of the model to not overestimate the CV risks. As advised by clinical experts, compared to the other events TIAs are likely heterogeneous and due to its nature, the symptoms of TIAs are often short and can easily be mistaken. Hence, when diagnosed the patient in the data used for calculating the risk of TIA could already have had several TIAs and including this could lead to an overestimation.

Modelling the relationship between LDL-C lowering and CV risk reduction

B26. Priority question. Please provide a clinical rationale or any supporting evidence as to why the relationship between LDL-C and CV risk using the CTTC meta-analysis based on statins is expected to hold true for:

a) Patients who are contraindicated to or cannot tolerate statins;

b) PCSK9 inhibitors.

Company response: When statins are contraindicated or not tolerated, patients in the model may receive ezetimibe, bempedoic acid, alirocumab or evolocumab. Studies have shown that the relationship between LDL-C reduction and CV events is similar between statin and non-statin treatments (e.g., Silverman et al. 2016). In this meta-regression analysis, a total of 312,175 participants with 39,645 major vascular events from 49 trials were included, spanning 9 different treatment modalities (statins, ezetimibe, PCSK9s, diet, bile acid sequestrants, ileal bypass surgery, fibrates, niacin, and cholesteryl ester transfer protein). The authors concluded that the use of statin and non-statin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar RRs of major vascular events per change in LDL-C. This analysis builds on prior observations in a smaller number of trials ((Robinson et al., 2005) (Robinson et al., 2009)2009). These findings are also supported by Mendelian randomization studies showing a strong association between the degree of lower LDL-C imparted by a genetic variant and the magnitude of the lower cardiovascular outcome risk in carriers of that variant, irrespective of the gene ((Ference et al., 2012)).

The CTTC meta-analysis was selected for the base-case analysis because it was based on patient-level data rather than aggregated published data, and for consistency of decision making, as this analysis was used (and preferred over the Navarese et al. (2015) analysis) in previous NICE appraisals (TA385, TA393, TA394). Bempedoic acid acts in the same cholesterol biosynthesis pathway as statins and upregulates LDL receptors by suppression of cholesterol synthesis (Section B.2.13). Hence, statin treatments could be considered most representative of the effect of LDL-C lowering from bempedoic acid.

B27. Priority question. The ERG has identified discrepancies between the rate ratios included in the economic model ('Default Data'A172:P206) and Table 55 of the CS. Please clarify if the values reported in the model are correct.

Company response: There is a discrepancy as the Table 55 in the CS report the risk of all types of stroke while the model, as intended, reports the risk of ischemic stroke. In line with comments from experts, we consider ischemic stroke a more relevant outcome and the model and, in extension, all results are therefore correct. Hence, 0.80 (0.75-0.86) as used in the model and for the presented results is the correct values. Table 55 updated with values for ischemic stroke rather that all-cause stroke is presented in Table 24.

Table 24. Updated Table 55. Rate Ratio for CV events per 1 mmol/L reduction in LDL C

	Mean (CI)	Mean (CI)	Mean (CI)	Mean (CI)[a]
MI	0.64 (0.43- 0.96)	0.76 (0.73-0.79)	0.85 (0.78-0.96)	[redacted]
UA	0.64 (0.43- 0.96)	0.76 (0.73-0.79)	0.85 (0.78-0.96)	[redacted]
SA	1	1	1	1
Revascularisation	0.64 (0.43- 0.96)	0.76 (0.73-0.78)	0.89 (0.82-0.96)	[redacted]
IS	0.64 (0.43- 0.96)	0.80 (0.75-0.86)	0.99 (0.86-1.08)	[redacted]
TIA	1	1	1	1
CV death	0.64 (0.40-1.04)	0.88 (0.84-0.91)	0.89 (0.73-1.01)	[redacted]
Source	Navarese et al. (2015)	(Cholesterol Treatment Trialists et al., 2015)	Navarese et al. (2018)	De novo meta-regression

CI = confidence interval; CV= cardiovascular; MI= myocardial infarction; SA=stable angina, TIA= transient ischaemic attack; UA=unstable angina,

B28. Priority question. Table 47 in Appendix E reports separate relative risks for 4 populations included in the company's submission.

a) Please clarify if these relative risks can be interpreted as rate ratios;

b) Please explain why these population-specific relative risks (or rate ratios) are not utilised in scenario analyses;

c) Please provide cost-effectiveness results using the population-specific relative risks (or rate ratios).

Company response: Relative risks were calculated based on data reported from the underlying publications. The relative risk based on data reported for the time closest to 12 weeks was calculated. This has been used as a proxy for rate ratios, which were not directly published..

They are used and presented in the CS labelled as "De novo meta-regression" in Table 69-72 in CS.

These values are also included in the model named “De novo meta-regression”.

Health related quality of life

B29. Priority question: The ERG’s clinical experts have advised that recurrent events have a greater impact on quality of life compared with primary events. Please justify why utility values for primary and recurrent events were assumed to be the same in the economic model.

a) Please provide a scenario making appropriate adjustments to event utilities for recurrent events, using evidence from the published literature, where available or clinical expert opinion to inform the adjustments. Alternatively, provide threshold analysis, testing different percentage decrements to utilities for recurrent events.

Company response: Similar to previous technology assessments (TA393 (NICE, 2016c) and TA394 (NICE, 2016b)), we did not identify any reliable utility estimates of recurrent survivors of each outcome in the literature. As the data used to estimate utility values (The Health Survey for England [HSE]) likely included patients with both one and recurrent events (data not presented for number of events) and could therefore capture the utility effect of multiple events, additional adjustments could result in double counting of the utility effect from CV events. Further, applying multiple adjustments on the same population (such as composite endpoints) has previously been criticised by ERGs and NICE. A scenario analysis where the utility-multiplier in recurrent health states are applied twice (extreme scenario) is presented in 0 for reference.

Table 25. Results with multiple utility adjustments after recurrent events

	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	NMB (£20,000)	NMB (£30,000)
Position 2a									
Bempedoic acid with background ezetimibe	14,085	11.82	8.65						
No further treatment/placebo with background ezetimibe	8,203	11.58	8.44	5,882	0.24	0.21	28,375	-1,736	337
Position 2b									
Bempedoic acid with background ezetimibe	18,672	10.07	6.55						
Alirocumab	41,516	10.15	6.61	-22,844	-0.09	-0.06	352,229	21,547	20,898
Evolocumab	41,950	10.19	6.64	-23,277	-0.13	-0.09	246,375	21,387	20,443
Position 4a									
Bempedoic acid with background ezetimibe	18,111	9.91	6.53						
No further treatment/placebo with background ezetimibe	12,690	9.80	6.45	5,421	0.11	0.08	66,916	-3,801	-2,991
Position 4b									
Bempedoic acid with background ezetimibe	18,090	9.35	6.10						
Alirocumab	40,210	9.63	6.32	-22,121	-0.28	-0.22	102,198	17,792	15,627
Alirocumab+EZE	40,430	9.67	6.34	-22,340	-0.32	-0.24	92,107	17,489	15,064
Evolocumab	40,919	9.81	6.46	-22,830	-0.46	-0.35	64,436	15,744	12,201

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

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B30. Please justify why a utility value of 1 was used to represent no CV disease ('Utilities'G14 of the economic model).

a) In the one-way sensitivity analyses, the upper bound is implausible (1.1). Please amend the no CV disease utility value to reflect either age-adjusted general population values or obtain from the literature a baseline utility value for a patient a high-risk ASCVD patient.

Company response: The utility value of 1 is not used to represent the utility in patients with no CV disease. The utility multiplier of 1 is used for this population but is multiplied with the general population utility as recommended in the Technical Support Document (TSD) produced by NICE's Decision Support Unit (Ara and Wailoo, 2011). This population, therefore, have a utility that reflects the general population. A 1.1 multiplier is possible if the no CV disease population has a higher utility than the general population, which is not likely but still possible (not an insignificant part of the general population has prior CV therefore reduced utility),therefore, we propose that this should be kept as it is presented in the model.

B31. Please explain why 50% male has been assumed for the EQ5D utility calculation in 'Default Data'H340:347?

Company response: According to the methodology proposed in the TSD produced by NICE's Decision Support Unit(Ara and Wailoo, 2011), the distribution in the source publication should be used for this calculation. In the source publication we did not identify the proportion of males, hence, a 50% assumption was made. This is in line with assumptions in previous appraisals using this source for utility multipliers (for instance, TA393). A different sex distribution would have a very limited impact on the results.

Resource use and costs

B32. Priority question: The ERG has several concerns with how health state costs have been implemented in the model. The study by Danese et al. 2016 presents total and incremental costs for first and second events as well as first and second events combined, which has been used in the model. The ERG's clinical experts have advised that recurrent events have a greater impact on resource use and costs compared with primary events. Furthermore, The company have assumed that a CV death is cost-saving compared with a non-

CV death based on data from Walker et al.,2016. The ERG considers this a perverse incentive.

a) Please justify why the costs for first and second events combined from Danese et al. 2016 was deemed appropriate to use in the model.

b) Please clarify why the incremental cost values were deemed appropriate to use to cost the model health states.

c) Please perform a scenario where total costs are used for all health states, including CV death.

    i. Please build on this scenario by using second event total costs from Danese et al. 2016 to cost recurrent events. Alternatively, threshold analysis exploring the impacts of increased costs for recurrent events would be acceptable. Please make this an on/off option in the model for the scenario.

Company response: An alternative approach to model the negative CV death cost (which is not counterintuitive but maybe perverse) would have been to add an even higher cost for non-CV related death. This would imply adding additional parameters and complexity to the model without adding any benefits in form of flexibility or accuracy. Hence, the base case approach was considered most appropriate.

The rational for why we used the costs for both first and second events group together were:

- The values for first and second event were consistent in most cases and the increased number of cases improve the certainty in the estimates
- Some of the costs are higher for the first event than the recurrent event, which is counterintuitive according to both us and the ERG clinical experts.

Total costs were considered for inclusion, but incremental costs was deemed more appropriate as this controls for differences in the patient population between the Danese et al. (2016) (Danese et al., 2016) study and the model. Using the total costs, it is also technically challenging to apply an accurate cost for the patient before they experience an event, as this cost varies between the different events and between the first and second event.

A scenario where we have applied total costs rather than incremental costs is presented in 0 together with a scenario where the cost for recurrent events are modelled using a separate cost in 0. However, the results using total costs are not accurate as this approach does not correctly control for the difference in costs for the patients before the first event. Therefore, we do not support the presented results for decision making purposes.

Table 26. Scenario using total costs for the health states

Position 2a									
	Total cost (£)	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**	**NMB (£20,000)**	**NMB (£30,000)**
Bempedoic acid with background ezetimibe	37,016	11.82	8.76						
No further treatment/placebo with background ezetimibe	30,716	11.58	8.57	6,301	0.24	0.20	31,852	-2,344	-366
Position 2b									
Bempedoic acid with background ezetimibe	35,543	10.07	6.94						
Alirocumab	58,501	10.15	7.00	-22,958	-0.09	-0.06	373,619	21,729	21,114
Evolocumab	58,986	10.19	7.03	-23,443	-0.13	-0.09	261,813	21,652	20,757
Position 4a									
Bempedoic acid with background ezetimibe	34,663	9.91	6.89						
No further treatment/placebo with background ezetimibe	29,102	9.80	6.81	5,561	0.11	0.08	72,589	-4,029	-3,262
Position 4b									
Bempedoic acid with background ezetimibe	33,882	9.35	6.48						
Alirocumab	56,369	9.63	6.69	-22,487	-0.28	-0.20	109,938	18,396	16,351
Alirocumab+EZE	56,634	9.67	6.71	-22,752	-0.32	-0.23	99,242	18,166	15,874
Evolocumab	57,315	9.81	6.82	-23,433	-0.46	-0.34	69,900	16,728	13,376

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

Table 27. Scenario using health state costs split on first and second events

Position 2a									
	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	NMB (£20,000)	NMB (£30,000)
Bempedoic acid with background ezetimibe	14,314	11.82	8.76						
No further treatment/placebo with background ezetimibe	8,458	11.58	8.57	5,856	0.24	0.20	29,605	-1,900	78
Position 2b									
Bempedoic acid with background ezetimibe	19,550	10.07	6.94						
Alirocumab	42,382	10.15	7.00	-22,832	-0.09	-0.06	371,573	21,603	20,988
Evolocumab	42,810	10.19	7.03	-23,260	-0.13	-0.09	259,767	21,469	20,573
Position 4a									
Bempedoic acid with background ezetimibe	18,953	9.91	6.89						
No further treatment/placebo with background ezetimibe	13,548	9.80	6.81	5,406	0.11	0.08	70,566	-3,874	-3,108
Position 4b									
Bempedoic acid with background ezetimibe	19,003	9.35	6.48						
Alirocumab	41,085	9.63	6.69	-22,082	-0.28	-0.20	107,957	17,991	15,945
Alirocumab+EZE	41,300	9.67	6.71	-22,297	-0.32	-0.23	97,259	17,712	15,419
Evolocumab	41,769	9.81	6.82	-22,766	-0.46	-0.34	67,912	16,062	12,709

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

Table 28. Scenario using total costs for health states and costs split on first and second events

Position 2a									
	Total cost (£)	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**	**NMB (£20,000)**	**NMB (£30,000)**
Bempedoic acid with background ezetimibe	38,191	11.82	8.76						
No further treatment/placebo with background ezetimibe	31,981	11.58	8.57	6,210	0.24	0.20	31,394	-2,254	-276
Position 2b									
Bempedoic acid with background ezetimibe	39,602	10.07	6.94						
Alirocumab	62,532	10.15	7.00	-22,930	-0.09	-0.06	373,170	21,701	21,087
Evolocumab	63,005	10.19	7.03	-23,403	-0.13	-0.09	261,365	21,612	20,717
Position 4a									
Bempedoic acid with background ezetimibe	38,545	9.91	6.89						
No further treatment/placebo with background ezetimibe	33,019	9.80	6.81	5,525	0.11	0.08	72,127	-3,993	-3,227
Position 4b									
Bempedoic acid with background ezetimibe	37,914	9.35	6.48						
Alirocumab	60,313	9.63	6.69	-22,399	-0.28	-0.20	109,509	18,308	16,263
Alirocumab+EZE	60,567	9.67	6.71	-22,653	-0.32	-0.23	98,813	18,068	15,776
Evolocumab	61,203	9.81	6.82	-23,290	-0.46	-0.34	69,474	16,585	13,233

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B33. The ERG cannot find reference in the CS to the additional cost for PSCK9i of £42 ('Costs'F79:F80) and has checked the source provided in the model, but cannot reconcile the cost.

a) Please clarify if this input is the "One-off cost of 1 hour of training with a nurse". If this correct, please explain why this cost is applied annually if it is a one-off cost, Also please explain how the cost of £42 was derived from the source.

b) If this parameter is not the "One-off cost of 1 hour of training with a nurse", please clarify this parameter and any assumptions being used.

Company response: The cost is only included in the first cycle and is therefore not applied annually in the model. We have clarified labeling in the 'Costs'- sheet to avoid further confusion.

The unit cost is based on PSSRU 2018 cost presented in Supplementary Table 1 (Curtis and Burns, 2018).

B34. Please clarify what the "pharmacy preparation" cost is in 'Costs'F66 of the economic model and explain how this is being used for the analysis and justify its inclusion.

Company response: Pharmacy preparation cost has been included in Technology Appraisals of several intravenous drugs (e.g., TA424) but we made a conservative assumption to also include this for subcutaneous and oral drugs. It can be expected that in some circumstances there may be pharmacy time used especially with regards to PCSK9 inhibitors. The parameter has a minimal impact on the cost-effectiveness results, as the cost is minor, and we made the conservative assumption that there is no difference between the treatment arms.

B35. Please provide a scenario analysis using the discontinuation rates observed in the CLEAR studies in all treatment arms.

Company response: We do not have a reliable estimate of this due to the length of the CLEAR studies. Using data for the first year of treatment is unlikely to reflect the long-term discontinuation rate, as discontinuation due to AEs is more likely to occurr early in the treatment period. We have obtained expert opinion that verified there is no informative discontiuation data across treatments as discontinuation can vary according to several factors; expert opinion agreed with our conservative approach of applying the same rates across treatments.

In CLEAR Tranquility, which is the bempedoic acid trial with most similar treatment burden to the patients simulated in the model (all patients receiving both bempedoic acid and ezetimibe), [redacted] discountinued bempedoic acid during the trial follow-up. (Esperion Therapeutics data on file, 2018b) The other CLEAR trials had similar discountinuation rates. A scenario using this rate is presented in Table 29.

Table 29. Scenario with results using a [redacted] discontinuation rate for all treatments

	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	NMB (£20,000)	NMB (£30,000)
Position 2a									
Bempedoic acid with background ezetimibe	13,073	11.75	8.71						
No further treatment/placebo with background ezetimibe	8,114	11.54	8.54	4,959	0.21	0.17	29,145	-1,556	145
Position 2b									
Bempedoic acid with background ezetimibe	17,801	9.97	6.87						
Alirocumab	37,321	10.05	6.92	-19,521	-0.08	-0.05	362,806	18,444	17,906
Evolocumab	37,677	10.08	6.95	-19,877	-0.11	-0.08	253,540	18,309	17,525
Position 4a									
Bempedoic acid with background ezetimibe	17,246	9.87	6.87						
No further treatment/placebo with background ezetimibe	12,591	9.78	6.80	4,654	0.09	0.07	69,195	-3,309	-2,636
Position 4b									
Bempedoic acid with background ezetimibe	17,298	9.30	6.45						
Alirocumab	36,290	9.54	6.63	-18,992	-0.25	-0.18	105,248	15,383	13,579
Alirocumab+EZE	36,467	9.57	6.65	-19,169	-0.28	-0.20	94,788	15,125	13,102
Evolocumab	36,836	9.70	6.74	-19,539	-0.41	-0.30	66,092	13,626	10,670

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B36. Pease clarify why fibrates have not been included in the cost estimates.

Company response: As in previous NICE assessments in this disease area (NICE, 2016a; NICE, 2016c; NICE, 2016d), fibrates are not included as a cost. This is because of the minor cost of these and no differences between the arms is expected in the model. Including fibrates in the model would make the model unnecessary complex and are not expected in to impact the cost effectiveness results materially.

Section C: Textual clarification and additional points

C1. Priority question. Please include the starting age of patients in the one-way sensitivity analysis (OWSA) using the range of ages in the CLEAR studies to inform the lower and upper values.

Company response: The starting age and the ranges of mean age in the CLEAR trials has been added to the model in sheet 'Input summary General' L26:P26 but was not an important (top 20) parameter to include in the tables or figures.

C2. Priority question. The ERG cannot reproduce the company's estimates for the OWSA (tabs 'OWSA Results' and 'OWSA calcs', cells AL:AN23 of the economic model) presented in Table 68. Please investigate and either correct or provide instructions on how to replicate the company's results.

Company response: Please follow the instructions specified below to run this analyses in line with the company submission:

- Update WTP in the PSA sheet to 30,000
- Select the relevant compartor
- Run OWSA

Using these selections produce Table 30.

Table 30. Summary of bempedoic acid deterministic sensitivity analyses

Position	Most influential parameters	Lower bound NMB	Upper bound NMB
2a	[redacted]	[redacted]	[redacted]
	Average reduction LDL-C - Intervention	−578	572
	Risk factor - all risks	−575	539
	Mean baseline LDL-C (mmol/L):	−540	522
2b	Average reduction LDL-C - AliMab	946	−934
	Average reduction LDL-C - Intervention	−769	761
	Annual rate - Discontinuation AliMab	−636	598
	[redacted]	[redacted]	[redacted]
4a	[redacted]	[redacted]	[redacted]

Position	Most influential parameters	Lower bound NMB	Upper bound NMB
	Risk factor - all risks	−280	263
	Average reduction LDL-C - Intervention	−222	222
	Mean baseline LDL-C (mmol/L):	−207	204
4b	Average reduction LDL-C - AliMab	945	−933
	[redacted]	[redacted]	[redacted]
	Mean baseline LDL-C (mmol/L):	532	−516
	Annual rate - Discontinuation AliMab	−534	504

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein-cholesterol; NMB = net monetary benefit at £30,000/QALY.

C3. In Table 64 of the CS, the following rates of events are reported: CV Death, 25%; IS, 52%; MI, 24%; UA, 12%; SA, 50%; TIA, 16%. The ERG cannot identify these rates in Section B.3.1.5.1 or the model, please clarify.

Company response: These are the rates that are applied based on the weighted average of 55-64 and 65-74 year in Ward et al (2007) (Ward et al., 2007). They are reported in the model in the Support_engine F65:L65. The values used for the calculation are presented in Section B.3.1.5.1 as listed in the table.

C4. In the CS, Table 13, please clarify whether all numbers not reported as n (%) relate to mean values with standard deviations.

Company response: The units for all data presented are specified in the first column of the table, in the heading of each section of data. In most cases, data are mean and standard deviation (e.g., "Lipid measures at baseline, mg/dL, mean (SD)"); in some cases data are mean and interquartile range (e.g., "TG, median (IQR), mg/dL").

C5. Please clarify why the number of patients with a prior CV event in each CLEAR trial is reported in the economic model ('CLEAR data input') and why the number of patients receiving primary and secondary prevention is not reported for each CLEAR trial in Table 13 of the CS.

Company response: The prior CV event data included in the economic model are descriptive data prepared during an analysis of the individual patient-level trial data which was performed in order to estimate the baseline LDL-C for each of the proposed positions in the treatment pathway. This analysis used (as far as possible) the definition of prior CVD in TA393 and TA394 (NICE, 2016b; NICE, 2016c), in order to reflect the characteristics of patients for whom alirocumab and evolocumab are/are not appropriate based on NICE recommendations for these products. The prior CV event data were included for information only; the primary purpose of the analysis was to estimate baseline LDL-C for use as baseline characteristics in the economic analyses.

Table 13 in the Company evidence submission (Document B) presents the baseline cardiovascular history as defined in the phase 3 bempedoic acid trials. In CLEAR Harmony and CLEAR Wisdom, this

was reported as prior ASCVD, while in CLEAR Serenity, this was reported as primary and secondary prevention. In CLEAR Tranquility, patients with recent history of CVD were excluded; therefore, CVD at baseline was not reported. The definitions of these terms in each of the trials are presented in the response to question A16 (Table 14).

C6. In Table 63 of the CS, the description for "No prior CV event (%)" reflects the % for a prior CV event, please clarify the correct description.

Company response: This is correct, the row should be labelled "Prior CV event (%)".

C7. In Table 57 of the CS, the age figures are different to the model tab "Default Data", Cells J353:J358 and SE is different to the model tab "Default Data", Cells I353:I358. Please check and confirm which is correct and amend where necessary.

Company response: Table 57 presents the correct values for this data. The standard error reported in the CS (Table 57) is standard deviation and was converted to standard error in the model.

Table 31. Alternative source for utility estimates

Health state	Utility multiplier	N	SD	Reference	Age (years)	Male	Age- and sex-adjusted multipliers
MI < 1 year	0.702	733	0.290	(Pockett et al., 2018)	67.4	0.704	0.86127
UA < 1 year	0.637	522	0.311		69.1	0.644	0.789991
IS < 1 year	0.496	13	0.362		75.9	0.759	0.636882
MI > 1 year	0.706	888	0.336		68.9	0.704	0.87297
UA > 1 year	0.611	635	0.352		70.6	0.644	0.763897
IS > 1 year	0.527	16	0.403		77.4	0.759	0.682906

IS= Ischaemic stroke; MI= myocardial infarction; SD = standard deviation; UA=unstable angina.

C8. Please split the adjustments reported in Table 74 of the CS into adjustments for primary and secondary prevention.

Company response: The split is presented in Table 32.

Table 32. CS split into adjustments for primary and secondary prevention.

Model/ analysis	De novo model	CG181 (NICE, 2016d)	TA385 (NICE, 2016a)	TA393 (NICE, 2016c)	TA394 (NICE, 2016b)
Age adjustments – Primary prevention - Baseline risk	No adjustment	No adjustment in base-case.	No adjustment	3% all non-fatal CV events. 5% all fatal CV events (only HeFH patients considered)	Unknown

Model/ analysis	De novo model	CG181 (NICE, 2016d)	TA385 (NICE, 2016a)	TA393 (NICE, 2016c)	TA394 (NICE, 2016b)
Age adjustments – Primary prevention – Over time risk	3% all non-fatal CV events. 5% all fatal CV events	0.03% for men, 0.008% for women	0.03% for male and 0.008% for female	3% all non-fatal CV events. 5% all fatal CV events (only HeFH patients considered)	Unknown
Age adjustments – Secondary prevention - Baseline risk	3% all non-fatal CV events. 5% all fatal CV events	Non-parametric adjustment based on age groups 40-54, 55-64, 65-74, 75-84 and 85+	Non-parametric adjustment based on age groups 40-54, 55-64, 65-74, 75-84 and 85+	3% all non-fatal CV events. 5% all fatal CV events	Unknown
Age adjustments – Secondary prevention – Over time	3% all non-fatal CV events. 5% all fatal CV events	Non-parametric adjustment based on age groups 40-54, 55-64, 65-74, 75-84 and 85+	Non-parametric adjustment based on age groups 40-54, 55-64, 65-74, 75-84 and 85+	3% all non-fatal CV events. 5% all fatal CV events	Unknown

CV = cardiovascular.

C9. Please provide the source and any calculations used to estimate "no threshold" in 'Country-Specific Data'B73:F84**.**

Company response: These data are available in Table 25 in the ERG report in TA393.

Appendix: Revised NMA Results

A1. Priority question. Please conduct revised NMAs for the statin-intolerant studies and maximally tolerated statin studies based on the suggestions detailed above.

Company response: Revised NMAs incorporating the ERG suggestions on page 3 were performed for the percent change in LDL-C at 12 weeks.

For the statin-intolerant network, GAUSS, GAUSS-3, and the 420 mg arm and the corresponding placebo arm of GAUSS-2 were excluded in accordance with the ERG request to exclude 420 mg Q4W doses of evolocumab. Krysiak 2011 was also excluded in line with the ERG request. Previously, the subgroup of Krysiak 2011 defined in the publication to have a "history of statin intolerance" was included, but the publication did not report concomitant therapies for this subset, hence the exclusion. The subgroup of patients within 1002-008 was retained. For this study and network, the included subgroup included for the analysis was defined as follows: Statin intolerant (for relevant patients only) defined as patient-reported inability to tolerate at least two statins due to skeletal muscle-related symptoms (other than those due to strain or trauma), such as pain, aches, weakness, or cramping, that began or increased during statin therapy and resolved when statin therapy was discontinued. Inability to tolerate at least two statins must have met both the following criteria:

- Inability to tolerate one statin at the lowest daily approved dose, defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg
  - Current treatment with less than the lowest daily approved dose of a statin (i.e., skipping days or intermittent therapy provided that the average daily dose was less than the lowest daily approved dose) was considered equivalent to not tolerating one statin at the lowest daily approved dose
- Inability to tolerate another statin at any dose

Based on the above and concomitant medication profile for this subgroup, we propose that it is appropriate for this subgroup to be included in the analysis. The ERG requested that the alirocumab 300 mg Q4W arm in ODYSSEY CHOICE be excluded. We can confirm that this was not included in the original analysis or in the analysis performed in response to priority question A1.

For the maximally tolerated statin NMA, the 420 mg Q4W dose of evolocumab was excluded from YUKAWA and YUKAWA-2. the original analysis included results from a pooled dose for YUKAWA-2. In the revised analysis, results for the 140 mg dose for YUKAWA-2 were included instead. The treatments arms included for ODYSSEY CHOICE-I did not include the 300 mg Q4W dose of alirocumab within the original analysis or within this analysis performed in response to priority question A1. In accordance with the request to exclude 420 mg doses, the 420 mg doses for LAPLACE-2 and LAPLACE-TIMI were also excluded. The following studies were excluded in accordance with the ERG request to exclude studies which exclusively recruited populations with type 1 or type 2 diabetes: ODYSSEY-DM, DM-DYSLIPIDEMIA, DM-INSULIN, BANTING, ODYSSEY LONGTERM, and BERSON. In accordance with the ERG request, studies that exclusively recruited populations with heterozygous familial hypercholesterolaemia (HeFH) have been excluded, specifically ODYSSEY FH I, ODYSSEY FH II,

ODYSSEY HIGH FH, RUTHERFORD-2, and RUTHERFORD. Analysis was not performed to consider HeFH patients separately (see the response for question A2). Some information on results for separate trials within the original NMA which did not exclude these can be found in the experimental node-splitting results provided in response to early ERG questions. For LAPLACE-2, only the moderate/high-dose statin arms were retained; low-dose statin arms were excluded. Further, in accordance with the ERG request to remove EvoMab 420 mg Q4W doses from YUKAWA and YUKAWA-2, the 420 mg doses from LAPLACE-2 were also removed for consistency. The dosing for DESCARTES was also 420 mg QM; therefore, DESCARTES has been removed from this network in accordance with the ERG request to exclude 420 mg Q4W doses from YUKAWA and YUKAWA-2. Per the ERG request for YUKAWA-2, the 5 mg atorvastatin arm was removed and the 20 mg arm was retained. The 5 mg arm has not been included within the statin-intolerant network; this group was not defined as statin intolerant within the publication. Per the request from the ERG for removal of Krysiak 2011 from the statin-intolerant network, the 5 mg arm from YUKAWA-2 has not been included in the statin-intolerant network.

Results for the statin-intolerant network analysis performed within the original submission and in response to ERG requests within question A1 are shown below. Whilst the overall heterogeneity in the statin-intolerant network have been reduced marginally, there remains considerable heterogeneity following the exclusion of studies within both networks of interest (see Figure 25 and Figure 26). The point estimates remain relatively similar for most treatments between both sets of analysis for the statin-intolerant and maximally tolerated networks, but in general, greater uncertainty is seen in the reduced networks of evidence.

The revised NMA results are compared with the original results below (copied from the final NICE submission, Section B.2.9.1). Results used in the cost-effectiveness analyses presented in the submission are highlighted in bolded text.

Table 33. NMA results for bempedoic acid in statin-intolerant studies

Treatment	Company evidence submission			Revised		
	Estimated difference in % change in LDL-C from baseline compared with ezetimibe					
	Mean	95% CrIs	*P* value	Mean	95% CrIs	*P* value
Bempedoic acid	[redacted]					
Bempedoic acid + ezetimibe						
Evolocumab						
EvoMab + ezetimibe[a]						
Alirocumab (75 mg)						
Alirocumab (150 mg)						

CrI = credible interval; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

Note: Other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe. No trial data were identified for alirocumab + ezetimibe.

[a] Evolocumab + ezetimibe estimates are based on data for 30 patients in GAUSS (Sullivan et al., 2012).

Table 34. NMA results for bempedoic acid + statin in maximally tolerated statin studies

	Company evidence submission			Revised		
	Estimated difference in % change in LDL-C from baseline compared with ezetimibe					
Treatment	**Mean**	**95% CrIs**	***P* value**	**Mean**	**95% CrIs**	***P* value**
Bempedoic acid + statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FDC + statin[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EvoMab + statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AliMab (75 mg) + statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AliMab (150 mg) + statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AliMab (75 mg) + statin + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AliMab (150 mg) + statin + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AliMab = alirocumab; CrI = credible interval; EvoMab = evolocumab; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

[a] These data are used in the economic model to represent the efficacy of bempedoic acid + ezetimibe separate tablets in patients receiving maximally tolerated statin. Pharmacokinetic studies have shown the two presentations to be equivalent (see Appendix M).

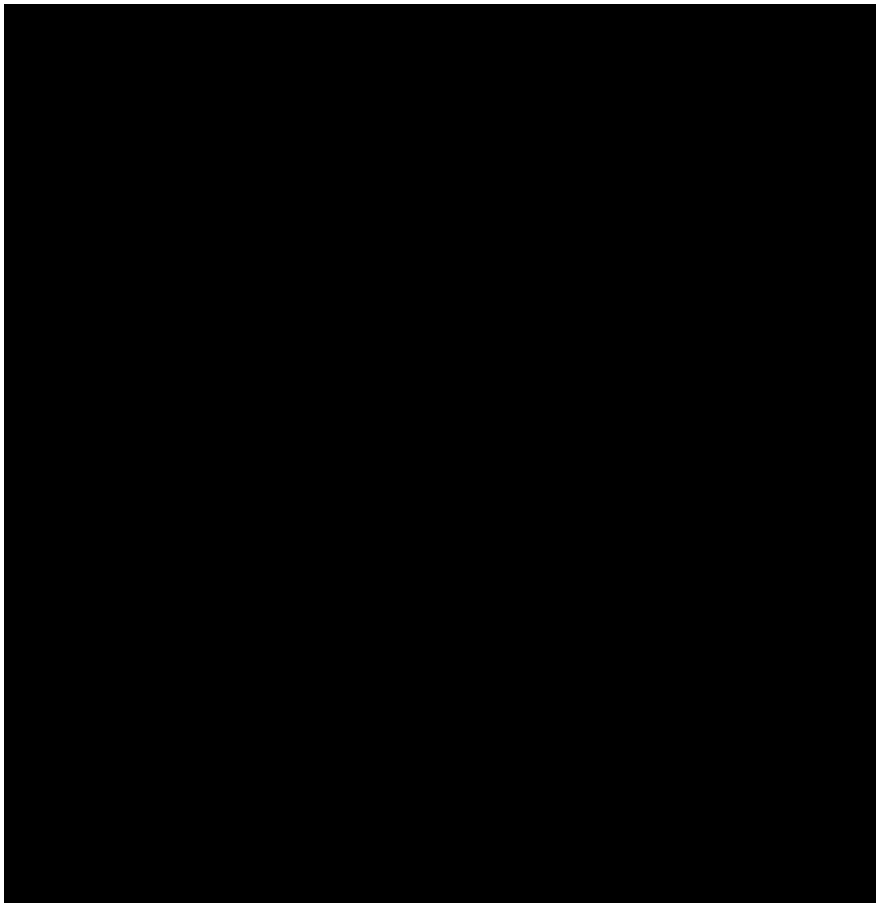
Note: other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe.

Results of the revised statin-intolerant NMA

Results from the Bayesian random-effects models for the reduced statin-intolerant network are shown below.

A high degree of heterogeneity was observed in the statin-intolerant population despite adjustment for baseline LDL, with I^2 of 66.1%. Cochran's Q was 14.8 with 5 degrees of freedom. The deviance information criterion for the fixed-effects model with covariate was 116.7 compared with 112.2 for the random-effects model and 115.2 compared with 111.3 for the models without baseline LDL-C included as a covariate. An explanatory variable that has not been included in the analysis may account for some of the underlying heterogeneity, such as the level of background ezetimibe use. Further information on fit statistics are provided in Table 35.

Figure 7. Statin-intolerant network



AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol.

Table 35. Fit statistics for statin-intolerant network: percentage change from baseline in LDL-C

Model	Baseline LDL-C	Total residual deviance	*pD*	DIC	Between study standard deviation (σ) (95% CrI)	Baseline LDL-C (95% CrI)
Fixed effects	−	99.460	15.7	115.2		
	✓	99.688	17.0	116.7		−0.210 (−0.669, 0.242)
Random effects	−	89.916	21.4	111.3	5.363 (1.093, 13.311)	
	✓	90.053	22.1	112.2	6.177 (1.470, 15.344)	−0.159 (−1.130, 0.947)

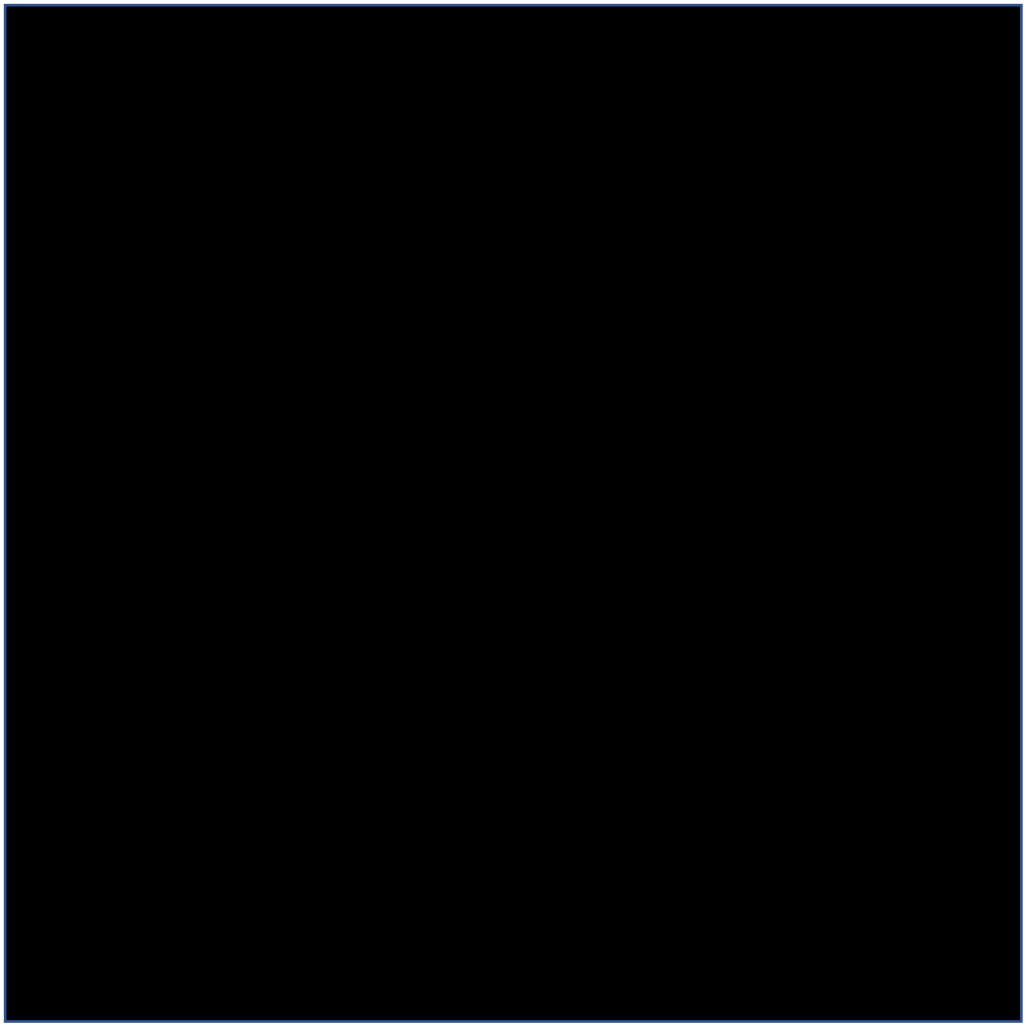
CrI = credible interval; DIC = deviance information criterion; LDL-C = low-density lipoprotein cholesterol; pD = effective number of parameters.

Total residual deviance is the measure of the error in the model (the lower the better).

For the effective number of parameters, the lower the better. The number of parameters in a fixed-effects model = n studies (10) + n treatments (7) − 1 + number of covariates (1) = 16. For a saturated model, the number is equal to the number of data points (total number of study arms + covariates) = 22. If a random-effects model gives a value close to 16, then a it suggests a fixed-effects model is likely to be adequate.

The deviance information criterion is the model error penalised by model complexity (the lower the better; a difference of > 5 is typically considered to be meaningful).

Figure 8. Predicted change from baseline in LDL-C: statin intolerant



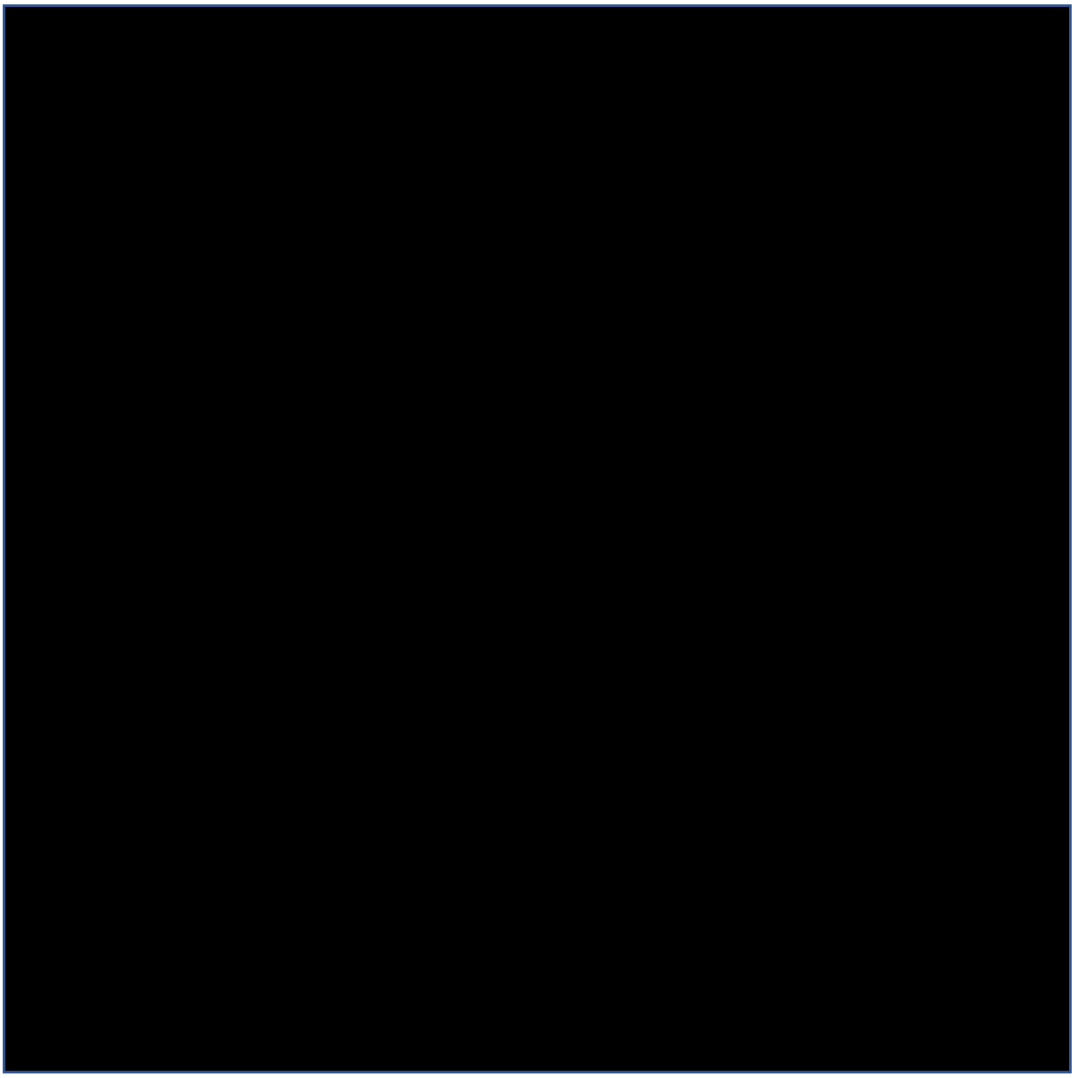
AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

Figure 9. Pairwise comparisons for predicted change from baseline in LDL-C: statin intolerant

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; MTC = mixed-treatment comparison.

Only significant differences are coloured. Reading horizontally, yellow to red shows a significant improvement relative to those treatments labelled on the vertical axes; blue indicates significantly worse.

Figure 10. Cumulative rankogram for predicted change from baseline in LDL-C: statin intolerant



AliMab = alirocumab; AUC = area under the curve; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; MTC = mixed-treatment comparison.

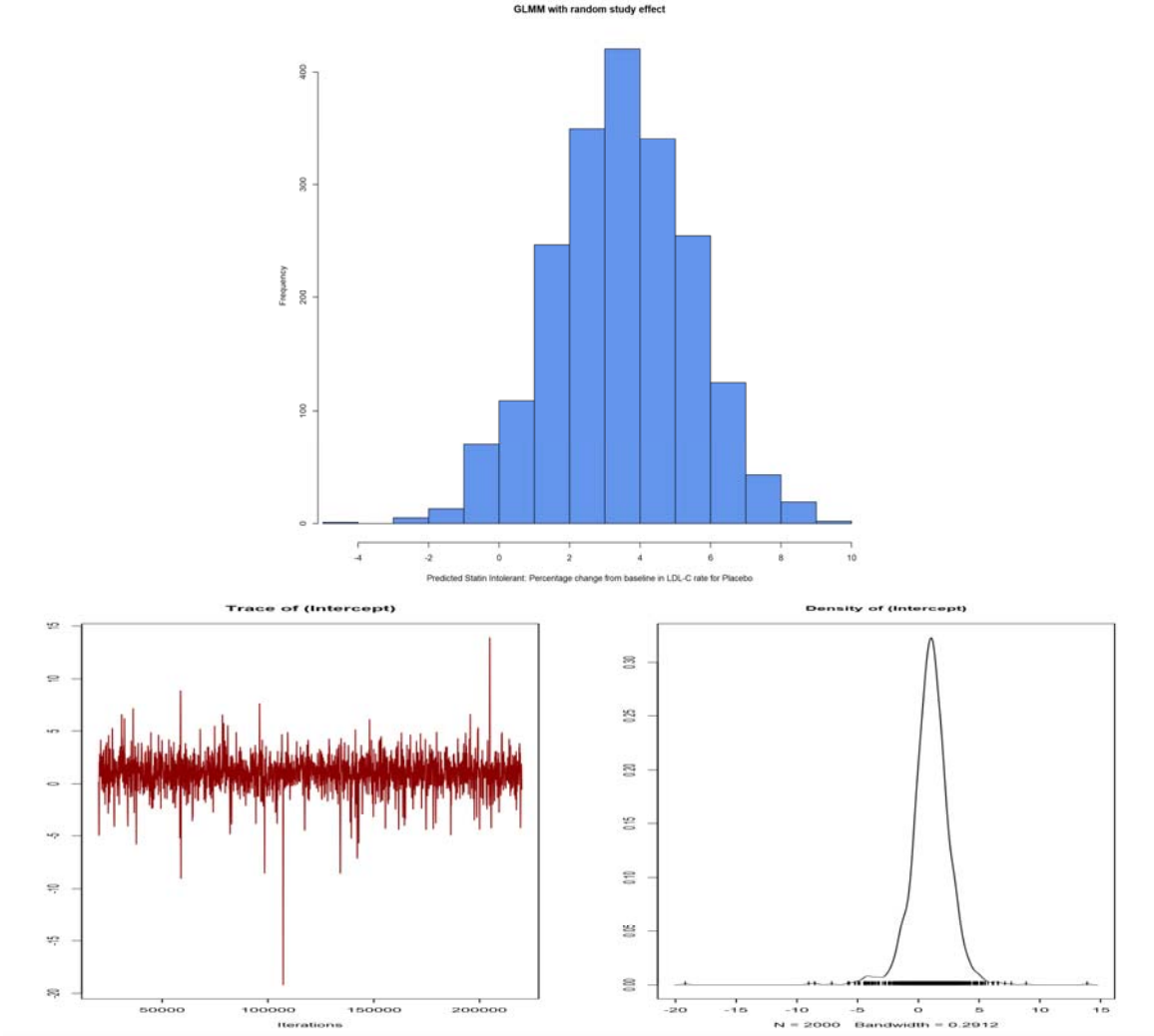
Figure 11. Placebo response for percentage change from baseline in LDL-C: statin intolerant

LDL-C = low-density lipoprotein cholesterol.

Figure 12. Duplicated pairwise comparisons: statin intolerant

AliMab = alirocumab; BA = bempedoic acid; CI = confidence interval; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; RE = random effects.

Figure 13. Placebo response – MCMC results: statin intolerant

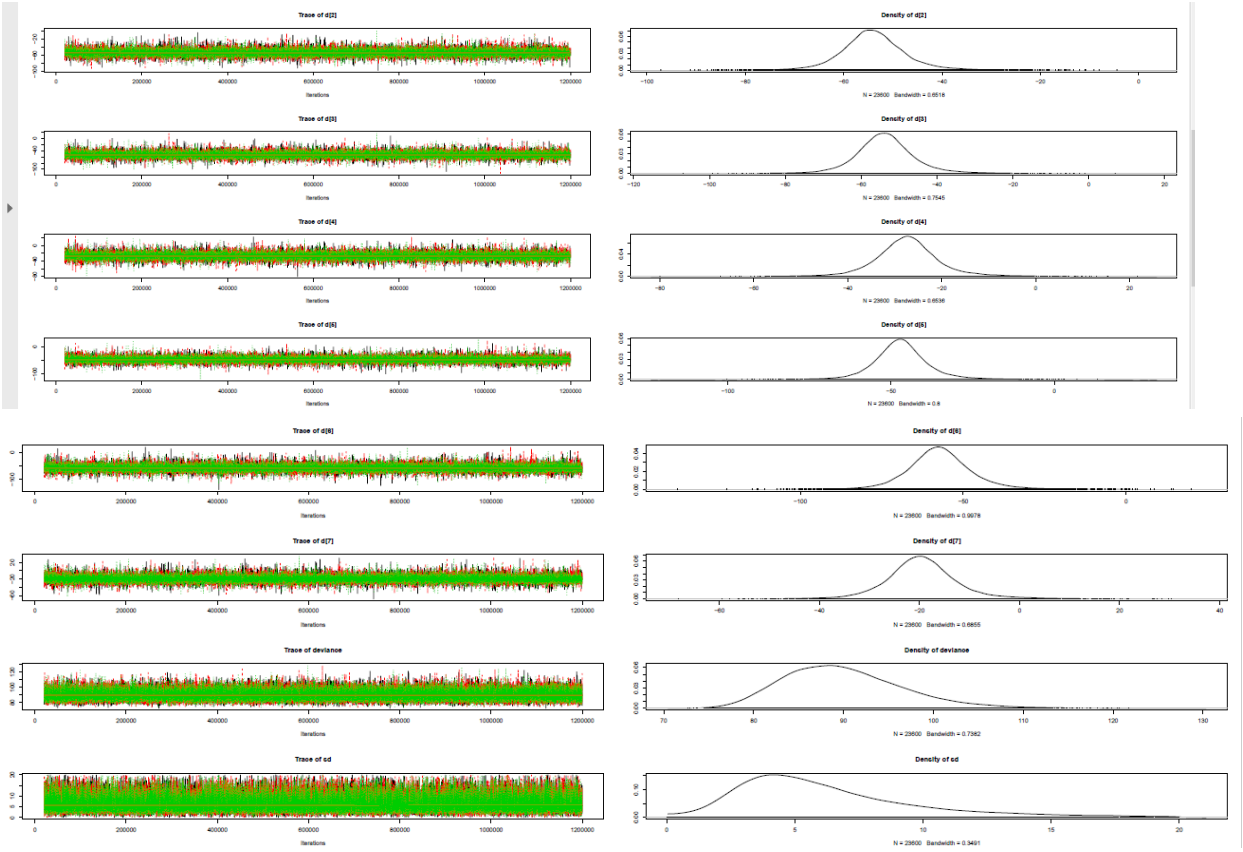


The model results for placebo response – MCMC were as follows:

	post.mean	l-95% CI	u-95% CI	eff.samp	pMCMC
(Intercept)	2.7966	-4.3707	9.3346	5953	0.299
covar.cen	0.1590	-0.3604	0.7224	6205	0.400

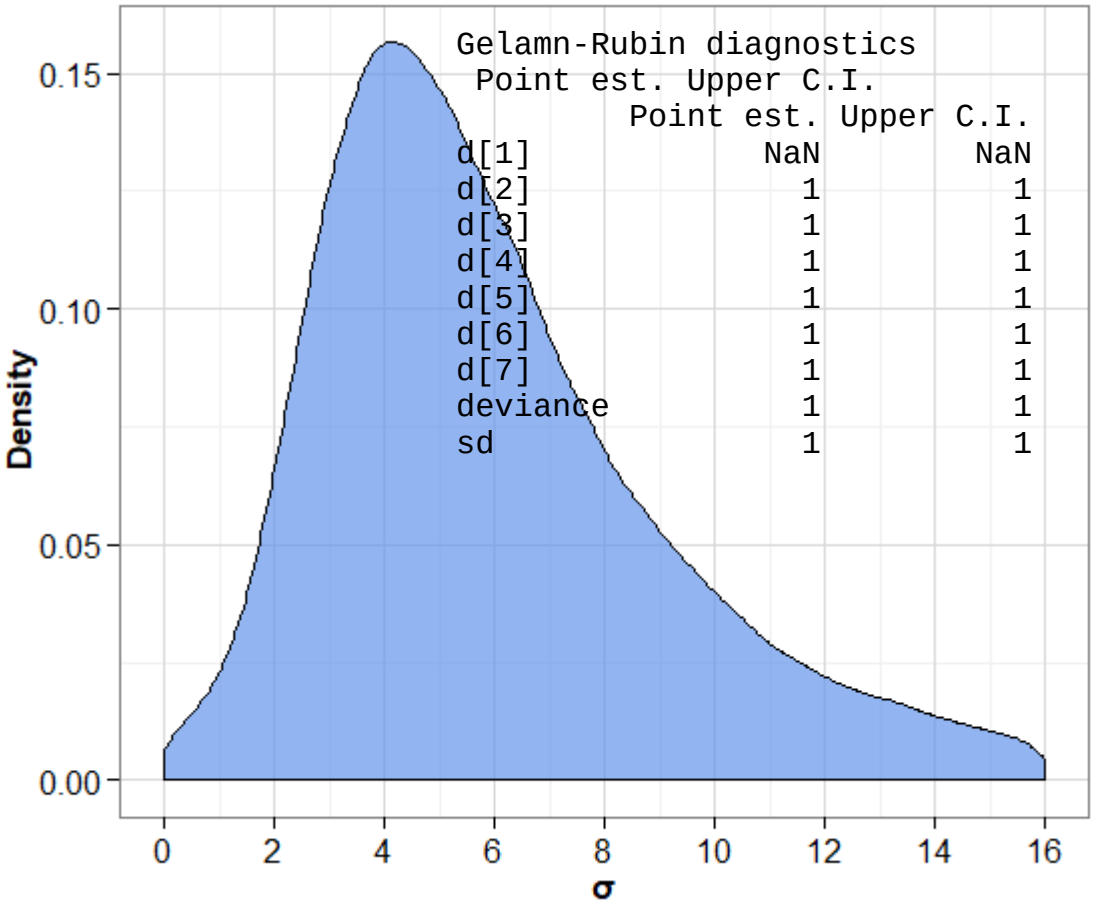
CI = confidence interval; GLMM = Generalised linear mixed model; LDL-C = low-density lipoprotein cholesterol; MCMC = Markov Chain Monte Carlo.

Figure 14. Bayesian NMA traces: statin intolerant



NMA = network meta-analysis.

Figure 15. Bayesian NMA – heterogeneity parameter and Gelman-Rubin diagnostics: statin intolerant

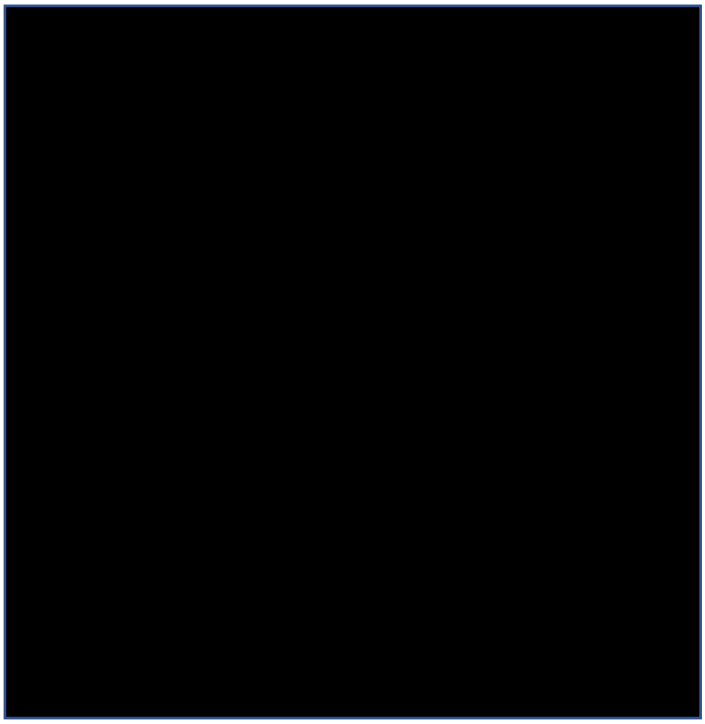


NMA = network meta-analysis.

Results of the revised maximally tolerated statin NMA

Results from the Bayesian random-effects models for the maximally tolerant network are shown below. Substantial heterogeneity was observed in the reduced maximally tolerated population despite adjustment for baseline LDL, with I^2 of 86.8%. Cochran's Q was 324.7 with 43 degrees of freedom. The deviance information criterion for the fixed-effects model with covariate was 719.7 compared with 509.3 for the random-effects model and 732.4 compared with 515.9 for the models without baseline LDL-C included as a covariate. The total residual deviance for the random-effects model was 108.5 compared with 670.7 for the fixed-effects model. For some treatment comparisons, a difference was observed in the direct and indirect evidence. An explanatory variable that has not been included in the analysis may account for some of the underlying heterogeneity, such as the level of background statin or ezetimibe use. Information on the fit statistics are shown in Table 36.

Figure 16. Network of evidence for maximally tolerated statin NMA



AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol.

Table 36. Fit statistics for maximally tolerated statin NMA: Percentage change from baseline in LDL-C

Model	Baseline LDL-C	Total residual deviance	pD	DIC	Between study standard deviation (σ) (95% CrI)	Baseline LDL-C (95% CrI)
Fixed effects	−	684.71	47.7	732.4		
	✓	670.65	49.1	719.7		0.061 (0.030, 0.092)
Random effects	−	409.456	106.5	515.9	10.014 (1.537, 7.368)	
	✓	408.51	100.8	509.3	10.07 (1.548, 7.400)	0.07 (−0.02, 0.064)

CrI = credible interval; DIC = deviance information criterion; LDL-C = low-density lipoprotein cholesterol; pD = effective number of parameters.

Total residual deviance is the measure of the error in the model (the lower the better).

For the effective number of parameters, the lower the better. The number of parameters in a fixed-effects model = n studies (40) + n treatments (9) − 1 + number of covariates (1) = 48. For a saturated model, the number is equal to the number of data points (total number of study arms + covariates) = 40. If a random-effects model gives a value close to 48, then a it suggests a fixed-effects model is likely to be adequate.

The deviance information criterion is the model error penalised by model complexity (the lower the better; a difference of > 5 is typically considered to be meaningful).

Figure 17. Predicted change from baseline in LDL-C: maximally tolerated statin NMA

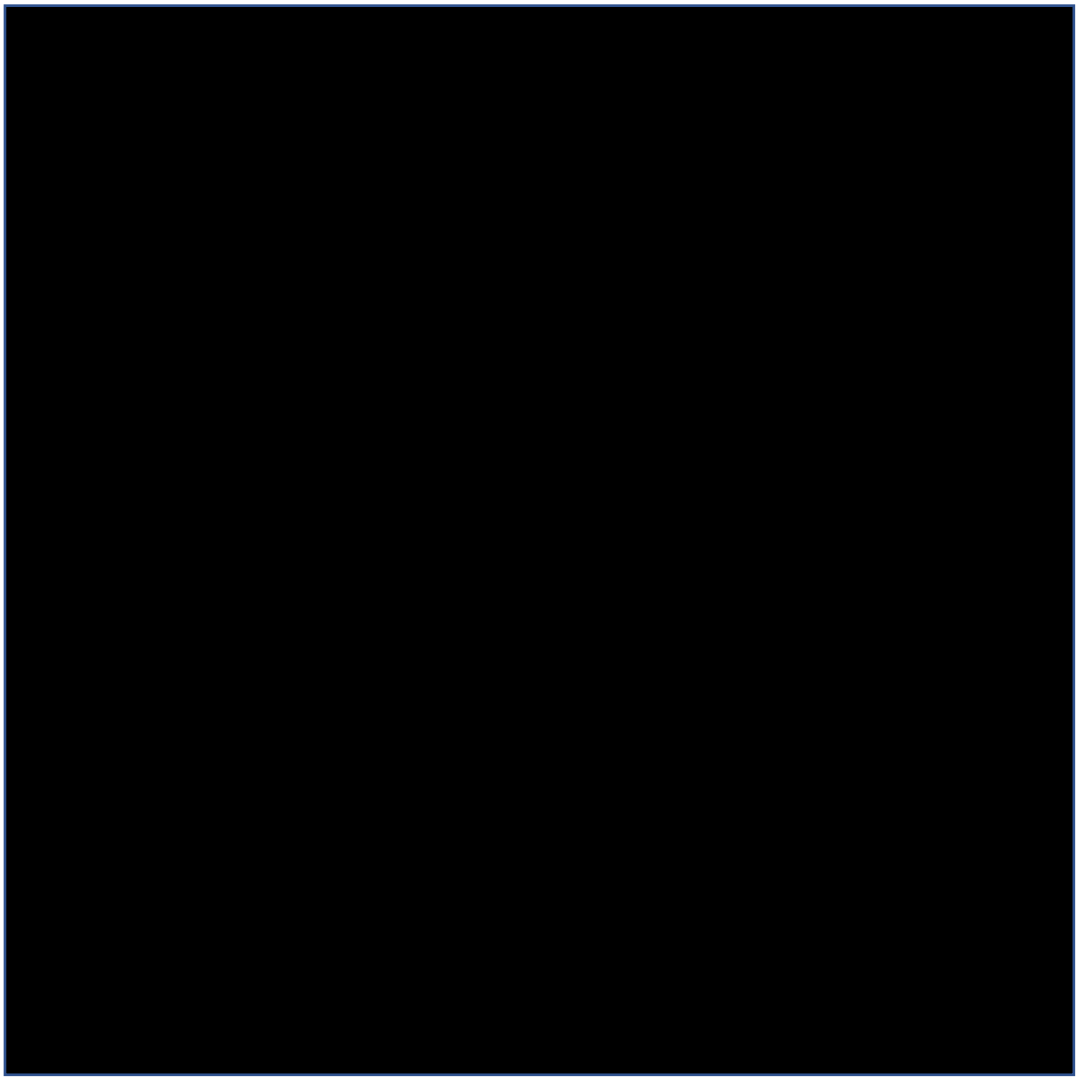
AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol.

Figure 18. Pairwise comparisons for predicted change from baseline in LDL-C: maximally tolerated statin NMA

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; MTC = mixed-treatment comparison.

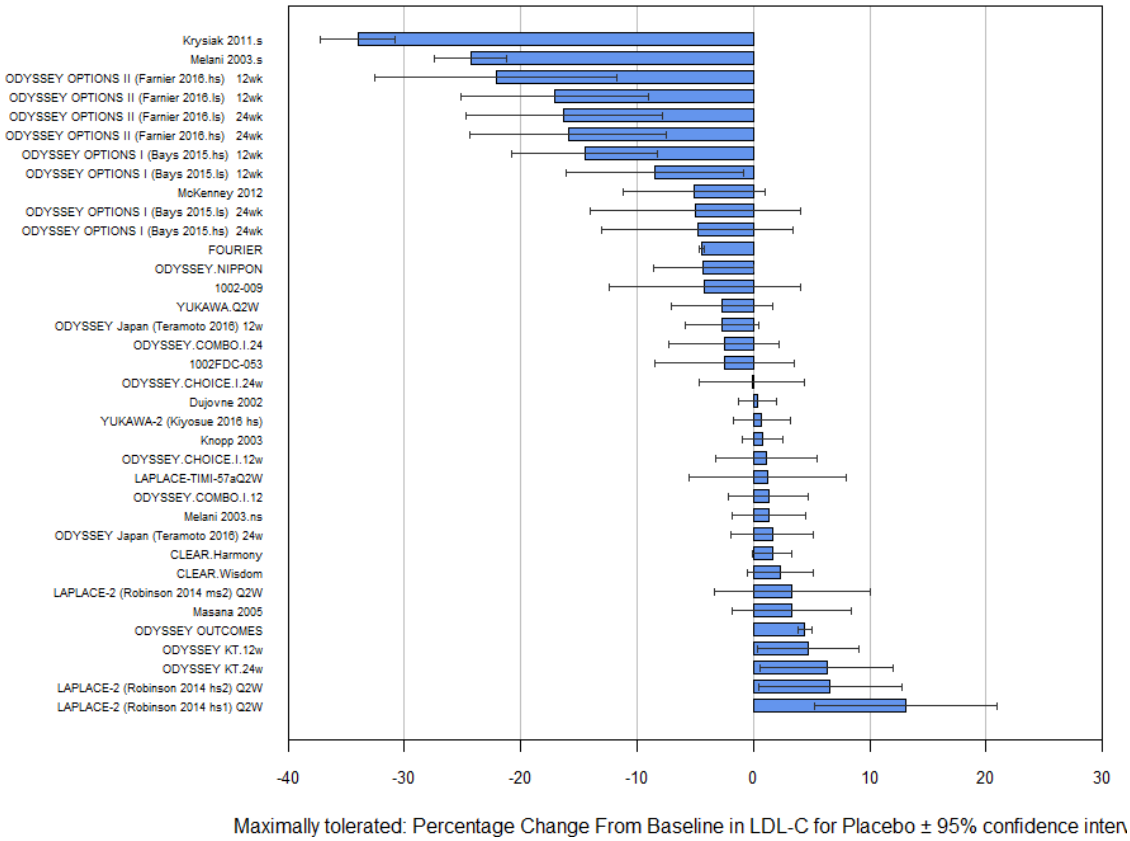
Only significant differences are coloured. Reading horizontally, yellow to red shows a significant improvement relative to those treatments labelled on the vertical axes; blue indicates significantly worse.

Figure 19. Cumulative rankogram for predicted change from baseline in LDL-C: maximally tolerated statin NMA



AliMab = alirocumab; AUC = area under the curve; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; MTC = mixed-treatment combination.

Figure 20. Placebo response for percentage change from baseline in LDL-C: maximally tolerated statin NMA

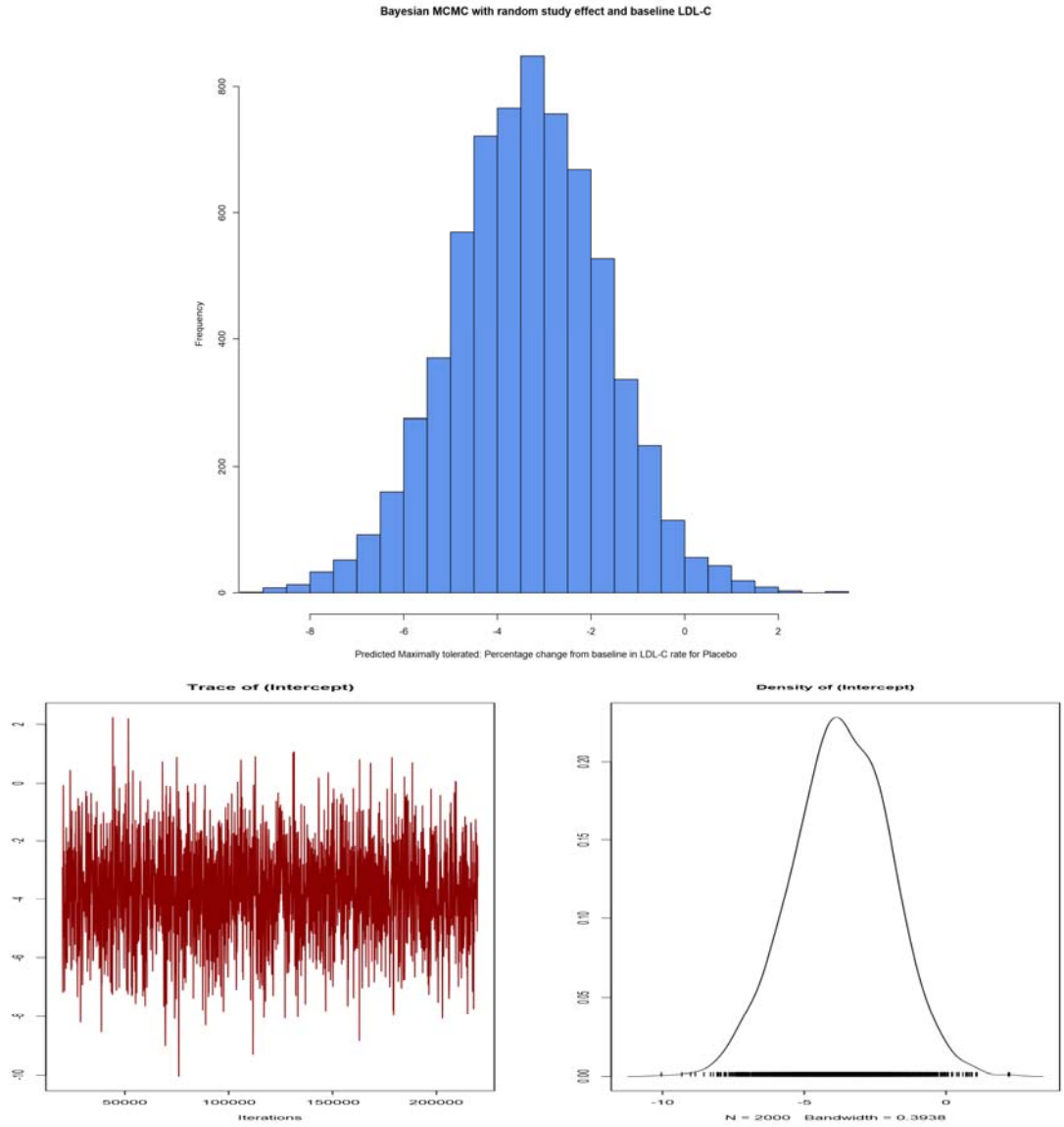


LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks.

Figure 21. Duplicated pairwise comparisons: maximally tolerated statin NMA

AliMab = alirocumab; BA = bempedoic acid; CI = confidence interval; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks; RE = random effects.

Figure 22. Placebo response – MCMC results: maximally tolerated statin NMA

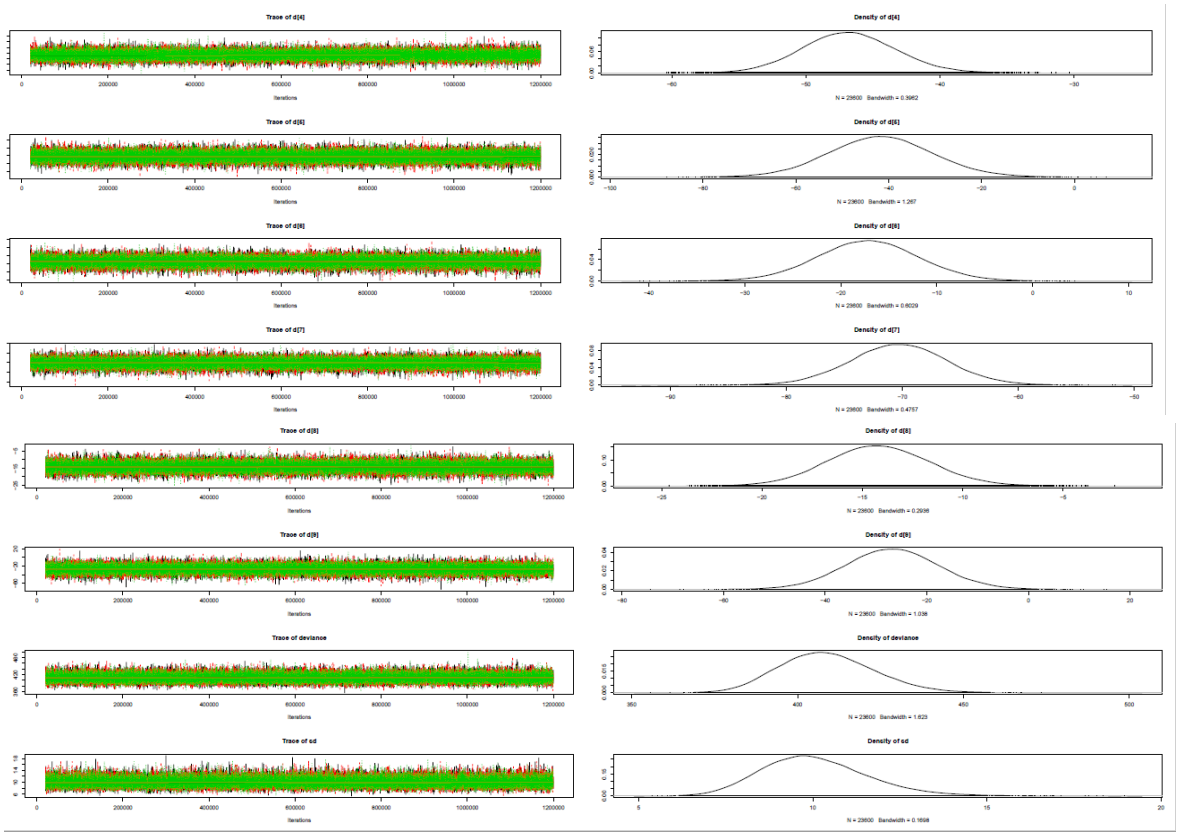


The model results for placebo response – MCMC were as follows:

	post.mean	l-95% CI	u-95% CI	eff.samp	pMCMC	
(Intercept)	-3.35392	-6.63262	-0.24588	4766	0.0384	*
covar.cen	-0.12353	-0.23301	-0.00705	6667	0.0330	*

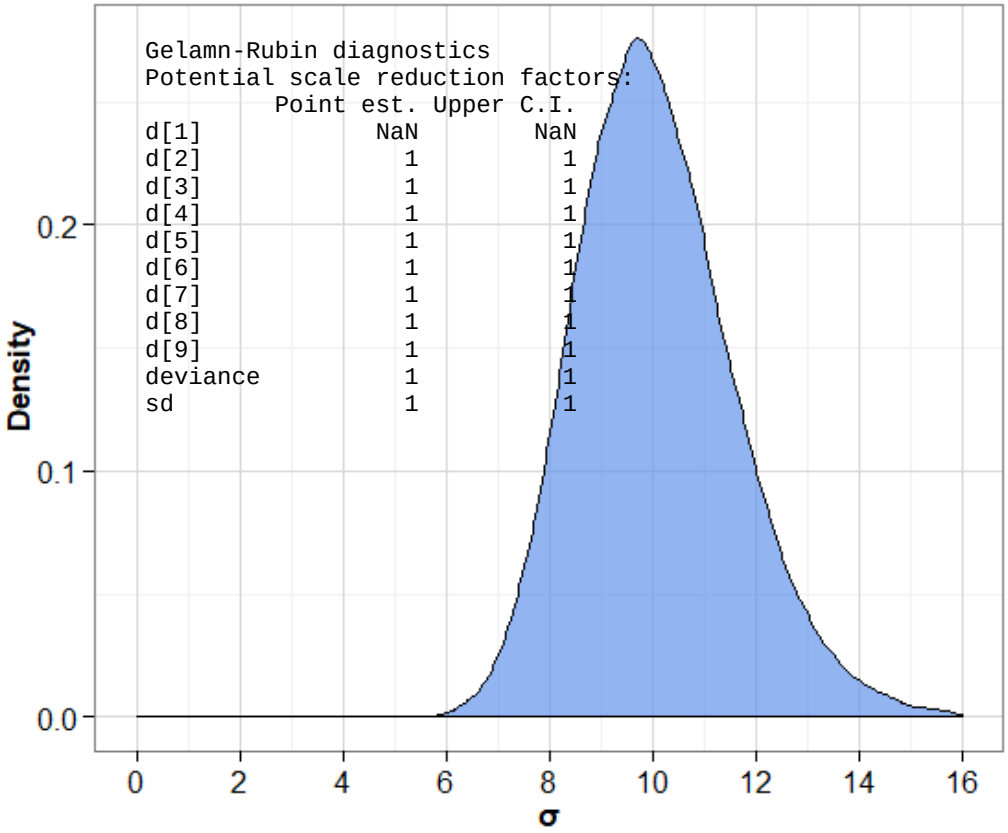
CI = confidence interval; GLMM = Generalised linear mixed model; LDL-C = low-density lipoprotein cholesterol; MCMC = Markov chain monte carlo.

Figure 23. Bayesian NMA traces: maximally tolerated statin NMA



NMA = network meta-analysis.

Figure 24. Bayesian NMA – heterogeneity parameter and Gelman-Rubin diagnostics: maximally tolerated statin NMA



NMA = network meta-analysis.

A8. Priority question. Please provide summary data tables for each of the studies included in the NMAs in response to questions A1, A2, A5, and A6 with details of the population or subgroup used, the intervention and dosage included in the NMAs, the mean baseline LDL-C and non-HDL-C for each study arm included, and the data included in the NMA (mean percentage change and standard deviation; as provided in table).

Company response: The data table used for the revised statin-intolerant network and maximally tolerated network, incorporating the ERG requests for A1 is shown below.

Table 37. Study arms included in the statin-intolerant NMA

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
1002-008	Statin intolerant subgroup	12	BA 180 mg once daily	[redacted]	[redacted]
1002-008	Statin intolerant subgroup	12	BA 180 mg + EZE 10 mg once daily	[redacted]	[redacted]
1002-008	Statin intolerant subgroup	12	EZE 10 mg once daily	[redacted]	[redacted]
CLEAR Serenity	Overall trial population	12	BA 180 mg once daily	[redacted]	[redacted]
CLEAR Serenity	Overall trial population	12	Placebo	[redacted]	[redacted]
CLEAR Tranquility	Overall trial population	12	BA 180 mg + EZE 10 mg once daily	[redacted]	[redacted]
CLEAR Tranquility	Overall trial population	12	EZE 10 mg once daily	[redacted]	[redacted]
GAUSS-2	Overall trial population	12	EvoMab 140 mg Q2W	−56.1	19.418
GAUSS-2	Overall trial population	12	EZE 10 mg once daily + placebo Q2W	−18.1	18.218
ODYSSEY alternative	Overall trial population	12	AliMab 75 mg Q2W	−47	21.327
ODYSSEY alternative	Overall trial population	12	EZE 10 mg once daily	−15.6	22.361
ODYSSEY alternative	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−45	24.695
ODYSSEY alternative	Overall trial population	24	EZE 10 mg once daily	−14.6	24.6
ODYSSEY CHOICE I	Moderate-to-very-high CVD risk and with statin-associated muscle symptoms (defined in protocol as muscle-related statin intolerance)	12	AliMab 75 mg Q2W	−51.8	17.64
ODYSSEY CHOICE I	Moderate-to-very-high CVD risk and with statin-associated muscle symptoms (defined in protocol as muscle-related statin intolerance)	12	Placebo	0.3	17.695
ODYSSEY CHOICE I	Moderate-to-very-high CVD risk and with statin-associated muscle symptoms (defined in protocol as muscle-related statin intolerance)	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−50.2	22.506
ODYSSEY CHOICE I	Moderate-to-very-high CVD risk and with statin-associated muscle symptoms (defined in protocol as muscle-related statin intolerance)	24	Placebo	−0.3	22.751

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
ODYSSEY CHOICE II	Overall trial population	12	AliMab 75 mg Q2W	−50.8	18.23
ODYSSEY CHOICE II	Overall trial population	12	Placebo	3.2	18.875
ODYSSEY CHOICE II	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−53.5	12.185
ODYSSEY CHOICE II	Overall trial population	24	Placebo	4.7	17.365

AliMab = alirocumab; BA = bempedoic acid; CVD = cardiovascular disease; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; Q2W = every 2 weeks; SD = standard deviation.

Table 38. Trial arms included in the maximally tolerated statin NMA

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
1002-009	Overall trial population	12	BA 180 mg once daily	[redacted]	[redacted]
1002-009	Overall trial population	12	Placebo	[redacted]	[redacted]
1002FDC-053	Overall trial population	12	BA 180 mg once daily	[redacted]	[redacted]
1002FDC-053	Overall trial population	12	BA 180 mg once daily + EZE 10 mg once daily	[redacted]	[redacted]
1002FDC-053	Overall trial population	12	EZE 10 mg once daily	[redacted]	[redacted]
1002FDC-053	Overall trial population	12	Placebo	[redacted]	[redacted]
CLEAR Harmony	Overall trial population	12	BA 180 mg once daily	[redacted]	[redacted]
CLEAR Harmony	Overall trial population	12	Placebo	[redacted]	[redacted]
CLEAR Wisdom	Overall trial population	12	BA 180 mg once daily	[redacted]	[redacted]
CLEAR Wisdom	Overall trial population	12	Placebo	[redacted]	[redacted]
Dujovne	Overall trial population	12	EZE 10 mg once daily	−16.86	14.19
Dujovne	Overall trial population	12	Placebo	0.36	12.48
FOURIER	Overall trial population	12	EvoMab either 140 mg every 2 weeks or 420 mg QM (according to patient preference)	−69.57	14.07
FOURIER	Overall trial population	12	Placebo	−4.46	14.07
Knopp	Overall trial population	12	EZE 10 mg once daily	−17.69	14.7
Knopp	Overall trial population	12	Placebo	0.79	12.43
Krysiak	Subgroup not statin intolerant	12	EZE 10 mg once daily	−46	8.89
Krysiak	Subgroup not statin intolerant	12	Placebo	−34	9.54
LAPLACE-2	Atorvastatin 80 mg	12	EvoMab 140 mg Q2W	−61.8	29.3
LAPLACE-2	Atorvastatin 80 mg	12	EZE 10 mg once daily	−16.9	28.95
LAPLACE-2	Atorvastatin 80 mg	12	Placebo Q2W	13.1	29.97
LAPLACE-2	Rosuvastatin 40 mg	12	EvoMab 140 mg Q2W	−59.1	23.65
LAPLACE-2	Rosuvastatin 40 mg	12	Placebo Q2W	6.6	23.48
LAPLACE-2	Simvastatin 40 mg	12	EvoMab 140 mg Q2W	−66.2	31.46
LAPLACE-2	Simvastatin 40 mg	12	Placebo Q2W	3.3	26.03

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
LAPLACE-TIMI-57	Overall trial population	12	EvoMab 140 mg Q2W	−68	31.35
LAPLACE-TIMI-57	Overall trial population	12	Placebo	1.23	30.38
Masana	Overall trial population	12	EZE 10 mg once daily	−23.7	33.91
Masana	Overall trial population	12	Placebo	3.3	22.96
McKenney	Overall trial population	12	AliMab 150 mg Q2W	−72.4	17.82
McKenney	Overall trial population	12	Placebo	−5.1	17.26
Melani	Overall trial population	12	EZE 10 mg once daily	−18.7	12.8
Melani	Overall trial population	12	Placebo	−24.3	12.9
Melani	Overall trial population	12	EZE 10 mg once daily + pooled pravastatin (10 mg, 20 mg, 40 mg)	−37.7	22.9
Melani	Overall trial population	12	Placebo + pooled pravastatin (10 mg, 20 mg, 40 mg)	−18.7	12.9
ODYSSEY Japan	Overall trial population	12	AliMab 75 mg Q2W	−64.2	13.2
ODYSSEY Japan	Overall trial population	12	Placebo	−2.7	13.58
ODYSSEY Japan	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−62.5	15.6
ODYSSEY Japan	Overall trial population	24	Placebo	1.6	15.27
ODYSSEY KT	Overall trial population	12	AliMab 75 mg Q2W	−57.9	21.67
ODYSSEY KT	Overall trial population	12	Placebo	4.7	22.22
ODYSSEY KT	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−57.1	29.55
ODYSSEY KT	Overall trial population	24	Placebo	6.3	29.29
ODYSSEY OPTIONS I	Atorvastatin 40 mg	12	AliMab 75 mg Q2W	−50.5	21.94
ODYSSEY OPTIONS I	Atorvastatin 40 mg	12	EZE 10 mg once daily	−29.7	21.94
ODYSSEY OPTIONS I	Atorvastatin 40 mg	12	Placebo	−14.5	21.94
ODYSSEY OPTIONS I	Atorvastatin 40 mg	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−54	29.48
ODYSSEY OPTIONS I	Atorvastatin 40 mg	24	EZE 10 mg once daily	−22.6	29.48
ODYSSEY OPTIONS I	Atorvastatin 40 mg	24	Placebo	−4.8	28.79

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
ODYSSEY OPTIONS I	Atorvastatin 20 mg	12	AliMab 75 mg Q2W	−48.4	29.44
ODYSSEY OPTIONS I	Atorvastatin 20 mg	12	EZE 10 mg once daily	−22.6	28.92
ODYSSEY OPTIONS I	Atorvastatin 20 mg	12	Placebo	−8.5	28.39
ODYSSEY OPTIONS I	Atorvastatin 20 mg	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−44.1	33.97
ODYSSEY OPTIONS I	Atorvastatin 20 mg	24	EZE 10 mg once daily	−20.5	34.86
ODYSSEY OPTIONS I	Atorvastatin 20 mg	24	Placebo	−5	34.73
ODYSSEY OPTIONS II	Rosuvastatin 20 mg	12	AliMab 75 mg Q2W	−32.3	38.21
ODYSSEY OPTIONS II	Rosuvastatin 20 mg	12	EZE 10 mg once daily	−19.3	39.31
ODYSSEY OPTIONS II	Rosuvastatin 20 mg	12	Placebo	−22.1	38.58
ODYSSEY OPTIONS II	Rosuvastatin 20 mg	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−36.3	31.6
ODYSSEY OPTIONS II	Rosuvastatin 20 mg	24	EZE 10 mg once daily	−11	32.03
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	24	Placebo	−15.9	31.3
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	12	AliMab 75 mg Q2W	−49.6	28.7
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	12	EZE 10 mg once daily	−17.4	29.1
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	12	Placebo	−17.1	28.41
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−50.6	30.1

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	24	EZE 10 mg once daily	−14.4	30.48
ODYSSEY OPTIONS II	Rosuvastatin 10 mg	24	Placebo	−16.3	29.79
ODYSSEY OUTCOMES	Overall trial population	17.4	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−55.8	29.18
ODYSSEY OUTCOMES	Overall trial population	17.4	Placebo	4.4	29.18
ODYSSEY CHOICE I	Maximally tolerated	12	AliMab 75 mg Q2W	−45.3	27.03
ODYSSEY CHOICE I	Maximally tolerated	12	Placebo	1.1	27.48
ODYSSEY CHOICE I	Maximally tolerated	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−51.6	28.77
ODYSSEY CHOICE I	Maximally tolerated	24	Placebo	−0.1	28.73
ODYSSEY COMBO I	Overall trial population	12	AliMab 75 mg Q2W	−46.5	26
ODYSSEY COMBO I	Overall trial population	12	Placebo	1.3	25.3
ODYSSEY COMBO I	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−47.9	29.1
ODYSSEY COMBO I	Overall trial population	24	Placebo	−2.5	24.9
ODYSSEY COMBO II	Overall trial population	12	AliMab 75 mg Q2W	−51.2	28.45
ODYSSEY COMBO II	Overall trial population	12	EZE 10 mg once daily	−21.8	27.94
ODYSSEY COMBO II	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated	−50.6	30.64
ODYSSEY COMBO II	Overall trial population	24	EZE 10 mg once daily	−20.7	29.5
ODYSSEY MONO	Overall trial population	12	AliMab 75 mg Q2W + EZE 10 mg	−48	21.63
ODYSSEY MONO	Overall trial population	12	EZE 10 mg once daily	−20	21.42
ODYSSEY MONO	Overall trial population	24	AliMab 75 mg Q2W/150 mg after 12 weeks if LDL-C still elevated + EZE 10 mg	−47.2	21.63
ODYSSEY MONO	Overall trial population	24	EZE 10 mg once daily	−15.6	22.14
ODYSSEY NIPPON	Overall trial population	12	AliMab 150 mg Q2W	−70.1	16.74
ODYSSEY NIPPON	Overall trial population	12	Placebo	−4.3	16.46

Study name	Population/subgroup	Time (weeks)	Treatment name and dosing schedule at or before timepoint	Mean % change LDL-C	SD
YUKAWA-2	Overall trial population	12	EvoMab 140 mg every 2 weeks + atorvastatin	−75.2	27.85
YUKAWA-2	Overall trial population	12	Placebo	0.71	8.77
YUKAWA	Overall trial population	12	EvoMab 140 mg Q2W	−71.3	15.86
YUKAWA	Overall trial population	12	Placebo	−2.7	15.86

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; Q2W = every 2 weeks; QM = every month; SD = standard deviation.

A10. Priority question. Please provide the I^2 and Cochran's Q test (with associated p-value) for all pairwise comparisons in the NMAs presented in response to questions A1, A2, A5, A6 and A7.

Company response: The results for I^2 and Cochran's Q are shown below for question A1 for the statin-intolerant and maximally tolerated network.

Figure 25. Heterogeneity/inconsistency statistics, statin-intolerant NMA

```
Quantifying heterogeneity / inconsistency:
tau^2 = 17.0404; I^2 = 66.1%

Tests of heterogeneity (within designs) and inconsistency
(between designs):
                    Q d.f. p-value
Total           14.77    5  0.0114
Within designs   2.55    2  0.2789
Between designs 12.21    3  0.0067

Decomposition of Cochran's Q
 treat1  treat2         Q df    pval.Q
  AliMab_150mg Placebo 2.3895248  1 0.1221508
   AliMab_75mg Placebo 0.1643898  1 0.6851467
        BA_EZE     EZE 0.1041147  1 0.7469466
```

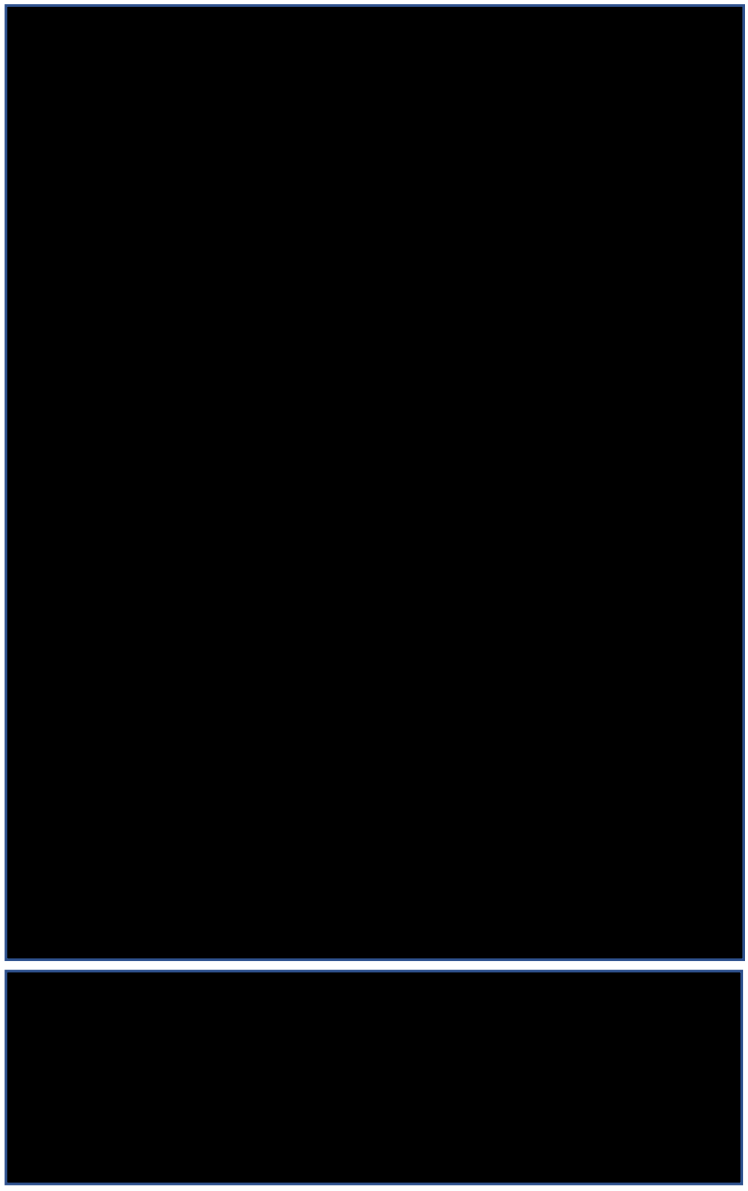
Figure 26. Heterogeneity/inconsistency statistics, maximally tolerated statin NMA

```
Quantifying heterogeneity/inconsistency:
tau^2 = 45.2615; I^2 = 86.8%

Tests of heterogeneity (within designs) and inconsistency
(between designs):
                     Q d.f.  p-value
Total           324.74   43 < 0.0001
Within designs  130.70   33 < 0.0001
Between designs 194.04   10 < 0.0001

Decomosition of Cochran's Q
          treat1     treat2           Q     df       pval.Q
       AliMab_150mg        EZE   1.7213563  4 7.868347e-01
       AliMab_150mg    Placebo  81.2236364  9 9.225953e-14
        AliMab_75mg        EZE   5.1678230  4 2.705072e-01
                 BA    Placebo   0.4643449  3 9.266519e-01
            EvoMab    Placebo  12.7520097  6 4.714751e-02
               EZE    Placebo  50.2183868 15 1.109087e-05
```

A11. Priority question. Please provide a comparison of loops in the NMAs where there is more than one loop forming an indirect comparison for the same direct treatment effect for the NMAs presented in response to questions A1, A2, A5, A6 and A7.

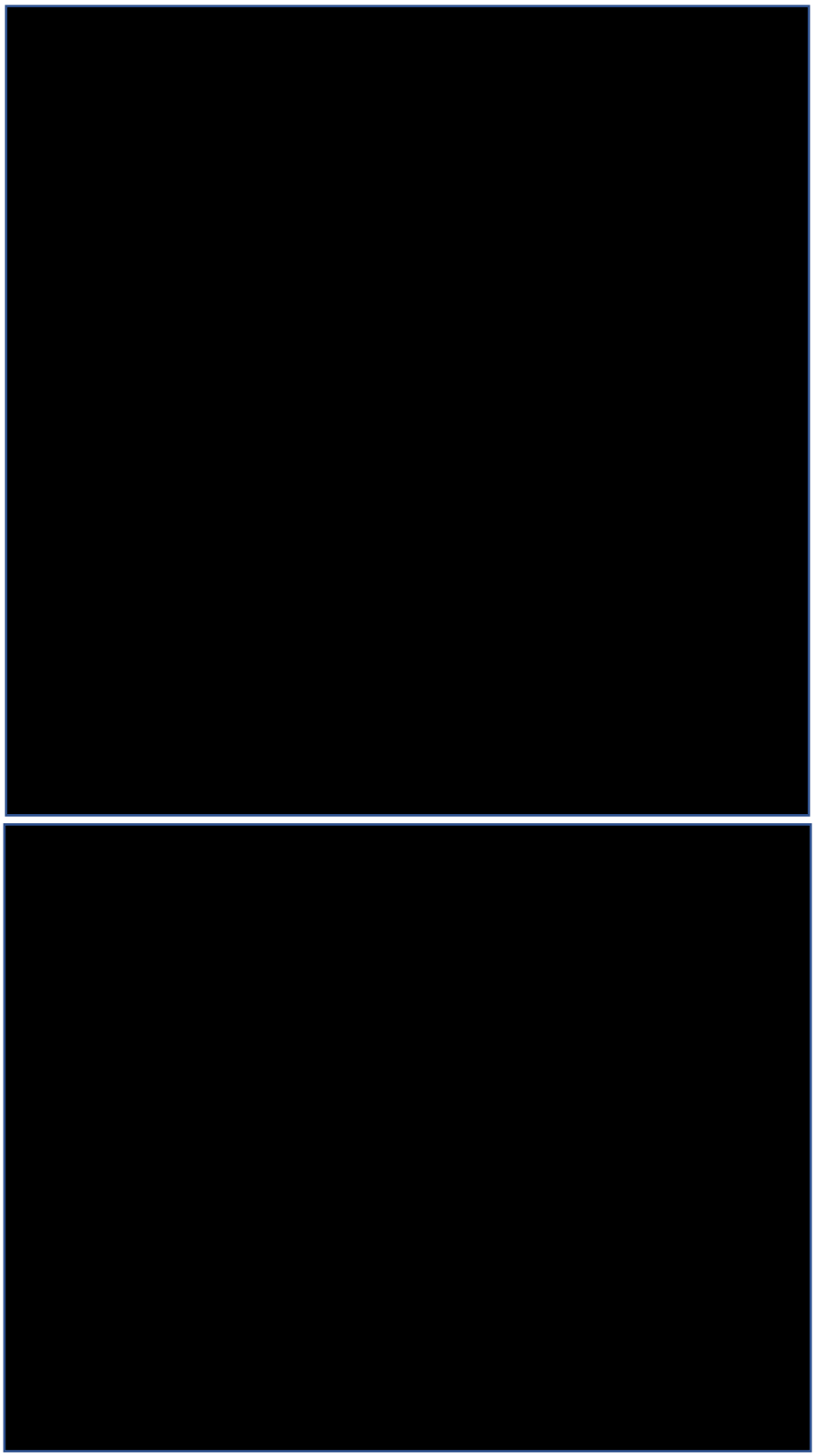
Company response: All indirect estimates were combined for the node-splitting analysis. The experimental node-splitting results provide more detail on how each study contributed to the heterogeneity and inconsistency, but they do not provide information on each look. The results are presented below.

Figure 27. Node splitting: statin intolerant NMA



AliMab = alirocumab; BA = bempedoic acid; CrI = credible interval; EZE = ezetimibe.

Figure 28. Experimental node splitting: statin intolerant NMA



AliMab = alirocumab; BA = bempedoic acid; CrI = credible interval; EZE = ezetimibe; NA = not available.

Clarification questions

Figure 29. Node splitting: maximally tolerated statin NMA

AliMab = alirocumab; BA = bempedoic acid; CrI = credible interval; EvoMab = evolocumab; EZE = ezetimibe.

Figure 30. Experimental node splitting: maximally tolerated statin NMA

Clarification questions

Clarification questions

AliMab = alirocumab; BA = bempedoic acid; CrI = credible interval; EvoMab = evolocumab; EZE = ezetimibe; NA = not available.

A12. Please provide fit statistics as presented in Table 29 of the company submission (CS) for the NMAs presented in response to questions A1, A2, A5, A6 and A7.

Company response: These are found in the model results above for A1.

B2. Priority question. Please provide cost-effectiveness results for populations 2 and 4 based on the clinical effectiveness analysis requested in clarification questions:

a) A1a (% change in LDL-C at 12 weeks);

b) A1b (% change in LDL-C at 24 weeks);

c) A5a (% change in LDL-C at 12 weeks); and

d) A5b (% change in LDL-C at 24 weeks).

Company response: The revised Company base-case cost-effectiveness results using the revised NMA from question A1a are presented in Table 39 (pairwise comparison) and Table 40 (fully incremental analysis). Results for A1b, A5a and A5b are not presented, as explained in responses to questions A1 (page **Error! Bookmark not defined.**) and A5 (page **Error! Bookmark not defined.**). The cost-effectiveness results using the revised NMA are consistent with those in the original Company evidence submission, and the overall conclusions remain the same.

Results in this appendix (B2 to C2) are presented using the updated NMA results.

Table 39. Revised Company base-case cost-effectiveness results for bempedoic acid versus comparators using the revised NMA (Appendix, question A1a)

	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) BA vs. comparator	NMB BA vs. comparator (£20,000)	NMB BA vs. comparator (£30,000)
Position 2a									
Bempedoic acid with background ezetimibe	14,125	11.76	8.71						
No further treatment/ placebo with background ezetimibe	8,278	11.51	8.51	5,847.18	0.25	0.21	28,521.35	−1,746.97	303.14
Position 2b									
Bempedoic acid with background ezetimibe	18,642	9.97	6.86						
Alirocumab	41,337	10.06	6.93	−22,695.14	−0.09	−0.07	342,007.65	21,367.96	20,704.38
Evolocumab	41,776	10.10	6.96	−23,134.35	−0.14	−0.10	236,401.09	21,177.14	20,198.53
Position 4a									
Bempedoic acid with background ezetimibe	18,110	9.91	6.89						
No further treatment/ placebo with background ezetimibe	12,690	9.80	6.81	5,420.08	0.11	0.08	69,452.43	−3,859.27	−3,078.87
Position 4b									
Bempedoic acid with background ezetimibe	18,089	9.35	6.48						
Alirocumab	40,289	9.67	6.72	−22,199.56	−0.32	−0.23	94,487.97	17,500.64	15,151.18
Alirocumab+EZE	40,297	9.60	6.67	−22,208.13	−0.25	−0.18	121,686.25	18,558.07	16,733.04
Evolocumab	41,126	9.91	6.89	−23,036.74	−0.57	−0.41	56,284.72	14,850.95	10,758.06

BA = bempedoic acid; EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; NMA = network meta-analysis; NMB = net monetary benefit; QALY = quality adjusted life-year.

Table 40. Revised company base-case results: fully incremental analysis using the revised NMA (Appendix, question A1a)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	8,278.06	11.51	8.51								
FDC	14,125.24	11.76	8.71	5,847.18	0.25	0.21	-1,746.97	-1,746.97	303.14	303.14	28,521.35
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,642.09	9.97	6.86								
Alirocumab	41,337.23	10.06	6.93	22,695.14	0.09	0.07	-21,367.96	-21,367.96	-20,704.38	-20,704.38	342,007.65
Evolocumab	41,776.44	10.10	6.96	23,134.35	0.14	0.10	-21,177.14	190.83	-20,198.53	505.85	13,942.32
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	12,689.96	9.80	6.81								
FDC	18,110.04	9.91	6.89	5,420.08	0.11	0.08	-3,859.27	-3,859.27	-3,078.87	-3,078.87	69,452.43
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,089.10	9.35	6.48								
Alirocumab	40,288.66	9.67	6.72	22,199.56	0.32	0.23	-17,500.64	-17,500.64	-15,151.18	-15,151.18	94,487.97
Evolocumab	41,125.85	9.91	6.89	23,036.74	0.57	0.41	-14,850.95	2,649.69	-10,758.06	4,393.13	4,801.91

FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NMB = net monetary benefit; QALY = quality-adjusted life-year.

DSA results with the updated NMA results

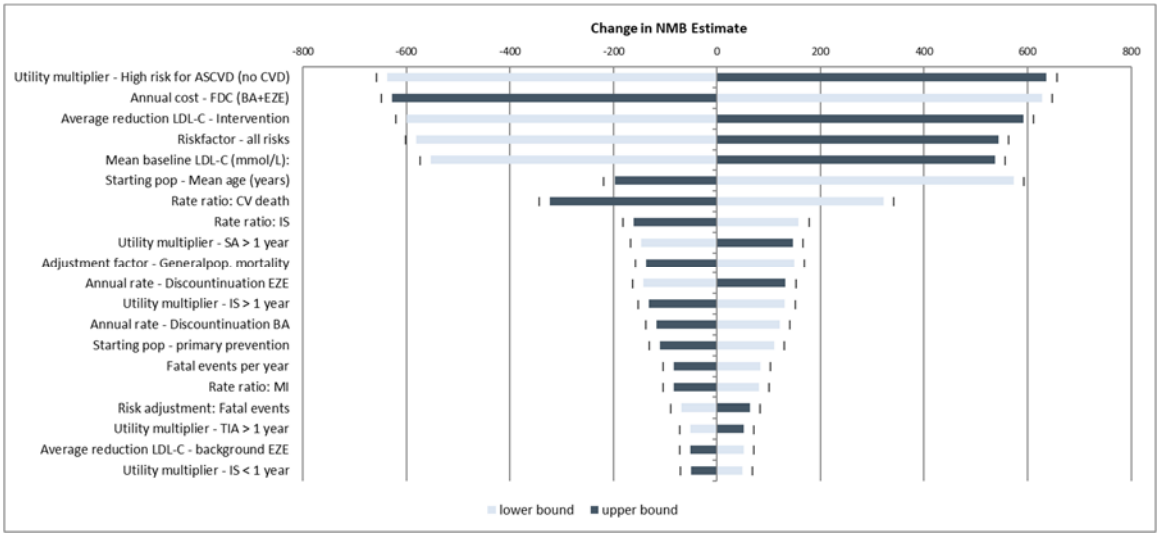
Table 41. Summary of bempedoic acid deterministic sensitivity analyses

Position	Most influential parameters	Lower Bound change in NMB	Upper Bound change in NMB
2a	Utility multiplier - High risk for ASCVD	-637	637
	Annual cost - FDC (BA+EZE)	[redacted]	[redacted]
	Average reduction LDL-C - Intervention	-599	592
	Risk factor - all risks	-581	543
2b	Annual costs - Alirocumab	-2823	2823
	Average reduction LDL-C - AliMab	897	-884
	Average reduction LDL-C - Intervention	-796	788
	Annual rate - Discontinuation AliMab	648	-600
4a	Annual cost - FDC (BA+EZE)	[redacted]	[redacted]
	Risk factor - all risks	-277	259
	Average reduction LDL-C - Intervention	-227	226
	Mean baseline LDL-C (mmol/L):	-210	207
4b	Annual costs - Alirocumab	-2753	2753
	Average reduction LDL-C - AliMab	938	-924
	Risk factor - all risks	942	-882
	Annual rate - Discontinuation AliMab	588	-545

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein-cholesterol; NMB = net monetary benefit at £30,000/QALY.

Deterministic sensitivity analyses using the updated NMA results are presented in the tornado diagrams in Figure 31 through Figure 34.

Figure 31. Tornado diagram – updated NMA – Position 2a – background treatment with EZE

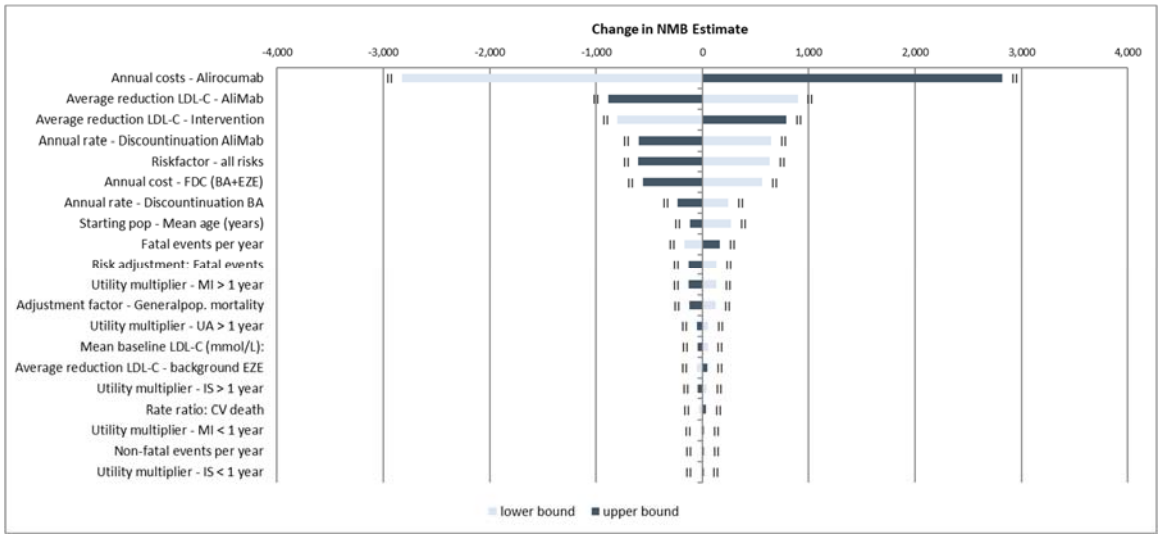


AE = adverse event; NMB = incremental cost-effectiveness ratio.

Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). NMB calculated using £30,000 per QALY.

Clarification questions

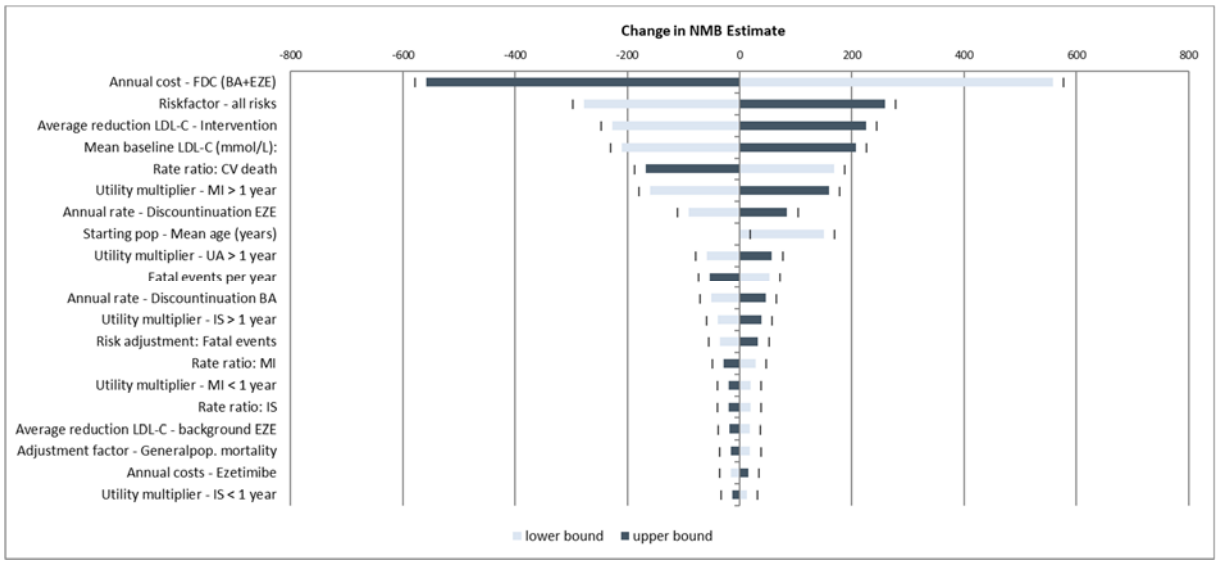
Figure 32. Tornado diagram – updated NMA – Position 2b - Alirocumab



AE = adverse event; NMB = incremental cost-effectiveness ratio.

Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). NMB calculated using £30,000 per QALY.

Figure 33. Tornado diagram – updated NMA – Position 4a – Background treatment with EZE + statin

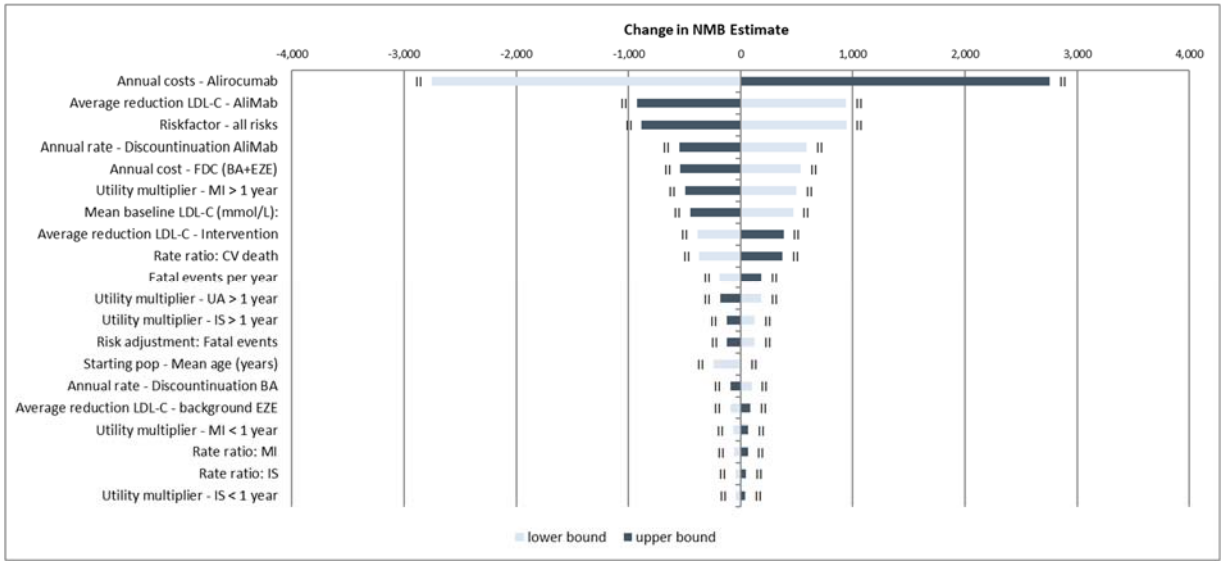


AE = adverse event; NMB = incremental cost-effectiveness ratio.

Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). NMB calculated using £30,000 per QALY.

Clarification questions

Figure 34. Tornado diagram – updated NMA – Position 4b - Alirocumab + statin



AE = adverse event; NMB = incremental cost-effectiveness ratio.

Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). NMB calculated using £30,000 per QALY.

PSA results using the updated NMA results

Acceptability curves with the updated NMA are presented in Figure 35 and Figure 36 and cost-effectiveness planes are presented in Figure 37 to Figure 40.

Table 42. Updated NMA - Results of the probabilistic sensitivity analysis for bempedoic acid

Position	Comparator	Deterministic NMB	Probabilistic mean NMB	95% CrIs for NMB	Probability of cost-effectiveness	
					£20,000/ QALY	£30,000/ QALY
2a	No further treatment/placebo with background ezetimibe	-£1,747	-£1,702	(2350, -4501)	15.4%	51.0%
2b	Alirocumab	£21,368	£21,519	(26394, 16481)	100.0%	99.9%
	Evolocumab	£21,177	£21,396	(15982, 26817)		
4a	No further treatment/placebo with background ezetimibe + statin	-£3,859	-£3,923	(-595, -6328)	1.4%	7.5%
4b	AliMab + statin	£17,501	£17,388	(23234, 10756)	99.9%	96.8%
	AliMab + ezetimibe +statin	£18,558	£18,471	(11406, 25264)		

Clarification questions

	EvoMab +statin	£14,851	£14,717	(6911, 21105)		

AliMab = alirocumab; CrI = credible interval; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NMB = net monetary benefit.

Note: the NMB is presented at £20,000 per QALY.

Figure 35. Cost-effectiveness acceptability curve – updated NMA – bempedoic acid when statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C

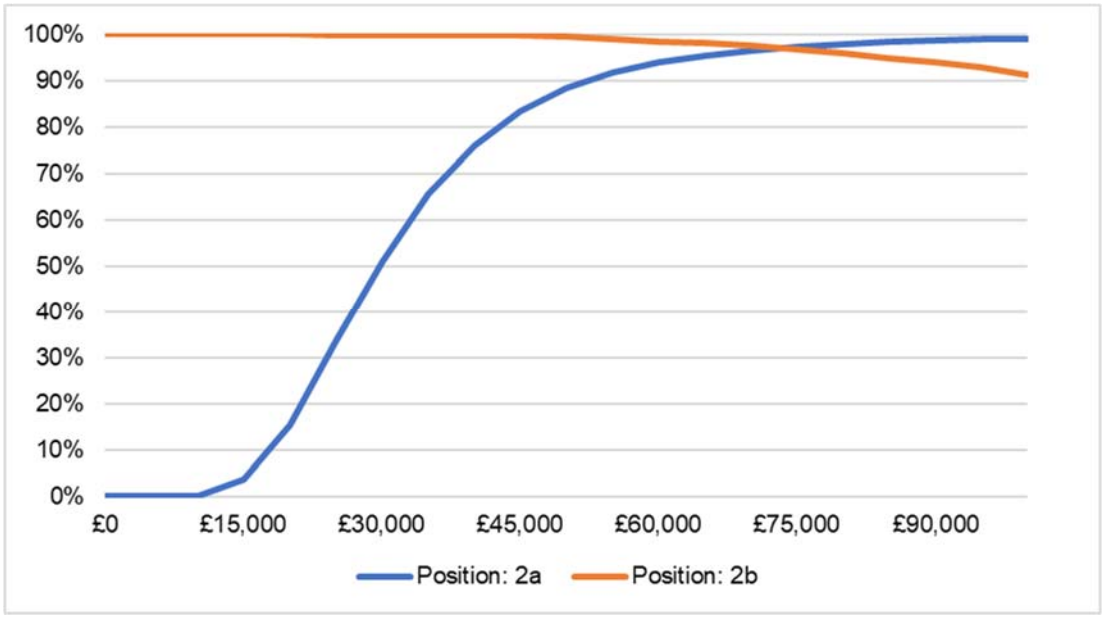
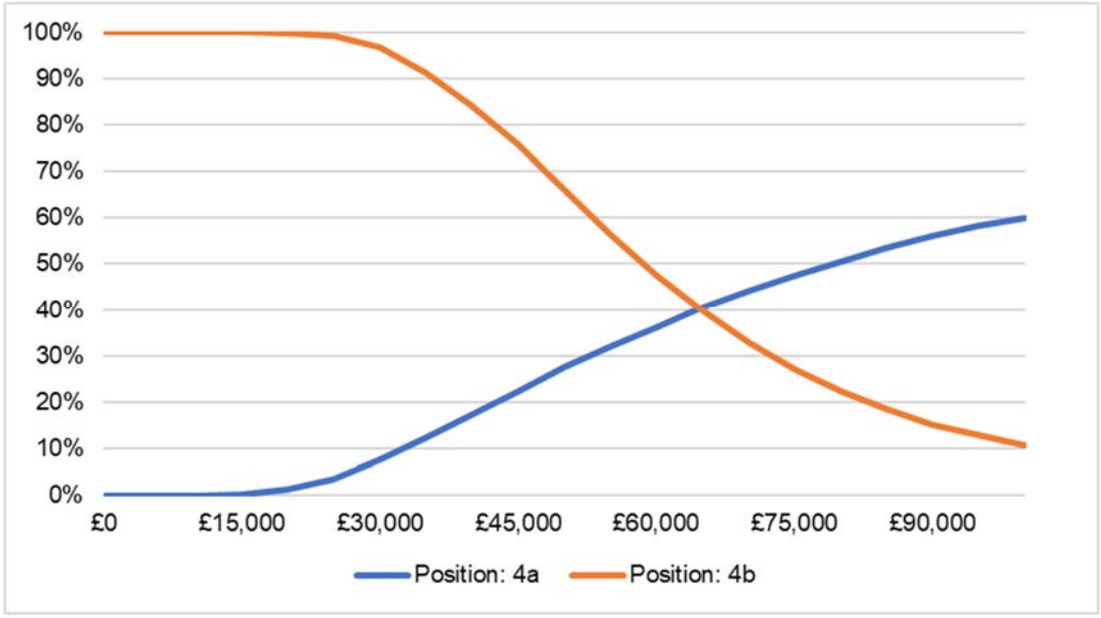


Figure 36. Cost-effectiveness acceptability curve – updated NMA – bempedoic acid when maximally tolerated statin dose and ezetimibe does not appropriately control LDL-C



Clarification questions

Figure 37. Cost-effectiveness plane – updated NMA – Position 2a

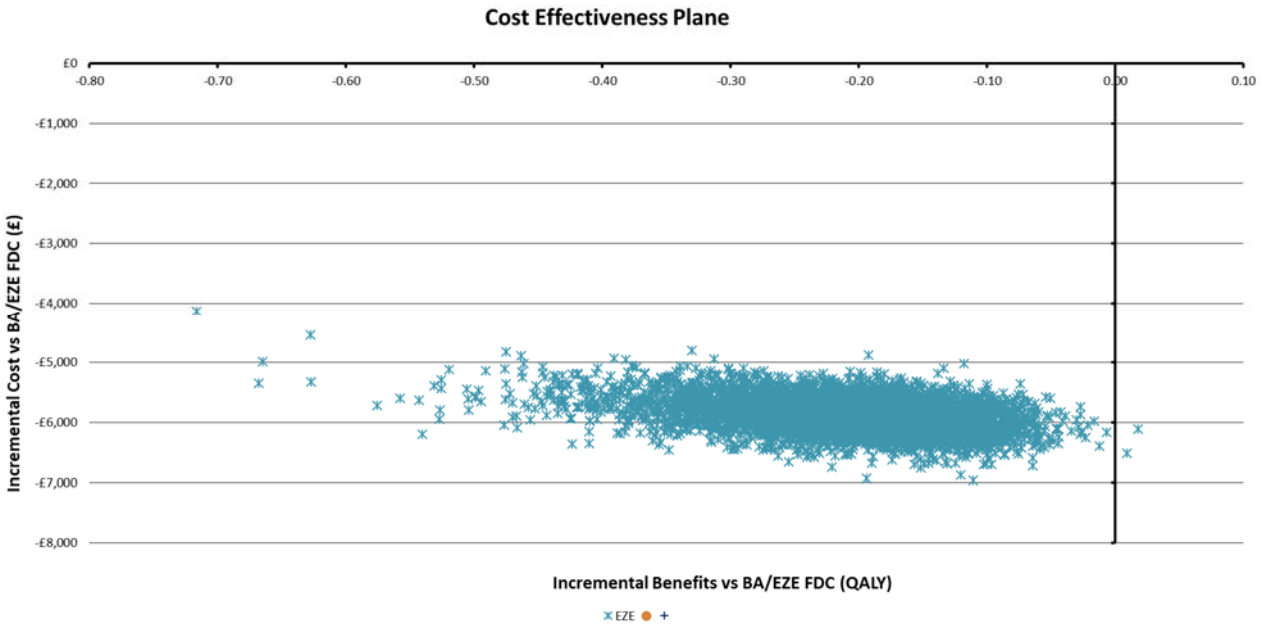


Figure 38. Cost-effectiveness plane – updated NMA – Position 2b

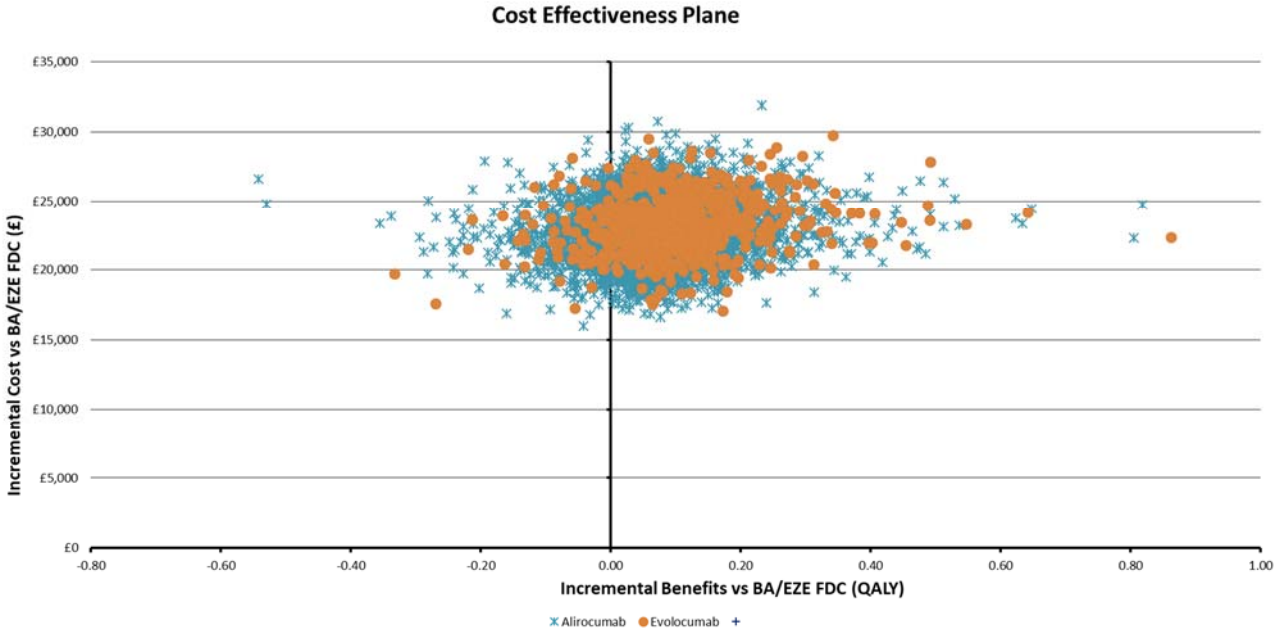


Figure 39. Cost-effectiveness plane – updated NMA – Position 4a

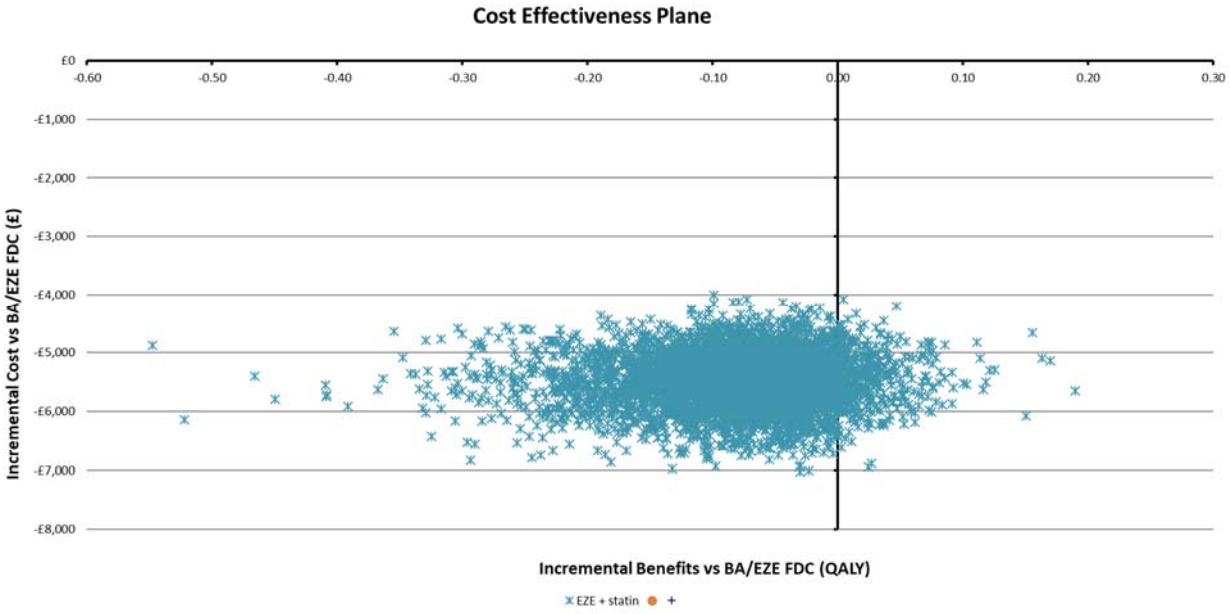
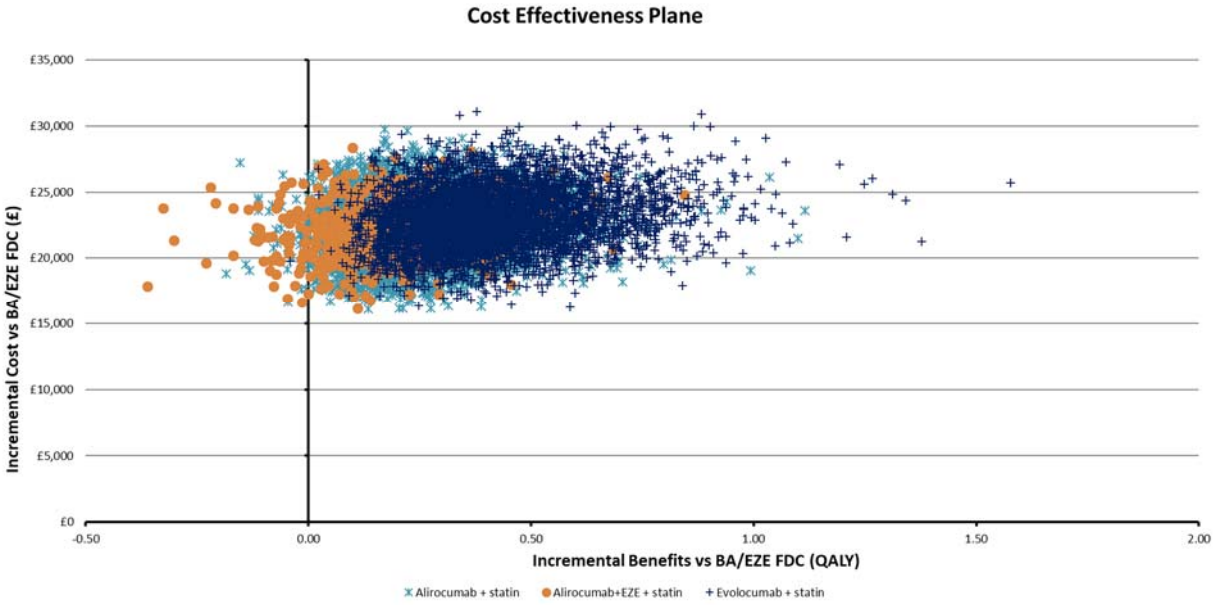


Figure 40. Cost-effectiveness plane – updated NMA – Position 4b



B6. Priority question. Table 51 in Ward et al. 2007 reports the distribution of secondary prevention patients by prior CV event and these include post-stable angina, post-unstable angina, post-MI post-TIA and post-stroke.

c) Please clarify why TIA and stable angina were not included as prior CV events for secondary prevention patients;

d) As a scenario analysis, please include TIA and stable angina as prior CV events for secondary prevention patients, using the distributions of prior CV events recorded in Ward et al. 2007

Company response: Prior transient ischaemic attack (TIA) and stable angina were not included as starting prior events to better align with the definition of prior CV/high risk in TA393 and TA394. This is also aligned with starting cohorts in TA385 and, therefore, makes our results more comparable with the technology assessments of the relevant comparators.

Table 43 presents the results for the four base-case positions (2a, 2b, 4a and 4b) if TIA and stable angina are included as starting populations. As can be seen in the table, this has a limited effect on the results.

Table 43. Scenario results populations if TIA and stable angina are included as starting populations

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	8,105.93	11.56	8.58								
FDC	13,953.01	11.81	8.79	5,847.08	0.25	0.20	-1,754.74	-1,754.74	291.43	291.43	28,575.73
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	17,889.47	10.22	7.21								
Alirocumab	40,944.54	10.31	7.28	23,055.07	0.09	0.07	-21,736.38	-21,736.38	-21,077.04	-21,077.04	349,668.29
Evolocumab	41,371.15	10.35	7.31	23,481.68	0.13	0.10	-21,536.95	199.44	-20,564.58	512.46	13,628.74
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	11,847.75	10.03	7.13								
FDC	17,324.22	10.13	7.21	5,476.48	0.10	0.08	-3,936.02	-3,936.02	-3,165.80	-3,165.80	71,102.09
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	17,446.16	9.59	6.80								
Alirocumab	39,915.13	9.90	7.04	22,468.97	0.31	0.23	-17,819.44	-17,819.44	-15,494.67	-15,494.67	96,650.44
Evolocumab	40,656.22	10.13	7.21	23,210.06	0.54	0.41	-15,106.87	2,712.57	-11,055.27	4,439.40	4,291.58

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit; TIA = transient ischaemic attack.

B12. Priority question. Please explain why primary prevention CV risks are not adjusted by age and/or gender.

b) As a scenario analysis, please apply rates each year of 0.03% for males and 0.008% for females, to reflect the methods employed in NICE CG181 and TA385, based on the evidence in Ward et al. 2007.

Company response: As the cohorts get older, the risk for the primary prevention cohort is adjusted for age and increased by each cycle in a similar way to the risk for subsequent CV events (secondary prevention).

But for the primary prevention cohort, the risk itself together with the LDL-C are the most important factors for deciding if a patient without prior CV event should receive treatment (defining the relevant cohort for the model), it is not appropriate to adjust the baseline risk for age/sex. Hence, the baseline CV risks in the primary prevention cohort are considered to be already representative of the cohort that should simulated to answer the decision problem.

A scenario with age-adjustments of 0.03% for males and 0.008% for females is presented in Table 44. However, for the primary prevention cohort, these adjustments are only applied for when the patients get older in the model and no adjustments to the baseline risks are performed as outlined in the paragraph above.

Table 44. Results using 0.03% for males and 0.008% for females for age adjustments.

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	7,921.27	12.05	8.92								
FDC	13,857.87	12.31	9.13	5,936.60	0.25	0.21	-1,778.35	-1,778.35	300.77	300.77	28,553.39
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,558.46	10.06	6.92								
Alirocumab	40,970.15	10.16	7.00	22,411.68	0.11	0.08	-20,899.79	-20,899.79	-20,143.84	-20,143.84	296,471.14
Evolocumab	41,423.06	10.21	7.03	22,864.59	0.16	0.11	-20,636.24	263.54	-19,522.07	621.77	12,643.11
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	12,766.90	10.00	6.95								
FDC	18,177.27	10.12	7.03	5,410.37	0.12	0.09	-3,696.48	-3,696.48	-2,839.54	-2,839.54	63,135.66
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,131.31	9.54	6.61								
Alirocumab	40,313.41	9.90	6.87	22,182.10	0.36	0.26	-16,976.93	-16,976.93	-14,374.34	-14,374.34	85,231.03
Evolocumab	41,225.09	10.17	7.06	23,093.78	0.63	0.45	-14,059.10	2,917.83	-9,541.76	4,832.58	4,761.34

BA=bempedoic, EZE=ezetimibe; FDC = bempedoic acid plus ezetimibe fixed-dose combination; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B14. Priority question. Page 160 of the CS states "*for example, a 10-year risk of 20% corresponds to a 1-year risk (annual probability) of 2.207%, so for a QRISK3 risk score of 20% (10-year risk), the values in Table 49 were all multiplied by 0.02207 to give the baseline transition probabilities from high risk for ASCVD to each CV event each year*" but this is not reflected in the model. Please explain this discrepancy and provide explicit details of how the transition probabilities were calculated and applied in the model.

b) Instead of adjusting a 10-year risk of 7.5% from the ESC guidelines, please provide a scenario analysis using a 10-year risk of 20% to reflect the methods in CG181 and TA385.

Company response: We see no discrepancy between what is stated in the dossier and how the risks are calculated in the model (Support_engine C61:T73). The methodology used in the model and described in the Company submission is in line with the approach in CG181 and TA393 (NICE, 2016c; NICE, 2016d). As stated in the dossier, the 20% is an example as the 10-year risk varies depending on the population that is selected in the model (see question B10). See question B16 for supporting details.

As described in the Company submission, the following approach is used to estimate baseline transition probabilities from high risk for ASCVD to each CV event each year:

- The 10-year risk of CV death in the high-risk population (7.5%) (Mach et al., 2019) was converted to a 10-year risk of CV events according to QRISK3 using the relative rate of death in Ward et al. (2007) via CG181 (NICE, 2016d). (See 'Default Data'!H146)
- The 10-year QRISK score was converted to yearly probabilities using
  - =1 – EXP(ln(1-"10-year probability (QRISK score)")/10)) (see Support_engine!D69)
  - The yearly probability of a QRISK event was multiplied with the relative rates in Table 49 to obtain probabilities from high risk for ASCVD to each CV event each year. (see Support_engine!F70:L70)

An exploratory scenario analysis with 20% 10-year risk for CV events is presented in Table 45. As ezetimibe is likely also to be used also in a populations with lower risk patients it is not unreasonable to assume that the patients relevant for bempedoic acid will have a higher mean 10-year risk for CV events than the patients considered in TA385.

Table 45. Scenario with 20% 10-year risk for CV events

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	7,170.07	12.09	9.02								
FDC	13,219.81	12.30	9.19	6,049.75	0.21	0.17	-2,593.62	-2,593.62	-865.55	-865.55	35,008.81
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,622.90	9.98	6.88								
Alirocumab	41,332.50	10.07	6.94	22,709.60	0.09	0.07	-21,386.34	-21,386.34	-20,724.70	-20,724.70	343,235.09
Evolocumab	41,771.82	10.12	6.97	23,148.93	0.14	0.10	-21,197.47	188.86	-20,221.75	502.95	13,987.02
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	12,647.54	9.82	6.83								
FDC	18,074.77	9.93	6.91	5,427.23	0.11	0.08	-3,875.48	-3,875.48	-3,099.61	-3,099.61	69,949.88
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,066.73	9.36	6.49								
Alirocumab	40,283.37	9.68	6.73	22,216.64	0.32	0.23	-17,534.21	-17,534.21	-15,192.99	-15,192.99	94,893.59
Evolocumab	41,120.09	9.93	6.90	23,053.35	0.56	0.41	-14,896.34	2,637.87	-10,817.83	4,375.16	4,816.20

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B24. Priority question. On page 169 of the CS it states “a recurrent cardiac event (MI, UA and SA) only affects the risk for cardiac events (MI, UA, SA and CV death) while a recurrent IS only affects the risk of IS and CV death” but the ERG’s clinical experts have advised that recurrent cardiac events also affect the risk for IS events, and that recurrent IS events also affect the risk for cardiac events. Please provide a scenario analysis where recurrent cardiac events also affect the risk for IS events.

Company response: This assumption was used as it was deemed most conservative and also in line with our understanding of TA393. A scenario where the recurrent cardiac events also affect the risk for IS events is presented in Table 46.

Table 46. Cost-effectiveness results when recurrent cardiac events also affect the risk for IS events

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	8,283.73	11.49	8.50								
FDC	14,126.81	11.74	8.70	5,843.09	0.25	0.21	-1,712.63	-1,712.63	352.60	352.60	28,292.70
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,649.79	9.93	6.84								
Alirocumab	41,299.84	10.02	6.90	22,650.05	0.09	0.07	-21,303.89	-21,303.89	-20,630.81	-20,630.81	336,514.96
Evolocumab	41,739.18	10.07	6.93	23,089.39	0.14	0.10	-21,104.18	199.72	-20,111.57	519.25	13,749.68
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	12,709.56	9.76	6.78								
FDC	18,118.62	9.87	6.86	5,409.06	0.11	0.08	-3,824.37	-3,824.37	-3,032.02	-3,032.02	68,266.46
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,098.54	9.31	6.45								
Alirocumab	40,252.20	9.63	6.69	22,153.66	0.33	0.24	-17,386.77	-17,386.77	-15,003.32	-15,003.32	92,947.98
Evolocumab	41,093.36	9.88	6.87	22,994.83	0.57	0.42	-14,690.27	2,696.50	-10,537.98	4,465.33	4,755.49

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B29. Priority question: The ERG's clinical experts have advised that recurrent events have a greater impact on quality of life compared with primary events. Please justify why utility values for primary and recurrent events were assumed to be the same in the economic model.

b) Please provide a scenario making appropriate adjustments to event utilities for recurrent events, using evidence from the published literature, where available or clinical expert opinion to inform the adjustments. Alternatively, provide threshold analysis, testing different percentage decrements to utilities for recurrent events.

Company response: Similar to previous technology assessments (TA393 (NICE, 2016c) and TA394 (NICE, 2016b)), we did not identify any reliable utility estimates of recurrent survivors of each outcome in the literature. As the data used to estimate utility values (The Health Survey for England [HSE]) likely included patients with both one and recurrent events (data not presented for number of events) and could therefore capture the utility effect of multiple events, additional adjustments could result in double counting of the utility effect from CV events. Further, applying multiple adjustments on the same population (such as composite endpoints) has previously been criticised by ERGs and NICE. A scenario analysis where the utility-multiplier in recurrent health states are applied twice (extreme scenario) is presented in Table 47 for reference.

Table 47. Results with multiple utility adjustments after recurrent events

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	8,278.06	11.51	8.38								
FDC	14,125.24	11.76	8.60	5,847.18	0.25	0.22	-1,545.59	-1,545.59	605.20	605.20	27,186.15
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,642.09	9.97	6.47								
Alirocumab	41,337.23	10.06	6.54	22,695.14	0.09	0.07	-21,292.43	-21,292.43	-20,591.07	-20,591.07	323,589.95
Evolocumab	41,776.44	10.10	6.58	23,134.35	0.14	0.10	-21,066.57	225.86	-20,032.68	558.39	13,207.96
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	12,689.96	9.80	6.45								
FDC	18,110.04	9.91	6.53	5,420.08	0.11	0.08	-3,769.30	-3,769.30	-2,943.91	-2,943.91	65,666.97
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	18,089.10	9.35	6.10								
Alirocumab	40,288.66	9.67	6.35	22,199.56	0.32	0.25	-17,228.47	-17,228.47	-14,742.92	-14,742.92	89,314.65
Evolocumab	41,125.85	9.91	6.53	23,036.74	0.57	0.43	-14,391.24	2,837.23	-10,068.49	4,674.43	4,556.82

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

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B32. Priority question: The ERG has several concerns with how health state costs have been implemented in the model. The study by Danese et al. 2016 presents total and incremental costs for first and second events as well as first and second events combined, which has been used in the model. The ERG's clinical experts have advised that recurrent events have a greater impact on resource use and costs compared with primary events. Furthermore, The company have assumed that a CV death is cost-saving compared with a non-CV death based on data from Walker et al.,2016. The ERG considers this a perverse incentive.

d) Please justify why the costs for first and second events combined from Danese et al. 2016 was deemed appropriate to use in the model.

e) Please clarify why the incremental cost values were deemed appropriate to use to cost the model health states.

f) Please perform a scenario where total costs are used for all health states, including CV death.

ii. Please build on this scenario by using second event total costs from Danese et al. 2016 to cost recurrent events. Alternatively, threshold analysis exploring the impacts of increased costs for recurrent events would be acceptable. Please make this an on/off option in the model for the scenario.

Company response: An alternative approach to model the negative CV death cost (which is not counterintuitive but maybe perverse) would have been to add an even higher cost for non-CV related death. This would imply adding additional parameters and complexity to the model without adding any benefits in form of flexibility or accuracy. Hence, the base case approach was considered most appropriate.

The rational for why we used the costs for both first and second events group together were:

- The values for first and second event were consistent in most cases and the increased number of cases improve the certainty in the estimates
- Some of the costs are higher for the first event than the recurrent event, which is counterintuitive according to both us and the ERG clinical experts.

Total costs were considered for inclusion, but incremental costs was deemed more appropriate as this

controls for differences in the patient population between the Danese et al. (2016) (Danese et al., 2016) study and the model. Using the total costs, it is also technically challenging to apply an accurate cost for the patient before they experience an event, as this cost varies between the different events and between the first and second event.

A scenario where we have applied total costs rather than incremental costs is presented in Table 48 together with a scenario where the cost for recurrent events are modelled using a separate cost in Table 49. However, the results using total costs are not accurate as this approach does not correctly control for the difference in costs for the patients before the first event. Therefore, we do not support the presented results for decision making purposes.

Table 48. Scenario using total costs for the health states

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	30,666.85	11.51	8.51								
FDC	36,948.77	11.76	8.71	6,281.91	0.25	0.21	-2,181.70	-2,181.70	-131.60	-131.60	30,641.91
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	35,381.97	9.97	6.86								
Alirocumab	58,199.45	10.06	6.93	22,817.48	0.09	0.07	-21,490.31	-21,490.31	-20,826.72	-20,826.72	343,851.34
Evolocumab	58,696.90	10.10	6.96	23,314.93	0.14	0.10	-21,357.72	132.59	-20,379.12	447.61	15,791.15
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	29,097.67	9.80	6.81								
FDC	34,660.19	9.91	6.89	5,562.51	0.11	0.08	-4,001.71	-4,001.71	-3,221.31	-3,221.31	71,277.60
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	33,878.92	9.35	6.48								
Alirocumab	56,499.85	9.67	6.72	22,620.93	0.32	0.23	-17,922.01	-17,922.01	-15,572.55	-15,572.55	96,281.45
Evolocumab	57,653.38	9.91	6.89	23,774.46	0.57	0.41	-15,588.67	2,333.35	-11,495.77	4,076.78	6,616.39

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

Table 49. Scenario using health state costs split on first and second events

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	8,541.12	11.51	8.51								
FDC	14,360.69	11.76	8.71	5,819.57	0.25	0.21	-1,719.36	-1,719.36	330.75	330.75	28,386.68
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	19,533.78	9.97	6.86								
Alirocumab	42,215.91	10.06	6.93	22,682.13	0.09	0.07	-21,354.95	-21,354.95	-20,691.37	-20,691.37	341,811.59
Evolocumab	42,649.05	10.10	6.96	23,115.26	0.14	0.10	-21,158.05	196.90	-20,179.45	511.92	13,749.58
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	13,548.36	9.80	6.81								
FDC	18,953.01	9.91	6.89	5,404.64	0.11	0.08	-3,843.84	-3,843.84	-3,063.44	-3,063.44	69,254.67
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	19,002.61	9.35	6.48								
Alirocumab	41,157.61	9.67	6.72	22,155.00	0.32	0.23	-17,456.09	-17,456.09	-15,106.63	-15,106.63	94,298.33
Evolocumab	41,962.16	9.91	6.89	22,959.56	0.57	0.41	-14,773.77	2,682.32	-10,680.87	4,425.76	4,614.75

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

Table 50. Scenario using total costs for health states and costs split on first and second events

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	31,960.32	11.51	8.51								
FDC	38,146.38	11.76	8.71	6,186.06	0.25	0.21	-2,085.85	-2,085.85	-35.75	-35.75	30,174.36
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	39,473.19	9.97	6.86								
Alirocumab	62,260.39	10.06	6.93	22,787.20	0.09	0.07	-21,460.03	-21,460.03	-20,796.44	-20,796.44	343,394.98
Evolocumab	62,743.79	10.10	6.96	23,270.60	0.14	0.10	-21,313.39	146.64	-20,334.78	461.66	15,345.12
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	33,016.36	9.80	6.81								
FDC	38,542.76	9.91	6.89	5,526.40	0.11	0.08	-3,965.59	-3,965.59	-3,185.19	-3,185.19	70,814.81
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	37,910.81	9.35	6.48								
Alirocumab	60,431.03	9.67	6.72	22,520.23	0.32	0.23	-17,821.31	-17,821.31	-15,471.85	-15,471.85	95,852.82
Evolocumab	61,512.06	9.91	6.89	23,601.25	0.57	0.41	-15,415.46	2,405.85	-11,322.57	4,149.28	6,200.54

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

B35. Please provide a scenario analysis using the discontinuation rates observed in the CLEAR studies in all treatment arms.

Company response: We do not have a reliable estimate of this due to the length of the CLEAR studies. Using data for the first year of treatment is unlikely to reflect the long-term discontinuation rate, as discontinuation due to AEs is more likely to occur early in the treatment period. We have obtained expert opinion that verified there is no informative discontinuation data across treatments as discontinuation can vary according to several factors; expert opinion agreed with our conservative approach of applying the same rates across treatments.

In CLEAR Tranquility, which is the bempedoic acid trial with most similar treatment burden to the patients simulated in the model (all patients receiving both bempedoic acid and ezetimibe), 9.4% discontinued bempedoic acid during the trial follow-up. (Esperion Therapeutics data on file, 2018b) The other CLEAR trials had similar discontinuation rates. A scenario using this rate is presented in Table 51.

Table 51. Scenario with results using a 9.4% discontinuation rate for all treatments

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£) incremental (QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	8,179.50	11.48	8.49								
FDC	13,113.48	11.69	8.67	4,933.99	0.21	0.18	-1,408.97	-1,408.97	353.54	353.54	27,994.10
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	17,781.97	9.88	6.81								
Alirocumab	37,199.55	9.97	6.87	19,417.58	0.08	0.06	-18,254.94	-18,254.94	-17,673.61	-17,673.61	334,023.22
Evolocumab	37,559.94	10.00	6.89	19,777.97	0.12	0.09	-18,063.57	191.37	-17,206.37	467.24	13,063.30
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	12,591.37	9.78	6.80								
FDC	17,245.19	9.87	6.87	4,653.82	0.09	0.07	-3,283.31	-3,283.31	-2,598.05	-2,598.05	67,913.62
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
FDC	17,297.51	9.29	6.44								
Alirocumab	36,344.00	9.58	6.65	19,046.50	0.28	0.21	-14,901.38	-14,901.38	-12,828.81	-12,828.81	91,898.33
Evolocumab	36,978.89	9.79	6.81	19,681.39	0.50	0.36	-12,463.90	2,437.47	-8,855.16	3,973.66	4,132.91

EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality adjusted life-year; NMB = net monetary benefit.

C2. Priority question. The ERG cannot reproduce the company's estimates for the OWSA (tabs 'OWSA Results' and 'OWSA calcs', cells AL:AN23 of the economic model) presented in Table 68. Please investigate and either correct or provide instructions on how to replicate the company's results.

Company response: Please follow the instructions specified below to run this analyses in line with the company submission:

- Update WTP in the PSA sheet to 30,000
- Select the relevant comparator
- Run OWSA

Using these selections produce Table 52.

Table 52. Summary of bempedoic acid deterministic sensitivity analyses

Position	Most influential parameters	Lower Bound change in NMB	Upper Bound change in NMB
2a	Utility multiplier - High risk for ASCVD	-637	637
	Annual cost - FDC (BA+EZE)	[redacted]	[redacted]
	Average reduction LDL-C - Intervention	-599	592
	Risk factor - all risks	-581	543
2b	Annual costs - Alirocumab	-2823	2823
	Average reduction LDL-C - AliMab	897	-884
	Average reduction LDL-C - Intervention	-796	788
	Annual rate - Discontinuation AliMab	648	-600
4a	Annual cost - FDC (BA+EZE)	[redacted]	[redacted]
	Risk factor - all risks	-277	259
	Average reduction LDL-C - Intervention	-227	226
	Mean baseline LDL-C (mmol/L):	-210	207
4b	Annual costs - Alirocumab	-2753	2753
	Average reduction LDL-C - AliMab	938	-924
	Risk factor - all risks	942	-882
	Annual rate - Discontinuation AliMab	588	-545

AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein-cholesterol; NMB = net monetary benefit at £30,000/QALY.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Simon Williams**
2. Name of organisation	HEART UK- The Cholesterol Charity

3. Job title or position	Head of Communications and Policy
4a. Brief description of the organisation (including who funds it). How many members does it have?	HEART UK is the Nation's Cholesterol Charity providing support to individuals with raised cholesterol, atherosclerosis and other lipid conditions. We provide high quality literature, a Cholesterol Helpline run by cardiac nurses and dietitians, an extensive website, a range of educational videos, the Ultimate Cholesterol Lowering Plan© and a range of electronic communication tools aimed at increasing the awareness of cholesterol. HEART UK also supports the health care professionals who work and care for patients (and their families) with raised and unhealthy patterns of high cholesterol and other dyslipidaemias. HEART UK hosts a world class annual scientific conference and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity maintains a health professional membership scheme, provides resources and training to health care professionals.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Daichii Sankyo, Sanofi and Amgen are members of the HEART UK Collaborative Group and pay an annual fee of £25,200

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have a Cholesterol Helpline with direct contact via telephone and email. The helpline supports people with information to make informed choices. Additionally we have an extensive website that receives over 4million views a year and engagement on social media.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	NHS Health Checks, which includes a cholesterol test, are important cornerstone of CVD prevention and can be the first indication of a need for treatment. However, NHS Health Checks are delivered inconsistently across the country with very poor uptake in many places. Diet and lifestyle advice and medication to treat high cholesterol following an NHS Health Check, where a patient has raised LDL-C

	also varies enormously across the country. Access to cholesterol testing is variable and we regularly hear reports of people being denied access to a test, including people where a family history indicates familial hypercholesterolaemia.
8. Is there an unmet need for patients with this condition?	Cardiovascular disease (CVD) is the underlying cause of 26% of all deaths in the UK, which includes heart attacks, strokes and dementia. This equates to approximately 160,000 deaths each year or an average of 435 people each day. At least, 42,000 of these deaths occur prematurely and, in many cases, can be prevented.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Those living in England's most deprived areas are almost 4 times as likely to die prematurely from CVD than those in the least deprived areas.

Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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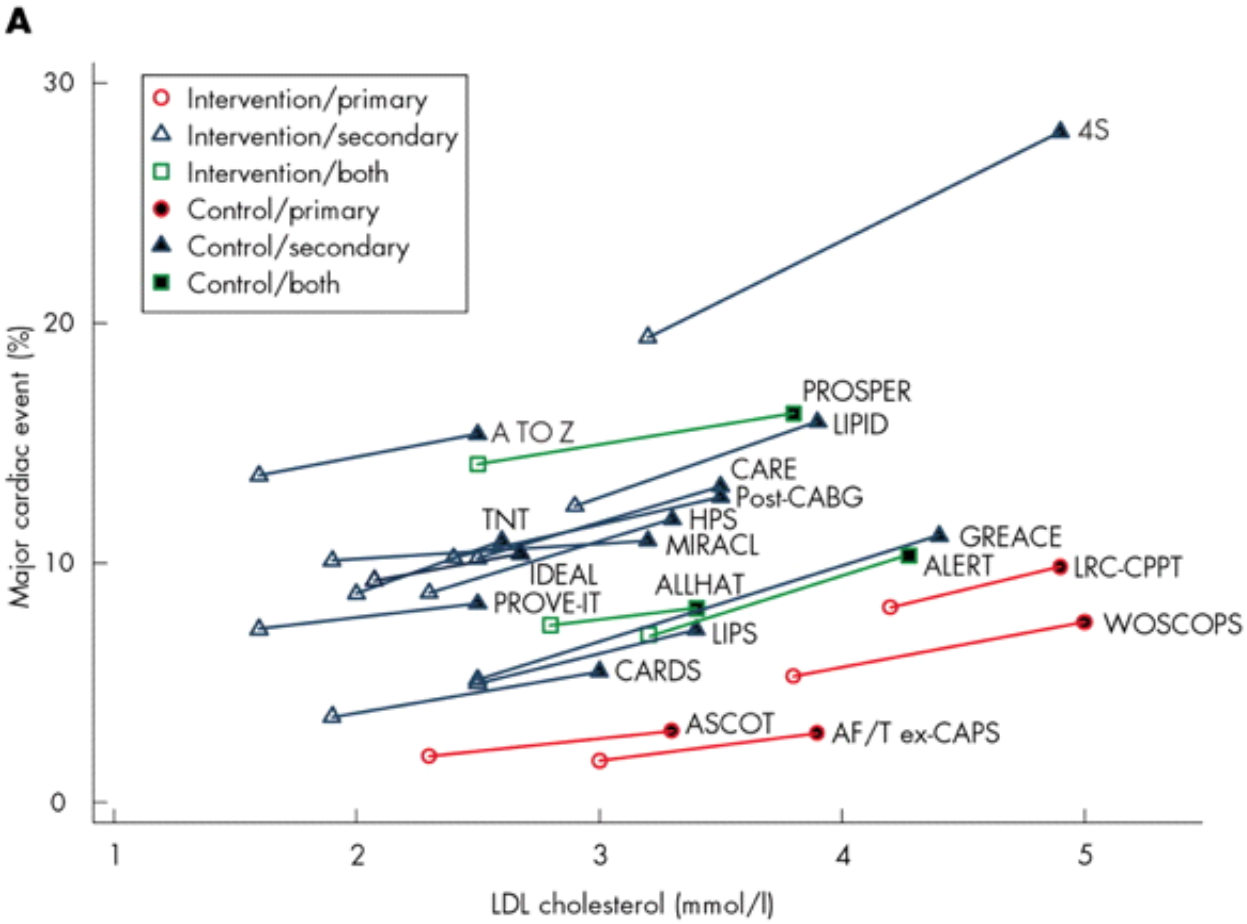
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The British Cardiovascular Society**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Professional organisation for cardiologists in the UK funded by membership fees**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**To lower plasma concentrations of LDL-cholesterol and thereby reduce the risk of cardiovascular events (myocardial infarction, stroke, cardiovascular death) in people with primary hypercholesterolaemia or mixed dyslipidaemia.**
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**Response to treatment can be judged by (1) extent of reduction of plasma LDL-cholesterol concentration and (2) the extent of reduction in clinical endpoints such as myocardial infarction, coronary intervention, stroke, and death.** **(1) The reduction in plasma LDL cholesterol concentration could be judged as (a) a proportionate reduction from the starting level or (b) in terms of absolute reduction expressed in mmol/L or mg/dL. Statin drugs (oral preparations which also lower plasma LDL-cholesterol concentration) vary in their ability to reduce LDL-cholesterol according to specific agent and dose.** **A reduction in plasma LDL-cholesterol concentration by >15% might be considered clinically significant. This is, however, an arbitrary figure, not least because the absolute benefit from LDL-cholesterol reduction is related at population level to the starting cardiovascular risk and to the duration of treatment. The graph below shows effects of plasma LDL-cholesterol reduction in a variety of primary and secondary prevention trials. High dose statins can reduce plasma LDL-cholesterol concentration by 50% or more.**



Bempedoic acid lowers plasma LDL cholesterol concentration by approximately 15-20%.
https://www.ncbi.nlm.nih.gov/pubmed/30922146
https://www.ncbi.nlm.nih.gov/pubmed/30865796

	(2) There are no current clinical endpoint outcome data for Bempedoic acid.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**There is a need for drugs to lower plasma LDL-cholesterol concentration, but this is largely met by existing drugs, notably the HMG Co-A reductase inhibitors, or statins. There is some unmet need in relation to statin intolerance, but this is a notoriously imprecise and difficult to define state. For patients with greatly elevated plasma LDL-cholesterol concentrations (>3.5- 4.0 mmol/L, depending upon the presence or absence of cardiovascular disease), PSK-9 inhibitors are recommended by NICE. Arguably there is a need for a safe, cheap oral preparation that would either (a) augment LDL-reduction with statins or (b) be available for use in patients who are intolerant of statins.** **Ezetimibe, which is orally administered, also lowers cholesterol by a comparable amount to bempedoic acid and arguably occupies this space.** **Bempedoic acid is a prodrug which is activated by a hepatic enzyme not present in skeletal muscle, it inhibits ATP-citrate lyase, an enzyme upstream of HMG CoA reductase in the cholesterol biosynthesis pathway. There are some data which suggest that ezetimibe and bempedoic acid could be used in combination (with or without a statin). This would increase the therapeutic options.** **Some small, short-duration trials have administered Bempedoic acid to patients who were previously intolerant of statins.** https://www.ncbi.nlm.nih.gov/pubmed/26073387 https://www.ncbi.nlm.nih.gov/pubmed/30922146
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	**Lowering plasma concentrations of LDL-cholesterol in people with primary hypercholesterolaemia or mixed dyslipidaemia is currently achieved as follows:** **For the secondary prevention of cardiovascular disease: statins; ezetimibe; PCK-9 inhibitors** **For the primary of cardiovascular disease: stains; ezetimibe; PCSK-9 inhibitors, plasma aphoresis**

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**Various. Recent European Society of Cardiology / European Atherosclerosis Society guidelines:** https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/09/12/15/13/2019-esc-eas-guidelines-for-dyslipidaemias
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**The overall pathways are well-defined. Debate continues regarding the plasma concentration of LDL-cholesterol or non-HDL cholesterol and the level of cardiovascular risk at which treatment should be initiated, and the targets for treatment. The general direction of travel is to aim for greater LDL-cholesterol reduction in secondary prevention. There is also an emerging case for earlier initiation and longer duration of LDL-cholesterol reduction in primary prevention, in keeping with the notion of '*lifetime risk*'**
• What impact would the technology have on the current pathway of care?	**Minimal impact on the main pathway. Bempedoic acid may provide alternative therapy for LDL-cholesterol lowering for statin intolerant patients; i.e. it would provide an additional parallel strand on the pathway. There may be an option to use Bempedoic acid in combination with ezetimibe in statin-intolerant patients. As stated above, the field of statin intolerance is fraught with subjectivity and uncertainty.**
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**See answer above**
• How does healthcare resource use differ	

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**If used, I would expect initiation in secondary care / specialist clinics, with ongoing treatment in primary care.**
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**Nil out of the ordinary. New drug, but orally administered. No broader implications for delivery.**
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**It is not better than the current standard of care. It offers an alternative for statin intolerant patients .**
• Do you expect the technology to increase length of life more than current care?	**No.** **It is not better than current standard of care. It offers an alternative.**
• Do you expect the technology to increase health-related quality of	**No**

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**Not known to me**
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	**It is not easier than current standard of care. It offers an alternative.**

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**No**
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	**No**
16. Do you consider the technology to be innovative in its potential to make a	

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	**No. it is a new class of drug. It offers an alternative. Current evidence does not suggest superiority.**
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	**Bempedoic acid was fairly well tolerated in a trial of approximately 2,000 people, but with limited duration of follow-up (12 months). There was an increase in plasma urate levels in treated patients. There may be an excess of muscle pain / spasm.** **https://www.ncbi.nlm.nih.gov/pubmed/30865796** **I am not aware of any formal quality of life study.**

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	**Broadly, yes.**
• If not, how could the results be extrapolated to the UK setting?	**N/A**
• What, in your view, are the most important outcomes, and were they measured in the trials?	*"The trial involved 2230 patients, of whom 1488 were assigned to receive bempedoic acid and 742 to receive placebo. The mean (Å}SD) LDL cholesterol level at baseline was 103.2Å}29.4 mg per deciliter. The incidence of adverse events (1167 of 1487 patients [78.5%] in the bempedoic acid group and 584 of 742 [78.7%] in the placebo group) and serious adverse events (216 patients [14.5%] and 104 [14.0%], respectively) did not differ substantially between the two groups during the intervention period, but the incidence of adverse events leading to discontinuation of the regimen was higher in the bempedoic acid group than in the placebo group (162 patients [10.9%] vs. 53 [7.1%]), as was the incidence of gout (18 patients [1.2%] vs. 2 [0.3%]). At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg per deciliter, representing a change of −16.5% from baseline (difference vs. placebo in change from baseline, –18.1 percentage points; 95% confidence interval, –20.0 to –16.1; P<0.001). Safety and efficacy findings were consistent, regardless of the intensity of background statin therapy."* Reproduced from abstract of Ray et al *N Engl J Med*, 2019.

	https://www.ncbi.nlm.nih.gov/pubmed/30865796
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	**Broadly, LDL-cholesterol reduction is associated with improved cardiovascular outcomes and it seems not to matter how that LDL-cholesterol reduction is effected. However, this does not take into account potential off-target effects.** **Anacetrapib, ezetimibe, and statins all reduce plasma LDL-cholesterol concentration and by different mechanisms. These interventions all show reduced rates of cardiovascular events commensurate with the observed reduction in plasma LDL-cholesterol concentration. However that does not mean that lowering LDL-cholesterol guarantees a risk reduction because there can be off-target effects (see torcetrapib; nicotinic acid; thiazolidinediones). Treatment effects on cardiovascular risk can only be assessed by randomised controlled trials which report clinical event rates as their primary outcome.**
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	**Not known to me.**
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**No**

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	**N/A**
21. How do data on real-world experience compare with the trial data?	**N/A**
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	**Not known to me**

22b. Consider whether these issues are different from issues with current care and why.	**N/A**
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- **New oral drug class**
- **Modest cholesterol reduction (approximately 16%) is demonstrated in patients already taking statins**
- **No clinical outcome data**
- **No long term safety data**
- **Less efficacious than injectable agents (e.g. anti-PSCK9 antibodies or siRNA for PCSK9)**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Kathryn Ryan**
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	**Consultant Chemical Pathologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment reduces LDL-C and therefore prevents cardiovascular disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in LDL-C by 20%.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, current treatments are not tolerated by a significant number of patients.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	By statins, ezetimibe and PCKS9i
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, CG71 CG181 TA 393 TA 394 TA 385
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, clear from guidelines listed above
• What impact would the technology have on the current pathway of care?	Provide an additional treatment option for patients who are statin intolerant or not treated to target on available treatment.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes

• How does healthcare resource use differ between the technology and current care?	Different mechanism of action and tolerability (in clinical trials).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In primary and secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment beyond cost of medication
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Potentially
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	It may do
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not known
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additions to current practice
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	no

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	no
• Does the use of the technology address any particular unmet need of the patient population?	yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Currently appears to be well tolerated
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Lipid reduction and tolerability - yes CV reduction – not designed to assess this
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Will need longer studies designed to assess CV benefit
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any
20. Are you aware of any relevant evidence that might	NO

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	N/A
22. How do data on real-world experience compare with the trial data?	Not known
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any

23b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Potentially well tolerated treatment which reduces LDL-C. Further studies will be required to assess impact on primary and secondary prevention of CV disease.
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

Single Technology Assessment Report

Source of funding

This report was commissioned by the National Institute for Health Research Systematic Reviews Programme as project number 129823T.

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, and clinical sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Charlotta Karner	Critical appraisal of the clinical evidence; cross checking of data; and assisted with drafting the clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Kayleigh Kew	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

AAT	aspartate aminotransferase
ACL	adenosine triphosphate citrate lyase
ACSVL1	acyl-CoA synthetase 1
AE	adverse event
ALT	alanine aminotransferase
Apo B	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
ATP	adenosine triphosphate
BA	bempedoic acid
BMI	body mass index
CE	cost-effectiveness
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CoA	coenzyme A
CrI	credible interval
CS	company submission
CSR	clinical study report
CTTC	Cholesterol Treatment Trialists Collaboration
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
ECG	electrocardiograms
eGFR	estimated glomerular filtration rate
ERG	Evidence review group
EZE	ezetimibe
FDC	Bempedoic acid plus ezetimibe fixed-dose combination
GP	general practitioner
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
hsCRP	high-sensitivity C-reactive protein
HTN	hypertension
IQR	interquartile range
ITT	intention to treat
IWRS	interactive web-response system
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LMT	lipid-modifying therapy
Lp(a)	lipoprotein(a)

LS	least squares
LY	life-year
MACE	major adverse cardiovascular events
MI	myocardial infarction
mITT	modified intention to treat
NA	not applicable
NCEP ATP-III	National Cholesterol Education Program adult treatment panel III
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit at £30,000 per QALY
NR	not reported
OLE	open-label extension
PBO	placebo
PCSK9	proprotein convertase subtilisin / kexin type 9
PCSK9i	proprotein convertase subtilisin / kexin type 9 inhibitor
PK	pharmacokinetic
PMM	pattern-mixture model
Q2W	every 2 weeks
QALY	quality-adjusted life year
QD	once daily
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	summary of product characteristics
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
THIN	The Health Improvement Network
TIA	transient ischaemic attack
UK	United Kingdom
VLDL	very low-density lipoprotein

1 Executive summary

1.1 Critique of the decision problem in the company's submission

The ERG has several concerns with the way in which the company has addressed the decision problem specified in the NICE final scope and with the clinical data presented for bempedoic acid and fixed dose combination bempedoic acid + ezetimibe (FDC). The NICE final scope specified separate comparators for the following populations:

- **Population 1:** When statins are contraindicated or not tolerated;
- **Population 2:** When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control low-density lipoprotein cholesterol (LDL-C);
- **Population 3:** When maximally tolerated statin dose does not appropriately control LDL-C; and
- **Population 4:** When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C.

The subpopulations addressed in the company submission are those in which the company considers bempedoic acid and/or FDC are likely to be used in clinical practice:

- **Subpopulation 2a:** When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;
- **Subpopulation 2b:** When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;
- **Subpopulation 4a:** When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,
- **Subpopulation 4b:** When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

The ERG considers there to be several issues in the company's approach to the decision problem, and these are detailed below:

- **Population:**
  - Clinical data presented for the intervention, bempedoic acid, that are used in the company's network meta-analyses and economic model are not exclusively in patients who have received prior ezetimibe despite this being the population in which the company is positioning bempedoic acid and FDC. The ERG's clinical

experts support the company view that bempedoic acid or FDC is unlikely to be used prior to ezetimibe although the ERG notes that [redacted]

- The ERG is also concerned by the high levels of clinical and statistical heterogeneity in the company's network meta-analyses (NMAs) and that some of the studies in the analyses may not reflect UK clinical practice.

- **Intervention:**
  - The ERG does not consider there to be suitable data for assessing FDC in patients when maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and notes the only data for bempedoic acid are from the pooled analysis of the *post hoc* subgroup data from CLEAR Harmony and CLEAR Wisdom.
- **Outcomes:**
  - The ERG notes that there are no clinical trial data presented in the company's submission (CS) for bempedoic or FDC for health-related quality of life, lipoprotein a or LDL apheresis.
  - Only 12-week outcome data are presented from the NMAs for the comparisons of bempedoic acid and FDC with the comparators specified in the scope although 24-week and 52-week data are available from some of the bempedoic acid studies.
  - None of the subgroups specified in the final scope (presence or risk of cardiovascular disease, people with heterozygous familial hypercholesterolaemia [HeFH], people with statin intolerance and severity of hypercholesterolaemia) are presented exclusively for the population of patients who have received prior ezetimibe.
  - However, the populations in the economic model include a mixture of both primary and secondary prevention patients and patients with and without HeFH.

1.2 Summary of the key issues in the clinical effectiveness evidence

The company is positioning bempedoic acid and FDC for use in patients after ezetimibe and has conducted two NMAs to address the populations specified in the NICE final scope:

- Patients in whom statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C; and
- Patients in whom maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C.

The ERG considers the key issues in the clinical effectiveness evidence directly relate to these two NMAs and that they are unfit for decision making due to clinical, methodological, and statistical heterogeneity. The ERG considers the key issues in the clinical effectiveness evidence to be:

1. **Clinical studies:**
    - The use of incorrect populations in the NMAs to address the population in whom ezetimibe does not appropriately control LDL-C with studies included that have a mix or even no patients with prior ezetimibe therapy; (Section 3.4.1)
    - Clinical heterogeneity in the studies included in the NMAs which includes differences between studies in terms of baseline cardiovascular risk, statin intensity, proportion of patients receiving lipid lowering therapy (LLT) for primary prevention, and proportions of patients with HeFH; (Section 3.4.1)
    - The company's updated NMAs may be missing studies of relevance; e.g. ODYSSEY Long Term is missing from the maximally tolerated statin NMA and yet the ERG considered it suitable for inclusion in the ERG's NMA. In addition, it appears that there is double counting of patients in the NMA through the use of 12- and 24-week data for some of the alirocumab trials. The ERG notes that alirocumab patients who have received 75 mg and also been uptitrated to 150 mg at 12 weeks may have been included in both the 75 mg and 150mg analyses albeit using data from different timepoints (12 weeks and 24 weeks, respectively) (Section 3.4.2).
2. **Data and analyses:**
    - No subgroup analyses based on primary or secondary prevention (CV risk) or presence of HeFH were conducted by the company despite being specified in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively). In addition, patients from these subgroups are included in the economic model. There is limited information reported in the clinical studies in the NMAs on the proportion of patients who are primary or secondary prevention and who do or don't have HeFH. In the absence of suitable subgroup analyses, the ERG does not consider it appropriate to assume no difference in treatment effect across potentially important subgroups of relevance in the economic model.
    - Data are mostly limited to 12-weeks in the company's NMAs, although treatment is likely to be long-term depending on patient response and tolerance. The ERG considers that there may be a slight waning of treatment effect with bempedoic acid beyond 12-weeks and is unable to comment as to whether similar waning would be seen for the comparators.(Section 3.4.1)
3. **NMA methodology:**

- The ERG was unable to replicate the results obtained from the company's NMAs and is unsure of the reason for this. The ERG also considers the company to have used incorrect methods to adjust for differences in baseline LDL-C in the NMAs which results in issues relating to the reliability of the results (Section 3.4.1).
- In addition, there were high levels of statistical heterogeneity in the results of the company's NMAs despite the inclusion of co-variate adjustment for baseline LDL-C differences and updates to the NMAs during the clarification stage suggesting that the results of the company's NMAs are unreliable:
  - for the company's statin intolerant NMA the I^2 is 66.1%;
  - for the company's maximally tolerated statin NMA the I^2 is 86.6% (Section 3.4.2).

- **ERG NMAs:**
  - The ERG conducted exploratory NMAs with data used only in the population of patients who have received prior ezetimibe and are assumed to continue ezetimibe throughout the study. However, the ERG was unable to include all the appropriate data from the bempedoic acid studies and the ERG's appraisal of studies was limited. As such, the results of the ERG's analyses should be interpreted with caution (Section 3.5).

1.3 Summary of the key issues in the cost effectiveness evidence

The ERG's main concerns are related to the reliability of the clinical effectiveness data on LDL-C used to inform the model; the proportion of primary prevention patients and patients with HeFH entering the model; the starting health state of secondary prevention patients in the model; the appropriateness of external data sources used to inform some baseline characteristics; the assumption that costs are benefits to treat CV events are not affected by the number of previous CV events; and, the costs associated with a CV-related death and ischemic stroke (IS). These issues are discussed in detail below, together with other topics worthy of consideration:

1. **Reliability of the clinical effectiveness data on LDL-C:** Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness for this appraisal. The revised NMAs provided by the company at the clarification stage remain unfit for decision making, principally due to the extent of the clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. To address these issues, the ERG performed additional

NMAs. Although the ERG's estimates are closer to a robust analysis they are still subject to limitations and should be interpreted with caution (Section 4.2.5.3).

An additional and related area of concern is that no subgroup analyses based on CV risk or presence of HeFH were conducted by the company despite being specified in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively). Moreover, given the high proportion of secondary prevention patients without HeFH entering the model, the ERG considers it unreliable to use treatment effectiveness estimates from a wider population with and without these characteristics. For these reasons, the ERG stresses its opinion that cost-effectiveness results by subgroup should be provided by the company in order to reflect the patients entering the model and in order to allow for consistent decision making with previous NICE appraisals (Section 4.2.5.3).

Finally, the ERG notes that the reductions in LDL-C recorded in the CLEAR trials at week 12 are not sustained at week 24 (CLEAR Serenity) or week 52 (CLEAR Harmony and CLEAR Wisdom). Therefore, assuming 12-week results are maintained for the duration of the model's time horizon, or until treatment is discontinued is questionable. The ERG's clinical experts also affirmed that the response at week 12 would be larger than the sustained response. As such, it is the ERG's view that the dataset including the latest outcomes available is the preferred approach to addressing this important area of uncertainty (Section 4.2.5.3).

2. **Proportion of primary prevention patients and patients with HeFH entering the model:** At baseline, over [redacted] of patients in subpopulations 2b, 4a and 4b had had a prior CV event while the majority of patients in subpopulation 2a (around [redacted] had not had a prior CV event. The ERG considers that including a small proportion of primary prevention patients in the subpopulations 2b, 4a and 4b and a small proportion of secondary prevention patients in subpopulation 2a is of limited benefit as it causes unnecessary "noise" (due to the additional complexities required to model primary and secondary prevention patients in the same model) and potentially leads to inappropriate conclusions for the "mixed" cohorts. Furthermore, the company modelled a high proportion of patients without HeFH [redacted] in each subpopulation. For these reasons, the ERG's preference is to adjust the company's "mixed"

cohorts into either a primary prevention cohort without HeFH (subpopulation 2a) or secondary prevention cohort without HeFH (subpopulations 2b, 4a and 4b) (Section 4.2.2.2).

3. **Starting health state of patients receiving secondary prevention:** Secondary prevention patients enter the model in one of the 0 to 1 year-post CV event health states, incurring the costs and benefits for an acute event. The ERG disagrees with this because the prior CV event could have occurred many years prior to entering the model. Moreover, patients with established CV disease in TA393, TA394 and TA385 entered a model in a post-event type health state associated with either "stable" or "established" CV disease. As such, the ERG considers it more appropriate to allocate the secondary prevention cohort to enter the model in the 3-year+ post-event state, associated with post-event costs and benefits, until a new event occurs (Section 4.2.4.1).

4. **Use of external data sources to inform baseline characteristics*:*** As treatment effectiveness data were taken from the CLEAR trials, the ERG considers that CV event history from those trials may be more appropriate to use in the economic analyses. Furthermore, the distribution of prior CV events in secondary prevention patients is a key driver in the model based on the ERG's exploratory analyses. As a result, the ERG stresses its opinion that prior CV event data from the CLEAR trials are made available (Section 4.2.2.2). Similarly, the ERG would prefer the company to enter patient characteristics from the CLEAR trials directly into the QRISK3 risk assessment tool to estimate the baseline risk of CV events in the primary prevention cohort to better reflect the treatment effectiveness data and patients that would be considered for bempedoic acid (Section 4.2.6.6).

5. **Baseline LDL-C in non-PCSK9i eligible subpopulations:** In the non-PCSK9i eligible subpopulations, the ERG found that the company used the baseline LDL-C levels of all patients in the CLEAR trials (population 2: [redacted]; population 4: [redacted]) and that these levels are notably higher than the levels of non-PCSK9i eligible patients in the CLEAR trials (subpopulation 2a: [redacted]; subpopulation 4a: [redacted]). This approach contradicts the company's decision to separate populations according to PCSK9i eligibility using NICE recommendations (Section 4.2.2.2).

6. **Health related quality of life data:** Subpopulations 2b, 4a and 4b are largely representative of secondary prevention patients and therefore the ERG disagrees with the use of the

regression equation used to estimate baseline utility for these populations, given it was derived from a population with no history of CV disease. Furthermore, the ERG notes that the baseline utility multipliers for the specific CV event history for these patients in subpopulations 2b, 4a and 4b, should be those reflective of a post-event because secondary prevention patients enter the model at cycle 0 with a history of CV disease. Additionally, the Ara and Brazier study (the source of utility values and multipliers used in the analysis) provided utility values for patients experiencing multiple events, which should be used to capture the impact of recurrent events in these patients' quality of life.

As for subpopulation 2a, the ERG agrees with the company's approach of using the Ara and Brazier regression derived from people with no history of CV events to estimate baseline utility, however after patients in subpopulation 2a experience their first event, recurrent events should accrue the utilities for multiple events (Section 4.2.9.1). Other key areas of concern include the company's decision to use the Ara and Brazier 1-year angina utility value to inform acute MI events and the lack of use of different time-point utilities for acute and post TIA events (Section 4.2.9.1).

7. **Health state cost data:** The ERG disagrees with combining first and secondary event costs in the model as Danese *et al*. 2017 provides first- and second-event related costs, which is an advantage of the study compared with previous sources of literature used in previous CVD models. Furthermore, clinical experts advising the ERG explained that the costs associated with second events are expected to be higher than costs associated with first events, therefore, given the data are available, costs of primary and secondary events should be estimated separately in the model (Section 4.2.10.6). The ERG also disagrees with the use of incremental costs for CV deaths as these result in a cost-saving event in the model, therefore benefiting the treatments associated with higher rates of CV deaths (Section 4.2.10.6). Furthermore, the ERG is unclear why the company used IS health state costs from CG181 that were similar to those criticised by the ERG in TA393, and not the costs that were proposed by the ERG in TA393 (Section 4.2.10.6).

8. **Comparator costs:** The clinical experts advising the ERG explained that patients on alirocumab and evelocumab are managed in a hospital setting and so would incur an annual cost of a hospital consultant visit. These costs were not included by the company or in previous related TAs, however, given the clear direction from the ERG's clinical experts, the ERG considers them important to include in the analyses (Section 4.2.10.4).

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The company's revised base case results are given in Table 1. The ERG's preferred assumptions for the cost-effectiveness analysis of bempedoic acid are outlined in Table 2 and the deterministic and probabilistic ICERs resulting from the ERG's preferred assumptions are given in Table 3. However, the ERG recommends that the cost-effectiveness results based on the ERG's NMAs on the percentage change in LDL-C from baseline are interpreted with caution. Due to time and resource constraints the ERG has been unable to fully assess all potentially relevant studies for inclusion in the networks and additionally not had access to the relevant subgroup data from the bempedoic acid studies. The ERG also notes that all patients in the ERG's NMA received ezetimibe; hence, all treatments assessed in the economic analyses are in addition to ezetimibe. Furthermore, no evidence on evolocumab was identified by the ERG in order to include this treatment as a comparator.

Table 1. Company's revised base case results

Treatment	Total cost	Total QALYs	Pairwise ICER (BA vs comparator)
Subpopulation 2a			
BA/EZE FDC	£14,125	8.71	-
EZE	£8,278	8.51	£28,521
Subpopulation 2b			
BA/EZE FDC	£18,642	6.86	-
AliMab	£41,337	6.93	£342,008
Evolocumab	£41,776	6.96	£236,401
Subpopulation 4a			
BA/EZE FDC	£18,110	6.89	-
EZE	£12,690	6.81	£69,452
Subpopulation 4b			
BA/EZE FDC	£18,089	6.48	-
AliMab	£40,289	6.72	£94,488
AliMab+EZE	£40,297	6.67	£121,686
Evolocumab	£41,126	6.89	£56,285

Abbreviations: AliMab, alirocumab; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years;
Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;
Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;
Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,
Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

Table 2. ERG's preferred assumptions for the economic analyses

#	Scenario	Section in ERG report	Subpopulation			
			2a	2b	4a	4b
0	Using a starting cohort of primary prevention patients without HeFH	Section 4.2.4.1	X			
0	Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	Section 4.2.4.1		X	X	X
1	Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe	Section 4.2.5.3	X	X	X	X
2	Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment	Section 4.2.2.2	X		X	
8	Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al*. 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	Table 24 in Section 4.2.9.1		X	X	X
9	Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • After patients in subpopulation 2a experience their first event, recurrent events accrue the utilities for multiple events reported in Table 24.	Table 25 in Section 4.2.9.1	X			
10	Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors	Section 4.2.10.2		X		X
11	Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	Section 4.2.10.6	X	X	X	X

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;
Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;
Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,
Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

Table 3. ERG's preferred base case ICERs, deterministic and probabilistic results

Subpopulation	Treatment	Total costs	Total QALYs	ICER
2a	Deterministic			
	EZE	£9,591	9.06	-
	BA/EZE FDC	£15,319	9.25	£29,856
	Probabilistic			
	EZE	£9,664	9.16	-
	BA/EZE FDC	£15,429	9.35	£30,218
2b	Deterministic			
	BA/EZE FDC	£23,204	12.29	-
	Ali + EZE	£48,247	12.56	£93,455
	Probabilistic			
	BA/EZE FDC	NC	NC	-
	Ali + EZE	NC	NC	NC
4a	Deterministic			
	EZE + statin	£16,731	9.05	-
	BA/EZE FDC	£22,352	9.14	£75,437
	Probabilistic			
	EZE + statin	£16,805	9.04	-
	BA/EZE FDC	£22,441	9.12	£73,723
4b	Deterministic			
	BA/EZE FDC	£22,296	8.69	
	Ali + EZE + statin	£46,869	9.15	£54,250
	Probabilistic			
	BA/EZE FDC	£22,394	8.71	-
	Ali + EZE + statin	£46,193	9.12	£58,929

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; EZE, ezetimibe; fixed dose combination; ICER, incremental cost-effectiveness ratio; NC, not calculable; QALYs, quality-adjusted life years
Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;
Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;
Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,
Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

2 Introduction and background

2.1 Introduction

The company submitted clinical and economic evidence to the National Institute for Health and Care Excellence (NICE) in support of bempedoic acid as a monotherapy and in a fixed dose combination (FDC) with ezetimibe for primary hypercholesterolemia (HC) and mixed dyslipidaemia. The company propose that bempedoic acid, alone or in the fixed dose combination with ezetimibe, will be used in two positions in the treatment pathway:

- When statins are contraindicated or not tolerated, and ezetimibe monotherapy does not appropriately control low-density lipoprotein cholesterol (LDL-C);
- When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C.

2.2 Background

In section B.1.3 of the company's submission (CS), the company provides an overview of the health condition (including the measurement of CV risk, disease burden, and epidemiology), current management recommended in UK and other guidelines, and the proposed position of the technology in the treatment pathway. The ERG considers the information provided by the company to be satisfactory but highlights several points raised by clinical experts in relation to the approach taken by the company in the text below.

The ERG's clinical experts were generally happy with the pathway put forward by the company, which indicates that statins are the preferred treatment for primary HC or mixed dyslipidaemia, followed by the addition of ezetimibe where required, and a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) inhibitor for patients meeting criteria set out in TA393 (alirocumab) and TA394 (evolocumab).[1, 2] The experts explained that a number of tools are used for estimating CV risk in primary care (e.g. QRISK3 and JBS-3), but they were happy with the overview provided by the company and the categories outlined in Table 4 of the CS. The ERG notes that the pathway covers patients at high risk of CV disease which includes, but is not limited to, people with primary HC and mixed dyslipidaemia (Figure 1). The clinical experts stressed that heterozygous familial HC (HeFH), non-familial HC and mixed dyslipidaemia each have distinct lipid profiles which may require different types and levels of treatment, and a common treatment effect (for LDL-C, non-HDL-C and CV outcomes) should not be assumed across them.

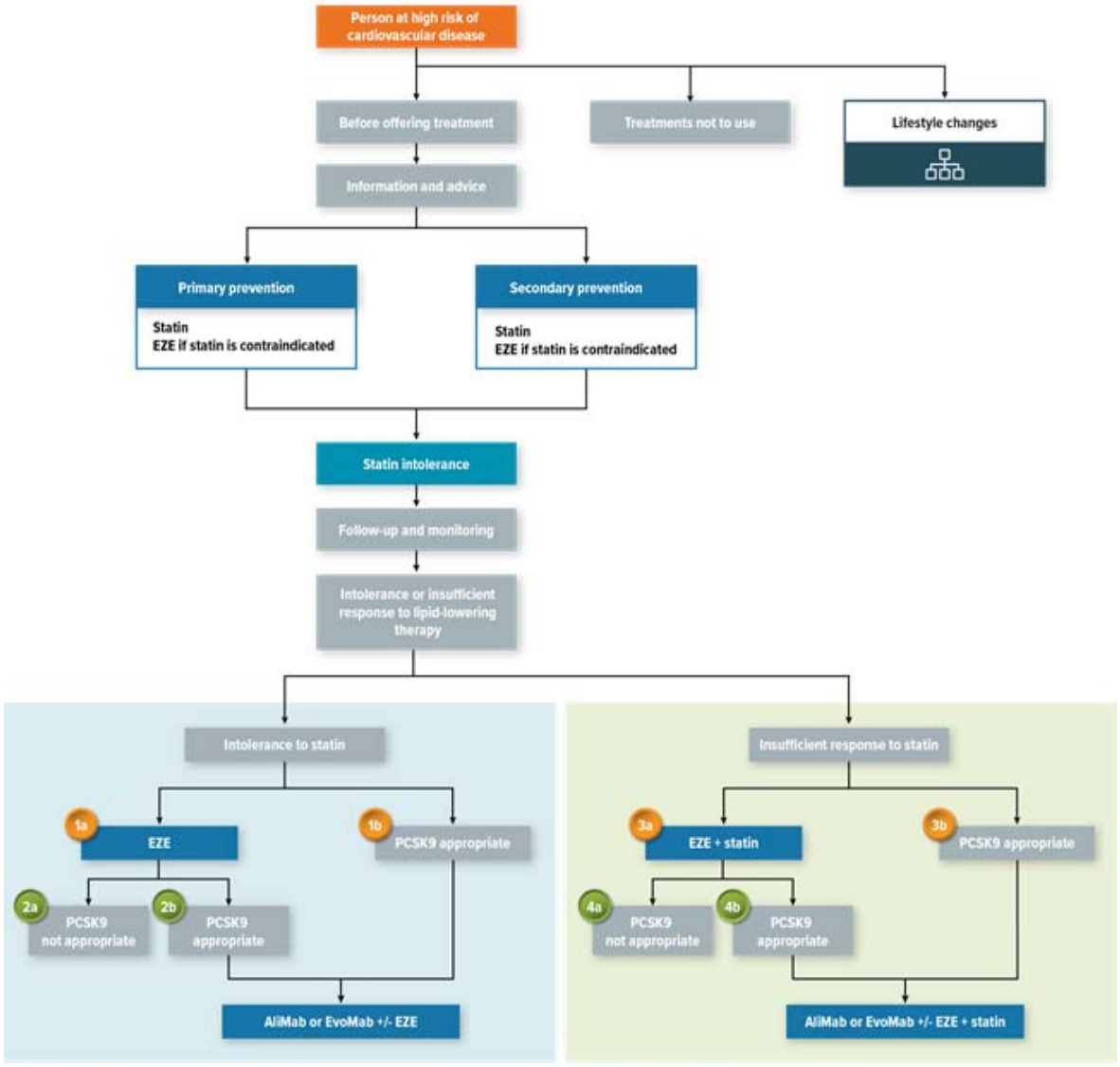
The company outlined the considerable disease burden associated with elevated LDL-C and gave an overview of the evidence base underpinning the association between LDL-C and risk of CV events (CS

Section B.1.3.1.1), which informs much of the cost-effectiveness analysis. In the absence of evidence for long-term CV outcomes with bempedoic acid or FDC, the ERG sought validation from clinical experts about the predictive nature of LDL-C. The experts advised that LDL-C is a common primary outcome in trials of cholesterol-lowering drugs and remains important in clinical practice, but clinical decision-making in terms of the treatment pathway for individual patients in the UK may also be driven by non-high-density lipoprotein cholesterol (non-HDL-C) levels.

In terms of eligibility for bempedoic acid, the ERG's clinical experts reported that the proportion of patients who cannot receive statins due to intolerance or contraindication may be higher than the 15% proposed by the company.[3, 4] The proportion who may be eligible for treatment because they are insufficiently controlled on statins may also be higher than the 29% proposed by the company,[5] but depends on the threshold used to gauge control. The ERG's clinical experts explained that some studies suggest up to 30% of patients receiving statins have a level of intolerance due to muscle symptoms and only a small proportion of patients reach guideline-defined LDL-C reduction targets through lifestyle changes and the use of statins.[6, 7]

The ERG heard from its clinical experts that, should bempedoic acid be recommended for primary HC and mixed dyslipidaemia, clinicians will most likely want to use it in addition to ezetimibe unless ezetimibe is contraindicated or not tolerated. The ERG's clinical experts expect ezetimibe to remain the treatment of choice when statins are contraindicated, not tolerated, or provide insufficient control, because CV benefit and clinical experience with ezetimibe is well established. The clinical experts added that bempedoic acid may be considered a viable alternative to ezetimibe if it is shown to have additional benefits beyond LDL-C such as lowering triglycerides for those with mixed dyslipidaemia or improving insulin resistance in those with comorbidities such as diabetes mellitus. The ERG's clinical experts' views corroborate the company's positioning of the technology for patients who remain uncontrolled on statins (where indicated and tolerated) and ezetimibe. The ERG notes that bempedoic acid could also potentially be considered for use after PCSK9i's although there are likely no or extremely limited clinical data from the bempedoic acid or FDC clinical trials to support this positioning.

Figure 1. NICE pathway and recommendations and the company's proposed placement of bempedoic acid and FDC (reproduced from CS, Figure 3)



Position	Background therapy	Intervention	Phase 3 trial evidence for BA / FDC
1	None	BA	CLEAR Serenity (1002-046)
		FDC	Position not clinically relevant
2	Ezetimibe	BA	CLEAR Tranquility (1002-048)
		FDC[a]	CLEAR Tranquility (1002-048) [SE]
3	Maximally tolerated stain	BA	CLEAR Harmony (1002-040); CLEAR Wisdom (1002-047)
		FDC	Position not clinically relevant
4	Maximally tolerated stain and ezetimibe	BA	CLEAR Harmony (1002-040); CLEAR Wisdom (1002-047); 1002FDC-053
		FDC[a]	1002FDC-053

Abbreviations: AliMab, alirocumab; EvoMab, evolocumab; EZE, ezetimibe; FDC, bempedoic acid and ezetimibe fixed-dose combination; NICE, National Institute for Health and Care Excellence; PCSK9, proprotein convertase subtilisin/kexin type 9.

2.3 Critique of the company's definition of the decision problem

Table 4. Summary of decision problem (adapted from Table 1, CS pages 14–16)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	Patients with primary hypercholesterolaemia or mixed dyslipidaemia	Patients with primary hypercholesterolaemia or mixed dyslipidaemia	NA	The ERG's clinical experts reported that the majority of patients in clinical practice don't have mixed dyslipidaemia, and that primary hypercholesterolaemia will include patients with HeFH. The ERG notes that the comparators in the NICE final scope are split based on population in terms of prior ezetimibe therapy. The ERG critique on this is therefore presented in the comparator critique row below.
Intervention	Bempedoic acid, alone or with a statin, with or without other lipid-lowering therapy Bempedoic acid in a fixed-dose combination (FDC) with ezetimibe, alone or with a statin	Bempedoic acid alone or with a statin, with or without other lipid-lowering therapy Bempedoic acid in a fixed-dose combination (FDC) with ezetimibe, alone or with a statin	NA	Appropriate. However, the details of the concomitant statin and lipid lowering therapy used in the bempedoic acid and FDC studies is limited.
Comparator(s)	When statins are contraindicated or not tolerated: •Ezetimibe •Evolocumab (with or without another lipid-lowering therapy) •Alirocumab (with or without another lipid-lowering therapy) When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C:	When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C: •No additional treatment on background ezetimibe (when evolocumab and alirocumab are not appropriate) •Evolocumab (with or without another lipid-lowering therapy) •Alirocumab (with or without another lipid-lowering therapy)	Comparisons are only presented when ezetimibe does not appropriately control LDL-C, because bempedoic acid and FDC are not expected to be used prior to ezetimibe in the treatment pathway. The comparator when ezetimibe does not appropriately control LDL-C and when evolocumab and alirocumab are not	The ERG's clinical experts support the company view that bempedoic acid or FDC is unlikely to be used prior to ezetimibe although the ERG notes that [redacted] The ERG's clinical experts agree with the comparators specified in the NICE final scope for the prior ezetimibe populations [redacted] The ERG is however concerned by the high levels of clinical and statistical heterogeneity in the company's NMAs

	•Ezetimibe (when evolocumab and alirocumab are not appropriate) •Evolocumab (with or without another lipid-lowering therapy) •Alirocumab (with or without another lipid-lowering therapy) When maximally tolerated statin, dose does not appropriately control LDL-C: •Ezetimibe with a statin •Evolocumab with a statin (with or without another lipid-lowering therapy) •Alirocumab with a statin (with or without another lipid-lowering therapy) When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: •Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate) •Evolocumab with a statin (with or without another lipid-lowering therapy) •Alirocumab with a statin (with or without another lipid-lowering therapy)	When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: •No additional treatment on background ezetimibe and statin (when evolocumab and alirocumab are not appropriate) •Evolocumab with a statin (with or without another lipid-lowering therapy) •Alirocumab with a statin (with or without another lipid-lowering therapy)	appropriate has been clarified as "no additional treatment on background ezetimibe," as patients are already receiving ezetimibe.	and that some of the studies in the analyses may not reflect UK clinical practice. The ERG is also concerned that the only data suitable for assessing bempedoic acid or FDC when statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C is from CLEAR Tranquility and limited to patients who had received 4-weeks prior ezetimibe or the pooled analysis of the *post hoc* subgroups in CLEAR Serenity and CLEAR Tranquility. The ERG does not consider there to be suitable data for assessing FDC in patients when maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and notes the only data for bempedoic acid are from the pooled analysis of the *post hoc* subgroup data from CLEAR Harmony and CLEAR Wisdom.
Outcomes	The outcome measures to be considered include: •Plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, apolipoprotein B, and lipoprotein A •Requirement of procedures including LDL apheresis and revascularisation	The outcome measures to be considered include: •Plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, apolipoprotein B, lipoprotein A, and total cholesterol	hsCRP was included as a secondary endpoint in the Phase 3 clinical trial programme for bempedoic acid and FDC with ezetimibe. hsCRP is an inflammatory marker associated with increased cardiovascular risk and is presented as supporting scientific evidence of	The ERG's clinical experts reported that LDL-C and non-HDL-C are the key biochemical markers of relevance and that hsCRP is of limited value. The ERG notes hsCRP was not an outcome specified in the NICE final scope and therefore does not discuss these results.

	•Fatal and non-fatal cardiovascular events •Mortality •Adverse effects of treatment •Health-related quality of life	•Inflammatory marker high-sensitivity C-reactive protein (hsCRP) •Requirement of procedures including LDL apheresis and revascularisation •Fatal and non-fatal cardiovascular events •Mortality •Adverse effects of treatment •Health-related quality of life	a biological effect (it is not used in the economic evaluation). Total cholesterol and triglycerides are lipid endpoints included in clinical guidelines ([8]), often reported in trials and included in the bempedoic acid trials. Lipoprotein a and apheresis data were not reported in the bempedoic acid or bempedoic acid + ezetimibe FDC trials.	The ERG also notes that no data on health-related quality of life with bempedoic acid or FDC were collected in the clinical trials presented in the review of clinical effectiveness. The only outcome considered in the company's NMAs was mean percentage change in LDL-C from baseline to 12-weeks. The ERG considers that later time-points should also have been explored in NMAs as there were some data from the bempedoic acid trials at 24 weeks and 52 weeks.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per scope	NA	NA

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: •Presence or risk of cardiovascular disease •People with heterozygous familial hypercholesterolaemia •People with statin intolerance •Severity of hypercholesterolaemia	Where the evidence allows, the following subgroups will be considered: •Presence or risk of cardiovascular disease •Patients with heterozygous familial hypercholesterolemia •Patients with statin intolerance •Severity of hypercholesterolaemia	NA	Some relevant subgroup data are presented individually and from pooled analyses of the bempedoic acid and/or FDC trials compared with placebo (or ezetimibe) or each other but no subgroup data are presented from the NMAs to enable comparison with the wider range of comparators specified in the NICE final scope.
Special considerations, including issues related to equity or equality	Guidance will be issued only in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Evidence is presented for treatment combinations in accordance with the anticipated wording of the marketing authorisation.	NA	NA

Abbreviations: AliMab, alirocumab; CVD, cardiovascular disease; EvoMab, evolocumab; FDC, bempedoic acid and ezetimibe fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

2.3.1 Population

Clinical effectiveness data in the CS for bempedoic acid are derived from four Phase 3 studies and two Phase 2 studies (CLEAR Harmony[9], CLEAR Wisdom[10], CLEAR Serenity[11], CLEAR Tranquility[12], and Study 1002-008[13], Study 1002-009[14], respectively) and clinical effectiveness data for bempedoic acid in a fixed dose combination with ezetimibe (FDC) are derived from study 1002FDC-053.[15] In addition, the company conducted two network meta-analyses (NMAs), one in patients in whom statins are contraindicated or not tolerated (statin intolerant NMA) and the other in patients in whom maximally tolerated statin dose does not appropriately control LDL-C (maximally tolerated statin NMA), both were populations specified alongside comparators in the NICE final scope. However, the NMAs were both associated with high levels of clinical and statistical heterogeneity even after adjustments made by the company in response to clarification questions. The ERG is therefore concerned about the suitability of the NMAs for decision making and addressing the NICE final scope. These concerns are discussed further in Section 3.4.

The population specified in the NICE final scope was people with primary hypercholesterolaemia or mixed dyslipidaemia. The ERG notes that the company reported in their factual accuracy response that all patients enrolled across the included bempedoic acid and FDC studies restricted enrolment to patients with primary hypercholesterolaemia and/or mixed dyslipidaemia. The ERG also notes that there was variation in the inclusion criteria between the included bempedoic acid and FDC studies beyond populations in whom statins are contraindicated or not tolerated and populations in whom maximally tolerated statin dose does not appropriately control LDL-C. A large proportion of patients across the studies were deemed to be at high cardiovascular (CV) risk and while it is unclear how many patients had heterozygous familial hypercholesterolaemia (HeFH) in each of the studies, some patients with HeFH (< 6%) were known to be enrolled in CLEAR Harmony and CLEAR Serenity. CLEAR Harmony and CLEAR Wisdom only recruited patients with high CV risk as patients were required to have ASCVD or HeFH (with or without ASCVD) at enrolment. Patients in CLEAR Tranquility were excluded if they had a history in the previous 12 months of clinically significant cardiovascular disease whereas in CLEAR Harmony, CLEAR Wisdom and CLEAR Serenity only patients with acute CV events such as MI or revascularisation in the 90 days prior to enrolment were excluded. The minimum LDL-C baseline threshold for study inclusion also varied between studies from ≥ 70 mg/dL to ≥ 130 mg/dL although LDL-C was included as a covariate in the NMAs. In addition to the variation among the bempedoic acid and FDC study populations, the ERG notes there was substantial clinical heterogeneity in the company's NMAs due to variation in the populations of the included studies. The ERG considers that these population differences in the studies in the

company's NMAs is likely to be contributing to the high levels of statistical heterogeneity seen in the NMAs and that the NMA results are thus subject to high levels of uncertainty.

The anticipated marketing authorisation for bempedoic acid is in [redacted]

The two Phase 2 bempedoic acid studies (1002-008[13] and 1002-009) and Study 1002FDC-053 were USA based studies and CLEAR Serenity was based in North America (USA and Canada). The three remaining Phase 3 studies included sites in Europe in addition to Canada and the USA, although it is unclear exactly how many patients were enrolled from UK sites. The ERG notes that the majority of patients enrolled in the bempedoic acid and FDC studies were white and the ERG's clinical experts reported that it is likely that the UK population would have a higher ethnic diversity. The background lipid modifying therapies received by patients in the clinical trials was also wider than that expected in the UK. However, in general the ERG's clinical experts consider the bempedoic acid and FDC trial populations largely representative of people in England eligible for bempedoic acid and FDC.

The subgroups of interest specified in the NICE final scope were presence or risk of CV disease, HeFH, statin intolerance and severity of hypercholesterolaemia. The ERG does not consider any of these subgroups to have been explored by the company in relation to any of the comparators specified in the NICE final scope. The ERG notes that some subgroup analyses for change in LDL-C were presented for the individual bempedoic acid and FDC trials (CS Section 2.7) but does not consider these suitable for drawing conclusions due to the small patient numbers in many of the subgroups. The results of these subgroup analyses are summarised in Section 3.3.2.

2.3.2 Intervention

Bempedoic acid (ETC-1002) is an oral, once daily, first-in-class cholesterol synthesis inhibitor. The brand name for bempedoic acid (ETC-1002) is [redacted] and it is administered as a 180 mg tablet. Bempedoic acid 180 mg is also available in a fixed dose combination tablet with 10 mg of ezetimibe (FDC) with the brand name [redacted]

Bempedoic acid is an adenosine triphosphate (ATP) citrate lyase (ACL) inhibitor that lowers LDL-C by reducing cholesterol biosynthesis and up-regulating the LDL receptor. Bempedoic acid requires coenzyme A activation by very long-chain ACSVL1 and this is primarily expressed in the liver. Bempedoic acid is inactive in skeletal muscle unlike statins but both bempedoic acid and statins work to inhibit cholesterol synthesis in the liver.

Ezetimibe is an NPC1L1 (sterol transporter) inhibitor, which inhibits gastrointestinal cholesterol absorption and upregulates LDL receptors. The FDC tablet contains 180 mg bempedoic acid and 10 mg ezetimibe, with bempedoic acid lowering LDL-C via inhibition of cholesterol synthesis, and ezetimibe via inhibition of cholesterol absorption in the intestine.

Bempedoic acid and FDC do not currently hold marketing authorisation approval from the European Medicines Agency (EMA) although CHMP positive opinion is anticipated in [redacted] and regulatory approval expected to be in [redacted]

The anticipated indication for bempedoic acid is in [redacted]

- [redacted]
- [redacted]

The anticipated indication for FDC is in [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The company uses data from studies of bempedoic acid + ezetimibe in separate tablets to demonstrate the efficacy of FDC in addition to the single tablet 1002FDC-053 study and provided data from pharmacokinetic studies to demonstrate bioequivalence (CS, Appendix M). The ERG acknowledges that the pharmacokinetic studies show some difference between the formulations (ezetimibe glucuronide and ezetimibe C_{max} was approximately [redacted] and [redacted] lower, respectively, for the FDC monolayer or FDC bilayer formulation relative to the individual tablets co-administered in study 1002FDC-034) but notes that the company does not consider these of clinical significance. The ERG's clinical experts reported that they would not expect separate single tablets to perform differently to a dual combination tablet.

2.3.3 Comparators

The comparators in the bempedoic acid and FDC studies included placebo tablets and ezetimibe alone. The NICE final scope specified separate comparators for patients dependent on their prior therapies as follows:

When statins are contraindicated or not tolerated (population 1):

- Ezetimibe;
- Evolocumab (with or without another lipid-lowering therapy);
- Alirocumab (with or without another lipid-lowering therapy).

When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C (population 2):

- Ezetimibe (when evolocumab and alirocumab are not appropriate);
- Evolocumab (with or without another lipid-lowering therapy);
- Alirocumab (with or without another lipid-lowering therapy).

When maximally tolerated statin, dose does not appropriately control LDL-C (population 3):

- Ezetimibe with a statin;
- Evolocumab with a statin (with or without another lipid-lowering therapy);
- Alirocumab with a statin (with or without another lipid-lowering therapy).

When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C (population 4):

- Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate);
- Evolocumab with a statin (with or without another lipid-lowering therapy);
- Alirocumab with a statin (with or without another lipid-lowering therapy).

The company reported in the CS and in their response to clarification questions that they did not anticipate bempedoic acid would be used prior to ezetimibe in the treatment pathway in the National Health Service (NHS) setting and therefore they presented cost-effectiveness results only for populations 2 and 4. The ERG notes that the CLEAR Harmony and CLEAR Wisdom trials provide clinical effectiveness data for bempedoic acid alone for population 3 but less than 10% of patients were on background ezetimibe at baseline and so they provide limited evidence for bempedoic acid in population 4. The company provides data from a pooled analysis of the patients on background ezetimibe in CLEAR Harmony and CLEAR Wisdom to support their argument that background ezetimibe does not influence the results; the pooled analysis is discussed is discussed in Section 3.2.3.2. The company considers the results from the full population of the bempedoic acid trials where there is a mix of patients who have and have not received prior ezetimibe at baseline

(population 3 and 4) are representative of the efficacy of bempedoic acid in the population of patients who have received prior ezetimibe (population 4). However, the ERG does not consider this to be a reliable conclusion based on the results of the pooled analyses discussed in Section 3.2.3.2.

In terms of populations 1 and 2, the ERG considers that CLEAR Serenity provides data for bempedoic acid in population 1 as less than 15% of patients were receiving background ezetimibe. The ERG notes that in CLEAR Tranquility all patients received background ezetimibe although it was possibly only during the 4-week run-in period prior to commencing bempedoic acid. Nevertheless, the ERG considers CLEAR Tranquility to provide the most robust evidence for bempedoic acid in population 2. The ERG also notes that the company provides data from a pooled analysis of the patients on background ezetimibe in CLEAR Tranquility and CLEAR Serenity to substantiate their assertion that background ezetimibe does not influence the results; the pooled analysis is discussed in Section 3.2.3.2. The company therefore considers the results from the full population of the bempedoic acid trials, where there is a mix of patients who have and have not received prior ezetimibe at baseline (population 1 and 2), are representative of the efficacy of bempedoic acid in the population of patients who have received prior ezetimibe (population 2). However, the ERG does not consider this to be a reliable conclusion based on the results of the pooled analyses discussed in Section 3.2.3.2.

With regards to FDC, the company reported in their clarification question response [redacted] The ERG notes that the FDC trial provides clinical data for FDC in patients on maximally tolerated statin although over 30% of patients were on no statin at baseline. The ERG also notes that no patients in the FDC trial were on ezetimibe at baseline and in the clarification response, the company reported that ezetimibe use within 5 weeks prior to baseline screening was an exclusion criterion. The ERG therefore considers the FDC trial comprises of a mixture of patients relevant to populations 1 and 3 but has concerns about extrapolating the data to population 4, which the company has done in the cost-effectiveness analysis. The company also presents data from two Phase 2 studies, one in patients where statins are contraindicated or not tolerated (Study 1002-008) and the other in patients where maximally tolerated statin dose does not appropriately control LDL-C (1002-009). The ERG notes from the publications of Study 1002-008 and Study 1002-009 that patients on prior ezetimibe would have been subject to a wash-out period of at least 5 weeks prior to randomisation and therefore considers that these studies only provide data for populations 1 and 3, respectively.

The company presented data for bempedoic acid and FDC versus ezetimibe, alirocumab and evolocumab from two network meta-analyses (NMAs):

- When statins are contraindicated or not tolerated;

- When maximally tolerated statin, dose does not appropriately control LDL-C.

The ERG notes that alirocumab 75 mg was considered as a separate treatment in the NMAs to alirocumab 150 mg. However, the ERG notes that for the 150 mg alirocumab dose some studies have been included in each of the NMAs to provide data for the 75 mg dose at 12-weeks and also 24-week data for 150 mg which originates from the 75 mg trial arm where patients could have been up titrated to 150 mg at 12 weeks. The ERG notes that the 24-week data uses the same baseline LDL-C values and thus considers it likely to be double-counting the 75mg patients by using a later data point to inform 150 mg. Additionally, it is unclear whether all patients in the 24-week data cut received the 150 mg dose of alirocumab and so potentially the efficacy of 150 mg is underestimated. The ERG also notes that the placebo arm in these studies also appears to be double counted by using 12 week and 24-week data, and is unclear why the 24-week data was included in the NMAs. The ERG also notes that alternative dosing schedules for evolocumab, namely 140 mg every two weeks (Q2W) and 420 mg once monthly (QM), were combined in the NMA as a single intervention. The company cited a review by Toth *et al.*2017[16] as justification and providing evidence of similar efficacy for the 140 mg Q2W and 420 mg QM evolocumab doses. The ERG does not consider the Toth review robust evidence for this assumption and highlights that existing NICE guidance does not recommend the use of the 420 mg dose. The ERG therefore suggested the company remove the data on the 420mg dose of evolocumab from the NMA in the clarification question stage and the ERG acknowledges that these doses were removed from the company's revised NMA's.

2.3.4 Outcomes

The ERG and its clinical experts consider the key measures of clinical relevance listed in the NICE final scope were captured and reported in the bempedoic acid and FDC studies although not all outcomes in the scope were captured in the trials. Of note, lipoprotein a, requirement for LDL apheresis and health-related quality of life (HRQoL) were not captured in either the bempedoic acid or FDC studies. Data on revascularisation and non-fatal cardiovascular events were only available for bempedoic acid from the CLEAR studies and no data were available for FDC. The ERG notes that reporting of safety data for FDC in the CS was limited compared with safety data for bempedoic acid alone. The ERG also notes that the only clinical trial data from the bempedoic acid and FDC trials used in the company's NMAs and economic model were change in LDL-C. The ERG also notes that data on clinical outcomes such as fatal and non-fatal cardiovascular events and mortality are limited by the low event rates and short follow-up in the clinical trials.

3 Clinical effectiveness

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia. The Evidence Review Group (ERG) has critiqued the details provided on:

- methods implemented to identify, screen and data extract relevant evidence;
- clinical efficacy of bempedoic acid and bempedoic acid in a fixed dose combination with ezetimibe (FDC);
- safety profile of bempedoic acid and FDC;
- assessment of comparative clinical effectiveness of bempedoic acid and FDC against relevant comparators.

A detailed description of an aspect of the company submission (CS) is provided only when the ERG disagrees with the company's assessment or proposal, or where the ERG has identified a potential area of concern that the ERG considers necessary to highlight to the Committee.

3.1 Critique of the literature review methods

The company conducted a systematic literature review (SLR) in May 2019 to identify efficacy and safety studies of bempedoic acid or FDC and comparator treatments for patients with primary hypercholesterolaemia or mixed dyslipidaemia when optimised lipid-lowering therapy including statins does not appropriately control LDL-C or when statins are contraindicated or not tolerated.

The clinical studies investigating bempedoic acid and FDC identified in the SLR as relevant for the NICE decision problem and that met the inclusion criteria for inclusion in the CS comprised of five Phase 3 studies (CLEAR Harmony[9], CLEAR Wisdom[10], CLEAR Serenity[11], CLEAR Tranquility[12] and Study 1002FDC-053[15]) and two Phase 2 studies (1002-008[13] and 1002-009[14]). The ERG notes that eight Phase 2 studies were excluded from the NMAs used in the economic model and seven of these were excluded due to not having 12-week outcome data for change in LDL-C and the eighth study was excluded as it investigated non-standard doses of bempedoic acid (doses < 180 mg). The company also reported that the excluded Phase 2 studies had small sample sizes ranging from 52 to 68 patients and so they did not expect them to have much influence had they been included in the meta-analyses. The ERG agrees with the exclusion of the Phase 2 studies of bempedoic acid investigating doses less than 180mg but considers studies with outcome data at timepoints other than 12 weeks should have been included and considered further for potential inclusion in the NMAs informing the economic model.

The company also highlighted that there was an ongoing open label extension (OLE) study (CLEAR-OLE [1002-050]) for safety that had enrolled patients who received bempedoic acid 180 mg QD for 78 weeks after completion of the 52-week CLEAR-HARMONY study. The OLE study was expected to report in [redacted]. In addition, a further Phase 3 global, CV outcomes trial is ongoing (CLEAR CVOT, 1002-043) to investigate bempedoic acid compared with placebo in patients with, or at high risk of, CVD who are statin intolerant. The CLEAR CVOT study is expected to report in [redacted].

Table 5 provides a summary of the included studies that provide clinical effectiveness data for bempedoic acid and/or FDC. Included studies investigating only comparator interventions (i.e. not bempedoic acid or FDC) that were used in the NMAs are detailed in Appendix 9.3.

Table 5. Summary of included trials providing clinical efficacy and safety evidence for bempedoic acid and/or FDC of bempedoic acid with ezetimibe (adapted from CS document B, Tables 9 and 10).

	Phase 3 Bempedoic acid trials				FDC trial	Phase 2 trials	
Study	**CLEAR Harmony 1002-040 (Ray *et al.* 2019b)**	**CLEAR Wisdom 1002-047 (Goldberg *et al.* 2019)**	**CLEAR Serenity 1002-046 (Laufs *et al.* 2019)**	**CLEAR Tranquility 1002-048 (Ballantyne *et al.* 2018)**	**1002FDC-053 (Ballantyne *et al.* 2019a)**	**1002-009 (Ballantyne *et al.* 2016)**	**1002-008 (Thompson *et al.* 2016)**
Study design	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Population	Adults with ASCVD, HeFH, or both	Adults at high CV risk due to ASCVD, HeFH, or both	Adults with hypercholesterolaemia and a history of intolerance to at least 2 statins	Adults with a history of statin intolerance who require additional LDL-C lowering	Adults at high CV risk due to ASCVD, HeFH, or multiple CVD risk factors	Hypercholesterol-aemia	Hypercholesterol-aemia +/- statin-related muscle symptoms
Background therapy	LMT including moderate-/high-intensity statin, ezetimibe, or fibrate	LMT including moderate-/high-intensity statin, cholesterol absorption inhibitors, bile acid sequestrants, fibrates, proprotein convertase subtilisin/kexin type 9 inhibitors, or niacin, either alone or in combination	LMT including no/low-dose statin or non-statin	LMT including no/ low-dose statin, fibrate, nicotinic acid, bile acid sequestrant, fish oil, eicosapentaenoic acid ethyl ester, omega-3 fatty acids, salmon oil, or sitosterol	No/moderate-/high-intensity statin	Low-/moderate-intensity statin	No statin
Intervention(s)	Bempedoic acid	Bempedoic acid	Bempedoic acid	Bempedoic acid with background ezetimibe (separate pills)	Bempedoic acid and ezetimibe FDC	Bempedoic acid 120 or 180 mg + statin	Bempedoic acid or bempedoic acid + ezetimibe
Comparator(s)	Placebo	Placebo	Placebo	Placebo with background ezetimibe	Bempedoic acid, ezetimibe, placebo	PBO + statin	Ezetimibe
Trial supports marketing authorisation application	Yes, for bempedoic acid	Yes, for bempedoic acid	Yes, for bempedoic acid	Yes, for bempedoic acid and FDC	Yes, for bempedoic acid+ezetimibe FDC	Yes	Yes
Trial used in the economic model	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Rationale for use/non-use in the model	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Efficacy in LDL-C reduction at 12 weeks	Bempedoic acid 180 mg was investigated at 12 weeks in patients receiving statin therapy	Bempedoic acid 180 mg was investigated at 12-weeks in statin-intolerant patients (subgroup)
Reported outcomes specified in the decision problem	% change LDL-C, non–HDL-C, TC, apo B, adverse effects	% change LDL-C, non–HDL-C, TC, apo B, adverse effects	% change LDL-C, non–HDL-C, TC, apo B, adverse effects	% change LDL-C, non–HDL-C, TC, apo B, adverse effects	% change LDL-C, non–HDL-C, TC, apo B, adverse effects	% change in LDL-C, non–HDL-C, apo B, AEs	% change in LDL-C, non–HDL-C, apo B

Abbreviations: AE, adverse events; Apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; Atorva, atorvastatin; CSR, clinical study report; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiograms; FDC, bempedoic acid and ezetimibe fixed-dose combination; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; Lp(a), lipoprotein (a); NCEP ATP-III, National Cholesterol Education Program Adult Treatment Panel III; PCSK9, proprotein convertase subtilisin kexin type 9; PBO, placebo; PK, pharmacokinetics; RCT, randomised controlled trial; SBP, systolic blood pressure; TC, total cholesterol; TEAE, treatment-emergent adverse event; TG, triglyceride; T2DM, type 2 diabetes mellitus; VLD, very low dose; VLDL, very low-density lipoprotein.

Overall, the ERG found the company's SLR to be of reasonable quality and likely to have identified all relevant studies; a summary of the ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem is presented in Table 6.

Table 6. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D.1.1 (pages 3–11)	Appropriate, but the ERG notes the search terms were broader than required by the NICE final scope as they included the comparator lomitapide. The ERG also notes that study design was restricted to RCTs but considers this appropriate.
Inclusion criteria	Appendix D.1.2, Table 5 (pages 11–13)	Appropriate although they did not restrict to patients on prior ezetimibe.
Screening	Appendix D.1.2 (page 11)	Appropriate
Data extraction	Appendix D.1.3 (page 13)	Appropriate
Tool for quality assessment of included study or studies	Section B.2.5, Tables 20-26 (page 90-99) and Appendix D.1.4 (pages 13-14) and D.2.5, Table's 11-25 (pages 67–80)	Appropriate.

Abbreviations: CS, company submission; ERG, Evidence Review Group.

3.2 Critique of trials of the technology of interest

The company included clinical effectiveness evidence from seven RCTs of bempedoic acid and/or FDC and three of these studies (Study 1002-008, CLEAR Serenity and CLEAR Tranquility) were used in the statin intolerant NMA with the remaining four studies (Study 1002-009, 1002FDC-053, CLEAR Harmony and CLEAR Wisdom) used in the maximally tolerated NMA. The RCTs all enrolled patients with primary hypercholesterolaemia and/or mixed dyslipidaemia. The company reported that in Study 1002-009 a total of 15% of the study population reported a history of statin intolerance. However, the company does not report further details on this subgroup, and whether or not they are suitable for inclusion in the maximally tolerated NMA, or even if it is possible to include this subgroup of Study 1002-009 in the statin intolerant NMA. The ERG also notes that in the 1002FDC-053 study it was reported that while patients were required to be inadequately controlled with their current maximally tolerated statin therapy, patients on statin doses lower than the lowest approved dose as well as no statin at all were also enrolled. The ERG therefore considers the population for study 1002FDC-053 may include some statin intolerant patients despite the whole study population being used by the company in the maximally tolerated statin NMA. The company also reported concerns regarding the data integrity from 3 sites in study 1002FDC-053 due to 34 patients from these sites having no detectable study drug at 12-weeks and that these sites were excluded from the *post hoc* efficacy and safety analyses.

The ERG generally agrees with the company's quality assessments of the bempedoic acid and FDC studies as being at overall low risk of bias for mean change in LDL-C at 12 weeks. The ERG's critique of the design and conduct, and internal and external validity, of the bempedoic acid and FDC studies is summarised in Table 7. A summary of the company's and the ERG's quality assessment of the bempedoic acid and FDC studies can be found in Appendix 9.1.

Table 7. Summary of ERG's critique of the design and conduct of the bempedoic acid and FDC trials evaluating the technologies of interest to the decision problem

Aspect of trial design or conduct	ERG's critique						
	Phase 3 Bempedoic acid trials				FDC trial	Phase 2 trials	
	CLEAR Harmony 1002-040 (Ray *et al.* 2019b)	CLEAR Wisdom 1002-047 (Goldberg *et al.* 2019)	CLEAR Serenity 1002-046 (Laufs *et al.* 2019)	CLEAR Tranquility 1002-048 (Ballantyne *et al.* 2018)	1002FDC-053 (Ballantyne *et al.* 2019a)	1002-009 (Ballantyne *et al.* 2016)	1002-008 (Thompson *et al.* 2016)
Key inclusion criteria	Fasting LDL-C ≥ 70 mg/dL at least 2 weeks before screening visit; high CV risk[a]; on maximally tolerated LMT, defined as maximally tolerated statin either alone or in combination with other LMTs, at stable doses for at least 4 weeks before screening.	Fasting LDL-C at week −5 ≥ 100 mg/dL and fasting LDL-C value at week −1 ≥ 70 mg/dL; high CV risk[a]; on maximally tolerated LMT, defined as maximally tolerated statin either alone or in combination with other LMTs, at stable doses for at least 4 weeks before screening.	History of statin intolerance[b] with fasting LDL-C ≥ 130 mg/dL (for primary prevention patients[c]) and ≥ 100 mg/dL (for those with HeFH) and/or had a secondary prevention indication.[d]	History of statin intolerance, treated with no more than low-dose statin therapy[a]; fasting LDL-C ≥ 100 mg/dL or ≥ 120 mg/dL if not on ezetimibe at baseline.	Maximally tolerated statin therapy at stable dose for at least 4 weeks before screening; fasting LDL-C at week 2: ASCVD and or HeFH: 100 mg/dL Multiple CV risk factors: ≥ 130 mg/dL	Patients on stable statin therapy[f] With fasting, calculated LDL-C levels from 115-220 mg/dL and a fasting TG level of ≤ 400 mg/dL after washout of lipid-regulating agents other than the statin.	Fasting, calculated LDL-C values ≥ 130 and ≤ 220 mg/dL and a fasting TG level ≤ 400 mg/dL after washout of lipid-regulating drugs. Statin-tolerant and statin-intolerant patients.[g]
Screening and/or run-in period	2-week screening, no run-in.	1-week screening and 4-week single blind placebo run-in.	1-week screening and 4-week single blind placebo run-in.	1-week screening and 4-week single blind ezetimibe 10 mg run-in.	No run-in reported. Note patients treated with ezetimibe in the 5 weeks prior to screening were excluded.	6-week screening and washout period of all lipid lowering therapies other than atorvastatin, simvastatin, rosuvastatin, or pravastatin.	5-week washout period of all lipid lowering therapies and single blind placebo run-in.

Randomisation	Appropriate. Patients randomised 2:1 to bempedoic acid 180 mg: placebo orally once daily for 52 weeks. Randomisation stratified by: CV risk (HeFH) and baseline statin intensity (low, moderate or high).	Appropriate. Patients randomised 2:1 to bempedoic acid 180 mg: placebo orally once daily for 52 weeks. Randomisation stratified by: CV risk (ASCVD alone or HeFH with or without ASCVD) and baseline statin intensity (low, moderate or high).	Appropriate. Patients randomised 2:1 to bempedoic acid 180 mg: placebo orally once daily for 26 weeks. Randomisation stratified by: treatment indication (primary prevention vs, secondary prevention and/or HeFH).	Appropriate. Patients randomised 2:1 to bempedoic acid 180 mg + ezetimibe 10 mg: placebo + ezetimibe 10 mg orally once daily for 12 weeks (note ezetimibe was continued in both arms as single-blind therapy from run-in phase). Randomisation not reported to be stratified.	Appropriate. Patients randomised 2:2:2:1 to FDC: bempedoic acid 180 mg: ezetimibe 10 mg: placebo orally once daily for 12-weeks. Randomisation was stratified by CVD risk category (ASCVD and/or HeFH vs. multiple CVD risk factors) and baseline statin intensity (high intensity vs. other).	Appropriate. Note 3-armed trial with only 2-arms of relevance to NICE final scope. Patients randomised 1:1to bempedoic acid 180 mg: placebo once daily for 12 weeks in addition to ongoing low or moderate intensity statin.[e] Randomisation stratified by history of statin intolerance.	Appropriate. Note 5-armed trial with only 3-arms of relevance to NICE final scope. Patients randomised 4:4:1 to bempedoic acid 180 mg: ezetimibe 10 mg: bempedoic acid 180 mg + ezetimibe 10 mg for 12 weeks. Randomisation stratified by history of statin intolerance.
Number randomised (N)	Bempedoic acid N = 1,488 Placebo N = 742	Bempedoic acid N = 522 Placebo N = 257	Bempedoic acid N = 234 Placebo N = 111	Bempedoic acid + Ezetimibe N = 181 Placebo + Ezetimibe N = 88	FDC N = 108 Bempedoic acid N = 110 Ezetimibe N = 109 Placebo N = 55 Note: *post hoc* efficacy population used in analyses due to data integrity concerns resulted in only 86, 88, 86 and 41 patients, respectively for each study arm.	Bempedoic acid N = 45 Placebo N = 45 Note: 15% of patients reported to have history of statin intolerance but no subgroup analyses provided in CS.	Bempedoic acid N = 100 Ezetimibe N = 99 Bempedoic acid + Ezetimibe N = 24 Note: approximately 50% of patients were statin intolerant (n = 50, 51 and 10, respectively) and the company uses the statin intolerant subgroup in the NMA.

Concealment of treatment allocation	Appropriate		
Baseline characteristics	Baseline characteristics in the ITT population were generally well balanced between the two groups. Minor imbalances between groups are discussed in Section 3.2.1.		
Masking appropriate	Appropriate Patients and investigators masked to treatment allocation throughout the study.		
No difference between groups in treatments given, other than randomised treatments.	No evidence to suggest that concomitant therapies differed between groups although clinical experts reported not all background treatments would be used in the UK.		
Dropouts (high drop out and any unexpected imbalance between groups)	Patient flow diagrams not presented in the CS but reported in the company's quality assessments that they were available for all studies other than CLEAR Harmony which is ongoing and that there were no concerns for any study regarding dropouts.		
ITT analysis carried out for outcomes assessed relevant to NICE final scope	ITT analysis reported for primary efficacy outcome (change from baseline to week 12 in calculated LDL-C) and other measures of plasma lipid and lipoproteins. Cardiovascular events, mortality and AE data presented using the safety population. Note overall safety was the primary outcome in CLEAR Harmony and LDL-C change was the principal secondary outcome (and the primary efficacy outcome).	*Post hoc* efficacy population used based on ITT population with exclusion of 3 study sites due to data integrity concerns. *Post hoc* efficacy analysis and ITT analysis reported for primary efficacy outcome (change from	mITT analysis (all randomised patients who had a baseline assessment, received at least 1 dose of study medication, and had at least 1 on-treatment assessment [excluding any assessment taken more than 2 days after a dose of study drug]) reported for primary efficacy outcome (change from baseline to week 12 in calculated LDL-C) and other measures of plasma lipid and lipoproteins. Cardiovascular events, mortality and AE data not presented in the CS although reported that the safety data from 10 Phase 2 studies were pooled (includes 8

					baseline to week 12 in calculated LDL-C) and other measures of plasma lipid and lipoproteins. Cardiovascular events not reported but mortality and AE data presented using the safety population.	studies not relevant to NICE final scope).	
Subgroup analyses	Pre-planned subgroup analyses were carried out based on stratification factors and baseline demographic characteristics.	Pre-planned subgroup analyses were carried out based on stratification factors and baseline demographic characteristics.	Pre-planned subgroup analyses were carried out based on stratification factors and baseline demographic characteristics.	Pre-planned subgroup analyses were carried out based on baseline demographic characteristics.	Pre-planned subgroup analyses were carried out based on stratification factors and baseline demographic characteristics.	Not reported.	Not reported.
Sample size and power calculation	Required sample size met and power calculation based on adverse effects rates.	Required sample size met and power calculation based on LDL-C.					
Handling of missing data in primary efficacy analysis	Missing data were imputed: Patients with missing lipid data at week 12 who were no longer taking study treatment were assumed to no longer be benefitting from study drug, and	Missing values for any of the laboratory evaluations were not imputed; that is, only observed case data were used.	Missing data were imputed using a PMM. For patients with missing data who had already discontinued the study drug (bempedoic acid or placebo), the missing	Missing values at week 12 were imputed using the multiple imputation method taking into account ongoing treatment. Patients who had missing values and	Missing values were imputed using a multiple imputation method, taking into account adherence to treatment.	For week 12 endpoint, missing values at week 12 were imputed using the last observation carried forward procedure.	For week 12 endpoint, missing values at week 12 were imputed using the last observation carried forward procedure.

	their missing value(s) were assumed to be similar to those of placebo patients who had data. Patients with missing lipid data at week 12 who were still taking study treatment were assumed to continue to benefit from study drug, and their missing value(s) were assumed to be similar to those who remained on study treatment and had data.		values were imputed using data from placebo group patients only. For patients who had missing data and were adherent to study treatment, their missing data were imputed using patient data from their respective treatment group.	were off treatment were imputed with placebo patient data only.			
Standard pair-wise meta-analysis	Pooled analysis with CLEAR Wisdom appropriate. However, no analysis conducted with the other studies of BA and placebo despite inclusion in the background statin NMA alongside CLEAR Wisdom, Study 1002FDC-053 and Study 1002-009.	Pooled analysis with CLEAR Harmony appropriate. However, no analysis conducted with the other studies of BA and placebo despite inclusion in the background statin NMA alongside CLEAR Harmony, Study 1002FDC-053 and Study 1002-009.	Pooled analysis with CLEAR Tranquility despite differences in background statin use (everyone in CLEAR Tranquility received ezetimibe and [redacted]).	Pooled analysis with CLEAR Serenity despite differences in background statin use (everyone in CLEAR Tranquility received ezetimibe and [redacted]). No analysis with Study 1002-008 conducted despite inclusion alongside Study 1002-008 in the statin	Not conducted despite inclusion of BA and placebo arms in the background statin NMA alongside CLEAR Harmony, CLEAR Wisdom, and Study 1002-009.	Not conducted despite inclusion in the background statin NMA alongside CLEAR Harmony, CLEAR Wisdom, and Study 1002FDC-053.	Not conducted despite inclusion alongside CLEAR Tranquility in the statin intolerant NMA.

				intolerant NMA.			
Network meta-analysis	Background statin NMA: BA, placebo	Background statin NMA: BA, placebo	Statin intolerant NMA: BA, placebo.	Statin intolerant NMA: BA+EZE, EZE	Background statin NMA: BA, BA+EZE (FDC), EZE, placebo	Background statin NMA: BA, placebo	Statin intolerant NMA: BA, BA+EZE, EZE

[a] Defined as either diagnosis of HeFH or ASCVD (with established CHD or CHD risk equivalents).
[b] Defined as the inability to tolerate at least two statins, one at a low dose, owing to a prior adverse event that started or increased during statin therapy and resolved or improved when statin therapy was discontinued. Patients who required lipid-lowering therapy based on national guidelines.
[c] Patients with coronary artery disease, symptomatic peripheral arterial disease, and/or cerebrovascular atherosclerotic disease.
[d] Very low-dose statin therapy was defined as an average daily dose of rosuvastatin < 5 mg, atorvastatin < 10 mg, simvastatin < 10 mg, lovastatin < 20 mg, pravastatin < 40 mg, fluvastatin < 40 mg, or pitavastatin < 2 mg.
[e] atorvastatin 10 mg or 20 mg; simvastatin 5 mg, 10 mg, or 20 mg; rosuvastatin 5 mg or 10 mg; or pravastatin 10 mg, 20 mg, or 40 mg.
[f] Stable statin therapy was defined as use of atorvastatin (10 or 20 mg), simvastatin (5, 10, or 20 mg), rosuvastatin (5 or 10 mg), or pravastatin (10, 20, or 40 mg) for at least 3 months before screening.
[g] Statin intolerance was defined as the inability to tolerate ≥ 2 statins because of muscle-related symptoms such as pain, weakness, or cramping that began or increased during statin therapy and resolved on statin discontinuation.
[h] Defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg.
[i] Average daily doses ≤ 40 mg prior to protocol amendment and < 40 mg after amendment.
Abbreviations: AE, adverse events; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CV, cardiovascular; CVD, cardiovascular disease; ERG, Evidence Review Group; EZE, ezetimibe; FDC, bempedoic acid and ezetimibe fixed-dose combination; HeFH, heterozygous familial hypercholesterolaemia; ITT, intention to treat; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; mITT, modified intention to treat; NICE, National Institute of Health and Care Excellence; NMA, network meta-analysis; TG, triglyceride.

3.2.1 Baseline characteristics

The baseline characteristics of patients in the seven included studies: Study 1002-008, Study 1002-009, CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, CLEAR Tranquility and Study 1002FDC-053, are presented in Appendix 9.2 and discussed below.

Baseline characteristics presented in the CS were much more limited for the two Phase 2 studies (Study 1002-008 and Study 1002-009) compared with the five Phase 3 studies. However, patient characteristics were generally well balanced across the trial arms in all seven included studies, although there were notable differences between the studies. There was insufficient data from the studies to establish the proportion of patients with primary hypercholesterolaemia or the proportion with mixed dyslipidaemia and the company reported in their clarification response that primary non-FH or mixed dyslipidaemia were not specified as subgroups of interest in the NICE final scope and therefore the company considers them not relevant.

As discussed in Section 2.3.3, the ERG notes that in CLEAR Wisdom and CLEAR Harmony less than 10% of patients were on background ezetimibe at baseline and in CLEAR Serenity this was less than

15%. In the response to clarification questions, the company reported that there were no patients in Study 1002FDC-053 on ezetimibe at baseline as all patients who had received ezetimibe in the 5-weeks prior to screening were excluded and the ERG also notes from the publications of Study 1002-008 and Study 1002-009 that patients on prior ezetimibe would have been subject to a wash-out period of at least 5 weeks prior to randomisation. In CLEAR Tranquility, there was a 4-week single-blind ezetimibe run-in phase prior to the 12-week double-blind treatment phase with bempedoic acid. The ERG is therefore concerned that with the exception of CLEAR Tranquility, the full trial populations of each of the bempedoic acid and FDC studies does not reflect the prior ezetimibe population in which the company is positioning bempedoic acid and FDC.

Baseline LDL-C values varied considerably between the studies from just over 100 mg/dL in CLEAR Harmony to around 160 mg/dL in Study 1002-008 (note: baseline LDL-C for Study 1002FDC-053 was reported as mmol/L and so not directly comparable). In terms of statin intensity at baseline, nearly 50% of patients in CLEAR Harmony and CLEAR Wisdom were on high intensity statins compared with only approximately 35% of patients in Study 1002FDC-053. The ERG also notes that in Study 1002FDC-053, over 30% of patients were on no statin at baseline and it is unclear whether these patients have been excluded from the NMA where the study has been used to provide data for patients on maximally tolerated statin. Additionally, the ERG considers data from this subgroup of patients on no statin should have been considered for inclusion in the statin intolerant NMA. The ERG also notes that approximately 15% of patients in CLEAR Wisdom and 7% in CLEAR Harmony were on low intensity statins at baseline although these studies are included in the maximally tolerated statin network.

Risk factors for CV disease were variable between studies in terms of how they were captured at baseline and trial inclusion criteria, with not all studies reporting risk factors such as the proportion of patients with HeFH, thus making it hard to make cross-comparisons between the studies with regards baseline CV risk. The 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 the other four bempedoic acid studies. The ERG notes that all patients in CLEAR Harmony, CLEAR Wisdom and Study 1002FDC-053 were required to be at high risk of CVD but they were not all necessarily secondary CV prevention, in fact it is reported that 4% of patients in CLEAR Wisdom were primary prevention and 96% were secondary prevention and/or HeFH. In CLEAR Serenity over 60% of patients were primary prevention. The ERG notes from the NCEP ATP-III risk category baseline data reported for the Phase 2 studies that approximately 40% of patients were low risk and

approximately 20% were at high or very high risk of CV events. The company did not present any baseline CV risk data for CLEAR Tranquility.

In terms of patient demographics in comparison to the UK population likely to be eligible for bempedoic acid, the ERG's clinical experts reported that the bempedoic acid and FDC studies were broadly representative although they would expect a 50:50 gender split, higher proportion of non-white ethnicity patients, higher proportion of diabetics and background statin therapy to most commonly be atorvastatin. In addition, more older patients would also be expected in clinical practice, but it is not uncommon for age to be lower in clinical trials.

3.2.2 Outcome assessment

The primary efficacy outcome in the bempedoic acid and FDC trials was change in LDL-C from baseline to 12-weeks, which entailed blood tests and was assessed in a double-blind manner with patients, the study Sponsor and all clinical site personnel (e.g., investigator, pharmacist) reported to be blinded to the treatment group assignment. Details on the assessment of outcomes was limited in the CS and due to time constraints, the ERG has not fully reviewed this for each included study as its clinical experts did not report any concerns regarding the outcome measures presented in the CS of relevance to the decision problem. In the Goldberg *et al.* 2019 publication of CLEAR Wisdom, the ERG notes that it is reported that quantification of lipids and biomarkers was performed at a central laboratory (Q2 Solutions).The ERG also notes that for CLEAR Harmony, it was reported in the paper by Ray *et al.* 2019 that designated clinical end points, including major adverse cardiac events, were adjudicated centrally by an independent expert committee whose members were unaware of the trial-group assignments of patients. In terms of adverse events, the ERG notes that monitoring of adverse events that occurred during the intervention period was conducted from the receipt of the first dose through 30 days after the receipt of the last dose of trial agent. The ERG also considers it important to highlight that whilst the primary efficacy outcome in all the relevant bempedoic acid and FDC trials was assessed at 12 weeks there was also data available on bempedoic acid at 52 weeks in the maximally tolerated statin studies from CLEAR Wisdom and CLEAR Harmony, and 24 weeks for the statin intolerant analysis from CLEAR Serenity, and these data for LDL-C are discussed in Section 3.3.1.

3.2.3 Pooled analysis/meta-analysis

3.2.3.1 Bempedoic acid versus placebo in statin intolerant or maximally tolerated statin populations

The company conducted two pooled analyses, one of CLEAR Harmony and CLEAR Wisdom (maximally tolerated statin studies), and the other of CLEAR Serenity and CLEAR Tranquility (statin intolerant studies). The company reported in the CS that the Phase 2 trials 1002-008 and 1002-009 were not included in a meta-analysis because patients received no statin (Phase 2 study 1002-008) or low-to-moderate-intensity statin (Phase 2 study 1002-009). In contrast, in CLEAR Harmony and CLEAR Wisdom patients were receiving stable maximally tolerated statin and in CLEAR Serenity and CLEAR Tranquility patients had a history of statin intolerance. The company further reported that, *"Bempedoic acid has greater efficacy in patients receiving no/low-dose statin than in patients receiving moderate to high background statin therapy (CS Section B.2.6.1). Therefore, the treatment effect for bempedoic acid in the Phase 2 trials is expected to be heterogeneous with that in the Phase 3 trials"* (CS Section B.2.8.1, page 122). However, firstly the ERG notes that the Phase 2 studies were both included in the company's NMAs albeit using subgroup data from the statin intolerant patients in Study 1002-008 and secondly, the ERG does not consider the data presented in CS Section B.2.6.1 or CS Section B.2.7.1 (subgroup analyses) to be suitable for drawing conclusions regarding the impact of background statin therapy on the treatment effect of bempedoic acid. The ERG notes that in CS Section B.2.7.1 the company presents forest plots with subgroup analyses for CLEAR Harmony and CLEAR Wisdom based on intensity of statin therapy and that both studies have non-significant p-values for tests of subgroup interaction for the intensity of statin therapy subgroup ($p = 0.18$, and $p = 0.51$, respectively). The ERG also notes that the company report in Section B.2.7.1.1 for CLEAR Harmony that efficacy did not vary across subgroups with the exception of those where the p-vale for interaction was statistically significant. In CLEAR Harmony the mean difference for change from baseline LDL-C to week 12 in the low or moderate statin intensity subgroup was -20.0 (-22.8 to -17.3) and in the high statin intensity subgroup it was -17.5 (95% CI -20.0 to -14.7). The ERG does not consider these data sufficient to either prove or disprove a difference in treatment effect based on baseline statin intensity as the subgroups were not powered to detect treatment differences but agrees that the difference based on the underpowered subgroup analysis is statistically non-significant. The ERG therefore considers the company's pooled analyses of bempedoic acid versus placebo studies potentially flawed – the analysis of the statin intolerant studies omits the statin intolerant subgroup of study 1002-008 and the maximally tolerated statin study pooled analysis

omits study 1002-009, as well as the bempedoic acid and placebo arms of relevance from study 1002FDC-053, which are also included in the company's NMA.

The methodology for conducting the pooled analyses is not reported in the CS and so the ERG is unable to comment on the suitability of the methods and recommends caution should be used in the interpreting the results of the pooled analyses. The ERG notes that the pooled analyses only provide further evidence for the efficacy of bempedoic acid compared with placebo and that given this is not a comparison of interest, and the potential flaws highlighted, the ERG reports only the individual trial-based results and the results from the company's NMAs. The results of the pooled analyses can be found in the CS Section B.2.8.1. It should also be noted that the ERG considers the company's NMAs to be flawed due to clinical heterogeneity arising in part from differences in the populations of the bempedoic acid trials but given the results of the NMAs inform the efficacy data in the economic model the ERG critiques and presents the results of the NMAs in Section 3.4.

3.2.3.2 Bempedoic acid added to background ezetimibe therapy

The company presented the results of a pooled analysis of the subgroups of patients in CLEAR Harmony and CLEAR Wisdom who had received ezetimibe as background lipid lowering therapy at baseline and the subgroup of patients who had not received background ezetimibe therapy. This analysis comprised of a maximum of [redacted] patients with background ezetimibe therapy from *post hoc* subgroups and all patients were also on maximally tolerated statins.

In addition, the company presented the results of a pooled analysis of the subgroups of patients in CLEAR Tranquility and CLEAR Serenity who had received ezetimibe as background lipid lowering therapy at baseline and the subgroup of patients who had not received background ezetimibe therapy. This analysis comprised of a maximum of [redacted] patients with background ezetimibe therapy from *post hoc* subgroups and all patients were statin intolerant.

The ERG considers these two pooled subgroup analyses of relevance to the NICE decision problem as the company is positioning bempedoic acid and FDC for use in patients on background ezetimibe, but the ERG is unable to critique the methods of the pooled analyses as no detail was provided in the CS. The results of the pooled analyses are discussed in Section 3.3.3 and should be interpreted with caution given the small patient numbers, *post hoc* nature and lack of methodology detail.

3.3 Clinical effectiveness results of the trials of the technology of interest

The results of the bempedoic acid and FDC studies were presented separately in the CS as Phase 3 bempedoic acid studies, Phase 2 bempedoic acid studies and finally, the FDC study. The ERG considers it more helpful to present and critique the results based on the study populations and how the studies are used in the NMAs in terms of statin intolerant patients and patients on maximally tolerated statins. The ERG therefore presents the clinical effectiveness results based on these two populations.

3.3.1 Plasma lipid and lipoprotein results

3.3.1.1 Bempedoic acid trials in statin intolerant population

The results of the bempedoic acid and bempedoic acid + ezetimibe studies in statin intolerant patients are summarised in

Table 8, although the ERG notes that the data provided in this table for mean percentage change in LDL-C from baseline for CLEAR Serenity differ slightly from the data reported as used in the company's NMA (bempedoic acid: −23.6% vs -22.58% and placebo -1.3% vs -1.17% in

Table 8 and Clarification response Table 37, respectively) and the ERG are unsure why this is the case. The ERG notes that in statin intolerant patients, bempedoic acid is associated with a greater least square (LS) mean percentage reduction in LDL-C at 12-weeks compared with placebo or ezetimibe across all three studies. However, as discussed in Section 3.2.1, the ERG considers it important to highlight that it is unclear exactly what proportion of patients were receiving lipid lowering therapy for primary prevention of CV disease or how many patients had HeFH in most of the studies; in CLEAR Serenity the population is known to be mixed with over 60% primary prevention and less than 3% of patients with HeFH.

In CLEAR Serenity, the only study with longer follow-up, the statistically significant reduction in LS mean percentage change in LDL-C with bempedoic acid compared with placebo was maintained at 24-weeks ($p < 0.001$). The ERG considers it important to highlight that in CLEAR Serenity reductions in LDL-C were observed at the first post-baseline study visit (week 4) and, while still showing a statistically significant reduction in LDL-C compared with placebo at 24-weeks, the mean reduction in LDL-C suggests a waning of treatment effect with bempedoic acid between 4 and 24 weeks (CS, Figure 5). In addition, a similar treatment waning was seen in CLEAR Tranquility between 4 weeks and the trial endpoint at 12 weeks (CS, Figure 6). The ERG therefore considers the latest timepoint

(24weeks) to be the most informative to the decision problem as patients in clinical practice would be expected to potentially take bempedoic acid for the rest of their lives and at least beyond 24 weeks. The ERG also considers it important to highlight that in CLEAR Tranquility there was a 4-week single-blind ezetimibe run-in phase prior to the 12-week double-blind treatment phase with bempedoic acid.

The ERG notes that in the company's NMA, the placebo arm from CLEAR Tranquility is used to inform ezetimibe and not placebo although patients in both the bempedoic acid and placebo arms had received a 4 week single blind run in with ezetimibe. In contrast, in study 1002-008, ezetimibe was commenced at the start of the double-blind treatment phase which was after a 5-week washout period of all other lipid lowering therapies and is also used to provide data on ezetimibe in the company's NMA. The ERG therefore considers the population of study 1002-008 and CLEAR Tranquility to differ in terms of background ezetimibe therapy and notes that the resulting efficacy estimates for LS mean percentage change in LDL-C from baseline to week 12 for both bempedoic acid + ezetimibe and ezetimibe monotherapy are substantially different in the two studies (bempedoic acid + ezetimibe -23.5% in CLEAR Tranquility and -49.61% in study 1002-008; ezetimibe 4.99% in CLEAR Tranquility and -19.82% in study 1002-008). However, the ERG also recommends caution in interpreting the results of naïve comparisons of the results of different studies given that there are also known differences in the baseline LDL values between studies and that it is included as a covariate in the NMAs. The ERG also notes that in CLEAR Serenity [redacted] in each trial arm had received prior ezetimibe therapy and the ERG therefore considers that clinical heterogeneity between the three statin intolerant studies in terms of prior ezetimibe therapy is likely to be one of the causes of the statistical heterogeneity in the NMA.

In terms of other lipid and lipoprotein mean percentage changes from baseline at 12-weeks, the ERG notes that there is a statistically significant reduction in non-HDL-C, total cholesterol, apolipoprotein b and HDL-C with bempedoic acid compared with placebo in CLEAR Serenity. The ERG's clinical experts reported that the impact of the reduction in HDL-C with bempedoic acid is not known, but higher values of HDL-C tend to be associated with lower cardiovascular risks and reduction of HDL-C is not usually an intended outcome in lipid lowering therapy to treat raised LDL-C. Triglycerides were not associated with a statistically significant mean percentage change at 12 weeks with bempedoic acid compared with placebo in CLEAR Serenity although they were associated with numerically higher levels and the ERG's clinical experts reported that high triglycerides are associated with increased cardiovascular risk.

Table 8. Plasma lipid and lipoprotein efficacy results of bempedoic acid and bempedoic acid + ezetimibe trials in statin intolerant population

Efficacy parameter	CLEAR Serenity (1002-046) (Esperion Therapeutics data on file, 2018c; Laufs *et al.* 2019)			CLEAR Tranquility (1002-048) (Ballantyne *et al.* 2018) (Esperion Therapeutics data on file, 2018d)			Study 1002-008 (Thompson *et al.* 2016) – statin intolerant subgroup			
	LS mean % change from baseline to week 12		Difference of LS means (95% CI; *P* value)	LS mean % change from baseline to week 12		Difference of LS means (95% CI; *P* value)	LS mean % change from baseline to week 12			
	Bempedoic acid (n = 234)	Placebo (n = 111)		Bempedoic acid + ezetimibe (n = 181)	Placebo + ezetimibe (n = 88)		Bempedoic acid + ezetimibe	Bempedoic acid (n = 99) [b]	Ezetimibe (n = 98) [b]	Bempedoic acid vs. ezetimibe P value
LDL-C, mg/dL	−23.6	−1.3%	-21.4 (−25.1 to −17.7; < 0.001)	−23.5	5.0	−28.5 (−34.4 to −22.5); < 0.001	-49.61 (5.98)	−31.41 (12.90)	−19.82 (10.02)	NR
Non–HDL-C, mg/dL	−19	−0.4	−17.9 (−21.1 to 14.8; < 0.001)	−18.4	5.2	−23.6 (−29.005 to −18.121); < 0.001	NR	−25.3 (1.1)[b]	−18.7 (1.2) [b]	< 0.0001 [b]
TC, mg/dL	−16.1	−0.6	−14.8 (−17.3 to −12.2; < 0.001)	−15.1	2.9	−18.0 (−21.940 to −14.030); < 0.001	NR	−20.7 (0.9) [b]	−14.3 (0.9) [b]	< 0.0001 [b]
Apo B, mg/dL	−15.5	−0.2	−15.0% (−18.1% to −11.9%; < 0.001)	−14.6	4.7	−19.3 (−23.908 to −14.732); < 0.001	NR	−21.3 (1.3) [b]	−15.2 (0.70) [b]	NR
HDL-C, mg/dL	−5.0 (16.53)	−0.1 (11.15)	-4.52 (−7.475 to −1.575; 0.003)	−7.3	1.4	NR; 0.002	NR	−4.8 (13.5) [b]	5.0 (1.4) [b]	< 0.0001 [b]
TG, mg/dL	7.6 (39.51)	6.7 (36.97)	0.43 (−8.166 to 9.027; 0.921)	NR	NR	NR	NR	−2.70 (46.2)[a, b]	7.0 (34.9)[a, b]	NR

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LS, least squares; NR, not reported; SD, standard deviation; TC, total cholesterol; TG, triglyceride.
Data are means (SD) unless otherwise stated.
[a] Data are medians (interquartile ranges).
[b] Data are for the whole ITT study population and therefore include statin tolerant and intolerant patients.

3.3.1.2 *Bempedoic acid studies in maximally tolerated statin population*

The results of the bempedoic acid and bempedoic acid + ezetimibe studies in maximally tolerated patients are summarised in Table 9. However, as discussed in Section 3.2.1, the ERG considers it important to highlight that the majority of patients in these studies were in patients at high risk of CV disease thus likely receiving lipid lowering therapy for secondary prevention of CV disease. Also, the ERG notes that it is unclear how many patients had HeFH. The ERG considers there to be limited data for the maximally tolerated statin population subgroup of patients on lipid lowering therapy for primary prevention or low risk of CV disease.

In the ITT analysis (all randomised patients regardless of treatment received) of CLEAR Harmony, at week 12 treatment with bempedoic acid resulted in a statistically significantly greater mean percentage reduction of the LDL-C level than was observed in the placebo group (difference of LS percentage mean change in LDL-C at 12 weeks compared with baseline with bempedoic acid compared with placebo, −18.1; 95% CI, −20.0 to −16.1; P < 0.001) in patients on maximally tolerated statin therapy as part of their LMT. The statistically significant treatment effects of bempedoic acid versus placebo in CLEAR Harmony were apparent from week 4 through week 52 although the ERG notes that there is a slight waning of treatment effect beyond 4-weeks (CS, Figure 4). CLEAR Wisdom also demonstrated a statistically significant reduction with bempedoic acid compared with placebo at week 12 that was sustained at week 52 (p < 0.001) but again with a slight waning of treatment effect between weeks 4 and 24 (Goldberg *et al.* 2019 Supplement 3, eTable 1). Bempedoic acid also demonstrated statistically significant reductions at week 12 from baseline compared with placebo for non–HDL-C, TC and apo B in both CLEAR Harmony and CLEAR Wisdom ($p < 0.001$ for all). The ERG considers it important to highlight that the company uses the 12-week efficacy data in the NMAs to inform the cost-effectiveness analysis and would prefer to see data from the latest timepoints with data (52 weeks) given the possible treatment waning effect with bempedoic acid.

Study 1002-009 utilised a mITT analysis and was only 12 weeks duration but it and Study 1002FDC-053, which was also only 12 weeks, demonstrated results consistent with CLEAR Harmony and CLEAR Wisdom for LDL-C, non-HDL-C, TC and apo B showing a statistically significant reduction with bempedoic acid compared with placebo (p < 0.001; Table 9). In terms of FDC, the results from study 1002FDC-053 suggest that patients on FDC have a significantly greater reduction in LDL-C at 12 weeks compared with patients on bempedoic acid alone (difference of least square [LS] mean FDC vs bempedoic acid -19.0, 95% CI -26.1 to -11.9; p <0.001) or ezetimibe alone (difference of LS mean FDC

vs ezetimibe -13.1, 95% CI -19.7 to -6.5; p <0.001). FDC also demonstrated statistically significant reductions at week 12 from baseline compared with bempedoic acid or ezetimibe for non-HDL-C, TC and apo B in study 1002FDC-053 (p < 0.003 for all; CS Table 29, page 111).

The ERG considers it important to highlight that the data presented in Table 9 for study 1002FDC-053 relate to the *post hoc* efficacy analysis population which is discussed in Section 3.2 and excludes 3 study sites. The ERG notes that the results from the ITT population are used in the company's NMA and that these are less favourable for FDC and bempedoic acid compared with the results for mean change in LDL-C at 12 weeks from baseline using the *post hoc* analysis population (ITT analysis: FDC -31.5 mg/dL, bempedoic acid -17.7 mg/dL and *post hoc* analysis: FDC -36.2 mg/dL, bempedoic acid -17.2 mg/dL). The ERG therefore considers the data in the NMA to be a potentially conservative estimate for FDC albeit not in patients on background ezetimibe therapy as discussed in Section 2.3.3.

The data from the four studies in maximally tolerated statin patients [redacted] No data were provided for FDC in the CS for HDL-C or TG.

Table 9. Plasma lipid and lipoprotein efficacy results of bempedoic acid and FDC studies in maximally tolerated statin population

Efficacy parameter	CLEAR Harmony (1002-040) (Ray *et al.* 2019a; Ray *et al.* 2019b)			CLEAR Wisdom (1002-047) (Esperion Therapeutics data on file, 2019c; Goldberg *et al*. 2019)			Study 1002-009 (Ballantyne *et al.* 2016)			1002FDC-053 (Ballantyne *et al.* 2019a; Ballantyne *et al.* 2019b; Esperion Therapeutics data on file, 2019d)				
	LS mean % change from baseline to week 12		Difference of LS means (95% CI; *P* value)	LS mean % change from baseline to week 12		Difference of LS means (95% CI; *P* value)	LS mean % change from baseline to week 12		P value	LS mean % change from baseline to week 12				Difference of LS means (95% CI; *P* value)
	Bempedoic acid (n = 1,488)	Placebo (n = 742)		Bempedoic acid (n = 499)[d]	Placebo (n = 253)[d]		Bempedoic acid (n = 43)	Placebo (n = 43)		FDC (n = 86)	Bempedoic acid (n = 88)	Ezetimibe (n = 86)	Placebo (n = 41)	FDC vs. bempedoic acid
LDL-C, mg/dL	−16.5 (0.52)	1.6 (0.86)	−18.1 (−20.0 to −16.1; < 0.001)	−15.1 (1.073)	2.4 (1.446)	−17.4 (−21 to −13.9; < 0.001)	−24.3 (4.2)	−4.2 −(4.2)	< 0.0001	−36.2	−17.2	−23.2	1.8	−19.0 (−26.1, −11.9); < 0.001
Non–HDL-C, mg/dL	−11.9 (0.48)	1.5 (0.76)	−13.3 (−15.1 to −11.6; < 0.001)	−10.8 (1.0)	2.3 (1.4)	−13.0 (−16.3 to −9.8; < 0.001)	−10.75 (0.952)	−1.8 (3.9)	< 0.01	−31.9	−14.1	−19.9	+1.8	−17.8 (−25.1, −10.5); < 0.001
TC, mg/dL	−10.3 (0.37)	0.8 (0.57)	−11.1 (−12.5 to −9.8; < 0.001)	−9.9 (0.7)	1.3 (1.0)	−11.2 (−13.6 to −8.8; < 0.001)	−15.3 (2.9)	−3.2 (2.9)	< 0.01	−26.4	−12.1	−16.0	−1.9	−14.2 (−20.4, −8.1); < 0.001
Apo B, mg/dL	−8.6 (0.47)	3.3 (0.70)	−11.9 (−13.6 to −10.2; < 0.001)	−9.3 (0.9)	3.7 (1.3)	−13.0 (−16.1 to −9.9; < 0.001)	−17.2 (3.4)	−5.5 (3.4)	< 0.01	−24.6	−11.8	−15.3	5.5	−12.8 (−20.3, −5.3); < 0.001
HDL-C, mg/dL	−5.92 (13.5)[b, c]	−0.09 (11.2)[b, c]		−6.4 (0.7)	−0.2 (0.9)	−6.13 (−8.4, −3.9; < 0.001)	−4.0 (2.7)	−2.0 (2.7)	NR	NR	[redacted]	[redacted]	[redacted]	NR

TG, mg/dL	2.90 (−15.8, 26.2)[b, c]	−0.33 (−16.9, 20.8)[b, c]		11.0 (2.3)	6.1 (2.3)	4.9 (−1.5, 11.3; 13)	−9.1 (47)	−3.0 (37)	NR	NR	[redacted]	5.63 (NR)	[redacted]	NR

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LS, least squares; NR, not reported; SD, standard deviation; TC, total cholesterol; TG, triglyceride.
Data are means (SD) unless otherwise stated.
[a] Data are medians (interquartile ranges).
[b] N = 1,427 for bempedoic acid group, and N = 726 for placebo group.
[c] Data are medians (Q1, Q3).
[d] Sample sizes varied for some outcomes. LDL-C and non–HDL-C: 498 for bempedoic acid group, and 253 for placebo group; Apo B: 479 for bempedoic acid group and 245 for placebo group; hsCRP: 467 for bempedoic acid group and 240 for placebo group
Note: Data for Study 1002-009 relate to mITT population and Study 1002FDC-053 relate to the post hoc analysis set.

3.3.2 Subgroup analysis results

As discussed in Section 2.3.4, the subgroups of particular interest to this appraisal as specified in the NICE final scope are presence or risk of CV disease, people with HeFH, people with statin intolerance and severity of hypercholesterolaemia but these are not addressed in relation to the comparators in the NICE final scope. Forest plots presenting the results of pre-specified subgroup analyses of each of the four Phase 3 bempedoic acid studies and the 1002FDC-053 study were provided in the CS Section 2.7. The subgroup analyses and categories varied between the studies but did include CV risk factors (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity and study 1002FDC-053), presence of HeFH (CLEAR Harmony and CLEAR Serenity), background statin intensity (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity and study 1002FDC-053) and baseline LDL-C values (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, CLEAR Tranquility and study 1002FDC-053). All subgroup analyses resulted in significant differences in the difference of least square percentage mean change in LDL-C at 12 weeks compared with baseline with FDC or bempedoic acid compared with placebo (or bempedoic acid + ezetimibe compared with placebo + ezetimibe in CLEAR Tranquility) with the exception of the non-white race subgroup in CLEAR Tranquility, which was possibly due to low patient numbers in the analysis. Tests for between subgroup and treatment interactions suggested that in general there was no significant difference in treatment effect across the various subgroup analyses with the exception of gender in CLEAR Harmony, BMI in CLEAR Wisdom, history of diabetes in CLEAR Serenity and background LMT in CLEAR Tranquility. The ERG notes that the company reports in their clarification responses that subgroups such as patients with HeFH are too small to be analysed separately, but the company also uses the data from the subgroup analyses to demonstrate similar efficacy across groups such as patients with and without HeFH, which the ERG considers to be contradictory. The ERG considers many of the subgroup analyses to be associated with low patient numbers and underpowered to detect between subgroup differences in treatment effectiveness.

The company also presented subgroup analysis results from study 1002FDC-053 for FDC compared with bempedoic acid although it highlighted that the study was not powered to detect a difference between the two treatments. The ERG notes that in general the subgroup results were consistent with the overall trial results demonstrating a significant reduction in mean percentage change in LDL-C at 12 weeks from baseline with FDC compared with bempedoic acid alone; the subgroups that showed no significant difference were race 'other' ($p = 0.154$), CV risk 'multiple CV risk factors' ($p = 0.391$), other intensity statin ($p = 0.322$) and BMI 25 to ≤ 30 ($p = 0.775$).

3.3.3 Bempedoic acid added to background ezetimibe therapy pooled analysis results

3.3.3.1 Statin intolerant population

In CLEAR Serenity and CLEAR Tranquility patients where the background dose of statin equalled none, or low-dose statin therapy patients, were randomised to bempedoic acid (N = 415) and placebo (N = 199). Of the bempedoic acid patients, [redacted] were treated with background ezetimibe at the time of randomisation and in the placebo group this was [redacted] patients. The company reported that in *post hoc* subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use. The LS mean reduction in LDL-C at week 12 from baseline for bempedoic acid compared with placebo was [redacted] versus [redacted] respectively, resulting in a difference from placebo for the LS means of [redacted] in patients taking ezetimibe. In the subgroup of patients not taking background ezetimibe at baseline, the percentage change from baseline LDL-C was [redacted] for bempedoic acid versus [redacted] for placebo, resulting in a difference from placebo for the LS means of [redacted] The ERG acknowledges that these subgroup data suggest similar results in terms of mean percentage LDL-C reduction regardless of background ezetimibe therapy but also notes that there is still a difference in the results of the analysis and does not consider a [redacted] difference between the presence and absence of background ezetimibe use at baseline to be clinically insignificant given that the trial was not designed or powered sufficiently to detect a statistical difference for this comparison. In addition, it is important to note that the analysis is based on *post-hoc* subgroups. The ERG does not consider the comparison the company has presented in their clarification response (A5, Table 6) between the mean percentage LDL-C change from baseline for bempedoic acid versus placebo from the prior ezetimibe pooled trial analysis and the NMA estimate for bempedoic acid + ezetimibe versus ezetimibe to be appropriate evidence to support the assertion that bempedoic acid treatment effect is unrelated to prior ezetimibe therapy. This is because the bempedoic acid + ezetimibe data in the NMA includes data from study 1002-008, where patients had not received prior ezetimibe (5-week washout of all lipid lowering therapies prior to commencing randomised treatment) in addition to the data from CLEAR Tranquility, where there was a 4-week run-in with ezetimibe in all randomised patients.

3.3.3.2 Maximally tolerated statin population

In CLEAR Harmony and CLEAR Wisdom, the two Phase 3 studies in patients treated with maximally tolerated statins at randomisation, [redacted] patients received ezetimibe background therapy of the 2,010 randomised to bempedoic acid and of the 999 patients randomised to placebo, [redacted] patients

received ezetimibe background therapy. The results of the *post hoc* subgroup analyses gave a LS mean change from baseline to week 12 in LDL-C for bempedoic acid compared with placebo of [redacted] versus [redacted], respectively, and a difference from placebo for the LS means of [redacted] in patients taking ezetimibe. The LS mean change from baseline was [redacted] (bempedoic acid) versus [redacted] (placebo), with a LS mean difference from placebo of [redacted] in patients not taking ezetimibe. The ERG acknowledges that these subgroup data suggest similar results in terms of mean percentage LDL-C reduction regardless of background ezetimibe therapy but also notes that there is still a [redacted] difference in the results of the analysis and the ERG does not consider this difference to be clinically insignificant given that the trial was not designed or powered sufficiently to detect a statistical difference for this comparison. In addition, it is important to note that the analysis is based on *post hoc* subgroups. The ERG does not consider the comparison the company has presented in their clarification response (A5, Table 6) between the mean percentage LDL-C change from baseline for bempedoic acid versus placebo from the prior ezetimibe pooled trial analysis and the NMA estimate for FDC versus ezetimibe to be appropriate evidence to support the assertion that bempedoic acid effect is unrelated to prior ezetimibe therapy. This is because the FDC data in the NMA is from the 1002FDC-053 study, where prior ezetimibe therapy was disallowed and patients underwent a 5-week washout period prior to commencing randomised treatment, therefore the ERG considers it to reflect patients who were not on background ezetimibe.

3.3.4 Adverse effects of treatment

The company presented safety data separately for bempedoic acid alone and in the FDC with ezetimibe. Safety data for bempedoic acid were available from four different safety sets with mixed background therapies and populations, and data for the FDC are based solely on study 1002FDC-053 (Table 10). Safety set 3 pools data for statin tolerant and intolerant populations and safety set 4 includes data from 10 Phase 2 studies, most of which were excluded from the clinical and cost-effectiveness analyses because they had less than 12 weeks' follow-up. The ERG therefore considers safety sets 1 and 2 for bempedoic acid and set 5 for the FDC the most appropriate to assess safety in line with the clinical effectiveness analyses. Tabulated safety results in the CS focused mainly on the overall Phase 3 pool (safety set 3) but a summary of individual Phase 3 study results was also presented. Where necessary, the ERG has therefore combined studies to represent safety sets 1 and 2 in line with the clinical effectiveness results.

Safety outcomes reported in the CS included the incidences of treatment-emergent adverse events (TEAEs, including all events, common events, serious events, fatal events, and events leading to

discontinuation of the study drug), TEAEs of special interest, positively adjudicated CV endpoints, and changes in clinical laboratory tests. Only very limited information was provided regarding the number and type of treatment-related adverse events (TRAEs). Mortality and CV outcomes are discussed in more detail in Section 3.3.5 and Section 3.3.6, respectively.

Table 10. Pooled safety sets presented in the company's submission

Safety set	Studies	Comparison groups	Background therapy	Population
1. High-Risk/Long-Term	CLEAR Harmony CLEAR Wisdom	Bempedoic acid (n = [redacted]) Placebo (n = [redacted])	Mix including ezetimibe and mod-high statin	High CV risk due to ASCVD and/or HeFH
2. No- or Low-Dose Statin	CLEAR Serenity CLEAR Tranquility	Bempedoic acid (n = [redacted]) Placebo (n = [redacted])	Mix including ezetimibe and no-or low dose statin	HC and history of statin intolerance
3. Overall Phase 3	CLEAR Harmony CLEAR Wisdom CLEAR Serenity CLEAR Tranquility	Bempedoic acid (n = [redacted]) Placebo (n = [redacted])	Mix across sets 1 and 2	Sets 1 and 2 combined
4. Overall Phase 2	1002-003, 1002-005, 1002-006, 1002-007, 1002-008, 1002-009, 1002-014, 1002-035, 1002-038, 1002-039	Bempedoic acid (n = [redacted]) Placebo (n = [redacted]) Ezetimibe (n = [redacted])	Mix including ezetimibe and no/ low/moderate/high statin	HC and mixed statin tolerance
5. FDC	1002FDC-053	Bempedoic acid (n = 110) BA + ezetimibe FDC (n = 108) Ezetimibe (n = 86) Placebo (n = 41)	Mix of no/low/ moderate/high statin	High CV risk due to ASCVD, HeFH, or multiple CVD risk factors

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; FDC, fixed-dose combination of bempedoic acid and ezetimibe; HC, hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; n, number of patients; NR, not reported. Exposures are expressed as means.
Sources: Information in the table were collated from descriptions in CS Section B.2.10.1 (pgs 131–132), Section B.2.10.2 (Table 42), and Section B.2.2 (Table 9).

3.3.4.1 Bempedoic acid trials

Table 11 gives a summary of adverse events for safety set 1 (CLEAR Wisdom and CLEAR Harmony) and safety set 2 (CLEAR Serenity and CLEAR Tranquility). The ERG notes that data for the high CV risk, statin tolerant population (safety set 1) is likely to be more robust than safety set 2 (statin intolerant population) because it includes more people who received bempedoic acid (n = [redacted]) and longer mean exposure ([redacted] days) than safety set 2 (n = [redacted] and [redacted] days, respectively).

The proportions of patients who had one or more treatment-emergent adverse event (TEAE) were similar between the bempedoic acid and placebo groups (Table 11), but the proportions were [redacted] in

safety set 1 ([redacted] vs [redacted] than safety set 2 (57.3% vs 51.5%). The same pattern is true for serious TEAEs, which were experienced by [redacted] vs [redacted] for bempedoic acid and placebo in safety set 1, and 4.6% vs 3.5% in safety set 2. CV events were more common in the high-risk safety set 1 than safety set 2, as expected and fatal TEAEs occurred in less than [redacted] of all groups. The proportion of TEAEs judged to be related to study treatment was not reported for safety set 1 or 2 or for each study separately.

In safety set 1 (high-risk population with background statins), SAEs by system organ class that either occurred more frequently in one group than the other or in at least 2% of patients in either group were infections and infestations ([redacted]), vascular disorders ([redacted]), cardiac disorders ([redacted]), and unstable angina ([redacted]). In safety set 2, injury, poisoning or procedural complications occurred less frequently in the bempedoic acid group than the placebo group ([redacted]) and unstable angina was uncommon in both groups but higher in the bempedoic acid group ([redacted]). The frequency of specific SAEs shown at the bottom of Table 11 was generally higher in safety set 1 than safety set 2. Treatment-related SAEs were not reported for safety set 1 or 2 or for each study separately but they were low and balanced between groups in the overall Phase 3 pool ([redacted] and [redacted] for the bempedoic acid and placebo groups, respectively; CS, Section B.2.10.1.4).

Table 11. Safety overview of bempedoic acid for the statin tolerant and intolerant populations (safety sets 1 and 2)

	Safety set 1 (high-risk/long-term, moderate-high background statin)		Safety set 2 (No- or low-dose statin)	
Comparison group	**Bempedoic acid**	**Placebo**	**Bempedoic acid**	**Placebo**
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean exposure (days)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 TEAE (%)	[redacted]	[redacted]	57.3	51.5
Patients with ≥ 1 serious TEAE (%)	[redacted]	[redacted]	4.6	3.5
Patients with ≥ 1 TEAE with a fatal outcome (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 TEAE leading to discontinuation of IMP (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any positively adjudicated CV or fatal clinical event (%)	5.5	6.8	[redacted]	[redacted]
Serious adverse events by system organ class (%)				
Infections and infestations	[redacted]	[redacted]	-	-
Vascular disorders	[redacted]	[redacted]	-	-
Cardiac disorders	[redacted]	[redacted]	-	-

Injury, poisoning and procedural complications	-	-	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]	[redacted]	[redacted]
AEs with a ≥ 1% difference between groups (%)				
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	3.1	7.1
Arthralgia	[redacted]	[redacted]	6.0*	4.5
Muscle spasms	[redacted]	[redacted]	3.9	4.0
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	2.6*	5.4*
Pain in extremity	[redacted]	[redacted]	3.4	2.0
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]
AAT increased	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAT, aspartate aminotransferase; AE, adverse event; TEAE, treatment-emergent adverse event.
Notes: The serious adverse events listed either occurred more commonly in one group than the other (>1% between groups) or in at least 2% of those taking bempedoic acid. Data marked with * were only reported for CLEAR Serenity.
Sources: Adverse event frequencies have been combined to reflect safety sets 1 and 2 from individual study results reported in CS Section B.2.10.1, Table 41.

Results for the overall Phase 3 (safety set 3) and overall Phase 2 (safety set 4) results have not been reproduced but can be found in Section B.2.10 of the CS. Briefly, [redacted] occurred more frequently in the overall Phase 3 pool with bempedoic acid than with placebo, and arthralgia, dizziness and [redacted] occurred more frequently with bempedoic acid than placebo in at least one of the safety pools (specific data not reported; CS, pg. 132). Adverse events of special interest reported only for the overall Phase 3 pool showed no increased risk of hypoglycaemia ([redacted]), metabolic acidosis (<[redacted]), new onset diabetes/hyperglycaemia ([redacted]) or neurocognitive disorders with bempedoic acid (CS Section B.2.10.1.7). However, increases in creatinine, uric acid, and liver function tests, and decreased haemoglobin were highlighted as more frequent in patients taking bempedoic acid than placebo. The company states that the elevations were asymptomatic and are therefore not considered potential or identified risks, but the ERG notes from the draft SmPC that they may require special consideration for some patients, such as those with a history of gout (which was considered a potential low but increased risk with bempedoic acid ([redacted]) compared with placebo ([redacted]) in the overall Phase 3 pool).

The ERG considers the data to illustrate generally low rates of adverse events with bempedoic acid and placebo, particularly in safety set 2. Where there are differences between groups, the rates in both groups are low. The ERG does not consider the extent of any of the differences in either population to suggest serious or unmanageable safety issues of bempedoic acid compared with

placebo. The data presented by the company are in line with the special warnings and precautions set out in the draft SmPC for bempedoic acid monotherapy provided in Appendix C.1 of the CS. While muscle symptoms are common adverse effects with statins, they do not appear to be associated with bempedoic acid alone, the draft SmPC highlights a [redacted]. The draft SmPC also [redacted].

The ERG notes that the none of the studies or safety sets are wholly reflective of bempedoic acid in combination with ezetimibe and maximally tolerated statins for the populations of interest (Table 10), where the company has positioned it in the UK. As such, there may be additional safety considerations associated with the drugs in combination that have not been captured fully by the studies.

3.3.4.2 FDC trial

The company presented safety data separately for the bempedoic acid plus ezetimibe FDC in section B.2.10.2, based on the 1002FDC-053 trial (see Table 10). Data were not reported as comprehensively as for the bempedoic acid trials and did not include types of SAE or AEs of special interest, but a summary was provided which has been adapted in Table 12.

Mean exposure was similar across groups and ranged from [redacted] days in the placebo group to [redacted] days in the FDC group. A similarly high proportion of patients in the FDC (62.4%) and bempedoic acid monotherapy groups (65.9%) had at least one TEAE, followed by the ezetimibe (54.7%) and placebo (43.9%) groups (Table 12). Rates of SAEs and discontinuations due to TEAEs were all between 8 and 12% in each of the active treatment groups (and lower in the placebo group), and there were no fatal TEAEs in any group. The proportion of TEAEs or serious TEAEs judged to be related to study treatment was not reported for the FDC study, but the company stated that most were judged not to be related (CS, Section B.2.10.2, pg. 141). The most common AE was nasopharyngitis which occurred in 6.8% of the bempedoic acid group, 4.7% of the FDC and ezetimibe groups and 0% of the placebo group. As for the bempedoic acid monotherapy trials, the ERG considers the data to illustrate generally low rates of adverse events across the FDC, bempedoic acid and ezetimibe groups, and differences between groups are not pronounced.

Table 12. Safety overview of bempedoic acid and ezetimibe FDC (safety set 5; adapted from CS, Table 42)

	FDC	Bempedoic acid	Ezetimibe	Placebo
N	108	110	86	41

Mean exposure (days)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 TEAE (%)	62.4	65.9	54.7	43.9
Patients with ≥ 1 serious TEAE (%)	9.4	8.0	10.5	2.4
Patients with ≥ 1 TEAE with a fatal outcome (%)	0	0	0	0
Patients with ≥ 1 TEAE leading to discontinuation of IMP (%)	8.2	10.2	11.6	4.9
Patients with any positively adjudicated CV or fatal clinical event (%)	Not performed			
AEs with a ≥ 1% difference between groups (%)				
Nasopharyngitis	4.7	6.8	4.7	0
Urinary tract infection	5.9	3.4	2.3	2.4
Arthralgia	1.2	4.5	3.5	2.4
Muscle spasms	2.4	1.1	4.7	0
Back pain	3.5	3.4	2.3	4.9
Bronchitis	3.5	0	3.5	0
Pain in extremity	2.4	2.3	1.2	2.4
Angina pectoris	NR	NR	NR	NR
Osteoarthritis	NR	NR	NR	NR
AAT increased	1.2	0	0	0

Abbreviations: AAT, aspartate aminotransferase; AE, adverse event; FDC, bempedoic acid and ezetimibe fixed-dose combination; TEAE, treatment-emergent adverse event.
Sources: CS Section B.2.10.2, Table 42.

The ERG considers the safety data presented by the company for the FDC in line with the special warnings and precautions set out in an updated draft SmPC provided by the company at the clarification stage, [redacted]

3.3.5 Mortality

Among the [redacted] patients in the four bempedoic acid placebo-controlled Phase 3 studies, there was a total of [redacted] fatal adverse events with [redacted] in patients treated with bempedoic acid and [redacted] in patients treated with placebo. The company reported that [redacted] fatal adverse events in the Phase 3 studies were determined [redacted]) by the investigator or the Sponsor Medical Monitor. The ERG notes that there were [redacted] fatal adverse events in the no or low dose statin pool of patients, although the ERG also notes that these were the shorter duration studies (12-weeks and 24-weeks rather than 52-weeks). In CLEAR Harmony, the incidence of fatal adverse events was [redacted] patients) in the bempedoic acid group and [redacted] patients) in the placebo group and in CLEAR Wisdom rates were slightly higher with [redacted] patients) in the bempedoic acid group and [redacted] patients) in the placebo group. The ERG notes that there was a higher rate of adjudicated cardiac deaths in the bempedoic acid patients in Safety set 1 (high-risk/long-term, moderate-high background statin studies) compared to in the placebo patients (0.5% versus 0.3%, respectively).

The company reported detailed information on fatal neoplasms (benign, malignant and unspecified) [redacted]

In summary, there was a low rate fatal adverse events in the Phase 3 bempedoic acid study's, but the ERG considers the current data to be unsuitable for assessing long-term mortality due to the relatively short follow-up and lack of statistical power to detect differences between treatment groups.

3.3.6 CV events

As discussed in Section 2.3.4, the only outcome data presented for bempedoic acid in relation to CV events was from descriptive analyses of the four Phase 3 CLEAR studies and preliminary data from the ongoing CLEAR-OLE study (detailed in Section 3.1). It should be noted that the CLEAR studies were not powered to detect differences between treatment groups in terms of CV events. All fatal events and potential CV events were assessed by a blinded independent clinical endpoints committee as part of the CV safety analysis. Events that were adjudicated as CV events included

The results suggest trends to lower rates of MACE in the bempedoic acid group when either the whole Phase 3 pool is considered or only the 52-week studies in high-risk patients (Table 13). The company also provided the results for time-to-first adjudicated MACE composite events and for the 5 component MACE (CV death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation or hospitalisation for unstable angina) the HR for bempedoic acid compared with placebo was 0.83 with a 95% confidence interval of 0.59 to -1.16. The inclusion of hospitalisations for heart failure did not substantially change the HR (0.90, 95% CI: 0.65 to 1.25). The ERG acknowledges that the studies are not powered to detect statistically significant between group changes but considers the data so far suggest no excess CV risk with bempedoic acid.

Table 13. Summary of the adjudicated MACE and non-MACE events with bempedoic acid (safety analysis set) (reproduced from Table 38, CS page 135)

	High-risk/long-term pool (pool 1)		Overall Phase 3 pool (pool 3)		CLEAR-OLE
	Bempedoic acid	PBO	Bempedoic acid	PBO	Bempedoic acid
Number in analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any positively adjudicated event (MACE or non-MACE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated MACE					
CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for unstable angina	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary revascularisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other adjudicated non-MACE events					
Non-CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-coronary arterial Revascularisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; PBO, placebo.
Source: Esperion Therapeutics data on file (17).

3.4 Critique of the network meta-analyses

3.4.1 Critique of the methods and included studies in the network meta-analyses

The company conducted two NMAs in order to compare bempedoic acid and bempedoic acid + ezetimibe (or FDC) with the comparators specified in the NICE final scope in the statin intolerant population and the maximally tolerated statin population. As discussed in Section 3.1, the company conducted a SLR to identify studies for inclusion in the two NMAs (statin intolerant NMA and maximally tolerated statin NMA). A total of 40 studies were included in the company's updated NMAs in their clarification response (compared to 53 studies in their original NMAs), 10 in the statin intolerant NMA, and 30 in the maximally tolerated statins NMA (See Section 3.4.2 for network diagrams). The ERG notes that the company are positioning bempedoic acid and FDC for use in patients who have received prior ezetimibe (Section 2.3), but the ERG is concerned that the data used to inform the NMAs includes patients on a mix of prior lipid lowering therapies (LLTs) with many patients not on background ezetimibe therapy – the inclusion criteria for the company's NMA

did not restrict studies based on the presence of background or concomitant ezetimibe therapy. The ERG's notes from its clinical experts that bempedoic acid is likely to be used after ezetimibe, as an add on therapy rather than a replacement for ezetimibe and therefore the ERG considers the studies in the NMA should have been restricted to those in patients on prior and concomitant ezetimibe.

In addition to concerns regarding the use of background ezetimibe and other LLTs in the studies used in the NMAs, the ERG notes that there is wide variability in other patient baseline characteristics which the ERG's clinical experts report could affect prognosis. For example, some patients in the statin intolerant NMA were on statins and some patients in the maximally tolerated statin NMA were not on statins at baseline and did not receive concomitant statin therapy during the study. The ERG also notes that some studies included washout periods of baseline LLTs, such as ezetimibe, prior to randomised treatment. Generally, there was a lack of consistent reporting of baseline patient characteristics and many studies did not report some of the key baseline characteristics of relevance to this decision problem, making it hard to fully cross compare studies (Appendix 9.3). The threshold used to define baseline LDL-C inclusion criteria varied between many of the included studies in both NMAs, with some studies permitting patients with LDL-C >70 mg/dL and others requiring a minimum LDL-C of 130 mg/dL. Study populations in terms of proportions with HEFH, primary non-familial hypercholesterolaemia and mixed dyslipidaemia were also not reported or variable between studies. Similarly, there was mixed populations across studies in terms of primary or secondary CV prevention although data were not reported for all studies to make detailed assessments of the comparability of the populations in the two NMAs. The ERG does however have concerns that the data extraction tables provided by the company were incomplete, in particular for the bempedoic acid studies where further information are likely available in the clinical study reports.

The ERG requested the company amend their NMAs during clarification and the ERG's suggestions for changes included that the company refine their inclusion criteria for the NMAs, for example:

- by removing studies exclusively in patients with HeFH or diabetes,
- ensuring doses of drugs included in the network were similar,
- using subgroup data to ensure that patients met the appropriate NMA population in terms of being on maximally tolerated statin dose or being statin intolerant.

The aim of this was to help address some of the clinical heterogeneity in the company's NMAs, although the ERG notes that substantial heterogeneity still remains. The ERG discusses only the results and studies included in the updated NMAs in this report as the company used the updated NMAs to inform their revised cost-effectiveness base case results.

The ERG is nevertheless still concerned by the studies included and excluded in the updated NMA but due to time constraints has been unable to fully assess all 43 studies included in the company's original NMAs in detail. The ERG's concerns about studies in the updated NMA still relate to the substantial clinical heterogeneity present. In addition, the ERG is concerned that the company erroneously removed ODYSSEY Long Term from the maximally tolerated statin NMA for having an exclusive diabetic population when less than 50% of patients were diabetic, and that the company erroneously included ODYSSEY Mono[18], a study where no one had received prior LLT and yet they should have been on maximally tolerated statin.

No subgroup analyses based on CV risk or presence of HeFH were conducted by the company although these were deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394). The ERG notes that the data available may limit the ability of the company to conduct these analyses in the prior ezetimibe population but nevertheless the ERG considers them to be potential subgroups of interest.

The company reported that the methods used for conducting the NMAs followed those recommended in the NICE decision support unit technical support documents and the ISPOR task force recommendations (Jansen *et al.* 2014[19]). The outcome used in the company's NMAs was percentage change from baseline LDL-C at 12 weeks. The ERG notes that the company have data on bempedoic acid from the 52-week CLEAR Harmony and CLEAR Wisdom trials and therefore requested during clarification that a later 24-week timepoint be used for the analyses. The company's response was that 12-weeks was the primary endpoint for the Phase 3 studies and the changes in efficacy for bempedoic acid between weeks 12 and 24 was non-significant (CQ response A1, page 6). The ERG does not consider this sufficient justification for the use of the 12-week data and notes that Figure 1 in the clarification response demonstrates a slight waning of treatment effect with bempedoic acid in terms of change in LDL-C from baseline at 24 weeks compared with at 12 weeks. The ERG also considers it important to highlight that bempedoic acid is a long-term treatment and therefore considers data from the latest timepoint more reflective of its effectiveness in clinical practice. The ERG notes that the comparators may have different treatment waning effects

and therefore it is not possible to predict the direction of any bias related to limiting the analyses to the earlier 12-week timepoint.

The NMAs conducted by the company make use of the code presented in NICE DSU TSD 2 but additionally include a covariate adjustment for baseline LDL-C. The ERG is concerned about the implementation of the covariate adjustment as it is applying an adjustment independent of the treatment effect when the rationale for the adjustment is due to the purported correlation between the two. The ERG considers that the impact of this will be to cause additional uncertainty in the analysis. In the opinion of the ERG, the company should have addressed this by using the IPD from the relevant CLEAR studies to establish the correlation between baseline LDL-C and treatment effect, and then assumed this correlation held across all studies included in the network. The required methods to adopt this approach are covered in NICE DSU TSD 20. The ERG also considers that further co-variate adjustments could have been included in the NMAs and that their inclusion may have helped to reduce the large amount of clinical and statistical heterogeneity present in the company's NMAs. The ERG notes that the company's rationale for not including further covariate adjustments was that potential variables of interest were not consistently reported across studies.

In terms of software to run the NMAs, the ERG notes that the company used recognised statistical packages (R software and JAGS) although limited detail were provided and so the ERG were unable to replicate the company's results. The company explored model fit and statistical heterogeneity in their NMA results using appropriate methods including monitoring for DIC, conducting node splitting, comparing indirect and direct estimates and calculation of Cochrane's Q. Results of these are discussed in Section 3.5.1.2.

At the request of the ERG, the company provided the code and the data set for its NMAs for the ERG to validate its analyses. The ERG started by attempting to validate the Statin Intolerant NMA. However, the ERG was unable to replicate the results presented by the company. This could be because:

- incomplete or inaccurate data were provided;
- the company incorrectly used standard deviations in the analyses that required the use of standard errors (although when the ERG estimated the standard errors the results obtained were still substantially different);

- some unforeseen difference in the way the analysis is specified and run between the company's use of R and JAGS, and the ERG's use of OpenBUGS.

However, in attempting the validation the ERG became aware of the following issues:

- the random effects NMA converges on the posterior distribution after a substantial number of iterations (1.2 million in the company's base case);
- the results appear to be sensitive both to the prior distributions specified and to the number iterations the model is run.

The ERG notes that these issues are not present when the company's NMA is run without the covariate adjustment for baseline LDL-C level. This further supports the view of the ERG that the correlation between treatment effect and baseline LDL-C would be more appropriately captured by following the recommendations in NICE DSU TSD 20.

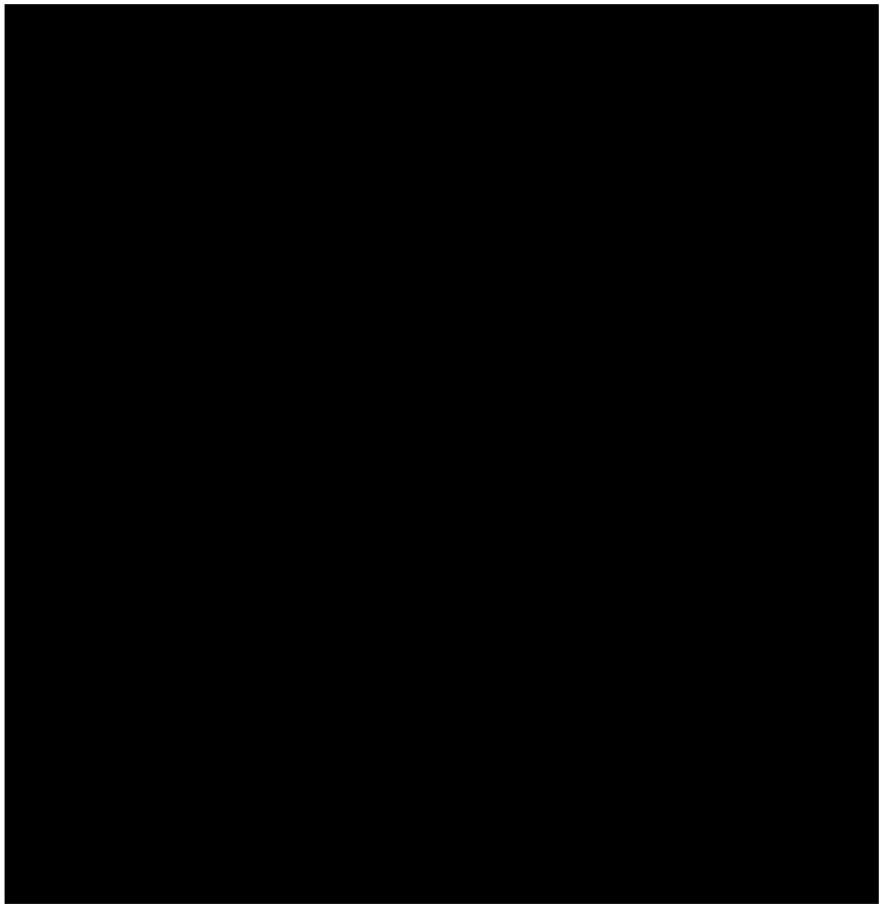
3.4.2 Network meta-analysis results

As discussed in Section 3.4.1, the ERG does not consider the results of either the company's original or updated NMAs to be suitable for addressing the prior ezetimibe population in which they are positioning bempedoic acid and the FDC in statin-intolerant or contra-indicated patients. In addition, the ERG has concerns about the robustness of the company's NMA methods and the presence of high levels of clinical and statistical heterogeneity. The ERG presents only the updated NMA results below as these are used in the company's economic model base case. However, the ERG notes that the results of the company's original NMAs were in keeping with the updated NMAs results. Nevertheless, the ERG recommends the results of the company's NMAs should be interpreted with considerable caution due to the high levels of clinical and statistical heterogeneity still present. In addition, it should be remembered that the NMAs do not directly address the population of interest, patients with prior ezetimibe. The ERG is also concerned about the company's NMA methodology as it appears that there is double counting of patients in the NMA through the use of 12 and 24 week data for some of the alirocumab trials. The ERG notes that alirocumab patients who have received 75 mg and also been uptitrated to 150 mg at 12 weeks may have been included in both the 75 mg and 150mg analyses albeit using data from different timepoints (12 weeks and 24 weeks, respectively).

3.4.2.1 Statin-intolerant NMA results

The network diagram for the seven included studies in the statin intolerant updated NMA lacks study name detail, nevertheless it indicates the number of trial arms for each direct comparison with data in the network (Figure 2). The ERG notes that even with adjustment for baseline LDL-C, there was an I^2 of 66.1% suggesting high levels of statistical heterogeneity in the network and the ERG therefore considers the results of the analysis are unlikely to be reliable. Cochrane's Q was 14.8 with 5 degrees of freedom and the DIC was 112.2 for the random-effects model which was slightly lower than that for the fixed effects model (116.7) and not changed by the removal of the baseline LDL-C covariate (111.3). The company reported in their clarification responses that, "An explanatory variable that has not been included in the analysis may account for some of the underlying heterogeneity, such as the level of background ezetimibe use.". The ERG considers this of great importance given that the population in which the company propose bempedoic acid will be used is in patients after ezetimibe therapy and as such they would be on background ezetimibe.

Figure 2. Statin-intolerant updated NMA network diagram (reproduced from Figure 7, Clarification response page 78)



AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol.

The results of the company's updated NMA suggest that compared with ezetimibe, bempedoic acid shows [redacted] in mean percentage LDL-C change from baseline (Table 14; [redacted]). [redacted]

Table 14. Company's updated NMA results in statin-intolerant patients (Adapted from CQ response appendix Table 33)

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value
Bempedoic acid	[redacted]	[redacted]	[redacted]
Bempedoic acid + ezetimibe	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]
EvoMab + ezetimibe[a]	[redacted]	[redacted]	[redacted]
Alirocumab (75 mg)	[redacted]	[redacted]	[redacted]
Alirocumab (150 mg)	[redacted]	[redacted]	[redacted]

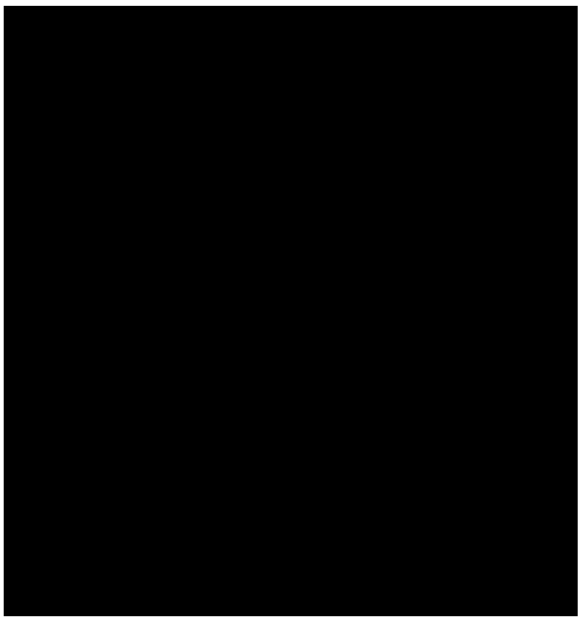
Abbreviations: CrI, credible interval; EvoMab, evolocumab; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis.
Note: Other treatments were included in the evidence network but were not reported in the table as they are not comparators. P value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe. No trial data were identified for alirocumab + ezetimibe.
a Evolocumab + ezetimibe estimates are based on data for 30 patients in GAUSS (Sullivan et al., 2012).
Results used in the cost-effectiveness analyses presented in the submission are highlighted in bolded text.

3.4.2.2 Maximally tolerated statin NMA results

The network diagram for the 33 included studies in the maximally tolerated statin updated NMA is lacking study name detail similar to the statin intolerant NMA network diagram, nevertheless it indicates the number of trial arms for each direct comparison with data in the network (Figure 3). The ERG notes that the I^2 is even higher in the maximally tolerated statin updated NMA compared to in the statin intolerant updated NMA suggesting the presence of substantial heterogeneity again (I^2 of 86.8%) and the ERG therefore considers the results of the analysis are unlikely to be reliable. Cochrane's Q was 324.7 with 43 degrees of freedom, which again is high. The DIC for the random effects model with the LDL-C covariate adjustment was 509.3 which was substantially lower than the DIC for the fixed-effects model with covariate adjustment (719.7) although the removal of the covariate from the random effects model had little effect on the DIC (515.9 without baseline LDL-C included as a covariate). The ERG notes that there was a difference observed in the direct and indirect evidence for some of the comparisons which is concerning as it suggests the NMA results may not be robust. The company again reported that, "An explanatory variable that has not been included in the analysis may account for some of the underlying heterogeneity, such as the level of

background statin or ezetimibe use". The ERG agrees that differences in the baseline characteristics of patients included in the studies in the NMA is likely to be a source of the heterogeneity.

Figure 3. Maximally tolerated statins network diagram for company's updated NMA (reproduced from Figure 16, clarification response page 88)



AliMab = alirocumab; BA = bempedoic acid; EvoMab = evolocumab; EZE = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol.

The results of the company's NMA suggest that compared with ezetimibe [redacted] in mean percentage LDL-C change from baseline (Table 15; [redacted], respectively). [redacted] compared with ezetimibe + statin. The ERG notes that alirocumab (150 mg) + statin + ezetimibe [redacted] compared with alirocumab (150 mg) + statin, [redacted] However, the ERG also notes that the [redacted]

Table 15. Company's updated NMA results in maximally tolerated statin patients (Adapted from CQ response appendix Table 34)

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value
Bempedoic acid + statin	[redacted]	[redacted]	[redacted]
FDC + statin[a]	[redacted]	[redacted]	[redacted]
EvoMab + statin	[redacted]	[redacted]	[redacted]
AliMab (75 mg) + statin	[redacted]	[redacted]	[redacted]
AliMab (150 mg) + statin	[redacted]	[redacted]	[redacted]
AliMab (75 mg) + statin + ezetimibe	[redacted]	[redacted]	[redacted]
AliMab (150 mg) + statin + ezetimibe	[redacted]	[redacted]	[redacted]

Treatment	Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
	Mean	95% CrIs	*P* value

Abbreviations: AliMab, alirocumab; CrI, credible interval; EvoMab, evolocumab; FDC, bempedoic acid and ezetimibe fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis.
[a] These data are used in the economic model to represent the efficacy of bempedoic acid + ezetimibe separate tablets in patients receiving maximally tolerated statin. Pharmacokinetic studies have shown the two presentations to be equivalent (see Appendix M).
Note: other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with ezetimibe.

3.5 ERG NMAs

3.5.1.1 Methods

Due to the ERGs concerns with the clinical, methodological and statistical heterogeneity in the company's NMAs the ERG explored alternative options. The ERG considers it important to highlight that the ERG NMAs are illustrative of potential alternatives and due to time and resource constraints the ERG has been unable to fully assess all potentially relevant studies for inclusion in its analyses. In addition, the ERG did not have access to the prior ezetimibe subgroup data for each of the company's bempedoic acid studies and therefore the ERG analyses are known to omit some relevant data on the key drug of interest. The ERG therefore recommends that the results of its analyses are interpreted with caution.

The ERG aimed to conduct NMAs for the statin intolerant population and the maximally tolerated statin population to address the population in which the company is positioning bempedoic acid and the FDC, that is in patients following ezetimibe therapy. The ERG therefore only considered studies or subgroups in patients with prior ezetimibe at baseline suitable for inclusion in its two NMAs. A consequence of this is that all randomised treatments are assumed to also be receiving ezetimibe; e.g. a treatment group receiving placebo is considered to be receiving ezetimibe in the analysis.

The ERG considers it important to highlight that the key assumption being made in the comparison of the ERG and company NMA results is that the use of data in patients with prior ezetimibe for all treatments in the ERG's NMA is the equivalent of the analyses in the company's NMAs where all patients are randomised to treatment + ezetimibe (where treatment also includes placebo or no treatment). This assumption is therefore also made for the comparison of alirocumab 150 mg in the ERG and company NMAs, in that in the ERG analysis alirocumab 150 mg + background ezetimibe is the equivalent to alirocumab 150 mg + ezetimibe in the company submission.

The ERG identified studies for inclusion in its NMAs from the studies included in the company's original NMAs – although, as mentioned, above the ERG was unable to include all the appropriate data from the bempedoic acid studies and the ERG's appraisal of studies was not sufficiently robust to enable reliable conclusions to be drawn from the results and so they should be considered exploratory.

The ERG used the same code that the company sourced from the example provided in NICE DSU TSD 2 and initially attempted to use the covariate adjustment implemented by the company. However, when using this adjustment the ERG's analyses demonstrated the same issues observed in the company's analyses (see Section 3.4.2) and so the ERG presents only unadjusted results. The ERG's results were based on a burn-in of 60,000 followed by results calculated from 60,000 iterations (i.e. when the sampling had converged on the posterior distribution), and with uninformed priors. The ERG used fixed and random effects models for its analyses with both NMAs providing similar DIC statistics for both models (Table 16). The ERG favoured the fixed effects results due the small number of studies informing each analysis (i.e. there was insufficient evidence to inform the between trial heterogeneity and so this was in effect "defined" by the uninformed prior assigned by the ERG in the random effects model).

Table 16. DIC for ERG's NMAs

Model	ERG's Statin intolerant NMA DIC	ERG's Maximally tolerated statin NMA DIC
Fixed Effects	27.32	20.81
Random effects	28.53	20.77

Abbreviations: DIC, deviance information criterion; ERG's, evidence review group's; NMA, network-metanalysis.

3.5.1.1.1 Statin intolerant ERG NMA studies

For the statin intolerant NMA, the ERG identified two studies with suitable data on patients who had received prior ezetimibe, CLEAR Tranquility and ODYSSEY CHOICE II.[20] CLEAR Tranquility provided data on bempedoic acid versus placebo and the ERG considered all patients to have received prior ezetimibe due to the 4-week single blind run-in. The ERG considers that CLEAR Serenity should also have been included to inform bempedoic acid versus placebo but unfortunately the ERG did not have access to the relevant subgroup data to enable its inclusion in the ERG NMA.

ODYSSEY CHOICE II was a 24-week three-armed randomised controlled trial with patients randomised to placebo, alirocumab 150 mg every four weeks (Q4W) or 75 mg every two weeks (Q2W), with dose adjustment to 150 mg Q2W at week 12 if week 8 predefined LDL-C target levels were not met. Following seeking clinical expert advice, the ERG concluded that the 24-week alirocumab data is relevant to UK clinical practice as if patients do not respond to the lower dose they would be up titrated and the ERG also notes that only 24-week data were available in the prior ezetimibe subgroup. The ERG considered the total dose from the 75 mg two weekly and 150 mg four weekly regimens to be equivalent and thus combined them in the NMA using only the 24-week data. The ERG notes that only 36% of the 75 mg two weekly patients and 49% of the 150 mg four weekly patients received the dose increase to 150 mg two weekly. The ERG also notes that 9.87% of patients in ODYSSEY CHOICE II did not meet the criteria for statin associated muscle symptoms (i.e. statin intolerance) although they were not receiving a statin and classed as moderate CV risk.

The ERG notes that there was a notable difference in baseline LDL-C between CLEAR Tranquility (mean baseline LDL-C of 123.0 mg/dL to 129.8 mg/dL for each study arm) and ODYSSEY CHOICE II (mean baseline LDL-C of 156.6 mg/dL to 167.5 mg/dL for each study arm) and as detailed above, this is not accounted for in the NMA due to issues with applying covariate adjustment for a treatment dependent variable (as described in Section 3.4.2).

In summary, only two studies were included in the ERG statin intolerant NMA and they provided data only for placebo, bempedoic acid and alirocumab 150mg. The ERG acknowledges that there are still sources of clinical heterogeneity even in this much reduced network of trials as 12-week data are used for bempedoic acid and 24-week data for alirocumab and 10% of patients in ODYSSEY CHOICE II may not have been statin intolerant or ineligible. However, the ERG considers the data in its 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.

3.5.1.1.2 Maximally tolerated statin ERG NMA studies

CLEAR Harmony provided data on bempedoic acid and placebo, although arm level data were not available which limited the methodology for the NMA. ODYSSEY LONG TERM was a randomised

controlled study in patients on maximally tolerated statins with or without other lipid lowering therapy and it reported subgroup data for patients on ezetimibe at baseline. Patients in ODYSSEY LONG TERM were randomised to alirocumab 150 mg every two weeks or placebo for 78 weeks with the primary analysis conducted at 24 weeks. The ERG notes that mean baseline LDL-C was similar between CLEAR Harmony (120.93 mg/dL) and ODYSSEY LONG TERM (122.3 mg/dL) and thus considers covariate adjustment for baseline difference is less important in this NMA.

In summary, there are two trials in the ERG's maximally tolerated statin NMA and they provide data for bempedoic acid, placebo and alirocumab 150 mg Q2W in patients on background ezetimibe. The ERG notes there is a difference in outcome measurement with 12-week data used from CLEAR Harmony and 24-week data from ODYSSEY LONG TERM but the ERG considers the company should have 24-week data from CLEAR Harmony in addition to further data on bempedoic acid from CLEAR Wisdom.

3.5.1.2 Results

As discussed in Section 3.5.1.1, the comparison of the ERG and company NMAs presented below assumes that the use of data in patients with a history of prior ezetimibe at baseline for all treatments in the ERG's NMA is the equivalent of the analyses in the company's NMAs where all patients are randomised to treatment + ezetimibe (where treatment also includes placebo or no treatment). The results presented from the ERG NMAs below are thus labelled as treatment + ezetimibe versus ezetimibe but actually reflect treatment + background ezetimibe versus placebo + background ezetimibe. The ERG has assumed that patients in the studies included in the ERG NMAs were allowed to continue on their background LLT's (including statin and/or ezetimibe).

3.5.1.2.1 Statin intolerant ERG NMA results

The results of the ERG analysis for the statin intolerant NMA are presented alongside the results from the company's updated NMA in Table 17. The ERG considers it important to highlight that the ERG's NMA comprises only patients with prior ezetimibe therapy at baseline, whereas the company NMA includes patients both with and without prior ezetimibe therapy. The placebo arm in the ERG analysis therefore contains patients on ezetimibe although it is not clear what proportion of patients remained on ezetimibe throughout the studies The difference in mean percentage change from baseline LDL-C with bempedoic acid compared to ezetimibe was [redacted] and ERG's (-28.38%) NMA [redacted] for bempedoic acid + background ezetimibe versus placebo + background ezetimibe, they

suggest no statistically significant difference although the trial informing bempedoic acid demonstrated a significant difference. The ERG notes that the difference in mean percentage change in LDL-C from baseline with bempedoic acid compared to ezetimibe in the NMA and CLEAR Tranquility were similar (-28.38, ERG NMA and -28.5, CLEAR Tranquility). The ERG considers that [redacted] is likely to be related to the small number of studies in the analysis compared to in the company's NMA. However, [redacted], the ERG considers the ERG NMA results are likely to be more accurate than the company's given the issues with the company's NMA highlighted in Section 3.4 .

Mean percentage change in LDL-C for alirocumab 150 mg cannot be compared between the ERG (-58.09%) and company [redacted] NMAs because in the company NMA patients in the alirocumab arm were not randomised to concomitant ezetimibe and so only patients in the ezetimibe arm have ezetimibe. In contrast, patients in both the alirocumab and placebo arms of the ERG NMA have received prior ezetimibe.

Table 17. ERGs statin intolerant NMA results and the company's updated NMA results.

	ERG's NMA			Company's updated NMA		
	Estimated difference in % change in LDL-C from baseline compared with ezetimibe			Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
Treatment	Mean	95% CrIs	*P* value	Mean	95% CrIs	*p*-value
Bempedoic acid + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AliMab 150 mg + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AliMab, alirocumab; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NMA, network meta-analysis.
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 alirocumab 150 mg alone versus ezetimibe, they therefore can not be compared with the ERG NMA results as patients in only one arm of the company's NMA have received ezetimibe whereas both treatment arms of the ERG's NMA have received ezetimibe.

3.5.1.2.2 Maximally tolerated statin ERG NMA results

The results of the ERG analysis for the maximally tolerated statin population are presented alongside the results from the equivalent treatments in company's updated NMA in Table 18. The ERG considers it important to highlight that the ERG's NMA comprises only patients with prior ezetimibe therapy at baseline, whereas the company NMA includes patients both with and without prior ezetimibe therapy. [redacted] However, the ERG considers the studies in its NMA to be more clinically

homogenous and to closer reflect the population of patients on prior ezetimibe therapy in which the company are positioning bempedoic acid. In addition, the ERG considers the ERG NMA results are likely to be more accurate than the company's given the issues with the company's NMA highlighted in Section 3.4.

Table 18. ERGs maximally tolerated statin NMA results and the company's updated NMA results.

	ERG's NMA			Company's updated NMA		
	Estimated difference in % change in LDL-C from baseline compared with ezetimibe			Estimated difference in % change in LDL-C from baseline compared with ezetimibe		
Treatment	Mean	95% CrIs	*P* value	Mean	95% CrIs	*P* value
Bempedoic acid +ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AliMab 150 mg + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AliMab, alirocumab; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NMA, network meta-analysis.
Note: *P* value relates to the difference in percentage change from baseline in LDL-C compared with placebo.

3.6 Conclusions of the clinical effectiveness section

The company submitted clinical evidence to the National Institute for Health and Care Excellence (NICE) in support of bempedoic acid as a monotherapy and in a fixed dose combination (FDC) with ezetimibe for primary hypercholesterolemia (HC) and mixed dyslipidaemia. The NICE final scope specified separate comparators for the following four populations:

- Population 1: When statins are contraindicated or not tolerated;
- Population 2: When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL C;
- Population 3: When maximally tolerated statin dose does not appropriately control LDL C; and
- Population 4: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL C.

However, the company propose that bempedoic acid, alone or in the FDC with ezetimibe, will be used in only populations 2 and 4. The clinical evidence submitted by the company comprised seven RCTs for bempedoic acid (one RCT included FDC) and two network meta-analyses (NMAs) but the

clinical data presented for bempedoic acid, are not presented separately for the prior ezetimibe populations specified for the comparators and in which the company is positioning bempedoic acid and FDC. The ERG's clinical experts support the company view that bempedoic acid or FDC is unlikely to be used prior to ezetimibe although the ERG notes that [redacted] The ERG also notes that there are subgroup data available from the bempedoic acid trials in patients who have received prior ezetimibe but that the main clinical data presented in the CS are for the whole trial populations. With the exception of the CLEAR Tranquility study, the bempedoic acid studies comprise mainly of patients who have either not received prior ezetimibe at baseline or who have undergone a washout period of prior lipid lowering therapies (LLTs). The ERG's clinical experts reported that in clinical practice, patients would be expected to continue on their prior LLTs alongside bempedoic acid and therefore studies with washout periods or lacking concomitant ezetimibe do not reflect how bempedoic acid would be used in the company's proposed positioning in clinical practice.

The two NMAs conducted by the company were for each of the two populations in which the company is positioning bempedoic acid and FDC:

- Population 2 = statin intolerant NMA; and
- Population 4 = maximally tolerated statin NMA.

The ERG considers the key issues in the clinical effectiveness evidence directly relate to these two NMAs and that they are unfit for decision making due to clinical, methodological, and statistical heterogeneity. The ERG's issues in the clinical effectiveness evidence include the use of incorrect populations in the NMAs to address the population in whom ezetimibe does not appropriately control LDL-C with studies included that have a mix or even no patients with prior ezetimibe therapy. In addition, there is substantial clinical heterogeneity in the studies included in the company's NMAs which includes differences between studies in terms of baseline cardiovascular risk, statin intensity, proportion of patients receiving lipid lowering therapy (LLT) for primary prevention, and proportions of patients with heterozygous familial hypercholesterolaemia (HeFH). The company's updated NMAs may also be missing studies of relevance (e.g. ODYSSEY Long Term) and use alirocumab study data from arms where up titration has occurred thus implying double counting (through the use of 12- and 24-week data).

The ERG considers the company to be making strong assumptions of efficacy in the absence of robust subgroup analyses for primary or secondary prevention (CV risk) patients and the presence of

HeFH, and notes that these were deemed important subgroups in the NICE final scope and in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively).

The ERG also has concerns with the methodology used by the company in the NMAs as the ERG was unable to replicate the results obtained from the company's NMAs. The ERG considers the company has used incorrect methods to adjust for differences in baseline LDL-C in the NMAs and should have followed the guidance provided in NICE DSU TSD 20. These methodological concerns along with the presence of high levels of statistical heterogeneity in the results of the company's NMAs, despite the inclusion of covariate adjustment for baseline LDL-C differences and updates to the NMAs during the clarification stage, suggest that the results of the company's NMAs are unreliable.

The ERG's exploratory NMAs used only the population of patients who have received prior ezetimibe and are assumed to continue ezetimibe throughout the study. However, the ERG was unable to include all of the appropriate data from the bempedoic acid studies and the ERG's appraisal of studies was limited. As such, the results of the ERG's analyses should also be interpreted with caution.

4 Cost effectiveness

4.1 ERG comment on the company's review of cost effectiveness evidence

The company carried out a systematic literature review (SLR), using a single search strategy, to identify existing cost-effectiveness evidence, health-related quality of life (HRQoL) evidence, and cost and resource use evidence of bempedoic acid and comparator interventions in adults with:

- hyperlipidaemia at high risk or with atherosclerotic cardiovascular disease (ASCVD) who require further lipid-lowering therapy despite statin treatment at the maximally tolerated dose or who are considered statin intolerant; and
- heterozygous familial hypercholesterolaemia (HeFH) and non-familial hypercholesterolaemia.

A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 19. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 19. Summary of ERG's critique of the methods implemented by the company to identify health economic evidence

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Searches	Appendix H	Appendix H	Appendix H	Appropriate.
Inclusion criteria	Table 49, appendix H	Table 49, appendix H	Table 49, appendix H	Restrictions to English-language and inclusion of publications from 2015 onward is reasonable. Unclear if PICOS criteria for intervention, comparators and outcomes is appropriate.
Screening	Appendix H	Appendix H	Appendix H	Appropriate.
Data extraction	Description in Appendix H Results in Table 51, Appendix H	Appendix H Results in Table 53, Appendix I	Appendix H Results in Table 56, Appendix J	Appropriate.
QA of included studies	Drummond checklist[21] in Appendix H	Studies assessed against NICE reference case[22] in Appendix I	No QA checklist completed	Drummond checklist appropriate. Checklists such as CASP (recommended in DSU TSD 9) would be preferred for HRQoL evidence.[23]

Abbreviations: CASP, Critical Appraisal Skills Programme; CS, company submission; DSU, Decision Support Unit; ERG, evidence review group; HRQoL health related quality of life; PICOS, population, intervention, comparator, outcome, study design; QA, quality assessment; TSD, Technical Support Document

Overall, a total of 26 cost-effectiveness studies, 18 HRQoL studies and 53 resource and cost use studies were included. The cost-effectiveness studies included four Health Technology Assessments (HTAs), including the NICE appraisal of alirocumab (TA393) and evolocumab (TA394), and the Scottish Medicine Appraisal (SMC) review of alirocumab (1147/16) and evolocumab (1148/16).[24-27] Nonetheless, the ERG is unclear why other relevant HTA assessments, such as TA385, and clinical guidelines (CGs), such as CG181, were not identified through the SLR.[28, 29]

Furthermore, the inclusion criteria for economic evaluations might have been too restrictive, as only incremental costs and outcomes seem to have been specified. Even though a broader specification of health economic terms in the inclusion criteria would have been preferred, the search terms used in the SLR were not restricted by the latter, thus the ERG considers this to have had a limited impact on results.

Overall, the ERG is moderately concerned that the company's search strategy might have missed relevant economic evaluations, and/or that the reporting of SLR's results is not very clear. For example, the company uses several studies to parameterise the model that have not been reported in the SLR. However, given that the company included all the relevant NICE technology assessments and CGs in their economic analysis (even the ones not identified in the SLR), the ERG does not anticipate the company's approach to the SLR to cause any major issues.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 20 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.[22, 30]

Table 20. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, direct effects on patients.
Perspective on costs	NHS and PSS	Yes.

Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, lifetime.
Synthesis of evidence on health effects	Based on systematic review	Partly, the company uses several studies to parameterise the model that have not been reported in the SLR.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Partly, the source included people with and without a history of CVD.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: ERG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year; SLR, systematic literature review

4.2.2 Population

The positions in the treatment pathway considered in the company's economic analysis are based on situations when ezetimibe does not appropriately control LDL-C and these situations cover two of the four populations included in the NICE final scope.[30] The two populations considered by the company are also split into subpopulations "a" and "b". Subpopulations "a" relate to situations when alirocumab or evolocumab are not appropriate and subpopulations "b" relate to situations when alirocumab or evolocumab are appropriate. To achieve this, the company considered the low-density lipoprotein cholesterol (LDL-C) concentrations (mmol/l) above which alirocumab and evolocumab are recommended by NICE (Table 5 of the CS, document B).

The four subpopulations considered for the economic analysis are:

- Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;

- Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;
- Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,
- Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

The company did not submit cost-effectiveness results for populations 1 (people in whom statins are contraindicated or not tolerated) and 3 (people in whom maximally tolerated statin dose does not appropriately control LDL-C) because the company did not anticipate bempedoic acid or bempedoic acid in a fixed-dose combination (FDC) with ezetimibe to be used prior to ezetimibe in the treatment pathway in the National Health Service (NHS). During the clarification stage, the company also noted that the [redacted]

The CLEAR studies, described in detail in Section 3.2, were used to inform the patient demographics at baseline in the company's model. Baseline demographics for each population are summarised in Table 21. Based on the proportion of prior CV events in the CLEAR studies, the simulated cohort in each population includes primary and secondary prevention patients. In consequence, subpopulations 4a, 4b and 2b are largely representative of a secondary prevention population, while subpopulation 2a is largely representative of a primary prevention population. For secondary prevention patients, CV event history was taken from Ward *et al.* 2007 and these estimates are outlined and critiqued in the following subsections.[31]

Table 21. Baseline characteristics based on the CLEAR studies (taken from the economic model)

Characteristic	Population 2[g] (no or low dose statin)	Population 4[h] (max dose statin)
Mean age, years	[redacted]	[redacted]
Female %	[redacted]	[redacted]
Diabetic %	[redacted]	[redacted]
HeFH %	[redacted]	[redacted]
Prior CV event % [b]	[redacted]	[redacted]
Prior CV event [b] and non-PCSK9i eligible % (subpopulation a)	[redacted]	[redacted]
Prior CV event [b] and PCSK9i eligible % (subpopulation b)	[redacted]	[redacted]
HeFH in secondary prevention %[c]	[redacted]	[redacted]
Recurrent/polyvascular CV event % [d]	[redacted]	[redacted]
Mean baseline LDL-C (mmol/L)		

Non-PCSK9i eligible (subpopulation a) [e]	[redacted]	[redacted]
Non-PCSK9i eligible data used to inform the economic analysis (subpopulation a) [e,f]	[redacted]	[redacted]
PCSK9i eligible data used to inform the economic analysis (subpopulation b) [e]	[redacted]	[redacted]

Abbreviations: CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin / kexin type 9 inhibitor

[a] rounded up to 65.0 for the analyses

[b] prior event implies more than zero prior events

[c] % only reported in CLEAR Harmony and this % was applied to all populations included in the economic analysis

[d] recurrent event implies more than one prior event

[e] based on NICE recommendations provided in Table 5 in the CS, document B

[f] for subpopulations 2a and 4a, the mean baseline LDL-C data from all patients included in the CLEAR trials were used in the economic analysis

[g] based on patients included in CLEAR Tranquility and CLEAR Serenity

[h] based on patients included in CLEAR Wisdom and CLEAR Harmony

4.2.2.1 Distribution of the secondary prevention patients at baseline

In line with CG181 and TA385, the company based the distribution of CV event history in secondary prevention patients on the data reported in Ward *et al.* 2007 (Table 22).[28, 29, 31] During the clarification stage, the company added that prior TIA and SA events were not included as prior CV events in the model to better align with the starting cohort in TA385, and the definition of prior CV/high risk in TA393 and TA394.[26, 27, 29] The ERG also considers it important to clarify that secondary prevention patients enter the model at cycle 0 having had a CV event before they enter the model.

Table 22. Distribution of the secondary prevention patients at the start of model time by age, sex, and type of prior CV event

Sex	Age (years)	Post-UA	Post-MI	Post-IS	Post-TIA	Post-SA
Male	65-74	20%	52%	28%	0%	0%
Female	65-74	21%	42%	38%	0%	0%

Abbreviations: IS, ischaemic stroke; MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina

As shown previously in Table 21, the proportion of males and proportion of patients with a prior CV event depends on the selected population for analysis. Thus, Table 23 provides the proportions that were used to allocate patients in the cohort into a starting health state, according to the selected population for analysis.

Table 23. Distribution of prior CV events by population, company's base case analyses

Prior CV event	Population 2 (no or low dose statin)		Population 4 (max dose statin)	
	a (non-PCSK9i eligible)	b (PCSK9i eligible)	a (non-PCSK9i eligible)	b (PCSK9i eligible)
UA	4.2%	20.0%	19.3%	19.5%
MI	9.5%	45.2%	47.5%	48.1%
IS	7.0%	33.2%	29.8%	30.2%
No prior CV event	79.3%	1.7%	3.5%	2.2%

Abbreviations: IS, ischaemic stroke; MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina

4.2.2.2 ERG critique

One of the ERG's main concerns is that the modelled population only covers part of the population included in the NICE final scope[30] and anticipated marketing authorisation presented in the CS for bempedoic acid due to the high proportion of patients with prior CV events (secondary prevention patients) and low proportion of patients with HeFH. Additional issues the ERG are concerned with include the distribution of secondary prevention patients at baseline, the lack of subgroup analyses, the baseline LDL-C used to inform non-PCSK9i eligible subpopulations and the use of polyvascular events to inform recurrent events. Each of these issues is described in turn below.

Proportion of patients with prior CV events and HeFH

Over [redacted] of patients in subpopulations 2b, 4a and 4b had had a prior CV event. As such, the ERG considers that including a small proportion of primary prevention patients in these subpopulations is of limited benefit as it causes unnecessary "noise" (due to the additional complexities required to model primary and secondary prevention patients in the same model) and potentially leads to inappropriate conclusions in a primary prevention population, for which there is little data. To address these issues, the ERG's preference is to model subpopulations 2b, 4a and 4b as secondary prevention populations. In this scenario, secondary prevention patients would be allocated into a starting health state based on the proportions given in Table 24 (based on Ward *et al.* 2007)[31].

Table 24. Distribution of prior CV events by population, 100% secondary prevention population

Prior CV event	Population 2 (low or no dose statin) b (PCSK9i eligible)	Population 4 (max dose statin)	
		a (non-PCSK9i eligible)	b (PCSK9i eligible)
UA	20.3%	20.0%	20.0%
MI	46.0%	49.2%	49.2%
IS	33.7%	30.9%	30.9%
No prior CV event	0.0%	0.0%	0.0%

Abbreviations: IS, ischaemic stroke; MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina

As for subpopulation 2a, the majority (around [redacted]) of patients did not have a CV history at baseline and therefore the ERG's preference is to model subpopulation 2a as a primary prevention population. The ERG's rationale for this decision is consistent with the ERG's rationale for modelling subpopulations 2b, 4a and 4b as secondary prevention populations.

What's more, the company modelled a high proportion of patients without HeFH [redacted] in each subpopulation. The prevalence of HeFH in a secondary prevention population was only reported in CLEAR Harmony and this may not be generalisable to all subpopulations considered by the company. As explained in Section 3.3.2, the small number of HeFH patients recorded in the CLEAR studies does not substantiate the company's assumption that the overall reduction in LDL-C is equally relevant for all populations. For these reasons, it is the ERG's preference to assume all subpopulations are representative of patients without HeFH. Results of the ERG's analyses that adjust the company's "mixed" cohort into either a primary prevention cohort (subpopulation 2a) or secondary prevention cohort (subpopulations 2b, 4a and 4b) are given in Section 6.

An additional and related area of concern of the ERG's is why the proportion of prior CV events in the model for each CLEAR study does not match the "not reported" values for prior CV events included in the CS (Table 13 of the CS, document B). In response to the ERG's clarification question, the company explained that the prior CV event data included in the model are descriptive data prepared during the CS to reflect the characteristics of patients for whom PCSK9i treatment are and are not appropriate. The company also added that the definition of a prior CV event varied across the CLEAR studies. In CLEAR Harmony and CLEAR Wisdom this was reported as prior ASCVD, while in CLEAR Serenity, this was reported as primary and secondary prevention. In CLEAR Tranquility, patients with recent history of CVD (documented within 3 months of screening) were excluded. However, the company's explanation only increases the ERG's concerns with the reliability of the company's cost-effectiveness results.

Distribution of the secondary prevention patients at baseline

As treatment effectiveness data were taken from the CLEAR trials, the ERG considers that CV event history from those trials may be more appropriate. For this reason, the ERG requested the company to conduct a scenario that used the distribution of secondary prevention patients by prior CV event from which the effectiveness data were derived. However, in their clarification response, the

company explained that these data are currently not available from the CLEAR trials. Nonetheless, the ERG considers it important to note that the distribution of prior CV events in secondary prevention patients is a key driver in the model based on the ERG's exploratory analyses. As shown in Section 6, using a cohort made up entirely of patients with prior IS events reduces the cost-effectiveness of bempedoic acid compared to its comparators, while a cohort made up entirely of patients with prior MI events increases the cost-effectiveness of bempedoic acid compared its comparators. As a result, the ERG stresses its opinion that prior CV event data from the CLEAR trials is made available.

Following another clarification request from the ERG, the company provided a scenario including prior TIA and SA events, based on the distribution of prior CV events reported in Ward *et al.* 2007.[31] Nonetheless, the impact on the cost-effectiveness results was found to be minimal in each population.

Subgroup analyses

An additional and related area of concern is that the company did not provide cost-effectiveness results for the subgroups specified in the NICE final scope (presence or risk of CVD, HeFH, statin intolerance and severity of HC).[30] However, in response to the ERG's clarification request, the company did not provide these results because they considered the treatment effect for bempedoic acid and the FDC with ezetimibe to be consistent across the subgroups. Nonetheless, the ERG is not convinced by the evidence in support of this claim provided by the company at the clarification stage Thus, the ERG reiterates that the NICE appraisals for aliroumab (TA393) and evoculumab (TA394) assessed treatments in the prevention of primary or secondary events (i.e. patients with or without CVD) separately and in the presence of HeFH or non-familial HC separately, and therefore stresses its opinion that cost-effectiveness results are provided by the company for these subgroups in order to allow consistent decision making.[26, 27]

Baseline LDL-C in non-PCSK9i eligible subpopulations

In the non-PCSK9i eligible subpopulations, the ERG found that the company used the baseline LDL-C levels of all patients in the CLEAR trials (population 2, [redacted]; population 4, [redacted]) and that these levels are notably higher than the levels of non-PCSK9i eligible patients in the CLEAR trials (subpopulation 2a, [redacted]; subpopulation 4a, [redacted]). In response to the ERG's clarification question, the company explained that this approach was appropriate because limited patients eligible for PCSK9i treatment

actually receive PCSK9i treatment according to clinical expert opinion from the Daiichi Sankyo Delphi panel (Daiichi Sankyo Europe data on file, 2019).[5] Following this, the ERG also sought clinical expert opinion who revealed that access to PCSK9i treatments is variable across different centres and regions. However, if a centre had access to PCSK9i treatments, the majority of patients eligible for PCSK9i treatment from that centre would receive PCSK9i treatment. Furthermore, the ERG considers that the company's rationale contradicts the company's separation of the populations into subpopulations according to PCSK9i eligibility. To address this issue, the ERG explored a scenario where the baseline LDL-C level in the non-PCSK9i eligible subpopulation is taken from non-PCSK9i eligible patients (subpopulation 2a, [redacted]; subpopulation 4a, [redacted]). Results of the ERG's analysis are reported in Section 6.

Recurrent/polyvascular events

The ERG notes that the proportion of patients with a recurrent event ([redacted]was only reported in the CLEAR Wisdom trial. This estimate also included polyvascular events. During the clarification stage, the company explained that patients with polyvascular events were included in the estimation of recurrent events as it was difficult to track recurrent events in the CLEAR data. The company also noted that their estimate ([redacted]was within the estimates from the alirocumab studies in TA393 (7% to 27%).[27] As there was no consensus between the ERG's clinical experts regarding the appropriateness of using polyvascular event data in the absence of recurrent CV event data, the ERG explored the impact of using an estimate of 7% in scenario analyses. Results of the ERG's analysis are reported in Section 6.

4.2.3 Interventions and comparators

The two interventions included in the CS are bempedoic acid alone or with a statin, with or without other lipid-lowering therapy and bempedoic acid in a FDC with ezetimibe, alone or with a statin. However, in the populations included in the company's economic analyses (populations 2 and 4) bempedoic acid is given with background ezetimibe. As such, the company did not provide any cost-effectiveness results for bempedoic acid alone or with a statin, with or without other lipid-lowering therapy.

Following this, the ERG sought clinical expert opinion on the use of bempedoic acid with or without ezetimibe in UK clinical practice. The ERG heard from clinical experts that, should bempedoic acid be recommended for primary HC and mixed dyslipidaemia, clinicians will most likely want to use it in

addition to ezetimibe, unless ezetimibe is contraindicated or not tolerated. As such, the ERG's clinical experts agreed with the company that bempedoic acid would be offered with ezetimibe (as separate tables or as a combined tablet) in populations 2 and 4.

In the economic analyses, data on bempedoic acid with background ezetimibe (as separate tablets) are used to represent the efficacy of bempedoic acid in a FDC with ezetimibe (as a combined tablet) in population 2, given the lack of FDC data in this population. Similarly, data on the FDC are used in the economic analyses to represent the efficacy of bempedoic acid with background ezetimibe in population 4. As explained in Section 2.3.2, pharmacokinetic studies have shown the two presentations to be equivalent, and therefore ERG considers it reasonable to assume equivalent efficacy between the two presentations in the absence of presentation-specific data. What's more, the company presented cost-effectiveness results for bempedoic acid in a FDC with ezetimibe and cost-effectiveness results for bempedoic acid with background ezetimibe. However, the cost-effectiveness results were the same given that the price (see Sections 4.2.10.1) and efficacy (see Section 4.2.5.1) of two presentations are equivalent.

The comparators considered in the economic analyses depend on the selected subpopulation for analysis and are as follows:

- Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate:
    - Ezetimibe
- Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate:
    - Evolocumab without another lipid-lowering therapy
    - Alirocumab without another lipid-lowering therapy
- Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate:
    - Ezetimibe with a statin
- Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate:
    - Evolocumab with a statin without another lipid-lowering therapy
    - Alirocumab with a statin with another lipid-lowering therapy (ezetimibe)
    - Alirocumab with a statin without another lipid-lowering therapy

No clinical evidence on evolocumab with another lipid-lowering therapy was identified to include this treatment as a comparator in subpopulation 2b or 4b. Moreover, no clinical evidence on alirocumab with another lipid lowering therapy was identified to include this comparator in subpopulation 2b. Nonetheless, the comparators included in the economic analyses are in line with the comparators included in the NICE final scope.[30]

The dosing regimens of the interventions and comparators included in the model are given in Table 36 of Section 4.2.10. The model also allows for treatment discontinuation and this is also described in Section 4.2.10.

4.2.4 Modelling approach and model structure (inc. perspective, time horizon and discounting)

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of bempedoic acid with background ezetimibe and bempedoic acid in a FDC with ezetimibe in populations 2 (low or no dose statin) and 4 (max dose statin).

The company used a Markov model structure (Figure 4) which included the following core health states on CV events: myocardial infarction (MI); unstable angina (UA); stable angina (SA); ischaemic stroke (IS); and, transient ischaemic attack (TIA). Each of these CV events 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.

In any of the post-CV event states, patients are able to transition to another event of the same type or to a different type of event, or they can remain in their post-event state. However, transitions from the IS health state to MI, UA, TIA, or SA 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 (regardless of Figure 4 indicating otherwise). The company also blocked transitions to SA from prior event health states, but the company did not provide a rationale for this decision. A proportion of patients in each health state may also undergo an elective revascularisation and patients are able to transition from any state to death.

Furthermore, a cycle length of one-year was implemented in the model with a half-cycle correction applied. The model time horizon was set to lifetime (55 years). The perspective of the analysis is based on the UK NHS, with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.[22] The company states that the adopted model structure is in line with previous NICE

HTA submissions and guidelines associated with the modelling of CV conditions, including TA393, TA394, TA385 and CG181.[26-29]

Figure 4. Structure of the cost-effectiveness model (reproduced from Figure 17 in document B of the CS)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease CVD, cardiovascular death; CS, company submission; MI, myocardial infarction; TIA, transient ischaemic attack

As touched upon in Section 4.2.2, the simulated cohort in each population includes primary and secondary prevention patients, based on the proportion of prior CV events in the CLEAR studies. As such, patients do not enter the model in the same health state. The starting states depend on whether patients receive treatment for primary or secondary prevention. Primary prevention patients (patients with no prior CV event) enter the "High risk for ASCVD" health state in the model, while secondary prevention patients (patients with a prior CV event) enter one of the primary CV health states according to the distribution of CV events reported in Ward *et al.* 2007 (see Section 4.2.2.1).[31]

The ERG also considers it important to note that a distinction is made between one CV event and recurrent events (two or more CV events) in the model. Thus, events are not split into secondary and tertiary events as inferred by Figure 4. Also, at the end of cycle 0 in the model, the proportion of recurrent events (two or more CV events) in the CLEAR studies ([redacted]) is applied to the distribution of primary CV events (secondary prevention patients). Following this, the cohort in the model is split into three different groups:

1. patients with no prior CV events (including primary prevention patients with no prior CV events);
2. patients with one CV event (including primary prevention patients who experience one CV event within the model and secondary prevention patients who experienced a CV event prior to entering the model); and,
3. patients with two or more CV events (including primary prevention patients who experience two or more CV events within the model, secondary prevention patients who experienced recurrent CV events prior to entering the model and secondary prevention patients who experience one or more CV events within the model).

Even though the company applies the same costs and benefits to any given CV event experienced as a primary event or recurrent event, the ERG considers it important to make this distinction to aid interpretation in Section 4.2.9 on resource use and costs and Section 4.2.10 on HRQoL.

4.2.4.1 ERG critique

The ERG considers that the company's model captures all relevant health states. However, the company's schematic model (Figure 4) is simplistic as it does not accurately illustrate how patients enter the model according to whether patients receive primary or secondary prevention, or reflect the blocked transitions from the IS state to other states.

One of the ERG's main concerns with the company's model relates to the starting state. Secondary prevention patients enter the model in one of the 0 to 1 year-post CV event health states, incurring the costs and benefits for an acute event. The ERG disagrees with this because the prior CV event could have occurred many years prior to entering the model. Moreover, patients with established CVD in TA393, TA394 and TA385 entered a model in a post-event type health state associated with either "stable" or "established" CVD.[26, 27, 29] To address this issue, the ERG allocated the secondary prevention cohort to enter the model in the 3-year+ post-event state, associated with post-event

costs and benefits, until a new event occurs as the ERG considers the 3-year+ post-event state to be equivalent to the "stable" or "established" CVD-type states included in the aforementioned appraisals. Results of the ERG's analysis are reported in Section 6.

Furthermore, although the annual cycle length used in the model was chosen to fit with the available data and align with previous TAs, the ERG's clinical experts advised that some patients suffer multiple events within the same year. For this reason, an annual cycle length may be too long to capture important changes in the health state of patients. Thus, it is possible that quality-adjusted life year (QALY) losses and costs are being underestimated with less effective treatments.

An additional and related area of concern with multiple events is the company's estimation of recurrent event costs and quality of life. In the economic analysis, primary events and recurrent events (two or more CV events) are associated with the same impacts on quality of life and resource use and costs, despite clinical expert opinion that recurrent events have larger impacts compared with primary events. This issue is explored further in Section 4.2.10.

Finally, two clinically plausible transition that are omitted from the model include transitions to a recurrent TIA and transitions to SA from prior event health states. The ERG does not consider the former to be a major issue given that TIAs are associated with small costs and a small reduction in benefits. Although the company has provided no rationale for the latter, the ERG notes that a SA health state was omitted from TA393 and the ERG expects this influenced the company's decision to block transitions to SA from prior event health states.[27] To explore the impact of enabling transitions to SA from prior event health states, the ERG performed a scenario where the background CV risks were set equal to the risks associated with UA. Results of the ERG's analysis are reported in Section 6.

4.2.5 Treatment effectiveness

4.2.5.1 Reduction in LDL-C

In the absence of CV event data from the clinical trials for bempedoic acid, the company used LDL-C reduction to estimate the impact of bempedoic acid on CV events. As mentioned previously in Section 3.4, the ERG had concerns about the treatment effect on LDL-C derived from the company's original NMAs given the extent of statistical heterogeneity observed. To address this issue, the company conducted revised NMAs at the clarification stage. Table 25 and Table 26 provide the LDL-C reduction data used in the revised model for population 2 and population 4, respectively. In line with

the company's initial economic analysis, the mean percentage reduction in LDL-C for bempedoic acid patients on background ezetimibe was assumed to be the same as the reduction for the FDC as pharmacokinetic studies have shown the two presentations to be equivalent. In addition, the company employed results for alirocumab using data on the 150 mg dose, but the company did not provide a rationale for this decision. However, the ERG's clinical experts fed back that the 150 mg dose is the most widely used dose for this indication and therefore the ERG does not consider this to be an issue. The ERG also adds that the results obtained from these NMAs are applied to the whole cohort included in each subpopulation.

Table 25. NMA data used in the economic analysis, population 2 (low or no dose statin) (adapted from Table 33 of the company's clarification responses)

Treatment [a]	Mean % change in LDL-C from baseline compared with ezetimibe [c]	95% CrIs
Bempedoic acid plus ezetimibe [b]	[redacted]	[redacted]
Evolocumab (140 mg Q2W)	[redacted]	[redacted]
Alirocumab (150 mg Q2W)	[redacted]	[redacted]

Abbreviations: CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; Q2W, per 2 weeks.
[a] No trial data were identified for alirocumab + ezetimibe, or evolocumab + ezetimibe
[b] These data are also used in the economic model to represent the efficacy of the FDC with ezetimibe
[c] Mean % change in LDL-C with baseline ezetimibe [redacted]

Table 26. NMA data used in the economic analysis, population 4 (max dose statin) (adapted from Table 34 of the company's clarification responses)

Treatment [a]	Mean % change in LDL-C from baseline compared with ezetimibe [c]	95% CrIs
FDC + statin [b]	[redacted]	[redacted]
Evolocumab (140 mg Q2W) + statin	[redacted]	[redacted]
Alirocumab (150 mg Q2W) + stain	[redacted]	[redacted]
Alirocumab (150 mg Q2W) + stain + ezetimibe	[redacted]	[redacted]

Abbreviations: CrI, credible interval; FDC, bempedoic acid and ezetimibe fixed-dose combination, LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; Q2W, per 2 weeks.
[a] No trial data were identified for evolocumab + statin + ezetimibe
[b] These data are also used in the economic model to represent the efficacy of bempedoic acid + ezetimibe as separate tablets
[c] Mean % change in LDL-C with baseline ezetimibe [redacted]

The company assumed that the treatment effect observed in LDL-C at week-12 remains constant for the duration of the model's time horizon, or until treatment is discontinued (described in Section 4.2.10). Once treatment is discontinued, any reductions in CV risk are stopped immediately as LDL-C levels returns to baseline.

As touched upon in Section 4.2.2, different mean baseline LDL-C levels are applied in the model depending on the selected population for analysis. Therefore, to derive the absolute reductions in LDL-C for each treatment (in order to model the relationship between absolute reductions in LDL-C and reductions in CV risk), the mean percentage change in LDL-C (adjusted for background ezetimibe treatment in positions 2 and 4) is multiplied by the baseline LDL-C level:

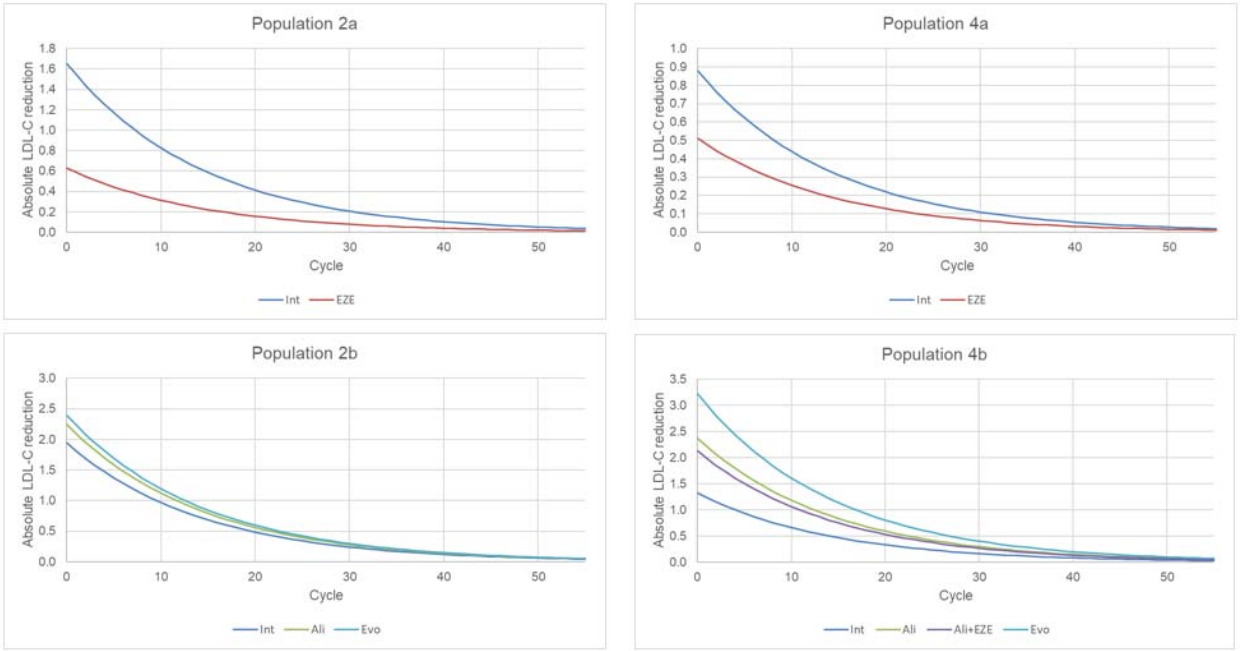
$$Absolute\ reduction\ in\ LDLC = L_0 - L_0 * (1 - (L_{eze} + L_{txi}) * On_{txi})$$

Where:

- L_0 is the mean baseline LDL-C level in mmol/L
- L_{eze} is the mean % reduction in LDL-C with background ezetimibe (see Table 25 and Table 26)
- L_{txi} is the mean % reduction in LDL-C with treatment i versus background ezetimibe (see Table 25 and Table 26)
- On_{txi} is the proportion of patients on treatment I (see discontinuation rates in Section 4.2.10)

The ERG has produced Figure 5 to illustrate the absolute reduction in LDL-C over the model's time horizon in each population.

Figure 5. Absolute reduction in LDL-C applied in the company's base case analyses



Abbreviations: Ali, alirocumab; Int, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; LDL-C = low-density lipoprotein-cholesterol

4.2.5.2 *Modelling the relationship between reductions in LDL-C and reductions in cardiovascular risk*

For the base-case analyses, the company chose the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis of 27 randomised controlled trials (RCTs) of statin therapies in 174,149 patients to provide the rate at which the risk of a CV event declines with the absolute reduction in LDL-C levels.[32] This was because it was based on patient-level data rather than aggregated published data, and for consistency of decision making, as this analysis was used (and preferred over the Navarese *et al*. 2018 analysis) in previous NICE appraisals including TA385, TA393 and TA394.[26, 27, 29, 33]

The company also added that the analysis by Navarese *et al.* 2018 was not used because the authors observed that the association between LDL-C reduction and CV risk was not present when baseline LDL-C levels were less than 100 mg/dL, while the rate ratio per unit reduction in LDL-C reported in the study included many large trials with mean baseline LDL-C less than 100 mg/dL (notably TNT, SEARCH, IMPROVE-IT, FOURIER, and SPIRE-1, contributing a total of 84,590 patients to the analysis). Therefore, the company concluded that the results from Navarese *et al.* 2018 may not be generalisable to the patient populations included in CLEAR studies, where the mean baseline LDL-C was estimated to range from 2.91 to 4.39 mg/dL (112 to 170 mmol/L).[33]

The rate ratio per unit reduction in LDL-C for various CV events obtained from the CTTC analysis and used to inform the base case analyses are given in Table 27.[32] The company assumed the rate ratios for SA and TIA were equal to 1, as there is no strong evidence supporting a relationship between these events and LDL-C.

Table 27. Rate Ratio for CV events per 1 mmol/L reduction in LDL-C (CTTC 2015)[32]

CV event	Mean (CI)
MI	0.76 (0.73-0.79)
UA	0.76 (0.73-0.79)
SA	1
Elective revascularisation	0.76 (0.73-0.78)
IS	0.80 (0.75-0.86)
TIA	1
CV death	0.88 (0.84-0.91)

Abbreviations: CI, confidence interval; CTTC, Cholesterol Treatment Trialists Collaboration; CV, cardiovascular; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina.

In addition to the CTTC meta-analysis, the company provided a *de novo* meta-regression that updates the meta-analysis of PCSK9 inhibitors by Navarese *et al.* 2018 to include studies reported

since the closing date of their systematic review.[32, 33] The purpose of the meta-regression was to estimate a pooled risk ratio for CV events by reduction in LDL-C across all the included studies.

The original meta-analysis by Navarese *et al*. 2018 reported data from 136,299 patients included in 34 RCTs.[33] To identify relevant studies that have been reported since Navarese *et al.* 2018, the company performed citation searching in PubMed to identify relevant publications which cited studies included in the analysis. Following this, the company identified two additional studies: ODYSSEY OUTCOMES (Schwartz *et al.* 2018) in 18,924 patents and HIJ-PROPER (Hagiwara *et al.* 2017) in 1,721 patients.[34, 35] The full list of trials included in the company's *de novo* meta-regression can be found in Table 31 of the CS, Appendix E.

The CV outcomes considered in the company's meta -regression include: CV mortality; MI; IS; revascularisation; and, major CV events. In the model, major CV events were used as a proxy for UA. The following covariates were also considered by the company: mean absolute change in LDL-C (time point closest to 12 weeks) and baseline LDL-C (study mean).

To assess whether baseline LDL-C may help in explaining some of the variation in CV events, the company compared results from the one covariate model (without baseline LDL-C) and two covariate model (with baseline LDL-C) by considering the following model fit statistics: Akaike Information Criterion (AIC), corrected AIC, Bayesian Information Criterion (BIC), R^2 (%) and Higgin I^2 (%). Model fit statistics are presented in Appendix E.4 of the CS and based on these statistics, the two covariate model produced a better fit than the one covariate model for all CV outcomes except for IS.

The parameters obtained from each regression model are given in Table 28, while the resulting rate ratios are given in Table 29. The company's scenario analysis employed data from the two covariate model and the results of this scenario are given in Section 5.1.2.

Table 28. Parameters for meta-regression model (taken from the economic model)

CV event	One covariate model		Two covariate model (with baseline LDL-C)		
	Intercept	Absolute change in LDL-C	Intercept	Absolute change in LDL-C	Baseline LDL-C
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CV, cardiovascular; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina.

Table 29. Rate Ratio for CV events per 1 mmol/L reduction in LDL-C (de novo meta-regression results taken from the economic model)

CV event	One covariate model [a]	Two covariate model (with baseline LDL-C) [b]			
		4a (2.91)	4b (4.38)	2a (3.74)	2b (4.39)
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA	1	1	1	1	1
Revascularisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIA	1	1	1	1	1
CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina.

a rate ratio = EXP(intercept+absolute change in LDL-C)

b rate ratio = EXP(intercept+absolute change in LDL-C+LDL-C adjust*baseline LDL-C)

4.2.5.3 ERG critique

One of the ERG's main concerns is the reliability of the company's NMAs on the % change in LDL-C from baseline. Additional areas of concern include the lack of subgroup analyses, the appropriateness of using 12-week data and the appropriateness of using the reduction in LDL-C levels to predict reductions in CV risk. For completeness, the ERG also provides comments on the company's updated meta-regression to estimate the relationship between LDL-C levels and CV risk. Each of these points is described in turn below.

Company's NMAs on the % change in LDL-C from baseline

Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness for this appraisal. As mentioned in Section 3.4, the revised NMAs provided by the company at the clarification stage remain unfit for decision making, principally due to the extent of clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. To address some of these issues, the ERG explored alternative networks to implement in the economic analyses (see Section 3.5). The data obtained from these networks are given in Table 30 and Table 31, while the results of the ERG's economic analyses are given in Section 6. However, the ERG recommends that the cost-effectiveness

results based on these networks are interpreted with caution due to time and resource constraints the ERG has been unable to fully assess all potentially relevant studies for inclusion in the networks and additionally not had access to the relevant subgroup data from the bempedoic acid studies (see Section 3.5).

The ERG also considers it important to highlight that the ERG NMA comprises only patients with prior ezetimibe therapy at baseline, whereas the company NMA includes patients both with and without prior ezetimibe therapy. As all patients in the ERG's NMA received ezetimibe, the ERG's analysis do not provide an estimate of ezetimibe compared with no treatment (see Section 3.5). To inform the mean percentage change in LDL-C with baseline ezetimibe in the model, the ERG has employed the estimates from the company's base case analysis. However, this is a pragmatic decision and the ERG would like more clarity from the company regarding the studies used to inform the mean percentage change in LDL-C with baseline ezetimibe.

Finally, no evidence on evolocumab was identified by the ERG in order to include this treatment as a comparator. As such, the only PCSK9i treatment included as a comparator is alirocumab.

Table 30. NMA data applied in the ERG's additional economic analyses, population 2 (low or no dose statin)

Treatment [a]	Mean % change in LDL-C from baseline compared with ezetimibe [b]	95% CrIs
BA/EZE FDC	[redacted]	[redacted]
Alirocumab (150 mg Q2W) + EZE	[redacted]	[redacted]

Abbreviations: BA, bempedoic acid; CrI, credible interval; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; Q2W, per 2 weeks.
[a] No trial data were identified for evolocumab + EZE
[b] Mean % change in LDL-C with baseline ezetimibe: [redacted]

Table 31. NMA data applied in the ERG's additional economic analyses, population 4 (max dose statin)

Treatment [a]	Mean % change in LDL-C from baseline compared with ezetimibe [b]	95% CrIs
BA/EZE FDC	[redacted]	[redacted]
Alirocumab (150 mg Q2W) + EZE + stain	[redacted]	[redacted]

Abbreviations: BA, bempedoic acid; CrI, credible interval; EZE, ezetimibe; FDC, fixed-dose combination, LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; Q2W, per 2 weeks.
[a] No trial data were identified for evolocumab + EZE + statin
[b] Mean % change in LDL-C with baseline ezetimibe [redacted]

Subgroup analyses

One of the ERG's main concerns about the company's approach to modelling treatment effectiveness is the lack of subgroup analyses. As mentioned previously in Section 3.4.1, the NICE appraisals for alirocumab (TA393) and evoculumab (TA394) resulted in recommendations for different subgroups and the ERG is therefore concerned that these subgroups are not considered separately in the CS.[26, 27] In response to the ERG's clarification request, the company did not provide these results because they considered the treatment effect for bempedoic acid and the FDC with ezetimibe to be consistent across patients with or without ASCVD, patients with HeFH, and differing severity of hypercholesterolaemia (as indicated by baseline LDL-C category). Nonetheless, the ERG is not convinced by the evidence in support of this claim provided by the company at the clarification stage.

Furthermore, the ERG considers there to be large discrepancies between the baseline characteristics of patients entering the model and the patients included in the company's networks to estimate the percentage change in LDL-C. In the economic analyses there is generally a large proportion of secondary prevention patients without HeFH entering the model and these proportions are either not reported or variable between the studies included in the trials in the company's networks. For these reasons, the ERG stresses its opinion that cost-effectiveness results by subgroup should be provided by the company in order to reflect the patients entering the model and in order to allow for consistent decision making with previous NICE appraisals.

12-week data

The ERG is also concerned with the appropriateness of assuming 12-week results are maintained for the duration of the model's time horizon, or until treatment is discontinued. The reductions in LDL-C recorded in the CLEAR trials at week 12 are not sustained at week 24 (CLEAR Serenity) or week 52 (CLEAR Harmony and CLEAR Wisdom), indicating treatment waning effects. The ERG's clinical experts also affirmed that the response at week 12 would be larger than the sustained response. As a result, the ERG asked the company to provide cost-effectiveness results based on 24-week data. However, the company did not comply with the ERG's request because they did not consider a non-significant change between LDL-C reductions at week 12 and week 24 to justify a deviation from the trials primary endpoint (Section 3.4.1). To address this issue, the ERG considered a scenario with diminishing treatment effects. However, the magnitude of treatment waning may be different across the different lipid lowering therapies under consideration, which makes a scenario analysis problematic due to the number of assumptions required. This also supports the ERG's view that the

dataset including the latest outcomes available is the preferred approach to addressing this important area of uncertainty.

Non-HDL-C

One issue regarding the company's estimation of CV events includes the appropriateness of using one lipoprotein (LDL-C) to predict reductions in CV risks. Although clinical experts considered reductions in LDL-C to be important, lipid profile assessments in UK clinical practice focus on non-HDL-C reductions which incorporate all lipoproteins, such as triglycerides, as these are considered to be more informative than reductions in LDL-C. Furthermore, the ERG's clinical experts expressed concerns that bempedoic acid may increase triglyceride levels and reduces HDL levels (see Section 3.3.1). The ERG also identified numerous sources including the latest recommendations of European and American Cardiological Associations and the Copenhagen City Heart Study, which indicate that non-HDL-C is more reliable than LDL-C at predicting the risk of CV events.[36, 37] For these reasons, the ERG asked the company to provide cost-effectiveness results using evidence from the published literature on the relationship between non-HCL-C and CV risk.

In their clarification response, the company reiterated that LDL-C has been accepted as a surrogate endpoint for the reduction of CV events. Thus, the company did not comply with the ERG's request as they wished to remain consistent with previous NICE appraisals in decision making. As an aside, the ERG considers the company's rationale here to be somewhat contradictory to their rationale not to provide the subgroup analyses requested by the ERG, which were requested in order to reflect subgroups deemed important in the recommendations made in previous NICE appraisals including TA393 and TA394 (see Section 3.4.1). Nonetheless, the company provided an analysis of CLEAR Harmony and CLEAR Wisdom which showed that treatment with bempedoic acid lowered non-HDL-C significantly more than did placebo at week 24: the mean change in non-HDL-C (mg/dL) from baseline to week 24 was [redacted] in the bempedoic acid group and [redacted] in the placebo group. In light of this, the ERG's concern that the risk of CV events in the bempedoic acid arm was potentially underestimated when triglyceride levels are ignored has been subdued.

Relationship between LDL-C and CV events (inc. updated meta-regression)

The ERG sought clinical expert opinion to ascertain if the relationship between LDL-C and CV events based on the CTTC meta-analysis of statin trials was accepted by clinicians in UK practice and if the relationship based on statins was expected to hold true for PCSK9i treatments.[32] The ERG's clinical

experts agreed with these points. During the clarification stage, the company also noted that studies including Silverman *et al.* 2016 have shown that the relationship between LDL-C reduction and CV events is similar between statin and non-statin treatments.[38] For these reasons, the ERG considers the use of the CTTC meta-analysis for the base case to be appropriate and consistent with previous NICE appraisals including TA385, TA393 and TA394.[26, 27, 29, 32]

Due to time constraints, the ERG was unable to replicate the company's searches, appraisal of identified abstracts and data extraction for the updated meta-regression. Nonetheless, the ERG considers the company's searches to identify relevant studies that have been reported since Navarese *et al.* 2018 to be pragmatic. Ideally, the ERG would have preferred a formal update of Navarese *et al.* 2018 using the same systematic review process conducted by the original authors. Although the company was at risk of missing relevant studies (i.e. publications which did not cite studies included in Navarese *et al.* 2018), the ERG is unaware of any key papers missed by the company (based on a naïve comparison with the studies included in the NMAs).[33]

4.2.6 Background cardiovascular risks

4.2.6.1 Background cardiovascular risks: primary prevention

The company explained that background CV risks in the model were calculated by converting the SCORE risk algorithm in European Society of Cardiology (ESC) guidelines for a high-risk population into a QRISK3 risk.[8] A high-risk population SCORE in ESC guidelines is represented by the 10-year risk of CV death (SCORE 5-10, 5%-10% risk of CV death). To calculate a 10-year QRISK3 risk, the company divided the midpoint (7.5%) obtained from the SCORE risk algorithm by the relative rate for CV death in Ward *et al.* 2007.[31] In population 4 this is equal to 29.4% (0.075/0.255) and in population 2 this is equal to 30.3% (0.075/0.247). The company assumed these 10-year QRISK3 risk estimates reflected the 10-year risk for MI, IS or CV death.

The company calculated the annual CV risk by converting the 10-year risk (probability) into a rate and then converting this rate into an annual risk (probability). Thus, a 10-year risk of 29.4% corresponds to an annual risk of 3.4%. The annual risk is then used to estimate annual risk for the different events based on the relative rates of first events in Ward *et al.* 2007.[31] The company noted that not all modelled CV events are included in QRISK3 (i.e. SA, UA, and TIA are not included). To resolve this, the company performed calculations by assuming the risk of SA, UA, and TIA events is

proportional to the number of events in Ward *et al.* 2007. The company noted that this approach is consistent with the approach in CG181 which was based on the QRISK2 assessment tool.[28]

Table 32. Background cardiovascular risks: primary prevention (taken from the economic model)

CV event	CV death	IS	MI	UA	SA	Elective revascularisation	TIA
Population 2 (no or low dose statin)							
Relative rates of first events in Ward *et al* 2007[a]	24.7%	51.7%	23.6%	12.4%	50.3%	0.0%	15.9%
Annual risk	0.9%	1.8%	0.8%	0.4%	1.8%	0.0%	0.6%
Population 4 (max dose statin)							
Relative rates of firs events in Ward *et al* 2007[a]	25.5%	47.1%	27.4%	13.1%	50.0%	0.0%	16.4%
Annual risk	0.9%	1.6%	0.9%	0.4%	1.7%	0.0%	0.6%

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina.
a Based on the average distribution for 55 to 64 and 65 to 74 year olds, and proportion of females included in the selected analysis

The company did not consider the prevalence of diabetes or HeFH when estimating baseline CV risks in the primary prevention population. The company's rationale for this was that the risk in the primary prevention cohort reflects a high-risk population and, therefore, the baseline risk applied for the primary prevention cohort should be considered as covering all relevant patients.

4.2.6.2 Background cardiovascular risk adjustments by baseline LDL-C

In the base case analyses, the company adjusted the baseline CV risk in the secondary prevention population (calculated using THIN data) by the baseline LDL-C levels (observed in the CLEAR trials) using a log-linear relationship between the reductions in LDL-C and reductions in CV risk observed in the CTTC 2015 analysis.[32] As described in Section 4.2.5.2, this analysis estimates the rate ratio per unit reduction in LDL-C ($\propto$) for various CV events. Based on this information, the company represented the relationship between CV event probability and LDL-C change, as in the TA393 submission:[27]

Equation 1) $\frac{E_{0i}-E_i}{E_{0i}} = 1 - \propto_i^{(L_0 - Li)}$

Equation 2) $E_i = E_{0i}[\propto_i^{(L_0 - Li)}]$

$$\text{Equation 3) } \ln(E_i) = \ln(E_{0i}) + (L_0 - Li)\ln(\propto_i),$$

Where:

- L_0 is the baseline LDL C level in mmol/L
- L_i is the new LDL C level in mmol/L
- E_{0i} is the 1-year probability for experiencing event i at the baseline LDL C level of L0
- E_i is the 1-year probability for experiencing event i at the LDL C level of Li
- $\propto_i$ is the rate ratio per unit change in LDL C for event i

These equations are used to adjust the CV risk based on the baseline LDL-C, i.e. if the patient cohort overall had a baseline LDL-C of L0, and an event rate of E0i, when considering a cohort with a baseline LDL C of Li, equation 2 is used to estimate the event rate Ei.

4.2.6.3 Background cardiovascular risks: secondary prevention

The company noted that QRISK risk estimates are not recommended for the high CV risk population.[28] Therefore, in line with TA393, background CV risks for secondary prevention patients are based on real-world UK data from THIN.[27] These were estimated separately according to the prevalence of diabetes, with diabetic patients having a higher risk for CV events than non-diabetic patients. In addition, risks for non-fatal CV events were inflated by 25% to account for under coding in registry data (Harrett *et al.* 2013).[39]

Event risks in patients with a history of TIA were not recorded from THIN in TA393 and, therefore, the company employed data from Ward *et al*. 2007 to reflect the data employed in CG181.[27, 28, 31] As for TIA event risks in patients with other types of CV event history, the company applied the ratio of TIA versus IS patients (266 versus 532) with a previous event in the Clinical Practice Research Database to estimate TIA risk.[40] The resulting annual CV event probabilities applied in the model are given in the CS, Table 48 of Document B.

The CV risks in the secondary prevention cohort were also adjusted for the prevalence of HeFH in the cohort [redacted] given that the CV risks in THIN were not reflective of a population with HeFH. In line with TA394, a risk multiplier of 6.1 based on Benn *et al.* 2012 was applied to patients with HeFH and previous events.[26, 41]

4.2.6.4 Background cardiovascular risk adjustment by age

In line with TA393, the company increased the risk for non-fatal CV events by 3% with each year of age and the risk of CV death by 5% with each year of age.[26] These estimates were based on Wilson *et al.* 2012 and reflected a high-risk patient group.[42] The company did not explore risk adjustments by

sex since background CV risks are taken from representative UK data sources and are therefore expected to be generalisable without any adjustments by sex.

4.2.6.5 Increased risk with multiple events

The company increased the risk of future CV events in patients with a prior CV event. This assumption was informed by a study in an English population which reported that the risk of death in survivors of recurrent MI was 1.5 times higher than that of survivors of a first MI (Smolina *et al.* 2012).[43] This was captured in the model by multiplying the baseline probability of CV death by 1.5 in all in patients entering the model with a prior CV event. The company also applied this increase to the baseline probability of a cardiac event for the subpopulations starting with a prior cardiac event, and the baseline probability of an IS event for the subpopulations starting with a prior IS event.

4.2.6.6 ERG critique

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. However, the ERG considers the company's interpretation of QRISK3 risk estimates for the primary prevention population to be misleading. The QRISK3 assessment tool is an algorithm that calculates a person's risk of developing a heart attack or stroke over the next 10 years. The factors included in this algorithm include smoking status, diabetes status, chronic kidney disease and atrial fibrillation, to name a few. However, the company's conversion from a 10-year risk of CV death into a QRISK3 score is not informed by this algorithm.[44]

To address this issue, the ERG requested the company to enter patient characteristics directly into the QRISK3 risk assessment tool to estimate the baseline risk of the primary prevention cohort that might be considered for bempedoic acid.[44] In response to the ERG, the company explained that individual patient-level data covering all the required data points were not easily available. As an alternative scenario, and following a clarification request from the ERG, the company provided cost-effectiveness results using a 10-year risk of 20% to reflect the QRISK2 risk employed in CG181 and TA385.[28, 29] The impact of using a 10-year risk of 20% on the cost-effectiveness results was negligible in subpopulations 2b, 4a and 4b. However, the impact in subpopulation 2a was notable (due to the larger proportion of patients entering the model in primary prevention) and increased the ICER from £28,521 to £35,009. Based on this exploratory analysis, the baseline risk of CV events in primary prevention patients is a key driver. As such, it is the ERG's view that the QRISK3 risk assessment tool

informed by patients included in the CLEAR trials is the preferred approach to addressing this important area of uncertainty.

Another concern of the ERG's is related to the increased risk of multiple events. Except for CV deaths, the company restricted adjustments to events of the same type. The ERG's clinical experts disagreed with the company's assumption and advised that recurrent cardiac events may also affect the risk for IS events, and that recurrent IS events may also affect the risk for cardiac events. As such, the ERG requested the company to provide a scenario analysis where recurrent cardiac events also affect the risk for IS events, with the caveat that the true multiplier for events of different types may be lower than the multiplier for events of the same type (i.e. between 1 and 1.5). Nonetheless, the impact on the cost-effectiveness results using the same multiplier was relatively small in each subpopulation.

4.2.7 Adverse events

No adverse events have been included in the economic analysis, as the company states that no preferred term was reported at an incidence > 2% higher in the bempedoic acid group compared with the placebo group in the High-Risk/Long-Term Pool or Overall Phase 3 Pool. The company also added that no adverse events were included in the economic evaluations submitted to NICE for TA385, TA393 or TA394.[26, 27, 29] The ERG consulted with its clinical experts who agreed that it was reasonable to exclude adverse events from the economic analysis as there are no relevant side effects of bempedoic acid or the comparators that could severely affect the management of the condition, or patients' quality of life.

4.2.8 All-cause mortality

The company modelled mortality due to CV events using the relationship between LDL-C levels and CV risk, using the methods outlined in Section 4.2.5. As for all-cause general population mortality, the company obtained estimates from national life tables provided by the Office of National Statistics (ONS) based on data for the years 2014-2016.[45] Then, the risk of CV death (due to the types of CV and stroke endpoint definitions for clinical trials reported in ESC guidelines)[46] was subtracted from the general population mortality data to derive the risk of death from other causes in the general population. The company stated that this approach avoided double-counting mortality due to CV events.

The ERG considers the company's approach to estimate all-cause cause mortality and non-CV morality reasonable. However, given that the definition of a CV death can vary between studies, the risk of CV deaths subtracted from the general population mortality could be over or under estimated. As a scenario analysis, the ERG explored the impact of using all-cause mortality without subtracting the risk of CV death. Results of the ERG's analysis are reported in Section 6.

4.2.9 Health-related quality of life

In their base case, the company applied multiplicatively age and sex adjusted health state utility multipliers to the estimated baseline utility in order to capture the impact of CV events. The company used the Ara and Brazier study, which estimated mean EQ-5D utility weights for members of the general population (N = 26,679) by history of different types of CV events within a year of a primary event, and in subsequent years following an event using data from the 2003 and 2006 Health Survey for England (HSE).[47] The study also estimated utility values for multiple events.

The company used the Ara and Brazier regression equation for individuals reporting no history of CVD in order to obtain the baseline gender and sex adjusted utility for every yearly cycle in the economic model, for both the primary and secondary prevention populations:

$$EQ - 5D = 0.9454933 + 0.0256466 \times \text{male} - 0.0002213 \times \text{age} - 0.0000294 \times \text{age2}$$

Subsequently, the estimated age and gender adjusted health state utility multipliers for CV events were multiplied by the baseline utility, in order to estimate health state related utility values (HSUVs) to be used in the model. The multipliers used in the company's analysis are reported in Table 33. The company estimated separate sets of baseline utilities for populations 2 and 4 in the model, given the difference in gender distribution across these populations ([redacted] female in population 2 and [redacted] female in population 4). Baseline utility was estimated for each model cycle as patients got older.

The company also used alternative utility values in scenario analyses. These consisted on the utility values used in CG181 and the utility values reported in Pockett *et al.* 2018.[28, 48]

Table 33. Age- and gender-adjusted cardiovascular multipliers (adapted from Table 56 in company's submission)

Health state	EQ-5D mean	N	SE	Age	Reference	Baseline adjusted utility		Age- and gender-adjusted multipliers^
						Population 4*	Population 2**	
SA < 1 year[a]	0.615	271	0.019	68.8	Ara and Brazier 2010[47]	0.809	0.801	0.765
SA > 1 year[a]	0.775	246	0.015	68.0		0.813	0.804	0.960
UA < 1 year[a]	0.615	271	0.019	68.8		0.809	0.801	0.765
UA > 1 year[a]	0.775	246	0.015	68.0		0.813	0.804	0.960
MI < 1 year[b]	0.615	271	0.019	68.8		0.809	0.801	0.765
MI > 1 year	0.742	206	0.019	65.1		0.825	0.816	0.906
IS < 1 year	0.626	76	0.038	67.9		0.813	0.805	0.775
IS > 1 year	0.668	291	0.018	66.8		0.818	0.809	0.822
TIA < 1 year	0.760	244	0.015	73.0	Luengo-Fernandez *et al*. 2013a[49]	0.791	0.782	0.968
TIA > 1 year	0.760	244	0.015	73.0		0.791	0.782	0.968

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; NR, not reported; SA, stable angina; SE, standard error; TIA, Transient ischaemic attack; UA, unstable angina.

[a] Mean utility for angina was used for both SA and UA.

[b] Health state utility multiplier assumed to be the same as acute SA and UA due to small sample size for acute MI (N=31).

* Estimated by the ERG using the Ara and Brazier equation adjusted for sex (using gender distribution from CLEAR studies for population 4) and age

** Estimated by the ERG using the Ara and Brazier equation adjusted for sex (using gender distribution from CLEAR studies for population 2) and age

^ Estimated by the company adjusted for sex (assuming 50% female/male distribution) and age.

Given that the 1-year post-IS HSUV was the lowest in the analysis, the company blocked any transitions from the IS state (first or subsequent years) to any other event states in order to prevent patients' quality of life to improve when experiencing a subsequent event.

4.2.9.1 ERG critique

The company's application of the different age adjusted multipliers to baseline utilities is in line with the Technical Support Document (TSD) 12 produced by NICE's Decision Support Unit (DSU).[50] In addition, the ERG agrees with the use of the Ara and Brazier utility data given these are from a single source and are representative of the population with and without CVD in England.[47] Nonetheless, the ERG is concerned with the choice of utility multipliers and regression equation used to estimate the baseline adjusted utility. The company's approach for the primary prevention population was to use the Ara and Brazier regression for people with no previous history of CV disease. Even though this is theoretically correct, [redacted] and [redacted] of patients in subpopulations 4a and 4b, respectively, had a history of previous CV events, and therefore cannot be considered a primary prevention population. Similarly, [redacted] of subpopulation 2b had a history of CV events. Therefore, these three populations should not be considered as primary prevention populations in the model (as discussed in Section 4.2.2 and Section 4.2.4). Furthermore, the population in Luengo-Fernandez *et al*. 2013a (used to derive the utility values for TIAs) also had a history of CV disease.[49]

Therefore, the ERG disagrees with the use of the regression equation derived for a population with no history of CV disease, as this does not accurately reflect the population underlying the effectiveness data used in the model. Ara and Brazier published three regressions to estimate baseline utility before CV events: the first in a "perfect health" population; the second in a population without previous CV events (used by the company); and a third, in the general population, with a mixed background of CV disease. While the third option is not a perfect match to subpopulations 4a, 4b, and 2b, the ERG considers that the regression for a population with a mixed background of history of CV events is more representative of the modelled population than the one used by the company. Therefore, the ERG replaced the regression used by the company to estimate age-adjusted baseline utilities for subpopulation 4a, 4b, and 2b in the model by the following regression:

$$EQ-5D = 0.9508566 + 0.0212126 \times \text{male} - 0.0002587 \times \text{age} - 0.0000332 \times \text{age2}$$

Furthermore, the ERG notes that the baseline utility multipliers for these patients in subpopulations 4a, 4b and 2b, should be those reflective of a post-event health state because secondary prevention patients enter the model at cycle 0 having had a CV event before they enter the model. Additionally, the Ara and Brazier study provided utility values for patients experiencing multiple events, which should be used to capture the impact of recurrent events in these patients' quality of life.

The ERG agrees with the use of the Ara and Brazier regression for no history of CV events and the use of utility values for primary events for subpopulation 2a, as [redacted] of patients did not have a CV history at baseline.

The company used the Ara and Brazier 1-year angina utility value (0.615) for acute MI events as it considered that the number of patients experiencing an MI in the study (31 patients) provided a small sample size. The ERG is unsure if the company's decision to use the Ara and Brazier 1-year angina utility value (0.615) for acute MI events is justifiable, especially when the 1-year post-event estimate used was the one reported for MI, thus breaking the correlation in utility decrease (or increase) between the chronic and stabilised MI event. Furthermore, primary MI events are associated with the highest utility value (0.721) amongst other CV events in Ara and Brazier, and in other sources such as Pockett *et al*. 2018 (0.702) thus, using a 0.615 utility value for MI in the model is overestimating the impact of the event on patients' quality of life.[47, 48]

Furthermore, the ERG is unclear why the company did not use the different time-point utilities for TIA events in Luengo-Fernandez *et al*. 2013a given that the latter provided 1; 6; 12; 24; and 60 months utility estimates for TIA events.[49]

Finally, the ERG disagrees with the company's approach to adjust for gender distribution twice (once in the calculation of the adjusted multipliers and again in the baseline utilities). Therefore, the ERG changed this in the model by removing the gender adjustment made by the company in the estimation of multipliers.

In conclusion, the ERG conducted two scenario analyses combining all the following assumptions, for subpopulation 2a and subpopulations 2b, 4a and 4b, respectively, and presents the results in Section 6:

- For all modelled populations:

    - Removed the gender adjustment made by the company in the estimation of multipliers;
    - Used the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al*. 2013a;[49]
    - Used the acute MI multiplier from Ara and Brazier in the analysis (reported in Table 24 for subpopulations 4a, 4b and 2b, and in Table 25 for subpopulation 2a, respectively).[47]
- For subpopulation 2b, 4a and 4b:
    - Used the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events. [47] These estimates and presented in Table 24.
- For population 2a:
    - Maintained the company's approach of using the Ara and Brazier regression for people with no history of CV events to estimate baseline utility.[47] The utility multipliers for this population are reported in Table 25. Nonetheless, the ERG notes that after patients in subpopulation 2a experience their first event, recurrent events should accrue the utilities for multiple events reported in Table 24.

The ERG notes that the utility multipliers in Table 34 and in Table 35 for females are above 1 for both acute and post-TIA events, and above 1 for acute TIAs for males. This is because the baseline utility for these events, derived with the Ara and Brazier equation for the background population, yields a higher utility value than the utility estimated in Luengo-Fernandez *et al*. 2013a. It is likely that the baseline utility in the latter study is overall higher than in Ara and Brazier population, given that the utility in the control group for TIA patients in Luengo-Fernandez *et al*. 2013a was 0.86 (compared with 0.776 and 0.755 for males and females, respectively, in the background population in Ara and Brazie, matched for age). Given that a multiplier higher than 1 implies that patients's utility after the CV event increases comparatively to their baseline utility, having a multiplier higher than 1 is not clinically plausible. Therefore, the ERG used the baseline utility in Luengo-Fernandez *et al*. 2013a (0.86) to estimate the utility multipliers for TIA events in the model whenever these were above 1 (as reported in Table 34 and in Table 35).[47, 49]

Table 34. Age-adjusted CV multipliers for a history of multiple CV events (subpopulations 4a, 4b and 2b)

Health state	EQ-5D mean	Reference	Baseline utility for males*	Baseline utility for females*	Age	Utility multipliers for males^	Utility multipliers for females^
Previous history of SA	0.775	Ara and Brazier 2010[47]	0.801	0.780	68.0	0.968	0.994
Previous history of UA	0.775		0.801	0.780	68.0	0.968	0.994
Previous history of MI	0.742		0.815	0.793	65.1	0.910	0.936
Previous history of IS	0.668		0.807	0.785	66.8	0.828	0.851
Previous history of TIA	0.760		0.776	0.755	73.0	0.979	**1.007**[2]
SA < 1 year[a]	0.541		0.801	0.780	67.9	0.675	0.693
SA > 1 year[a]	0.715		0.794	0.773	69.4	0.900	0.925
UA < 1 year[a]	0.541		0.801	0.780	67.9	0.675	0.693
UA > 1 year[a]	0.715		0.794	0.773	69.4	0.900	0.925
MI < 1 year	0.431		0.807	0.786	66.7	0.534	0.548
MI > 1 year	0.685		0.795	0.774	69.2	0.861	0.885
IS < 1 year	0.479		0.774	0.752	73.5	0.619	0.637
IS > 1 year	0.641		0.789	0.768	70.4	0.812	0.835
TIA < 1 year	0.760	Luengo-Fernandez *et al.* 2013a[49]	0.776	0.755	73.0	0.979	**1.007**[2]
TIA > 1 year	0.780		0.776	0.755	73.0	**1.005**[1]	**1.033**[3]

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; NR, not reported; SA, stable angina; SE, standard error; TIA, Transient ischaemic attack; UA, unstable angina.

[a] Mean utility for angina was used for both SA and UA.

*Estimated by the ERG using the Ara and Brazier equation for the general population adjusted for sex and age

^Estimated by the ERG for subpopulations 2b, 4a and 4b (multiple CV events history)

[1,2,3] Replaced by 0.907; 0.884; and 0.907; respectively, in the ERG's analysis

Table 35. Age-adjusted CV multipliers for primary CV events (subpopulation 2a)

Health state	EQ-5D mean	Reference	Baseline utility for males*	Baseline utility for females*	Age	Utility multipliers for males^	Utility multipliers for females^
Stable	-	-	**	**	**	1	1
SA < 1 year[a]	0.615	Ara and Brazier 2010[47]	0.817	0.791	68.8	0.753	0.777
SA > 1 year[a]	0.775		0.820	0.794	68.0	0.945	0.975
UA < 1 year[a]	0.615		0.817	0.791	68.8	0.753	0.777
UA > 1 year[a]	0.775		0.820	0.794	68.0	0.945	0.975
MI < 1 year	0.721		0.831	0.805	65.4	0.868	0.895
MI > 1 year	0.742		0.832	0.806	65.1	0.892	0.920
IS < 1 year	0.626		0.821	0.795	67.9	0.763	0.787
IS > 1 year	0.668		0.825	0.800	66.8	0.810	0.836
TIA < 1 year	0.760	Lueng-Fernandez *et al.* 2013a[49]	0.798	0.773	73.0	0.952	0.984
TIA > 1 year	0.780		0.798	0.773	73.0	0.977	**1.009**[1]

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; NR, not reported; SA, stable angina; SE, standard error; TIA, Transient ischaemic attack; UA, unstable angina.

[a] Mean utility for angina was used for both SA and UA.

*Estimated by the ERG using the Ara and Brazier equation for the general population adjusted for sex and age

** These change in each cycle of the model

^Estimated by the ERG for subpopulation 2a (primary CV events)
[1] Replaced by 0.907 in the ERG's analysis

4.2.10 Resource use and costs

Costs in the company's submission comprised of the intervention and comparators' acquisition and administration costs, disease monitoring and management costs (i.e. health state costs).

4.2.10.1 Intervention and comparator costs

Drug costs associated with the intervention and comparators were taken from the pharmaceutical electronic market information tool (eMit), the British National Formulary (BNF 2019), or MIMS 2019.[51-53] The company's model included the option to consider bempedoic acid as a single agent, or as a FDC with ezetimibe, based on the doses [redacted]. Nonetheless, as discussed in Section 4.2.3, in both populations 2 and 4, bempedoic acid is given with background ezetimibe. Therefore, the cost of the intervention (whether this consists of bempedoic acid with background ezetimibe or the FDC regimen) is always the same in the model (as seen in Table 36). Background atorvastatin was included in the treatment cost for 89% of patients in population 4 and 22% of patients in population 2.

The list prices of alirocumab and evolocumab included in the company's economic analyses are given in Table 36. However, both alirocumab and evolocumab are recommended on the basis of the discount agreed in the patient access scheme (PAS) with the Department of Health. The results of the economic analyses incorporating the approved PAS for alirocumab and evolocumab can be found in a confidential appendix produced by the ERG.

The company did not include any administration costs for oral drugs, while alirocumab and evolocumab were assumed to have a one-off £42 administration cost at the beginning of treatment. The intervention and comparator costs included a £9.89 annual pharmacy preparation cost.

Treatment costs were estimated based on drugs' discontinuation rates taken from a long-term study of evolocumab (Koren *et al*. 2019).[54] The company considered that the absolute discontinuation rates are not expected to be important model drivers however, the relative rates across treatments would be important. Therefore, the company assumed that all patients had the same discontinuation rate of 6.7%.

Table 36. Intervention and comparator acquisition costs

Treatment	Dose	Pack size	Pack price	Annual Cost
Bempedoic acid	180 mg daily	28	[redacted]	[redacted]

Treatment	Dose	Pack size	Pack price	Annual Cost
FDC	180 mg with 10 mg daily	28	[redacted]	[redacted]
Bempedoic acid with combination with background ezetimibe	180 mg with 10 mg daily	28	[redacted]	[redacted]
Ezetimibe	10 mg daily	28	£1.86	£24.26
Atorvastatin	10 mg daily	28	£0.68	£8.87
	20 mg daily	28	£0.97	£12.65
	40 mg daily	28	£1.22	£15.91
	80 mg daily	28	£1.82	£23.74
Alirocumab	150 mg per 2 weeks	1	£168.00	£4,383.00
Evolocumab	140 mg per 2 weeks	1	£170.10	£4,437.79

Abbreviations: FDC, bempedoic acid and ezetimibe fixed-dose combination; MIMS, Monthly Index of Medical Specialities
Source: British Medical Association RPS (2019); MIMS (2019).

4.2.10.2 ERG critique

The ERG is unclear what the one-off administration cost of £42 for alirocumab and evolocumab is meant to capture. The CS refers to a one-off 1-hour training with a nurse but also refers that these treatments are prescribed by specialists in the secondary setting. The ERG asked the company to clarify this, however, the company pointed the ERG to a table in the Personal Social Services Research Unit (PSSRU 2018) where the closest value to £42 corresponds to unit cost of a district nurse.[55] Clinical experts advising the ERG said that alirocumab and evelocumab treatment is initiated in the hospital setting with a nurse appointment to teach patients how to self-administer the drugs. Given that the cost of an hour hospital appointment with a nurse (Band 5) is £37 and £45 for a specialist nurse (Band 6), the ERG did not change the £42 estimate in the model (PSSRU 2018). Furthermore, the £42 estimate in the model is in between the one-off administration cost accepted in TAA393 (none) and TA394 (£84).[26, 27]

Even though the company used the same discontinuation rate across treatment arms in the model, this does not translate into the relative difference in discontinuation being the same across treatments. This is because different treatments are associated with different probabilities of CV events, which in turn are associated with different probabilities of death thus, the number of patients alive (used to estimate the probability of discontinuation) is different across treatments in every cycle.

Following a clarification request from the ERG, the company ran a scenario analysis using the discontinuation rate observed in the CLEAR studies for all treatments in the model ([redacted]). However, the impact of this change on the cost-effectiveness results was negligible.

4.2.10.3 Disease monitoring costs

The company estimated monitoring costs associated with all treatments in the model. These are reported in Table 37.

Table 37. Monitoring costs

Resource use	1st year	Subsequent years	Source	Cost	Source
Routine appointments:					
Appointment to take blood sample (with health care assistant)	2	1	CG181[28]	£6.66	PSSRU 2018[55]
GP appointment	2	2		£37.40	
Blood tests:					
Total cholesterol	2	1	CG181[28]	£1.03	Assumption
HDL cholesterol	2	1		£1.03	
Liver transaminase (ALT or AST)	2	1		£1.03	
Total annual monitoring costs, first year				£94.29	
Total annual monitoring costs, subsequent years				£84.55	

Abbreviations: ALT, alanine amino transferase; AST, aspartate aminotransferase; CG, Clinical Guideline; HDL, high-density lipid; GP, general practitioner; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, Technology Appraisal.

4.2.10.4 ERG critique

The clinical experts advising the ERG explained that patients on alirocumab and evelocumab are managed in the hospital setting and so would incur an annual cost of a hospital consultant visit. The ERG notes this is inconsistent with the monitoring schedules accepted in TA393 and TA394, which did not anticipate additional monitoring for alirocumab and evolocumab compared to current therapy.[26, 27] However, given the clear direction from the ERG's clinical experts involved in the prescribing and monitoring of PCSK9i treatments, the ERG added the cost of an annual hospital appointment of £128 for follow-up treatments (NHS reference cost, cardiologist outpatients attendance, code WF01B) and a one-off initial cost of £163 (NHS reference cost, cardiologist outpatients attendance, code WF01A) for patients receiving PCSK9 inhibitors.[56] Results of the ERG's analysis are reported in Section 6.

4.2.10.5 Disease management costs (i.e. health state costs)

In order to estimate health state-related costs, the company used cost and resource use data from a large UK study of patients treated with lipid-modifying therapy (Danese *et al*. 2017).[57] The company also used a UK registry study (Walker *et al*. 2016) to estimate the costs associated with CV deaths and CG181 to estimate the costs associated with SA.[58] The company included an option in the model to use CG181 costs for all CV events. The costs used by the company are reported in Table 38 together with the costs used in CG181 (and TA393).[27, 28] Table 38 also reports alternative cost estimates presented in Danese *et al*. 2017.[57] The study estimated total and incremental costs associated with CV events, where for the analyses of incremental costs the 12-month period before the first CV event was used as the baseline for calculating all cost differences, including for those in the second event cohort. The study reported costs for primary and secondary events separately (and combined), along with the respective post-event costs. The company used the combined incremental costs reported in the study. The company also assumed that post-event costs incur for the rest of patients' lives unless another event occurs, in which case the cost of the new event (followed by the post-event costs) are considered.

During the clarification stage, the ERG asked the company why combined (primary and secondary) event costs had been used instead of the separate primary and secondary event costs. The ERG also asked for a rationale for using incremental (as opposed to total) event-related costs, especially considering that this resulted in applying a negative cost (i.e. a cost saving) for each CV-related death in the analysis. The company explained that the use of combined costs was due to the costs of first and second events being consistent in most cases and that some of the first-event costs were higher than the recurrent events, which was counterintuitive to both the company and the ERG's clinical expert opinion. Furthermore, the company explained that the use of incremental costs allowed to take into account differences in the patient populations between Danese *et al*. 2017 and the modelled population.[57]

Table 38. CV-events-related costs

Health state	CG181 and TA393	Danese incremental costs primary event	Danese total costs primary event	Danese incremental costs secondary event	Danese total costs secondary event	Used by the company
SA	£8,042.05	NR	NR	NR	NR	£7,907.06
Post-SA	£249.49	NR	NR	NR	NR	£245.31
UA	£3,444.07	£2,227.43	£3,202.40	£2,544.53	£4,012.46	£2,469.42
Post-UA	£400.23	£335.71	£2,127.87	£691.79	£2,907.39	£381.40
MI	£3,469.02	£4,369.95	£5,414.73	£4,396.11	£5,913.40	£4,861.80
Post-MI	£819.17	£942.83	£2,402.64	£1,415.12	£3,973.71	£979.98
Revascularisation	£3,952.41	£5,759.80	£6,994.70	£5,951.88	£6,776.90	£5,682.03
CV death	£1,220.45	NR	NR	NR	NR	£-236.11
IS	£4,253.89	£3,589.91	£4,486.33	£4,673.38	£5,731.46	£4,205.58
Post-IS	£161.13	£994.13	£2,582.50	£697.38	£2,933.82	£974.56
TIA	£600.87	£1,570.86	£2,543.86	£1,853.73	£2,795.28	£2,011.49
Post-TIA	£128.91	£720.34	£2,414.33	£1,729.22	£3,410.86	£810.38

Abbreviations: CG, Clinical Guideline; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; NR, not reported; SA, stable angina; TA, Technology Appraisal; TIA, Transient ischaemic attack; UA, unstable angina.

All costs are inflated to 2018 prices.

For Danese *et al*. 2017 event costs include costs incurred 6 months after the event while post-event costs include costs incurred from months 7 to 36 after the event.[57]

For CG181/TA393 event costs include costs incurred 6 months after the event while post-event costs include costs incurred from months 7 to 12 after the event.[27, 28]

4.2.10.6 ERG critique

The ERG also agrees with the company that Danese *et al*. 2017 provides a good match to the relevant model population, as it only includes patients with lipid-lowering therapy.[57] The ERG also agrees with the company's use of incremental (relative to 12 months before the first CV event) costs from Danese *et al*. 2017 instead of total costs. This is mainly because comparison of total event costs in Danese *et al*. 2017 with CG181 and TA393 indicates that total costs in the former study might be generally overestimated when compared with previously accepted CVD event costs (CG181 and TA393), particularly with regards to post-event costs.[27, 28, 57] The reason for this difference in post-event costs across studies is unclear to the ERG, as Danese *et al*. 2017 was conducted using data from UK patients managed in the NHS. However, it is possible that this difference in post-event costs is driven by the fact that in Danese *et al*. 2017 the post-event estimates included 7 to 36-month annualised costs, while post-event costs in CG181 included only 7 to 12-month costs.

However, the ERG has three main concerns with the use of Danese *et al*. 2017 in the analysis, which relate to the use of incremental costs for CV deaths; the use of combined costs; and the time-points used to estimate costs.[57]

The ERG disagrees with the use of incremental costs for CV deaths as these result in a cost-saving event in the model, therefore benefiting the treatments associated with higher rates of CV deaths.

The ERG also disagrees with the use of combined event costs as Danese *et al*. 2017 provides first- and second-event related costs, which is an advantage of the study compared with previous sources of literature used in previous CVD models.[57] Furthermore, clinical experts advising the ERG explained that the costs associated with second events are expected to be higher than costs associated with first events, therefore, given the data are available, costs of primary and secondary events should be estimated separately in the model. Furthermore, the only event for which second event costs were lower than first event costs was the post-IS state for incremental costs and revascularisation for total costs (Table 38). As a result of clarification, the company provided a scenario analysis where primary and recurrent events were costed separately. Overall, the cost savings generated with bempedoic acid compared with other treatments decreased in the company's scenario analysis, but these cost savings never exceeded £100 in either of the subpopulations.

Similar to the issue raised in Section 4.2.10, the ERG considers that subpopulation 4a, 4b and 2b are secondary prevention populations. Therefore, the ERG costed any events experienced by these populations as secondary events in the model, with the exception of SA events as there were no data available for primary and secondary events, thus, the ERG used the costs reported in CG181. Results of the ERG's analysis are reported in Section 6. Furthermore, as discussed in Section 4.2.4, the ERG allocated these secondary prevention populations to begin the model in the 3-year+ post-event state, therefore, with a baseline annual post-event cost, and every year after that until a new event (and respective cost) occurs.

The ERG notes that the costs of an acute SA event are higher than those reported for an acute UA episode, in CG181 and in both the company's and ERG's analyses. The ERG's clinical expert advised that this is unexpected, as UA is a more serious and complicated event than SA. However, previous TAs (TA393 and TA385) and CG181 did not report any concerns with this difference in costs.[27-29]

Additionally, the ERG considers that the costs of SA and post-SA have been incorrectly inflated in the company's base case, as these should have been inflated from 2014 to 2018 costs, resulting in £8,042 and £250, respectively (as opposed to £7,907 and £245). The ERG corrected this in the model and reports results in Section 6.

Finally, the company's scenario analyses using CG181 costs replaced the cost of IS and post-IS in CG181 by those proposed by the ERG in TA393. These consist of £8,959 for acute IS and £1,839 for post-IS in 2018 prices. The ERG's rationale in TA393 was the CG181 costs for IS (£4,254 acute and £161 post-event) were too low. However, the ERG notes that the company's base case IS costs are £4,206 and £975 for acute and post-events, respectively, therefore not dissimilar (mainly for the acute event) to those proposed in CG181. Therefore, the ERG finds it inconsistent that the company would not use the values proposed in TA393 in their base case.[27, 28]

In conclusion, the ERG conducted one scenario analyses combining all the following assumptions, and presents the results in Section 6:

1. Using first and second event incremental costs from Danese *et al*. 2017 separately, in the analysis;[57]
2. Given that Danese *et al*. 2017 does not include an estimate for CV-related deaths, the ERG used the total cost estimate available in CG181 inflated to 2018 costs (£1,220) instead of an incremental cost as assumed in the company's base case analysis;[28, 57]

3. Given the ERG concerns in TA393 with IS costs, the ERG replaced the Danese *et al*. 2017 IS costs by £8,959 for acute IS and £1,839 for post-IS in 2018 prices (CG181).[27, 28, 57]

5 Cost effectiveness results

In response to the Evidence Review Group's (ERG's) clarification questions, the company submitted revised results which incorporated revised network meta analyses (NMAs). These revised results are presented here using list prices. Results incorporating the approved patient access scheme (PAS) for alirocumab and evolocumab can be found in a confidential appendix produced by the ERG.

The company presented separate cost-effectiveness results for bempedoic acid in a fixed dose combination (FDC) with ezetimibe and cost-effectiveness results for bempedoic acid with background ezetimibe. However, given that the cost-effectiveness results are equivalent (because the price and efficacy of the two presentations are equivalent), only one set of results is reported by the ERG.

5.1.1 Company's base case results

Table 39 to Table 42 provide the company's discounted base case results in each subpopulation compared to bempedoic acid (i.e. pairwise incremental cost-effectiveness ratios, ICERs). In subpopulations 2b and 4b bempedoic acid generates less quality-adjusted life years (QALYs) and less costs compared to its comparators, resulting in an ICER in the south-west quadrant of the cost-effectiveness plane. To aid interpretation, the ERG has produced cost-effectiveness planes for each subpopulation in Figure 6 including willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY. In short, treatments that lie below this threshold could be considered cost-effective.

Table 39. Company's deterministic base case results, population 2a

Results per patient	BA/EZE FDC	EZE	Incremental value
Total costs	£14,125	£8,278	£5,847
QALYs	8.71	8.51	0.21
LYs	11.76	11.51	0.25
ICER (cost per QALY)	-	-	£28,521

Abbreviations: BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

Table 40. Company's deterministic base case results, population 2b

Results per patient	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
				(1-2)	(1-3)
Total costs	£18,642	£41,337	£41,776	-£22,695	-£23,134
QALYs	6.86	6.93	6.96	-0.07	-0.10

LYs	9.97	10.06	10.10	-0.09	-0.14
ICER (cost per QALY)	-	-	-	£342,008*	£236,401*

Abbreviations: BA, bempedoic acid; Evo, evolocumab FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

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

Table 41. Company's deterministic base case results, population 4a

Results per patient	BA/EZE FDC	EZE	Incremental value
Total costs	£18,110	£12,690	£5,420
QALYs	6.89	6.81	0.08
LYs	9.91	9.80	0.11
ICER (cost per QALY)	-	-	£69,452

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

Note: all treatments in addition to statin therapy

Table 42. Company's deterministic base case results, population 4b

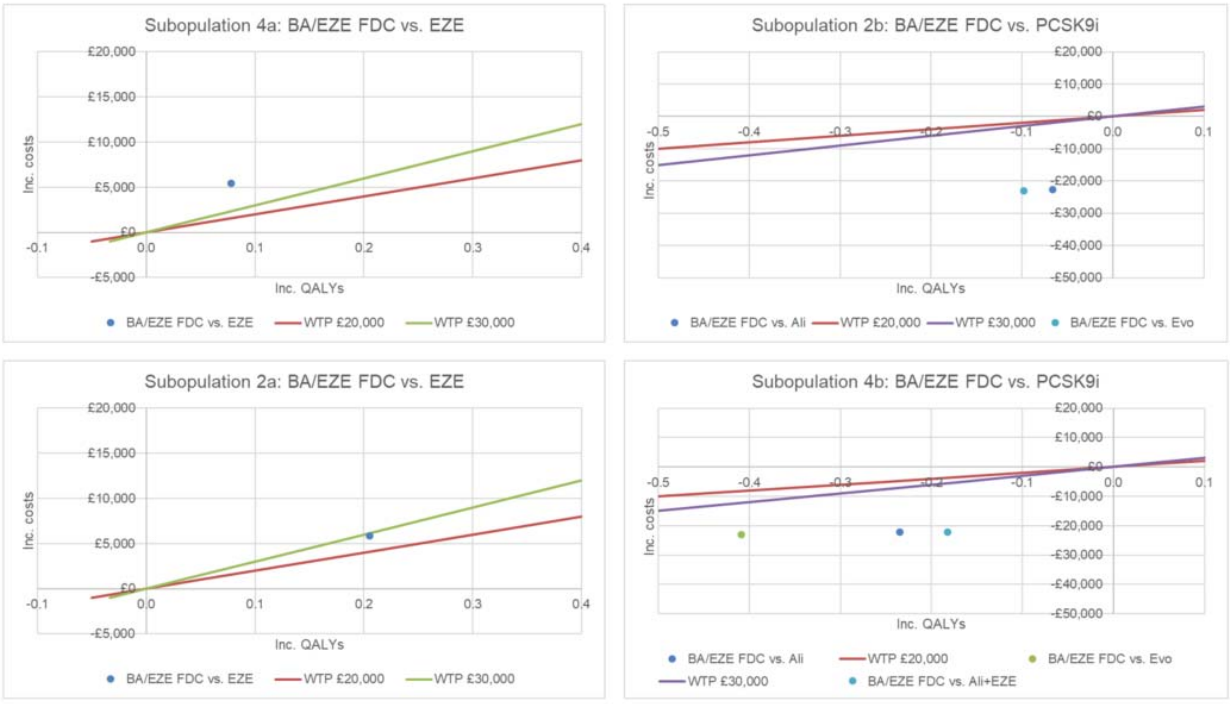
Results per patient	BA/EZE FDC (1)	Ali (2)	Ali + EZE (3)	Evo (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Total costs	£18,089	£40,289	£40,297	£41,126	-£22,200	-£22,208	-£23,037
QALYs	6.48	6.72	6.67	6.89	-0.23	-0.18	-0.41
LYs	9.35	9.67	9.60	9.91	-0.32	-0.25	-0.57
ICER (cost per QALY)	-	-	-	-	£94,488*	£121,686*	£56,285*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; Lys, life years; QALYs, quality-adjusted life years

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

Note: all treatments in addition to statin therapy

Figure 6. Company's deterministic results, cost-effectiveness planes (produced by the ERG)



Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; PCSK9i, proprotein convertase subtilisin / kexin type 9 inhibitor; QALYs, quality-adjusted life years; WTP, willingness to pay
Note: all treatments in population 4 in addition to statin therapy

Table 43 and Table 44 provide the fully incremental results in subpopulations 2b and 4b, respectively. In subpopulation 2b, alirocumab is extendedly dominated by evolocumab (i.e. the ICER for alirocumab is greater than that of a more effective intervention, evolocumab). Then, the decision in subpopulation 2b reduces to a comparison with evolocumab.

Table 43. Company's deterministic base case results, population 2b, fully incremental

Treatment	Cost	QALYs	Inc cost	Inc QALY	ICER
BA/EZE FDC	£18,642	6.86	-	-	-
Ali	£41,337	6.93	£22,695	0.07	£342,008
Evo	£41,776	6.96	£439	0.03	£13,942

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

In subpopulation 4b, alirocumab plus ezetimibe is dominated by alirocumab (i.e. alirocumab plus ezetimibe is more expensive and less effective than alirocumab). Subsequently, alirocumab is extendedly dominated by evolocumab (i.e. the ICER for alirocumab is greater than that of a more effective intervention, evolocumab). Then, the decision in subpopulation 4b reduces to a comparison with evolocumab.

Table 44. Company's deterministic base case results, population 4b, fully incremental

Treatment	Cost	QALYs	Inc cost	Inc QALY	ICER
BA/EZE FDC	£18,089	6.48	-	-	-
Ali	£40,289	6.72	£22,200	0.23	£94,488
Ali + EZE	£40,297	6.67	£9	-0.05	-£163
Evo	£41,126	6.89	£829	0.23	£3,654*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab FDC, EZE, ezetimibe; fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
*ICER for Evo vs. Ali £4,802
Note: all treatments in addition to statin therapy

5.1.2 *Company's sensitivity analyses*

5.1.2.1 *Probabilistic sensitivity analysis (PSA)*

PSA was undertaken using 5,000 iterations. The ERG considers the parameters and respective distributions chosen for PSA, outlined in Table 64 of the company submission (CS), to be generally sound. In addition, for data obtained from the NMA, the company used the CODA output from JAGS on low-density lipoprotein cholesterol (LDL-C) reductions to ensure the correlation between each sample is retained (i.e. the same iteration for each sample is used for all treatments). The cost-effectiveness planes produced by the company are presented in Figure 7 to Figure 10.

However, in the company's clarification letter the company did not present the total costs and QALYs associated with each treatment. As such, the ERG ran the PSA using 5,000 iterations to extract these results in order to calculate ICERs (Table 45). Following this, the ERG considers the PSA results to be comparable to the deterministic base-case results.

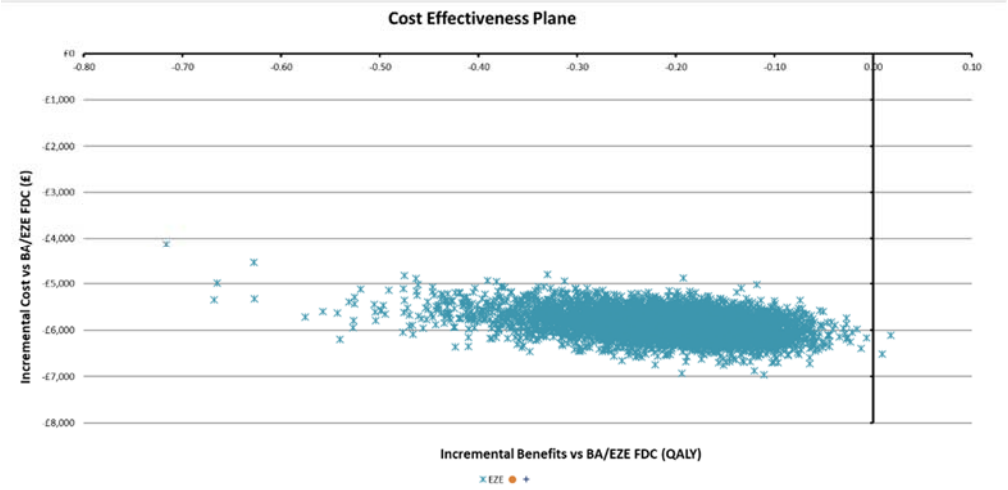
Table 45. PSA results produced by the ERG

Treatment	Total costs	Total QALYs	Pairwise ICER with BA/EZE FDC
Population 2a			
EZE	£8,382	8.61	-
BA/EZE FDC	£14,255	8.82	£28,262
Population 2b			
BA/EZE FDC	£18,899	6.99	-
Alirocumab	£41,791	7.05	£340,370
Evolocumab	£42,237	7.08	£259,311
Population 4a			
EZE + statin	£11,953	7.05	-
BA/EZE FDC	£17,427	7.13	£69,657
Population 4b			
BA/EZE FDC	£18,103	6.49	-
Ali + statin	£40,263	6.73	£93,373
Ali + EZE + statin	£40,283	6.67	£118,617

Evo + statin	£41,116	6.90	£55,817

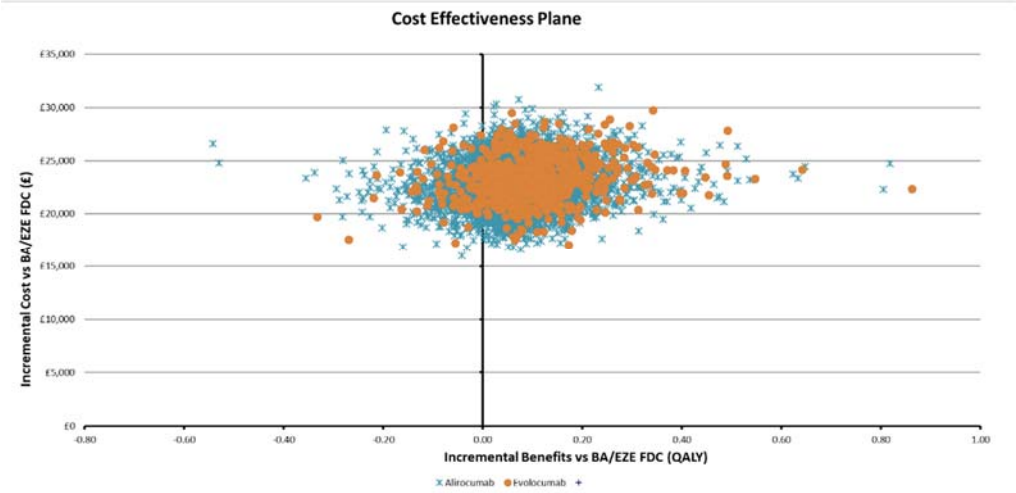
Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab FDC, EZE, ezetimibe; fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 7. Cost-effectiveness plane - population 2a, EZE vs BA/EZE FDC (reproduced from Figure 37 in the company's clarification responses)



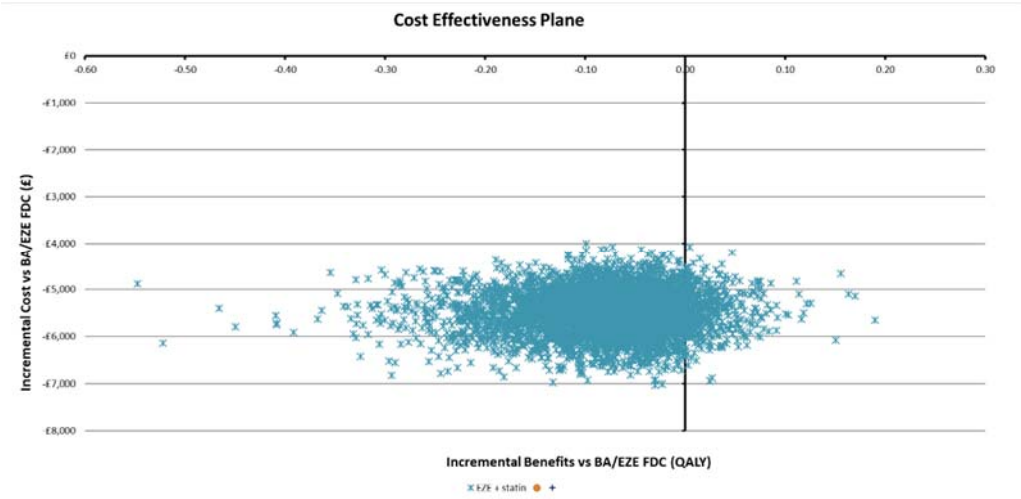
Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; QALYs, quality-adjusted life years

Figure 8. Cost-effectiveness plane – population 2b, PCSK9i vs BA/EZE FDC (reproduced from Figure 38 in the company's clarification responses)



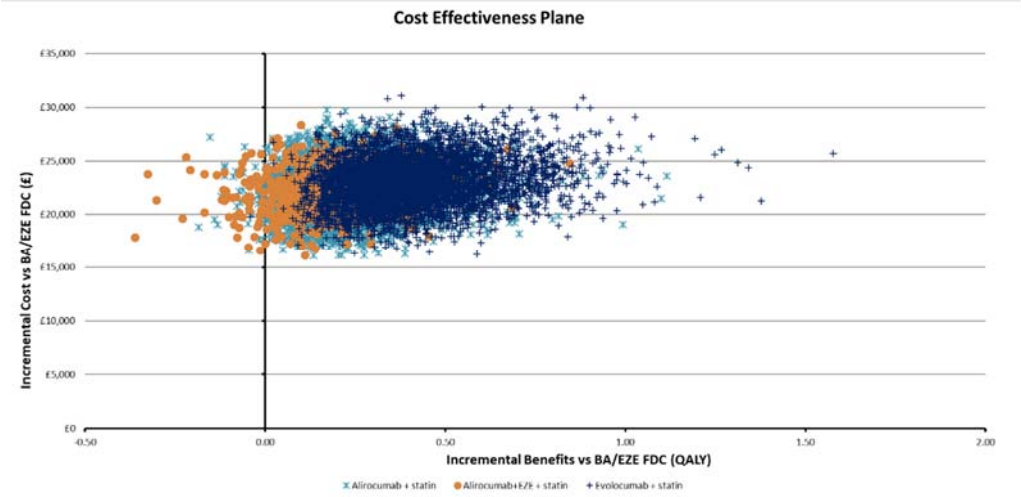
Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab EZE, ezetimibe; FDC, fixed dose combination; PCSK9i, proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years

Figure 9. Cost-effectiveness plane – population 4a, EZE vs BA/EZE FDC (reproduced from Figure 39 in the company's clarification responses)



Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; QALYs, quality-adjusted life years

Figure 10. Cost-effectiveness plane – population 4b, PCSK9i vs BA/EZE FDC (reproduced from Figure 40 in the company's clarification responses)

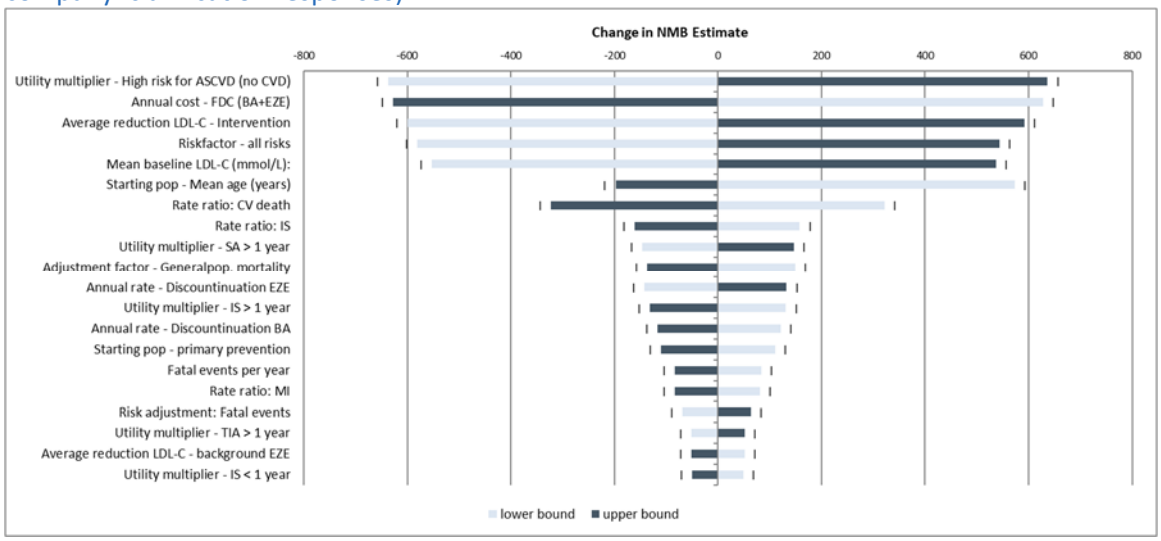


Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab EZE, ezetimibe; FDC, fixed dose combination; PCSK9i, proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years

5.1.2.2 One-way sensitivity analysis (OWSA)

The company carried out OWSAs to assess the impact of varying model parameters by ±10% of the mean. Figure 11 to Figure 14 display tornado diagrams of the 20 most influential parameters from the OWSA, in terms of impact on net monetary benefit (NMB) using a WTP of £30,000 per QALY.

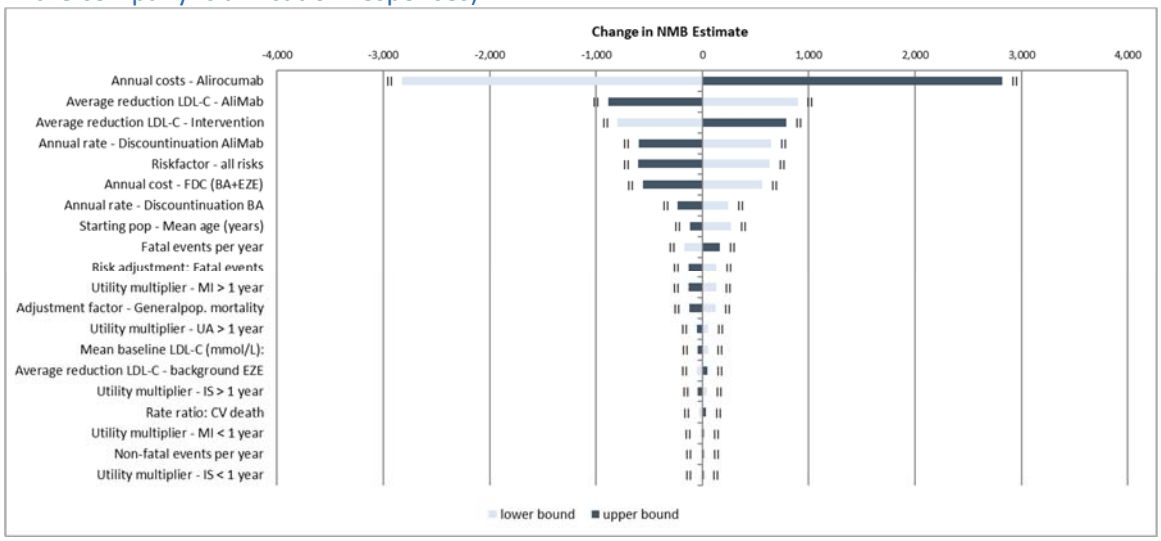
Figure 11. Tornado diagram – population 2a, BA/EZE FDC vs EZE (reproduced from Figure 31 in the company' clarification responses)



Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). Base case NMB £303

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CV, cardiovascular; CVD, cardiovascular disease; EZE, ezetimibe; DC, fixed dose combination; ICER, incremental cost-effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMB, net monetary benefit; QALYs, quality-adjusted life years; TIA, transient ischemic attack

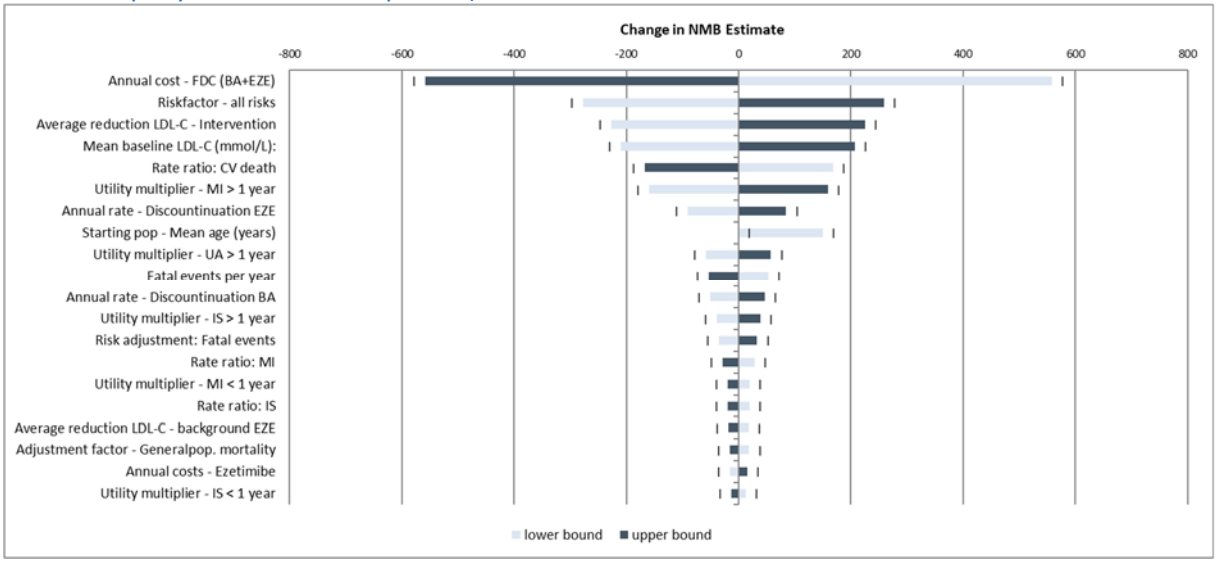
Figure 12. Tornado diagram – population 2b – BA/EZE FDC vs alirocumab (reproduced from Figure 32 in the company' clarification responses)



Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). Base case NMB £20,704

Abbreviations: BA, bempedoic acid; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMB, net monetary benefit; QALYs, quality-adjusted life years; TIA, transient ischemic attack

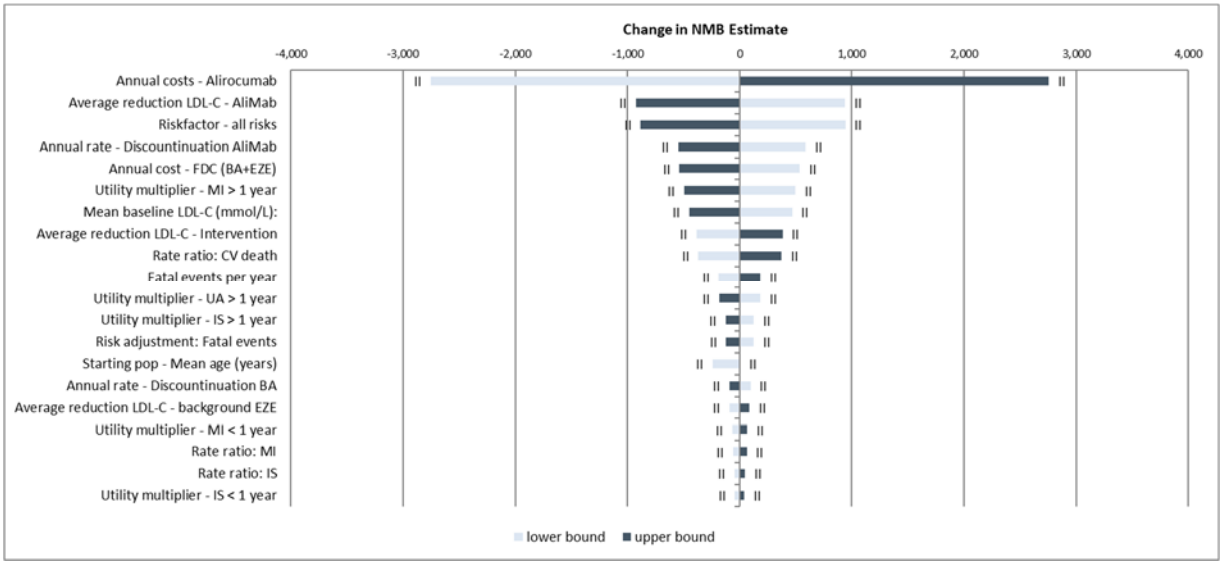
Figure 13.Tornado diagram – population 4a, BA/EZE FDC vs EZE + statin (reproduced from Figure 33 in the company' clarification responses)



Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). Base case NMB -£3,079

Abbreviations: BA, bempedoic acid; CV, cardiovascular; EZE, ezetimibe; DC, fixed dose combination; ICER, incremental cost-effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMB, net monetary benefit; QALYs, quality-adjusted life years; TIA, transient ischemic attack

Figure 14. Tornado diagram - population 4b, BA/EZE FDC vs alirocumab + statin (reproduced from Figure 34 in the company' clarification responses)



Note: the quadrant where the NMB falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates). Base case NMB £15,151

Abbreviations: BA, bempedoic acid; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMB, net monetary benefit; QALYs, quality-adjusted life years; TIA, transient ischemic attack

In summary, the main drivers of the model in each subpopulation include: the annual acquisition cost of the intervention or comparator, the average reduction in LDL-C obtained from the NMA, the baseline LDL-C and the discontinuation rate.

Other drivers in the model the utility multiplier for patients at high risk at atherosclerotic cardiovascular disease (ASCVD) and the risk factor for all risks. However, in the company's base case analyses, these parameters were set to 1. The former was informed by general population utilities while the latter was informed by rate ratios according to the type of cardiovascular (CV) event. As such, their inclusion in the company's OWSA is not meaningful. Furthermore, the company included utility multipliers higher than 1 in their sensitivity analysis (1.10 for patients at high risk for ASCVD). As noted in Section 4.2.9.1, having a multiplier higher than 1 is not clinically plausible as this implies that patients' utility after the CV event increases comparatively to their baseline utility.

Finally, the company did not consider the variation in model parameters recorded in the original sources. As such, the lower and upper bounds considered by the company (±10%) are arbitrary.

5.1.2.3 Scenario analyses

In the CS the company carried out scenario analyses changing assumptions surrounding the following parameters:

1. Discount rate for benefits (base case: 3.5%; scenario: 1.5%);
2. Relationship between LDL-C and CV events (base case: Cholesterol Treatment Trialists Collaboration (CTTC); scenario: de novo meta regression with a covariate for baseline LDL-C);[32]
3. Utility estimates (base case: Ara and Brazier 2010 and Luengo-Fernandez *et al.* 2013; scenario: CG181);[28, 47, 49] and,
4. Health state costs (base case: Danese *et al.* 2016 and Walker *et al*. 2016; scenario: TA393).[27, 40, 58]

During the clarification stage, the company did not update the results of these scenario analyses using the revised NMAs. For completeness, the ERG ran the company's scenario analyses in the revised model and provides the results in Table 46 to Table 49.

Table 46. Results of scenario analyses – population 2a, produced by the ERG

	BA/EZE FDC	EZE	Incremental value
Discount rate benefits 1.5%			
Total costs	£14,125	£8,278	£5,847
QALYs	10.18	9.91	0.27
ICER	-	-	£21,930
De novo meta regression for relationship between LDL-C and CV events			
Total costs	£14,254	£8,248	£6,006
QALYs	8.74	8.47	0.27
ICER	-	-	£22,299
TA393 health state costs			
Total costs	£16,599	£10,945	£5,654
QALYs	8.71	8.51	0.21
ICER	-	-	£27,577
CG181 utility estimates			
Total costs	£14,125	£8,278	£5,847
QALYs	8.27	8.06	0.21
ICER	-	-	£27,877

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack

Table 47. Results of scenario analyses – population 2b, produced by the ERG

	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
				1-2	1-3
Discount rate benefits 1.5%					
Total costs	£18,642	£41,337	£41,776	-£22,695	-£23,134
QALYs	7.89	7.97	8.01	-0.08	-0.12
ICER	-	-	-	£270,975*	£187,220*
De novo meta regression for relationship between LDL-C and CV events					
Total costs	£19,096	£42,539	£43,106	-£23,443	-£24,010
QALYs	7.04	7.16	7.22	-0.12	-0.18
ICER	-	-	-	£194,910*	£135,919*
TA393 health state costs					
Total costs	£22,685	£45,364	£45,796	-£22,679	-£23,111
QALYs	6.86	6.93	6.96	-0.07	-0.10
ICER	-	-	-	£341,767*	£236,160*
CG181 utility estimates					
Total costs	£18,642	£41,337	£41,776	-£22,695	-£23,134
QALYs	6.13	6.19	6.22	-0.06	-0.09
ICER	-	-	-	£373,066*	£257,879*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack

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

Table 48. Results of scenario analyses – population 4a, produced by the ERG

	BA/EZE FDC	EZE	Incremental value
Discount rate benefits 1.5%			
Total costs	£18,110	£12,690	£5,420
QALYs	7.92	7.82	0.10
ICER	-	-	£55,362
De novo meta regression for relationship between LDL-C and CV events			
Total costs	£18,017	£12,630	£5,387
QALYs	6.82	6.75	0.07
ICER	-	-	£77,725
TA393 health state costs			
Total costs	£21,571	£16,175	£5,395
QALYs	6.89	6.81	0.08
ICER	-	-	£69,135
CG181 utility estimates			
Total costs	£18,110	£12,690	£5,420
QALYs	6.20	6.12	0.07
ICER	-	-	£74,868

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack

Table 49. Results of scenario analyses – population 4b, produced by the ERG

	BA/EZE FDC (1)	Ali (2)	Ali + EZE (3)	Evo (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Discount rate benefits 1.5%							
Total costs	£18,089	£40,289	£40,297	£41,126	-£22,200	-£22,208	-£23,037
QALYs	7.39	7.68	7.62	7.90	-0.29	-0.23	-0.51
ICER	-	-	-	-	£75,735*	£97,605*	£45,006*
De novo meta regression for relationship between LDL-C and CV events							
Total costs	£18,262	£41,595	£41,413	£43,040	-£23,333	-£23,151	-£24,778
QALYs	6.54	6.97	6.87	7.27	-0.43	-0.33	-0.73
ICER	-	-	-	-	£54,551*	£69,227*	£34,021*
TA393 health state costs							
Total costs	£21,694	£43,825	£43,849	£44,609	-£22,130	-£22,155	-£22,915
QALYs	6.48	6.72	6.67	6.89	-0.23	-0.18	-0.41
ICER	-	-	-	-	£94,193*	£121,393*	£55,987*
CG181 utility estimates							
Total costs	£18,089	£40,289	£40,297	£41,126	-£22,200	-£22,208	-£23,037

QALYs	5.82	6.03	5.99	6.20	-0.22	-0.17	-0.38
ICER	-	-	-	-	£102,194*	£131,606*	£60,885*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack

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

5.1.3 Model validation and face validity check

To test the internal validity of the model, the CS reports that a health economist working for a vendor and not involved in model development validated input data (including the original sources), model results, calculations (including the testing extreme values), data references, model interface, and Visual Basic for Applications code.

As a face validity check, the company sought external validation from a UK advisory board on the following:

- Model structure;
- Comparators and position in the treatment pathway;
- Methodology of the NMA and *de novo* meta-regression;
- Selection of the meta-analysis for the association between LDL-C lowering and cardiovascular risk for the base-case analysis; and
- Validation of resource use and costs included in the economic model.

The company also performed a comparison of the model inputs with those for other relevant models used in previous NICE appraisals for alirocumab (TA393), evoculumab (TA394) and ezetimibe (TA385) and previous NICE guidance in CVD (CG181).[26-29] The findings of these comparisons are given in Table 74 of the CS.

6 Additional economic analysis undertaken by the ERG

Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness for this appraisal. As mentioned throughout this report, the revised network meta-analyses (NMAs) provided by the company at the clarification stage remain unfit for decision making, principally due to the extent of the clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. Thus, the individual incremental cost-effectiveness ratios (ICERs) presented in Section 6.1 and Section 6.2 which employ the company's NMAs are purely to demonstrate the direction and magnitude of the ERG's assumptions on the ICER.

6.1 Model corrections

The ERG described one implementation error in Section 4.2.10.6 of this report related to the calculation of health state costs. The ERG considers that the costs of SA and post-SA have been incorrectly inflated in the company's base case, as these should have been inflated from 2014 to 2018 costs, resulting in £8,042 and £250, respectively (as opposed to £7,907 and £245). Pairwise results including this correction are provided in Table 50 to Table 53.

Table 50. Company's corrected base case, population 2a

Results per patient	BA/EZE FDC	EZE	Incremental value
Total costs	£14,148	£8,300	£5,848
QALYs	8.71	8.51	0.21
ICER	-	-	£28,527

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 51. Company's corrected base case, population 2b

Results per patient	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
				(1-2)	(1-3)
Total costs	£18,643	£41,338	£41,777	-£22,695	-£23,134
QALYs	6.86	6.93	6.96	-0.07	-0.10
ICER	-	-	-	£342,008*	£236,401*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

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

Table 52. Company's corrected base case, population 4a

Results per patient	BA/EZE FDC	EZE	Incremental value
Total costs	£18,111	£12,691	£5,420
QALYs	6.89	6.81	0.08

ICER	-	-	£69,453

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 53. Company's corrected base case, population 4b

Results per patient	BA/EZE FDC (1)	Ali (2)	Ali + Eze (3)	Evo (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Total costs	£18,090	£40,289	£40,298	£41,126	-£22,200	-£22,208	-£23,037
QALYs	6.48	6.72	6.67	6.89	-0.23	-0.18	-0.41
ICER	-	-	-	-	£94,488*	£121,686*	£56,285*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

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

6.2 Exploratory and sensitivity analyses undertaken by the ERG

In Section 4 of this report, the ERG has described several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the ICER. One of these scenarios adjusts the cohort of patients entering the model and is fundamental in determining how subsequent scenarios are applied in the model.

As described in Section 4.2.2, subpopulation 2a is representative of patients receiving primary prevention (patients without a prior CV event), subpopulations 2b, 4a and 4b are largely representative of patients receiving secondary prevention (patients with a prior CV event) and all subpopulations are largely representative of patients without heterozygous familial hypercholesterolaemia (HeFH). As such, the ERG has adjusted the company's "mixed" model into either a primary prevention model without HeFH (subpopulation 2a) or secondary prevention model without HeFH (subpopulations 2b, 4a and 4b). Consequently, this limits bempedoic acid to being assessed in the populations for which there is data on bempedoic acid and reduces the complexities in the model required to model primary and secondary prevention patients in the same model.

Due to time constraints, the ERG has performed its additional analyses on top of this adjustment. However, results on top of the company's base case would not be informative, primarily because secondary prevention patients enter the company's model in the wrong health state. As explained in Section 4.2.4, secondary prevention patients enter the company's model in one of the 0 to 1 year-post CV event health states, incurring the costs and benefits for an acute event. The ERG disagrees with this because the prior CV event could have occurred many years prior to entering the model. As

such, the ERG allocated the secondary prevention cohort to enter the model in the 3-year+ post-event state, associated with post-event costs and benefits, until a new event occurs.

The scenarios that the ERG has produced are summarised in Table 54.

Table 54. Scenario analyses undertaken by the ERG

#	Scenario	Section in ERG report	Population			
			2a	2b	4a	4b
0	Using a starting cohort of primary prevention patients without HeFH	Section 4.2.4.1	X			
0	Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	Section 4.2.4.1		X	X	X
1	Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe	Section 4.2.5.3	X	X	X	X
2	Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment	Section 4.2.2.2	X		X	
3	Using a lower estimate for recurrent/polyvascular events (7%)	Section 4.2.2.2		X	X	X
4	Using prior IS events to inform the history of all secondary prevention patients to explore the impact of alternative distributions of prior CV events	Section 4.2.2.2		X	X	X
5	Using prior MI events to inform the history of all secondary prevention patients to explore the impact of alternative distributions of prior CV events	Section 4.2.2.2		X	X	X
6	Including transitions to the SA state from prior event states in all subpopulations	Section 4.2.4.1	X	X	X	X
7	Using all-cause mortality without subtracting the risk of CV death in all subpopulations	Section 4.2.8	X	X	X	X
8	Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	Table 24 in Section 4.2.9.1		X	X	X
9	Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier	Table 25 in Section 4.2.9.1	X			

	• After patients in subpopulation 2a experience their first event, recurrent events accrue the utilities for multiple events reported in Table 24.					
10	Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors	Section 4.2.10.2		X		X
11	Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	Section 4.2.10.6	X	X	X	X

Abbreviations: CG, Clinical Guideline; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9 proprotein convertase subtilisin kexin type 9; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

6.3 ERG scenario analysis

Table 55 to Table 58 present the results of the ERG exploratory analyses described in Section 6.2.

Scenarios are performed in addition to the model correction and the ERG's redefined populations.

Table 55. Results of the ERG's scenario analyses, population 2a

	Results per patient	BA/EZE FDC	EZE	Incremental value
0	**Corrected company base case**			
	Total costs	£14,148	£8,300	£5,848
	QALYs	8.71	8.51	0.21
	ICER	-	-	£28,527
0	**Primary prevention cohort, no HeFH**			
	Total costs (£)	£12,992	£7,018	£5,973
	QALYs	9.25	9.06	0.19
	ICER	-	-	£31,504
1	**ERG's NMA on LDL-C**			
	Total costs (£)	£12,984	£7,018	£5,966
	QALYs	9.26	9.06	0.20
	ICER	-	-	£30,504
2	**Using the baseline LDL-C level from non-PCSK9i eligible patients in the non-PCSK9i eligible subpopulations**			
	Total costs (£)	£12,995	£7,012	£5,984
	QALYs	9.26	9.07	0.18
	ICER	-	-	£32,517
6	**Including transitions to the SA state from prior event states**			
	Total costs (£)	£13,191	£7,224	£5,967

	QALYs	9.25	9.06	0.19
	ICER	-	-	£31,591
7	**Using all-cause mortality without subtracting the risk of CV death**			
	Total costs (£)	£12,515	£6,667	£5,847
	QALYs	8.95	8.77	0.18
	ICER	-	-	£33,329
9	**Alternative utility assumptions**			
	Total costs (£)	£12,992	£7,018	£5,973
	QALYs	9.24	9.05	0.19
	ICER	-	-	£31,162
11	**Alternative health state cost assumptions**			
	Total costs (£)	£15,329	£9,604	£5,726
	QALYs	9.25	9.06	0.19
	ICER	-	-	£30,198

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

Table 56. Results of the ERG's scenario analyses, population 2b

	Results per patient	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
					(1-2)	(1-3)
0	**Corrected company base case**					
	Total costs	£18,643	£41,338	£41,777	-£22,695	-£23,134
	QALYs	6.86	6.93	6.96	-0.07	-0.10
	ICER	-	-	-	£342,008	£236,401
0	**Secondary prevention cohort entering 3-year+ post-event states, no HeFH**					
	Total costs	£17,471	£40,817	£41,256	-£23,346	-£23,785
	QALYs	7.20	7.25	7.28	-0.06	-0.09
	ICER	-	-	-	£398,880	£275,430
1	**ERG's NMA on LDL-C†**					
	Total costs	£17,475	£41,505	NA	-£24,030	NA
	QALYs	7.20	7.45	NA	-0.24	NA
	ICER	-	-	-	£99,488	NA
3	**Using a lower proportion of recurrent/polyvascular events (7%)**					
	Total costs	£17,639	£41,218	£41,660	-£23,579	-£24,020
	QALYs	7.30	7.36	7.39	-0.06	-0.09
	ICER	-	-	-	£405,339	£279,938
4	**Using prior IS events to inform the history of all secondary prevention patients**					
	Total costs	£17,849	£40,521	£40,968	-£22,672	-£23,119
	QALYs	6.41	6.46	6.49	-0.05	-0.08
	ICER	-	-	-	£424,501	£293,004
5	**Using prior MI events to inform the history of all secondary prevention patients**					
	Total costs	£18,755	£42,470	£42,918	-£23,716	-£24,164

	QALYs	7.49	7.55	7.58	-0.06	-0.09
	ICER	-	-	-	£400,241	£276,551
6	**Including transitions to the SA state from prior event states**					
	Total costs	£17,860	£41,235	£41,675	-£23,375	-£23,815
	QALYs	7.22	7.28	7.30	-0.06	-0.09
	ICER	-	-	-	£400,674	£276,664
7	**Using all-cause mortality without subtracting the risk of CV death**					
	Total costs	£17,006	£39,948	£40,376	-£22,942	-£23,371
	QALYs	7.00	7.06	7.08	-0.06	-0.08
	ICER	-	-	-	£416,776	£287,797
9	**Alternative utility assumptions**					
	Total costs	£17,471	£40,817	£41,256	-£23,346	-£23,785
	QALYs	12.28	12.36	12.40	-0.09	-0.13
	ICER	-	-	-	£274,467	£188,501
10	**Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors**					
	Total costs	£17,471	£41,828	£42,270	-£24,357	-£24,798
	QALYs	7.20	7.25	7.28	-0.06	-0.09
	ICER	-	-	-	£416,156	£287,165
11	**Alternative health state cost assumptions**					
	Total costs	£23,201	£46,543	£46,980	-£23,342	-£23,779
	QALYs	7.20	7.25	7.28	-0.06	-0.09
	ICER	-	-	-	£398,809	£275,361

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

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

†Comparison with Ali+EZE

Table 57. Results of the ERG's scenario analyses, population 4a

	Results per patient	BA/EZE FDC	EZE	Incremental value
0	**Corrected company base case**			
	Total costs	£18,111	£12,691	£5,420
	QALYs	6.89	6.81	0.08
	ICER	-	-	£69,453
0	**Secondary prevention cohort entering 3-year+ post-event states, no HeFH**			
	Total costs	£17,045	£11,468	£5,577
	QALYs	7.18	7.11	0.07
	ICER	-	-	£82,286
1	**ERG's NMA on LDL-C**			
	Total costs	£17,055	£11,468	£5,587
	QALYs	7.20	7.11	0.08
	ICER	-	-	£66,343

2	**Using the baseline LDL-C level from non-PCSK9i eligible patients in the non-PCSK9i eligible subpopulations**			
	Total costs	£17,079	£11,460	£5,619
	QALYs	7.26	7.20	0.06
	ICER	-	-	£97,388
3	**Using a lower proportion of recurrent/polyvascular events (7%)**			
	Total costs	£17,205	£11,574	£5,631
	QALYs	7.28	7.22	0.07
	ICER	-	-	£83,877
4	**Using prior IS events to inform the history of all secondary prevention patients**			
	Total costs	£17,514	£12,074	£5,441
	QALYs	6.38	6.32	0.06
	ICER	-	-	£87,484
5	**Using prior MI events to inform the history of all secondary prevention patients**			
	Total costs	£18,251	£12,585	£5,667
	QALYs	7.44	7.37	0.07
	ICER	-	-	£83,109
6	**Including transitions to the SA state from prior event states**			
	Total costs	£17,437	£11,853	£5,584
	QALYs	7.20	7.13	0.07
	ICER	-	-	£82,698
7	**Using all-cause mortality without subtracting the risk of CV death**			
	Total costs	£16,465	£11,021	£5,444
	QALYs	6.92	6.86	0.06
	ICER	-	-	£86,764
9	**Alternative utility assumptions**			
	Total costs	£17,045	£11,468	£5,577
	QALYs	9.02	8.94	0.08
	ICER	-	-	£66,611
11	**Alternative health state cost assumptions**			
	Total costs	£22,321	£16,751	£5,570
	QALYs	7.18	7.11	0.07
	ICER	-	-	£82,185

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

Note: all treatments in addition to statin therapy

Table 58. Results of the ERG's scenario analyses, population 4b

	Results per patient	BA/EZE FDC (1)	Ali (2)	Ali + Eze (3)	Evo (4)	Incremental value		
						(1-2)	(1-3)	(1-4)
0	**Corrected company base case**							
	Total costs	£18,090	£40,289	£40,298	£41,126	-£22,200	-£22,208	-£23,037
	QALYs	6.48	6.72	6.67	6.89	-0.23	-0.18	-0.41

	ICER	-	-	-	-	£94,488	£121,686	£56,285
0	**Secondary prevention cohort entering 3-year+ post-event states, no HeFH**							
	Total costs	£16,955	£39,810	£39,842	£40,595	-£22,855	-£22,887	-£23,640
	QALYs	6.83	7.03	6.99	7.18	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£111,482	£143,849	£65,992
1	**ERG's adjusted NMA on LDL-C†**							
	Total costs	£16,965	NA	£40,572	NA	NA	-£23,607	NA
	QALYs	6.85	NA	7.25	NA	NA	-0.39	NA
	ICER	-	-	-	-	NA	£60,123	NA
3	**Using a lower proportion of recurrent/polyvascular events (7%)**							
	Total costs	£17,119	£40,202	£40,237	£40,982	-£23,082	-£23,118	-£23,862
	QALYs	6.93	7.13	7.09	7.29	-0.20	-0.16	-0.36
	ICER	-	-	-	-	£113,225	£146,057	£67,086
4	**Using prior IS events to inform the history of all secondary prevention patients**							
	Total costs	£17,233	£39,511	£39,507	£40,385	-£22,277	-£22,274	-£23,152
	QALYs	6.07	6.25	6.21	6.39	-0.18	-0.14	-0.32
	ICER	-	-	-	-	£120,894	£156,131	£71,341
5	**Using prior MI events to inform the history of all secondary prevention patients**							
	Total costs	£18,111	£41,311	£41,339	£42,121	-£23,200	-£23,227	-£24,010
	QALYs	7.07	7.28	7.23	7.44	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£111,463	£143,662	£66,220
6	**Including transitions to the SA state from prior event states**							
	Total costs	£17,351	£40,237	£40,269	£41,021	-£22,886	-£22,918	-£23,670
	QALYs	6.85	7.05	7.01	7.21	-0.20	-0.16	-0.36
	ICER	-	-	-	-	£112,029	£144,561	£66,308
7	**Using all-cause mortality without subtracting the risk of CV death**							
	Total costs	£16,408	£38,744	£38,782	£39,488	-£22,336	-£22,374	-£23,080
	QALYs	6.60	6.79	6.75	6.94	-0.19	-0.15	-0.33
	ICER	-	-	-	-	£117,267	£151,307	£69,431
9	**Alternative utility assumptions**							
	Total costs	£16,955	£39,810	£39,842	£40,595	-£22,855	-£22,887	-£23,640
	QALYs	8.67	8.90	8.84	9.08	-0.23	-0.18	-0.41
	ICER	-	-	-	-	£98,379	£130,348	£57,525
10	**Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors**							
	Total costs	£16,955	£40,802	£40,829	£41,599	-£23,846	-£23,874	-£24,644
	QALYs	6.83	7.03	6.99	7.18	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£116,316	£150,055	£68,793
11	**Alternative health state cost assumptions**							
	Total costs	£22,290	£45,120	£45,157	£45,890	-£22,830	-£22,867	-£23,600
	QALYs	6.83	7.03	6.99	7.18	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£111,360	£143,724	£65,879

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase

subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack
Note: all treatments in addition to statin therapy
*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. bempedoic acid generates less QALYs than comparators but is also less costly).
†Comparison with Ali+EZE

6.4 ERG preferred assumptions

The ERG's preferred assumptions are given in Table 59 while Table 60 to Table 63 present the cumulative results based on those preferred assumptions. As noted in Section 4.2.5.3 the cost-effectiveness results informed by the ERG's NMAs must be interpreted with caution due to time and resource constraints the ERG has been unable to fully assess all potentially relevant studies for inclusion in the networks and additionally not had access to the relevant subgroup data from the bempedoic acid studies (see Section 3.5).

Table 64 presents the deterministic and probabilistic ERG preferred base case ICERs in each subpopulation. PSA was undertaken using 5,000 iterations and incorporates the CODA obtained from the ERG's NMAs. Due to time constraints, the ERG was unable to make the utility multipliers and health state costs included in its preferred assumptions probabilistic. Even so, the ERG considers the PSA results to be informative to assess the simultaneous effects informed by the ERG's NMAs. Furthermore, the ERG was unable to produce PSA results for subpopulation 2b given that inputs for the CODA for alirocumab plus ezetimibe were not included in the model.

Table 59. ERG's preferred assumptions

#	Scenario	Section in ERG report	Population			
			2a	2b	4a	4b
0	Using a starting cohort of primary prevention patients without HeFH	Section 4.2.4.1	X			
0	Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	Section 4.2.4.1		X	X	X
1	Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	Section 4.2.5.3	X	X	X	X
2	Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment	Section 4.2.2.2	X		X	
8	Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al*. 2013a;	Table 24 in Section 4.2.9.1		X	X	X

	• Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events					
9	Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • After patients in subpopulation 2a experience their first event, recurrent events accrue the utilities for multiple events reported in Table 24.	Table 25 in Section 4.2.9.1	X			
10	Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9i treatment	Section 4.2.10.2		X		X
11	Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	Section 4.2.10.6	X	X	X	X

Abbreviations: CG, Clinical Guideline; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; TA, Technology Appraisal; TIA, transient ischemic attack

Table 60. ERG's preferred assumptions, cumulative results, population 2a, BA/EZE FDC vs EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	£5,848	0.21	£28,527
Using a starting cohort of primary prevention patients without HeFH	£5,973	0.19	£31,504
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	£5,966	0.20	£30,504
Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment	£5,976	0.19	£31,484
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months'	£5,976	0.19	£31,153

estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • After patients in subpopulation 2a experience their first event, recurrent events accrue the utilities for multiple events reported in Table 24.			
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	£5,727	0.19	£29,856

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack

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

Table 61. ERG's preferred assumptions, cumulative results, population 2b, BA/EZE FDC vs Ali + EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	NA†	NA†	NA†
Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	NA†	NA†	NA†
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	-£24,030	-0.24	£99,488*
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	-£24,030	-0.27	£89,677*
Adding the cost of an annual hospital appointment (£128) and a one-off initial training	-£25,057	-0.27	£93,508*

inhibitors			
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al*. 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	-£25,043	-0.27	£93,455*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

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

†Ali+EZE is not a comparator in the company's base case

Table 62. ERG's preferred assumptions, cumulative results, population 4a, BA/EZE FDC vs EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	£5,420	0.08	£69,453
Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	£5,577	0.07	£82,286
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	£5,587	0.08	£66,343
Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment	£5,628	0.07	£78,472
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	£5,628	0.07	£75,524
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al*. 2017 separately, in the analysis;	£5,622	0.07	£75,437

• Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)			
Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack			

Table 63. ERG's preferred assumptions, cumulative results, population 4b, BA/EZE FDC vs Ali + EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	-£22,208	-0.18	£121,686
Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	-£22,887	-0.16	£143,849
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	-£23,607	-0.39	£60,123*
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	-£23,607	-0.45	£52,116*
Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors	-£24,615	-0.45	£53,343*
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al*. 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	-£24,573	-0.45	£54,250*
Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER,			

incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

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

Table 64. ERG's preferred base case ICERs, deterministic and probabilistic results

Subpopulation	Treatment	Total costs	Total QALYs	ICER
2a	Deterministic			
	EZE	£9,591	9.06	-
	BA/EZE FDC	£15,319	9.25	£29,856
	Probabilistic			
	EZE	£9,664	9.16	-
	BA/EZE FDC	£15,429	9.35	£30,218
2b	Deterministic			
	BA/EZE FDC	£23,204	12.29	-
	Ali + EZE	£48,247	12.56	£93,455
	Probabilistic			
	BA/EZE FDC	NC	NC	-
	Ali + EZE	NC	NC	NC
4a	Deterministic			
	EZE + statin	£16,731	9.05	-
	BA/EZE FDC	£22,352	9.14	£75,437
	Probabilistic			
	EZE + statin	£16,805	9.04	-
	BA/EZE FDC	£22,441	9.12	£73,723
4b	Deterministic			
	BA/EZE FDC	£22,296	8.69	
	Ali + EZE + statin	£46,869	9.15	£54,250
	Probabilistic			
	BA/EZE FDC	£22,394	8.71	-
	Ali + EZE + statin	£46,193	9.12	£58,929

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; EZE, ezetimibe; fixed dose combination; ICER, incremental cost-effectiveness ratio; NC, not calculable; QALYs, quality-adjusted life years

6.5 Conclusions of the cost effectiveness sections

Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness for this appraisal. The revised network meta-analyses (NMAs) provided by the company at the clarification stage remain unfit for decision making, principally due to the extent of clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. To address some of these issues, the

ERG explored alternative networks to implement in the economic analyses. However, the ERG recommends that the cost-effectiveness results based on these networks are interpreted with caution. Due to time and resource constraints the ERG has been unable to fully assess all potentially relevant studies for inclusion in the networks and additionally not had access to the relevant subgroup data from the bempedoic acid studies.

Another key area of concern is that no subgroup analyses based on cardiovascular (CV) risk or presence of heterozygous familial hypercholesterolaemia (HeFH) were conducted by the company, despite being requested in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively). Moreover, given the high proportion of secondary prevention patients without HeFH included in the economic analyses, the ERG considers it unreliable to use treatment effectiveness estimates from a wider population with and without these characteristics. For these reasons, the ERG stresses its opinion that cost-effectiveness results by subgroup should be provided by the company in order to reflect the patients entering the model and in order to allow for consistent decision making with previous NICE appraisals.

The ERG is also concerned with the imbalance between the sources used to inform treatment effectiveness and the sources used to inform baseline characteristics and background CV. As treatment effectiveness data were taken from the CLEAR trials, the ERG considers that CV event history and background CV risks in these trials may be more appropriate to use in the economic analyses. Given that these are key drivers in the model, the ERG stresses its opinion that these data from the CLEAR trials are made available. If the company reiterates its position from the clarification response that these data are not yet available, the ERG is confused as to why the company does not have access to the data collected in its own trials?

Furthermore, the ERG disagrees with allocating secondary prevention patients to enter the model in one of the 0 to 1 year-post CV event health states, incurring the costs and benefits for an acute event. The ERG considers it more appropriate to allocate the secondary prevention cohort to enter the model in the 3-year+ post-event state, associated with post-event costs and benefits, until a new event occurs. An additional and related area of concern is that primary events and recurrent events (two or more CV events) are associated with the same impacts on costs and benefits in the model, despite clinical expert opinion that recurrent events have larger impacts compared with primary events.

In terms of results, the ERG's preferred base case assumptions for bempedoic acid compared to ezetimibe in the statin intolerant population led to an incremental cost-effectiveness ratio (ICER) close to NICE's upper threshold of £30,000 (£29,856). Nonetheless, the ERG's preferred base case ICER is not too dissimilar to the company's base case ICER (£28,521).

As for the maximally tolerated statin population, the company's base case ICER for bempedoic acid compared to ezetimibe was already above NICE's upper threshold of £30,000 (£69,452) and the ERG's preferred assumptions increased the ICER to £75,437.

When patients are eligible for PCSK9i treatment in either the statin intolerant population or maximally tolerated statin population, bempedoic acid generates less quality-adjusted life years (QALYs) and less costs compared to PCSK9i treatment in the company's base case analyses and in each of the ERG's scenario analyses.

7 End of Life

The company did not submit a case for end of life and the ERG agrees with this decision.

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9 Appendices

9.1 Baseline characteristics tables

Table 65. Baseline characteristics of the bempedoic acid statin intolerant studies

	CLEAR Serenity[11]		CLEAR Tranquility[12]		1002-009[14]	
	BA	Placebo	BA	Placebo	BA	Placebo
Number randomised	234	111	181	88	45	45
Age, years, mean (SD)	65.2 (9.7)	65.1 (9.2)	63.8 (10.8)	63.7 (11.3)	57 (10)	56 (10)
Male, no. (%)	101 (43.2)	50 (45)	72 (39.78)	32 (36.4)	14 (31)	23 (51)
Race, no. (%)						
Black or African American	16 (6.8)	10 (9)	11 (6.1)	10 (11.4)	NR	NR
White	211 (90.2)	96 (86.5)	165 (91.2)	75 (85.2)	37 (82)	37 (82)
BMI, kg/m^2, mean (SD)	30.1 (5.8)	30.6 (5.2)	29.5 (4.7)	30.5 (5.8)	30 (6)	31 (6)
CV risk factor, no. (%)						
Primary prevention	144 (61.5)	67 (60.4)	NR	NR	NR	NR
Secondary prevention	90 (38.5)	44 (39.6)	NR	NR	NR	NR
ASCVD	NR	NR	NR	NR	NR	NR
ASCVD only	NR	NR	NR	NR	NR	NR
HeFH	4 (1.7)	3 (2.7)	NR	NR	NR	NR
HeFH with/without ASCVD	NR	NR	NR	NR	NR	NR
Cardiac disorder, n (%)	NR	NR	49 (27.1)	22 (25.0)	NR	NR
DM	63 (26.9)	26 (23.4)	35 (19.3)	17 (19.3)	NR	NR
HTN	158 (67.5)	75 (67.6)	111 (61.3)	51 (58.0)	NR	NR
Impaired fasting glucose	NR	NR	NR	NR	NR	NR
Lipid measures at baseline, mg/dL, mean (SD)						
TC	245.7 (47.3)	241.1(44.3)	218.2 (35.9)	208.6 (35.7)	229 (29)	212 (24)
LDL-C	158.5 (40.4)	155.6 (38.8)	129.8 (30.9)	123.0 (27.2)	142 (28)	131 (22)
Non–HDL-C	193.5 (45.1)	190.7 (43.8)	162.4 (35.4)	151.6 (32.7)	NR	NR
HDL-C	52.2 (14.5)	50.4 (14.4)	55.8 (16.3)	57.1 (21.3)	55 (14)	54 (14)
Apo B	141.0 (31.6)	141.9 (30.4)	123.3 (26.5)	115.8 (23.5)	NR	NR
TG, median (IQR), mg/dL	156.5 (114.5-219)	164 (120-225.5)	153.0 (112.0-209.0)	135.5 (99.8-175.8)	145 (122-196)	119 (82-159)
hsCRP, median (IQR), mg/dL	2.92 (1.34-5.29)	2.78 (1.21-5.15)	2.21 (1.10-4.00)	2.26 (1.06-4.50)	1.8 (1.20-4.00)	1.8 (1.10-4.60)
LMT at Baseline, no. (%)						
Statins with or without other LMTs	NR	NR	NR	NR	NR	NR
Statins only	18 (7.7)	11 (9.9)	NR	NR	NR	NR
Statins with other LMT	NR	NR	NR	NR	NR	NR

Very low-dose statin	18 (7.7)	11 (9.9)	NR	NR	NR	NR
No LMT	[redacted]	[redacted]	NR	NR	NR	NR
Other LMT only (non-statin)	83 (35.5)	33 (29.7)	NR	NR	NR	NR
Concomitant LMT, no. (%)						
Statin	[redacted]	[redacted]	59 (32.6)	25 (28.4)	NR	NR
Ezetimibe	[redacted]	[redacted]			NR	NR
Fibrate	[redacted]	[redacted]	7 (3.9)	3 (3.4)	NR	NR
Nicotinic acid	NR	NR	3 (1.7)	4 (4.6)	NR	NR
Bile acid sequestrant	NR	NR	1 (0.6)	1 (1.1)	NR	NR
Other[b]	NR	NR	19 (10.5)	8 (9.2)	NR	NR
None	NR	NR	NR	NR	NR	NR
Statin therapy intensity, no. (%)						
Low	NR	NR	NR	NR	NR	NR
Moderate	NR	NR	NR	NR	NR	NR
High	NR	NR	NR	NR	NR	NR
eGFR category at baseline, no. (%)						
Normal: ≥ 90	58 (24.8)	16 (14.4)	45 (24.9)	17 (19.3)	NR	NR
Mild: 60 to < 90	139 (59.4)	69 (62.2)	110 (60.8)	57 (64.8)	NR	NR
Moderate: 30 to < 60 mL	NR	NR	NR	NR	NR	NR
Severe: 15 to < 30	NR	NR	NR	NR	NR	NR
Renal impairment: < 60	37 (15.8)	26 (23.4)	26 (14.4)	14 (15.9)	NR	NR
Reasons for statin intolerance, no. (%)						
Muscle symptoms	217 (92.7)	105 (94.6)	NR	NR	NR	NR
GIT symptoms	26 (11.1)	9 (8.1)	NR	NR	NR	NR
Elevated liver enzymes	15 (6.4)	7 (6.3)	NR	NR	NR	NR
Generalised fatigue	12 (5.1)	3 (2.7)	NR	NR	NR	NR
Cognitive decline	7 (3.0)	3 (2.7)	NR	NR	NR	NR
Elevated CK	2 (0.9)	1 (0.9)	NR	NR	NR	NR
Depression	1 (0.4)	0	NR	NR	NR	NR

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; apo B, apolipoprotein B; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FDC, bempedoic acid and ezetimibe fixed-dose combination; GIT, gastrointestinal; HDL C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; hsCRP, high-sensitivity C-reactive protein; LDL C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; NR, not reported; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Note: Data are means (standard deviations) unless otherwise specified.

Table 66. Baseline characteristics of the bempedoic acid maximally tolerated statin studies

	CLEAR Harmony[9]		CLEAR Wisdom[10]		1002FDC-053[15]				1002-008[13]		
	BA	Placebo	BA	Placebo	FDC	BA	Eze	Placebo	BA	BA+ Eze	Eze
Number randomised	1,488	742	522	257	86	88	86	41	100 (51)	24 (12)	99 (51)
Age, years, mean (SD)	65.8 (9.1)	66.8 (8.6)	64.1 (8.8)	64.7 (8.7)	62.2 (9.5)	65.0 (9.8)	65.1 (8.9)	65.6 (8.4)	59 (9)	59 (9)	60 (10)
Male, no. (%)	1,099 (73.9)	529 (71.3)	328 (62.8)	168 (65.4)	42 (48.8)	40 (45.5)	43 (50.0)	24 (58.5)	49 (49)	11 (48)	45 (46)
Race, no. (%)											
Black or African American	[redacted]	[redacted]	24 (4.6)	12 (4.7)	16 (18.6)	17 (19.3)	12 (14.0)	7 (17.1)	NR	NR	NR
White	1,423 (95.6)	716 (96.5)	491 (94.1)	244 (94.9)	67 (77.9)	70 (79.5)	72 (83.7)	34 (82.9)	91 (91)	22 (92)	87 (88)
BMI, kg/m^2, mean (SD)	29.74 (4.9)	29.4 (4.5)	30.0 (5.2)	30.6 (5.0)	31.1 (6.3)	30.6 (5.5)	29.9 (4.4)	30.7 (4.2)	31 (5)	28 (5)	30 (5)
CV risk factor, no. (%)											
Primary prevention	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Secondary prevention	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ASCVD	1,449 (97.4)	727 (98.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR
ASCVD only	[redacted]	[redacted]	495 (94.8)	241 (93.8)	NR	NR	NR	NR	NR	NR	NR
ASCVD and/or HeFH	NR	NR	NR	NR	53 (61.6)	55 (62.5)	54 (62.8)	26 (63.4)	NR	NR	NR
HeFH	56 (3.8)	23 (3.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR
HeFH with/without ASCVD	[redacted]	[redacted]	27 (5.2)	16 (6.2)	NR	NR	NR	NR	NR	NR	NR
Cardiac disorder, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DM	425 (28.6)	212 (28.6)	155 (29.7)	81 (31.5)	35 (40.7)	45 (51.1)	43 (50.0)	17 (41.5)	NR	NR	NR
HTN	1,174 (78.9)	594 (80.1)	438 (83.9)	224 (87.2)	74 (86.0)	77 (87.5)	71 (82.6)	35 (85.4)	NR	NR	NR
Impaired fasting glucose	NR	NR	9 (1.7)	5 (1.9)	NR	NR	NR	NR	NR	NR	NR
Lipid measures at baseline, mg/dL, mean (SD)											

TC	179.7 (35.1)	178.6 (35.6)	202.1 (42.7)	204.8 (46.1)	6.14 (1.26)	5.83 (1.12)	5.98 (1.31)	5.98 (1.30)	253 (33)	246 (32)	248 (32)
LDL-C	103.6 (29.1)	102.3 (30.0)	119.4 (37.7)	122.4 (38.3)	3.93 (1.05)	3.75 (0.99)	3.85 (1.08)	3.95 (1.21)	166 (24)	162 (27)	165 (25)
Non–HDL-C	130.9 (33.7)	129.4 (33.9)	150.7 (42.7)	153.7 (44.4)	4.87 (1.21)	4.54 (1.05)	4.66 (1.22)	4.68 (1.29)	NR	NR	NR
HDL-C	48.7 (11.9)	49.3 (11.5)	51.4 (12.9)	51.1 (13.1)	1.27 (0.38)	1.29 (0.32)	1.33 (0.41)	1.30 (0.36)	52 (13)	52 (16)	49 (12)
Apo B	88.5 (21.6)	86.8 (21.8)	116.2 (29.6)	118.6 (30.5)	121.1 (30.9)	113.4 (26.4)	115.5 (31.3)	115.1 (32.5)	NR	NR	NR
TG, median (IQR), mg/dL	126 (98-166)	123 (96-170)	139.3 (102.5-190.0)	143.0 (106.0-189.0)	1.77 (1.20-2.36)	1.59 (1.22-2.15)	1.62 (1.24-2.40)	1.57 (1.18-1.90)	162 (38-371)	151 (50-343)	163 (64-434)
hsCRP, median (IQR), mg/dL	1.49 (0.74-3.28)	1.51 (0.79-3.33)	1.61 (0.87-3.46)	1.88 (0.92-3.79)	3.1 (1.7-6.2)	2.9 (1.4-5.0)	2.8 (1.3-5.9)	3.0 (1.3-5.5)	2.50 (0.1-20.3)	2.60 (0.3-31.7)	1.25 (0.2-4.7)
LMT at Baseline, no. (%)											
Statins with or without other LMTs	1,485 (99.8)	742 (100)	470 (90.0)	228 (88.7)	NR	NR	NR	NR	NR	NR	NR
Statins only	1,271 (85.4)	641 (86.4)	416 (79.7)	196 (76.3)	NR	NR	NR	NR	NR	NR	NR
Statins with other LMT	214 (14.4)	101 (13.6)	54 (10.3)	32 (12.5)	NR	NR	NR	NR	NR	NR	NR
Very low-dose statin	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No LMT	2 (0.1)	0	30 (5.7)	14 (5.4)	NR	NR	NR	NR	NR	NR	NR
Other LMT only (nonstatin)	1 (0.1)	0	22 (4.2)	15 (5.8)	NR	NR	NR	NR	NR	NR	NR
Concomitant LMT, no. (%)											
Statin	1,485 (99.8)	742 (100)	470 (90.0)	228 (88.7)	53 (61.6)[a]	61 (69.4)[a]	54 (62.8)[a]	27 (65.8)[a]	NR	NR	NR
Ezetimibe	116 (7.8)	56 (7.5)	38 (7.3)	24 (9.3)	NR	NR	NR	NR	NR	NR	NR
Fibrate	54 (3.6)	26 (3.5)	26 (5.0)	19 (7.4)	NR	NR	NR	NR	NR	NR	NR

Nicotinic acid	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bile acid sequestrant	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
None	2 (0.1)	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Statin therapy intensity, no. (%)											
Low	100 (6.7)	48 (6.5)	78 (14.9)	40 (15.6)	NR	NR	NR	NR	NR	NR	NR
Moderate	646 (43.4)	324 (43.7)	166 (31.8)	82 (31.9)	NR	NR	NR	NR	NR	NR	NR
High	742 (49.9)	370 (49.9)	278 (53.3)	135 (52.5)	NR	NR	NR	NR	NR	NR	NR
eGFR (mL/min/1.73m2) renal impairment category at baseline, no. (%)											
Normal: ≥ 90	320 (21.5)	167 (22.5)	107 (20.5)	56 (21.8)	30 (34.9)	27 (30.7)	29 (33.7)	19 (46.3)	NR	NR	NR
Mild: 60 to < 90	946 (63.6)	468 (63.1)	338 (64.8)	164 (63.8)	40 (46.5)	41 (46.6)	43 (50.0)	14 (34.1)	NR	NR	NR
Moderate: 30 to < 60 mL	222 (14.9)	107 (14.4)	77 (14.8)	37 (14.4)	NR	NR	NR	NR	NR	NR	NR
Severe: 15 to < 30	NR	NR	1 (0.2)	1 (0.4)	NR	NR	NR	NR	NR	NR	NR
Renal impairment: < 60	NR	NR	NR	NR	16 (18.6)	20 (22.7)	14 (16.3)	8 (19.5)	NR	NR	NR

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; apo B, apolipoprotein B; BMI, body mass index; CK, Creatine kinase; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FDC, bempedoic acid and ezetimibe fixed-dose combination; GIT, gastrointestinal; HDL C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; NR, not reported; SD; standard deviation; TC, total cholesterol; TG, triglyceride.

Note: Data are means (standard deviations) unless otherwise specified.

[a] Calculated from high statin intensity plus other statin statin intensity in Company submission, Table 17.

9.2 Quality assessment tables

Table 67. Overview of quality assessments for the bempedoic acid statin intolerant studies

Study question	CLEAR Serenity		CLEAR Tranquility		1002-009	
	CS	ERG	CS	ERG	CS	ERG
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Not clear	Not clear	No	No
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	No	No	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Unclear	Unclear
Did the authors of the study publication declare any conflicts of interest?	Yes	Yes	Unclear	Unclear	Yes	Yes
Does the trial reflect routine clinical practice in England?	Yes	Yes	Unclear	Unclear	Yes	Yes

Abbreviations: CS, company's submission; ERG, evidence review group; ITT, intention to treat; NA, not applicable.

Table 68. Overview of quality assessments for the bempedoic acid maximally tolerated statin studies

Study question	CLEAR Harmony		CLEAR Wisdom		1002FDC-053		1002-008	
	CS	ERG	CS	ERG	CS	ERG	CS	ERG
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	NA	NA	No	No	No	No	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NA	NA	No	No	No	No	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors of the study publication declare any conflicts of interest?	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes
Does the trial reflect routine clinical practice in England?	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Abbreviations: CS, company's submission; ERG, evidence review group; ITT, intention to treat; NA, not applicable.								

9.3 Summary of studies in the company's updated NMAs

Table 69. Summary of studies in the statin intolerant updated company NMA

Study	Relevant arms	Background ezetimibe[a] (%)	N	Concomitant statin	Other permitted LMT	LDL-C inclusion (mg/dL)	Prior CV event (%)	HeFH (%)	% T2D
1002-008[13] (statin intolerant subgroup)	1) BA 2) BA + EZE 3) EZE	0%[c] 100%[c] 100%[c]	223	None (for statin intolerant subgroup)	Bile acid sequestrants, fibrates	≥130 or ≥100 (depending on LMT washout)	Excluded	NR	NR
CLEAR Serenity[11]	1) BA 2) PBO	NR NR	345	Mixed very low	Bile acid sequestrants, fibrates, PCSK9i	≥130 (≥100 w/ HeFH or ASCVD)	NR	1.7% 2.7%	NR
CLEAR Tranquility[12]	1) BA + EZE 2) EZE	100% 100%	269	Mixed low	Ezetimibe (given open-label) and others	>100	27.1% 25.0%	NR	NR
GAUSS-2[59]	1) EVO 140 Q2W 2) EZE + Q2W PBO (SCI)	0% 100%	154	Mixed non-intensive	33% on lipid lowering therapies	≥100	NR (high, mod, low risk)	NR	19% 22%
ODYSSEY Alternative[60]	1) ALI 75 Q2W[b] 2) EZE	0% 100%	251	Mixed low (lowest approved dose)	Bile acid sequestrants and others but ezetimibe and fibrates prohibited	≥100 (high risk), ≥70 (very high)	NR (mod, high, very high risk)	NR	28.6% 19.2%
ODYSSEY CHOICE I[61] (statin intolerant subgroup)	1) ALI 75 Q2W[b] 2) PBO (SCI)	8.1% 15.1%	110	None	Stable LMT except fibrates	≥100 (high/mod risk) ≥70 (v.high risk)	NR (mod, high, very high risk)	0.0% 1.4%	10.3% 23.3%
ODYSSEY CHOICE II[20]	1) ALI 75 Q2W[b] 2) PBO (SCI)	60.3% 60.3%	174	None	Two thirds receiving fenofibrate or ezetimibe	≥100 (high/mod risk) ≥70 (v.high risk)	NR (mod, high, very high risk)	12.9% 8.6%	19.0% 15.5%

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ALI, alirocumab; BA, bempedoic acid 180 mg once daily; CV, cardiovascular; EVO, evolocumab; EZE, ezetimibe 10 mg once daily; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; mg/dL, milligrams per decilitre; NMA, network meta-analysis; NR, not reported; PBO, placebo; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q2W, once every two weeks; SCI, subcutaneous injection; T2D, type 2 diabetes mellitus.

[a] Proportion of patients on ezetimibe at baseline as background therapy or as part of trial intervention

[b] Escalation to 150 mg Q2W after 12 weeks if LDL-C still elevated; Some or all of the following background treatments were permitted that may impact plasma lipid levels, provided they were kept stable prior to screening/during the study: hormone replacement, thyroid replacement, obesity medication, Omega 3 fatty acids, and diabetes medications.

[c] Patients underwent a 5-week washout of all lipid-regulating drugs, including ezetimibe

Table 70. Summary of studies in the maximally-tolerated statin updated company NMA

Study	Relevant arms	Background ezetimibe* (%)	Total N	Concomitant statin	Other permitted LMT	LDL-C inclusion	Prior CV event	HeFH	% T2D
1002-009[14]	1) BA 2) PBO	NR NR	90	Mixed (non-intensive)	None[e]	≥115 (after washout)	NR	NR	NR
1002FDC-053[15]	1) BA 2) BA + EZE 3) EZE 4) PBOI	0%[d] 100%[d] 100%[d] 0%[d]	382	Mixed (high, other, none)	None[e]	≥130 (≥100 w/ HeFH or ASCVD)	NR	NR	NR
CLEAR Harmony[9]	1) BA 2) PBO	7.8% 7.5%	2230	Mixed (high, mod, low)	Ezetimibe, bile acid sequestrants, fibrates, PCSK9i (w/ conditions).	≥70	NR	3.8% 3.1%	NR
CLEAR Wisdom[10]	1) BA 2) PBO	7.3% 9.3%	779	Mixed (high, mod, low)		≥100 (screen), ≥70 (baseline)	82.8% 79.8%	5.2% 6.2%	NR
Dujovne 2002[62]	1) EZE 2) PBO	100% 0%	892	NR	Stable CV regimens	≥130 to 250 (after washout)	NR	NR	NR
FOURIER[63]	1) EVO[b] 2) PBO (SCI)	5.3% 5.2%	27564	All intensive (at least ator 20mg daily or equivalent)	Required optimised tx (statin +/- ezetimibe)	≥70 on optimised tx	NR	NR	NR
Knopp 2003[64]	1) EZE 2) PBO	100% 0%	827	None	None[e]	≥130 to 250 (after washout)	3% 8%	NR	NR
Krysiak 2011[65] (not statin intolerant subgroup)	1) EZE 2) PBO	100% 0%	66	None	NR	>130	NR	6% 3%	NR

LAPLACE-2[66] (atorv 80, rosu 40 and sim 40 groups)[a]	1) EVO 140 Q2W 2) EZE 3) PBO (SCI)	0% 100% 0%	NR	All intensive: ator 80, rosu 40 or sim 40 mg daily	None[e]	≥80 (intensive statin) ≥100 (non-intensive statin)	NR	NR	3.6–31.5% across statin groups
LAPLACE-TIMI-57[67]	1) EVO 140 Q2W 2) PBO (SCI)	13% 9%	156	All (no details)	Statin +/- ezetimibe required	>85	NR	NR	19.0% 12.0%
Masana 2005[68]	1) EZE 2) PBO	100% 0%	433	Unclear	Unclear	50 to 160	NR	NR	NR
McKenney 2012[69]	1) ALI 150 Q2W 2) PBO (SCI)	NR NR	62	All taking 10–40mg ator	None[e]	≥100 on stable statin	NR	NR	9.7% 0.0%
Melani 2003[70]	1) EZE 2) PBO 3) EZE + statin 4) PBO + statin	100% 0% 100% 0%	538	All prav 10, 20 or 40 mg daily in groups 3) and 4)	NR	70–115 (converted from mmol)	NR	NR	NR
ODYSSEY Japan[71]	1) ALI 75 Q2W[c] 2) PBO (SCI)	NR NR	108	Mixed (stable)	Required stable statin +/- other LMT	NR	NR	18.8% 19.4%	NR
ODYSSEY KT[72]	1) ALI 75 Q2W[c] 2) PBO (SCI)	14.4% 11.8%	NR	All intensive	Ezetimibe and others	NR	NR	NR	NR
ODYSSEY OPTIONS I[73] (ator 20 and 40 groups)[a]	1) ALI 75 Q2W[c] 2) EZE 3) PBO	0% 100% 0%	NR	All non-intensive (ator 20 or 40 mg)	Other statins and ezetimibe prohibited	≥100 (high risk) ≥70 (v.high risk)	NR	NR	34.0–57.9% across statin groups
ODYSSEY OPTIONS II[74] (rosu 10 and 20 groups)[a]	1) ALI 75 Q2W[c] 2) EZE 3) PBO	0% 100% 0%	NR	All non-intensive (rosu 10 or 20 mg)	Other statins and ezetimibe prohibited	≥100 (high risk) ≥70 (v.high risk)	NR	13.6% 13.9% NR	33.3–47.6% across statin groups
ODYSSEY OUTCOMES[35]	1) ALI 75 Q2W[c] 2) PBO (SCI)	NR NR	NR	All intensive	NR	Elevated atherogenic levels despite intensive statin	NR	NR	NR

ODYSSEY CHOICE I[61] (max tolerated subgroup)	1) ALI 75 Q2W[c] 2) PBO (SCI)	11.5% 14.0%	235	All intensive (max tolerated rosu 20-40mg, ator 40-80mg, or simv 80mg)	All stable LMTs permitted except fibrates	NR	NR (mod, to v.high risk)	7.7% 7.6%	28.2% 31.8%
ODYSSEY COMBO I[75]	1) ALI 75 Q2W[c] 2) PBO (SCI)	7.2% 10.3%	316	All intensive (max tolerated rosu 20-40mg, ator 40-80mg, or simv 80mg)	Ezetimibe, bile acid sequestrants and others permitted	≥100 (high risk) ≥70 (w/ CVD)	NR (high risk)	NR	45.0% 39.3%
ODYSSEY COMBO II[20]	ALI 75 Q2W[c] 2) PBO	0% 100%	720	All intensive (max tolerated rosu 20-40mg, ator 40-80mg, or simv 80mg)	NR	≥100 (high risk) ≥70 (w/ CVD)	NR	NR	30.3% 31.5%
ODYSSEY MONO[18]	1) ALI[c] + EZE 2) EZE	100% 100%	103	None	None for at least 4 weeks prior to screen	100–190	NR	NR	5.8% 2.0%
ODYSSEY NIPPON[76]	1) ALI 150 Q2W 2) PBO (SCI)	26.4% 19.6%	109	Mixed low (ator 5 mg)	LMTs allowed but not specified	NR	NR	24.5% 25.0%	NR
YUKAWA-2[77]	1) EVO 140 Q2W + statin 2) PBO (SCI)	NR NR	99	All low (ator 5 mg)	Stable LMT allowed	≥100 after statin + LMT (including ezetimibe) run-in	NR	6% 5%	47% 51%
YUKAWA[78]	1) EVO 140 Q2W 2) PBO (SCI)	NR NR	104	Mixed non-intensive (≤20mg ator, rosu, pita, prava)	Stable LMT allowed	≥100 after statin + LMT (including ezetimibe) run-in	NR (high)	NR	40.4% 30.8%

Abbreviations: ator, atorvastatin; ASCVD, atherosclerotic cardiovascular disease; ALI, alirocumab; BA, bempedoic acid 180 mg once daily; CV/D, cardiovascular disease; EVO, evolocumab; EZE, ezetimibe 10 mg once daily; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; mg/dL, milligrams per decilitre; NMA, network meta-analysis; NR, not reported; PBO, placebo; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; pita, pitavastatin; prav, pravastatin; Q2W, once every two weeks; rosu, rosuvastatin; simv, simvastatin SCI, subcutaneous injection; T2D, type 2 diabetes mellitus.

* Proportion of patients on ezetimibe at baseline as background therapy or as part of trial intervention

[a] Studies with multiple baseline subgroups according to background statin type and dose;

[b] 140 mg Q2W or 420 mg QM depending on patient preference;

[c] Escalation to 150 mg Q2W after 12 weeks if LDL-C still elevated;

[d] Patients underwent a 5-week washout of all lipid-regulating drugs, including ezetimibe

[e] Some or all of the following background treatments were permitted that may impact plasma lipid levels, provided they were kept stable prior to screening/during the study: hormone replacement, thyroid replacement, obesity medication, Omega 3 fatty acids, and diabetes medications.

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Erratum to ERG report

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This document contains errata in respect of the ERG report that include an implementation error in the ERG's scenario analysis using alternative utility assumptions in subpopulations 2b, 4a and 4b. The table below lists the page to be replaced in the original document and the nature of the change:

Page number	Change
26	Values in Table 3 corrected
86	Text and number relating to CLEAR Harmony baseline LDL-C corrected
149-152	QALYs and ICERs for scenario 9 in Tables 56 to 58 corrected
155-158	Values in Tables 61 to 64 corrected
160	ICER corrected from £75,437 to £76,831

Abbreviations: ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALYs, quality adjusted life years

Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;

Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;

Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,

Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

Table 3. ERG's preferred base case ICERs, deterministic and probabilistic results

Subpopulation	Treatment	Total costs	Total QALYs	ICER
2a	Deterministic			
	EZE	£9,591	9.06	-
	BA/EZE FDC	£15,319	9.25	£29,856
	Probabilistic			
	EZE	£9,664	9.16	-
	BA/EZE FDC	£15,429	9.35	£30,218
2b	Deterministic			
	BA/EZE FDC	£23,204	7.03	-
	Ali + EZE	£48,247	7.28	£100,856
	Probabilistic			
	BA/EZE FDC	NC	NC	-
	Ali + EZE	NC	NC	NC
4a	Deterministic			
	EZE + statin	£16,731	6.97	-
	BA/EZE FDC	£22,352	7.06	£76,831
	Probabilistic			
	EZE + statin	£16,736	6.97	-
	BA/EZE FDC	£22,358	7.04	£81,456
4b	Deterministic			
	BA/EZE FDC	£22,296	6.62	
	Ali + EZE + statin	£46,869	7.02	£61,274
	Probabilistic			
	BA/EZE FDC	£22,364	6.61	-
	Ali + EZE + statin	£46,107	7.00	£62,314

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; EZE, ezetimibe; fixed dose combination; ICER, incremental cost-effectiveness ratio; NC, not calculable; QALYs, quality-adjusted life years

Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;

Subpopulation 2b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate;

Subpopulation 4a: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate; and,

Subpopulation 4b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

CLEAR Harmony provided data on bempedoic acid and placebo, although arm level data were not available which limited the methodology for the NMA. ODYSSEY LONG TERM was a randomised controlled study in patients on maximally tolerated statins with or without other lipid lowering therapy and it reported subgroup data for patients on ezetimibe at baseline. Patients in ODYSSEY LONG TERM were randomised to alirocumab 150 mg every two weeks or placebo for 78 weeks with the primary analysis conducted at 24 weeks. The ERG notes that mean baseline LDL-C for CLEAR Harmony (103.2 mg/dL) and ODYSSEY LONG TERM (122.3 mg/dL) are slightly different but as for the statin intolerant NMA, this is not accounted for in the NMA due to issues with applying covariate adjustment for a treatment dependent variable (as described in Section 3.4.2).

In summary, there are two trials in the ERG's maximally tolerated statin NMA and they provide data for bempedoic acid, placebo and alirocumab 150 mg Q2W in patients on background ezetimibe. The ERG notes there is a difference in outcome measurement with 12-week data used from CLEAR Harmony and 24-week data from ODYSSEY LONG TERM but the ERG considers the company should have 24-week data from CLEAR Harmony in addition to further data on bempedoic acid from CLEAR Wisdom.

3.5.1.2 Results

As discussed in Section 3.5.1.1, the comparison of the ERG and company NMAs presented below assumes that the use of data in patients with a history of prior ezetimibe at baseline for all treatments in the ERG's NMA is the equivalent of the analyses in the company's NMAs where all patients are randomised to treatment + ezetimibe (where treatment also includes placebo or no treatment). The results presented from the ERG NMAs below are thus labelled as treatment + ezetimibe versus ezetimibe but actually reflect treatment + background ezetimibe versus placebo + background ezetimibe. The ERG has assumed that patients in the studies included in the ERG NMAs were allowed to continue on their background LLT's (including statin and/or ezetimibe).

3.5.1.2.1 Statin intolerant ERG NMA results

The results of the ERG analysis for the statin intolerant NMA are presented alongside the results from the company's updated NMA in Table 17. The ERG considers it important to highlight that the ERG's NMA comprises only patients with prior ezetimibe therapy at baseline, whereas the company NMA includes patients both with and without prior ezetimibe therapy. The placebo arm in the ERG analysis therefore contains patients on ezetimibe although it is not clear what proportion of patients remained on ezetimibe throughout the studies. The difference in mean percentage change from

	QALYs	9.25	9.06	0.19
	ICER	-	-	£31,591
7	**Using all-cause mortality without subtracting the risk of CV death**			
	Total costs (£)	£12,515	£6,667	£5,847
	QALYs	8.95	8.77	0.18
	ICER	-	-	£33,329
9	**Alternative utility assumptions**			
	Total costs (£)	£12,992	£7,018	£5,973
	QALYs	9.24	9.05	0.19
	ICER	-	-	£31,162
11	**Alternative health state cost assumptions**			
	Total costs (£)	£15,329	£9,604	£5,726
	QALYs	9.25	9.06	0.19
	ICER	-	-	£30,198

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

Table 56. Results of the ERG's scenario analyses, population 2b

	Results per patient	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
					(1-2)	(1-3)
0	**Corrected company base case**					
	Total costs	£18,643	£41,338	£41,777	-£22,695	-£23,134
	QALYs	6.86	6.93	6.96	-0.07	-0.10
	ICER	-	-	-	£342,008	£236,401
0	**Secondary prevention cohort entering 3-year+ post-event states, no HeFH**					
	Total costs	£17,471	£40,817	£41,256	-£23,346	-£23,785
	QALYs	7.20	7.25	7.28	-0.06	-0.09
	ICER	-	-	-	£398,880	£275,430
1	**ERG's NMA on LDL-C†**					
	Total costs	£17,475	£41,505	NA	-£24,030	NA
	QALYs	7.20	7.45	NA	-0.24	NA
	ICER	-	-	-	£99,488	NA
3	**Using a lower proportion of recurrent/polyvascular events (7%)**					
	Total costs	£17,639	£41,218	£41,660	-£23,579	-£24,020
	QALYs	7.30	7.36	7.39	-0.06	-0.09
	ICER	-	-	-	£405,339	£279,938
4	**Using prior IS events to inform the history of all secondary prevention patients**					
	Total costs	£17,849	£40,521	£40,968	-£22,672	-£23,119
	QALYs	6.41	6.46	6.49	-0.05	-0.08
	ICER	-	-	-	£424,501	£293,004
5	**Using prior MI events to inform the history of all secondary prevention patients**					
	Total costs	£18,755	£42,470	£42,918	-£23,716	-£24,164

	QALYs	7.49	7.55	7.58	-0.06	-0.09
	ICER	-	-	-	£400,241	£276,551
6	**Including transitions to the SA state from prior event states**					
	Total costs	£17,860	£41,235	£41,675	-£23,375	-£23,815
	QALYs	7.22	7.28	7.30	-0.06	-0.09
	ICER	-	-	-	£400,674	£276,664
7	**Using all-cause mortality without subtracting the risk of CV death**					
	Total costs	£17,006	£39,948	£40,376	-£22,942	-£23,371
	QALYs	7.00	7.06	7.08	-0.06	-0.08
	ICER	-	-	-	£416,776	£287,797
9	**Alternative utility assumptions**					
	Total costs	£17,471	£40,817	£41,256	-£23,346	-£23,785
	QALYs	7.02	7.08	7.11	-0.06	-0.09
	ICER	-	-	-	£387,304	£267,513
10	**Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors**					
	Total costs	£17,471	£41,828	£42,270	-£24,357	-£24,798
	QALYs	7.20	7.25	7.28	-0.06	-0.09
	ICER	-	-	-	£416,156	£287,165
11	**Alternative health state cost assumptions**					
	Total costs	£23,201	£46,543	£46,980	-£23,342	-£23,779
	QALYs	7.20	7.25	7.28	-0.06	-0.09
	ICER	-	-	-	£398,809	£275,361

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

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

†Comparison with Ali+EZE

Table 57. Results of the ERG's scenario analyses, population 4a

	Results per patient	BA/EZE FDC	EZE	Incremental value
0	**Corrected company base case**			
	Total costs	£18,111	£12,691	£5,420
	QALYs	6.89	6.81	0.08
	ICER	-	-	£69,453
0	**Secondary prevention cohort entering 3-year+ post-event states, no HeFH**			
	Total costs	£17,045	£11,468	£5,577
	QALYs	7.18	7.11	0.07
	ICER	-	-	£82,286
1	**ERG's NMA on LDL-C**			
	Total costs	£17,055	£11,468	£5,587
	QALYs	7.20	7.11	0.08
	ICER	-	-	£66,343

2	**Using the baseline LDL-C level from non-PCSK9i eligible patients in the non-PCSK9i eligible subpopulations**			
	Total costs	£17,079	£11,460	£5,619
	QALYs	7.26	7.20	0.06
	ICER	-	-	£97,388
3	**Using a lower proportion of recurrent/polyvascular events (7%)**			
	Total costs	£17,205	£11,574	£5,631
	QALYs	7.28	7.22	0.07
	ICER	-	-	£83,877
4	**Using prior IS events to inform the history of all secondary prevention patients**			
	Total costs	£17,514	£12,074	£5,441
	QALYs	6.38	6.32	0.06
	ICER	-	-	£87,484
5	**Using prior MI events to inform the history of all secondary prevention patients**			
	Total costs	£18,251	£12,585	£5,667
	QALYs	7.44	7.37	0.07
	ICER	-	-	£83,109
6	**Including transitions to the SA state from prior event states**			
	Total costs	£17,437	£11,853	£5,584
	QALYs	7.20	7.13	0.07
	ICER	-	-	£82,698
7	**Using all-cause mortality without subtracting the risk of CV death**			
	Total costs	£16,465	£11,021	£5,444
	QALYs	6.92	6.86	0.06
	ICER	-	-	£86,764
9	**Alternative utility assumptions**			
	Total costs	£17,045	£11,468	£5,577
	QALYs	6.95	6.88	0.07
	ICER	-	-	£80,567
11	**Alternative health state cost assumptions**			
	Total costs	£22,321	£16,751	£5,570
	QALYs	7.18	7.11	0.07
	ICER	-	-	£82,185

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

Note: all treatments in addition to statin therapy

Table 58. Results of the ERG's scenario analyses, population 4b

	Results per patient	BA/EZE FDC (1)	Ali (2)	Ali + Eze (3)	Evo (4)	Incremental value		
						(1-2)	(1-3)	(1-4)
0	**Corrected company base case**							
	Total costs	£18,090	£40,289	£40,298	£41,126	-£22,200	-£22,208	-£23,037
	QALYs	6.48	6.72	6.67	6.89	-0.23	-0.18	-0.41

	ICER	-	-	-	-	£94,488	£121,686	£56,285
0	**Secondary prevention cohort entering 3-year+ post-event states, no HeFH**							
	Total costs	£16,955	£39,810	£39,842	£40,595	-£22,855	-£22,887	-£23,640
	QALYs	6.83	7.03	6.99	7.18	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£111,482	£143,849	£65,992
1	**ERG's adjusted NMA on LDL-C†**							
	Total costs	£16,965	NA	£40,572	NA	NA	-£23,607	NA
	QALYs	6.85	NA	7.25	NA	NA	-0.39	NA
	ICER	-	-	-	-	NA	£60,123	NA
3	**Using a lower proportion of recurrent/polyvascular events (7%)**							
	Total costs	£17,119	£40,202	£40,237	£40,982	-£23,082	-£23,118	-£23,862
	QALYs	6.93	7.13	7.09	7.29	-0.20	-0.16	-0.36
	ICER	-	-	-	-	£113,225	£146,057	£67,086
4	**Using prior IS events to inform the history of all secondary prevention patients**							
	Total costs	£17,233	£39,511	£39,507	£40,385	-£22,277	-£22,274	-£23,152
	QALYs	6.07	6.25	6.21	6.39	-0.18	-0.14	-0.32
	ICER	-	-	-	-	£120,894	£156,131	£71,341
5	**Using prior MI events to inform the history of all secondary prevention patients**							
	Total costs	£18,111	£41,311	£41,339	£42,121	-£23,200	-£23,227	-£24,010
	QALYs	7.07	7.28	7.23	7.44	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£111,463	£143,662	£66,220
6	**Including transitions to the SA state from prior event states**							
	Total costs	£17,351	£40,237	£40,269	£41,021	-£22,886	-£22,918	-£23,670
	QALYs	6.85	7.05	7.01	7.21	-0.20	-0.16	-0.36
	ICER	-	-	-	-	£112,029	£144,561	£66,308
7	**Using all-cause mortality without subtracting the risk of CV death**							
	Total costs	£16,408	£38,744	£38,782	£39,488	-£22,336	-£22,374	-£23,080
	QALYs	6.60	6.79	6.75	6.94	-0.19	-0.15	-0.33
	ICER	-	-	-	-	£117,267	£151,307	£69,431
9	**Alternative utility assumptions**							
	Total costs	£16,955	£39,810	£39,842	£40,595	-£22,855	-£22,887	-£23,640
	QALYs	6.59	6.80	6.75	6.96	-0.21	-0.16	-0.37
	ICER	-	-	-	-	£108,907	£140,473	£64,558
10	**Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors**							
	Total costs	£16,955	£40,802	£40,829	£41,599	-£23,846	-£23,874	-£24,644
	QALYs	6.83	7.03	6.99	7.18	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£116,316	£150,055	£68,793
11	**Alternative health state cost assumptions**							
	Total costs	£22,290	£45,120	£45,157	£45,890	-£22,830	-£22,867	-£23,600
	QALYs	6.83	7.03	6.99	7.18	-0.21	-0.16	-0.36
	ICER	-	-	-	-	£111,360	£143,724	£65,879

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NMA, network meta-analysis; PCSK9i proprotein convertase

estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • After patients in subpopulation 2a experience their first event, recurrent events accrue the utilities for multiple events reported in Table 24.			
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	£5,727	0.19	£29,856

Abbreviations: BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; TA, Technology Appraisal; TIA, transient ischemic attack

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

Table 61. ERG's preferred assumptions, cumulative results, population 2b, BA/EZE FDC vs Ali + EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	NA†	NA†	NA†
Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	NA†	NA†	NA†
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	-£24,030	-0.24	£99,488*
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	-£24,030	-0.25	£96,779*
Adding the cost of an annual hospital appointment (£128) and a one-off initial training	-£25,057	-0.25	£100,913*

cost (£163) for patients receiving PCSK9 inhibitors			
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al*. 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	-£25,043	-0.25	£100,856*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

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

†Ali+EZE is not a comparator in the company's base case

Table 62. ERG's preferred assumptions, cumulative results, population 4a, BA/EZE FDC vs EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	£5,420	0.08	£69,453
Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	£5,577	0.07	£82,286
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	£5,587	0.08	£66,343
Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment	£5,628	0.07	£78,472
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	£5,628	0.07	£76,920
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al*. 2017 separately, in the analysis;	£5,622	0.07	£76,831

• Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al.* 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)			

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack

Table 63. ERG's preferred assumptions, cumulative results, population 4b, BA/EZE FDC vs Ali + EZE

Preferred assumption	Incremental costs	Incremental QALYs	Cumulative ICER
Corrected company base case	-£22,208	-0.18	£121,686
Using a starting cohort of secondary prevention patients without HeFH, allocated to begin the model in the 3-year+ post-event state	-£22,887	-0.16	£143,849
Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe, unadjusted	-£23,607	-0.39	£60,123*
Combining the following utility assumptions: • Removing the gender adjustment made by the company in the estimation of multipliers; • Using the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez *et al.* 2013a; • Using the acute MI multiplier from Ara and Brazier • Using the regression from Ara and Brazier for people with a mixed background of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events	-£23,607	-0.40	£58,863*
Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors	-£24,615	-0.40	£61,378*
Combining the following assumptions on health state costs: • Using first and second event incremental costs from Danese *et al.* 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese *et al*. 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices)	-£24,573	-0.40	£61,274*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CG, Clinical Guideline; CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost effectiveness ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI,

myocardial infarction; PCSK9i proprotein convertase subtilisin kexin type 9 inhibitor; QALYs, quality-adjusted life years; SA, stable angina; TA, Technology Appraisal; TIA, transient ischemic attack
*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. bempedoic acid generates less QALYs than comparators but is also less costly).

Table 64. ERG's preferred base case ICERs, deterministic and probabilistic results

Subpopulation	Treatment	Total costs	Total QALYs	ICER
2a	Deterministic			
	EZE	£9,591	9.06	-
	BA/EZE FDC	£15,319	9.25	£29,856
	Probabilistic			
	EZE	£9,664	9.16	-
	BA/EZE FDC	£15,429	9.35	£30,218
2b	Deterministic			
	BA/EZE FDC	£23,204	7.03	-
	Ali + EZE	£48,247	7.28	£100,856
	Probabilistic			
	BA/EZE FDC	NC	NC	-
	Ali + EZE	NC	NC	NC
4a	Deterministic			
	EZE + statin	£16,731	6.97	-
	BA/EZE FDC	£22,352	7.05	£76,831
	Probabilistic			
	EZE + statin	£16,736	6.97	-
	BA/EZE FDC	£22,358	7.04	£81,456
4b	Deterministic			
	BA/EZE FDC	£22,296	6.62	
	Ali + EZE + statin	£46,869	7.02	£61,274
	Probabilistic			
	BA/EZE FDC	£22,364	6.61	-
	Ali + EZE + statin	£46,107	7.00	£62,314

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; EZE, ezetimibe; fixed dose combination; ICER, incremental cost-effectiveness ratio; NC, not calculable; QALYs, quality-adjusted life years

6.5 Conclusions of the cost effectiveness sections

Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness for this appraisal. The revised network meta-analyses (NMAs) provided by the company at the clarification stage remain unfit for decision making, principally due to the extent of clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. To address some of these issues, the ERG explored alternative networks to implement in the economic analyses. However, the ERG

In terms of results, the ERG's preferred base case assumptions for bempedoic acid compared to ezetimibe in the statin intolerant population led to an incremental cost-effectiveness ratio (ICER) close to NICE's upper threshold of £30,000 (£29,856). Nonetheless, the ERG's preferred base case ICER is not too dissimilar to the company's base case ICER (£28,521).

As for the maximally tolerated statin population, the company's base case ICER for bempedoic acid compared to ezetimibe was already above NICE's upper threshold of £30,000 (£69,452) and the ERG's preferred assumptions increased the ICER to £76,831.

When patients are eligible for PCSK9i treatment in either the statin intolerant population or maximally tolerated statin population, bempedoic acid generates less quality-adjusted life years (QALYs) and less costs compared to PCSK9i treatment in the company's base case analyses and in each of the ERG's scenario analyses.

7 End of Life

The company did not submit a case for end of life and the ERG agrees with this decision.

8 References

1. NICE. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Technology appraisal guidance [TA394]. National Institute for Health and Care Excellence, 2016.
2. NICE. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Technology appraisal guidance [TA393]. National Institute for Health and Care Excellence, 2016.
3. Daiichi Sankyo Europe data on file. Physician survey in hypercholesterolaemia in the United Kingdom Delphi panel discussion guide. 2019.
4. NICE. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. Technology appraisal guidance [TA385]. National Institute for Health and Care Excellence, 2016.
5. Daiichi Sankyo Europe data on file. Delphi panel UK. 2019.
6. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. National Institute for Health and Care Excellence, 2016.
7. NICE. Familial hypercholesterolaemia: identification and management. Clinical guideline [CG71]. National Institute for Health and Care Excellence, 2017 Nov. Report No.
8. Mach F, Baigent C, Catapano A, Koskinas K, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019: 1-78. [Epub ahead of print].
9. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med* 2019; **380**: 1022-32.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **12pm on 24 February 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inaccurate statement regarding clinical evidence presented in the Company evidence submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17, section 1.1 states: "*Clinical data presented for the intervention, bempedoic acid, are not presented separately for the prior ezetimibe populations specified for the comparators and in which the company is positioning bempedoic acid and FDC*" Clinical data separately for patients with prior ezetimibe treatment were presented (Company Evidence Submission, Document B, section B.2.8.2; Figure 7; and results of the CLEAR Tranquility trial in which all patients had a 4-week run-in period of ezetimibe treatment). In addition, the language used is ambiguous; "*the prior ezetimibe populations"* could be interpreted as the populations prior to ezetimibe treatment.	This statement should be removed.	The statement asserts that the company did not present clinical data for bempedoic acid separately for patients with prior ezetimibe therapy, which is incorrect. The Company evidence submission included all available subgroup analyses which demonstrated that the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use (Document B, section B.2.8.2 and Figure 7).	Thank you for highlighting this inaccuracy. The text in the ERG report related to this issue has been amended to reflect the data presented in the CS in relation to the NICE Final Scope.

Issue 2 Inaccurate statement regarding the anticipated marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17, section 1.1 states: "*The ERG's clinical experts support the company view that bempedoic acid or FDC is unlikely to be used prior to ezetimibe although the ERG notes that* [redacted]." Page 31, section 2.3, Table 4 states: *"It is unclear from this statement that the marketing authorisation would not permit use of FDC prior to ezetimibe."*	The statement should be amended to read, "*The ERG's clinical experts support the company view that bempedoic acid or FDC is unlikely to be used prior to ezetimibe although the ERG notes that* [redacted]."	The statement is potentially misleading with respect to the marketing authorisation for FDC.	Thank you for highlighting this inaccuracy. The text in the ERG report related to this issue has been amended as requested by the company.

Issue 3 Misleading statement regarding the bempedoic acid and FDC trial populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, section 1.1 states: "*It is unclear what proportion of patients in the relevant bempedoic acid and FDC studies have primary hypercholesterolaemia or mixed dyslipidaemia, the population specified in the NICE final scope.*" Page 31, section 2.3, Table 4 states: "*It is unclear what proportion of patients in some of the relevant bempedoic acid and FDC studies have primary hypercholesterolaemia or mixed dyslipidaemia, however,* [redacted]" Page 36, section 2.3.1 states: "*The ERG notes that it is not clear if all patients enrolled across the included bempedoic acid and FDC studies restricted enrolment to patients with primary hypercholesterolaemia and/or mixed dyslipidaemia*."	These statements should be removed.	All patients in the bempedoic acid and FDC studies have either primary hypercholesterolaemia or mixed dyslipidaemia. We believe this was clear in the Company evidence submission, and no question was raised about this by the ERG. The ERG raised questions about the proportion of patients with primary hypercholesterolaemia and separately with mixed dyslipidaemia (ERG Clarification Questions A16 and A21); however, no question was asked regarding the proportion of patients in the trials that have either primary hypercholesterolaemia or mixed dyslipidaemia (combined). The statement is misleading as it suggests that some patients in the bempedoic acid and FDC trials may not	Thank you for highlighting this inaccuracy. All text in the ERG report related to this issue has been amended.

		have either primary hypercholesterolaemia or mixed dyslipidaemia, and may not be relevant to the population specified in the NICE final scope. This is not correct.	

Issue 4 Inaccurate statement regarding the clinical evidence for FDC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, section 1.1 states: "*The ERG does not consider there to be suitable data for assessing FDC in patients when maximally tolerated statin dose with ezetimibe does not appropriately control LDL C and notes the only data for bempedoic acid are from the pooled analysis of the post hoc subgroup data from CLEAR Harmony and CLEAR Wisdom.*" The Company has provided to the ERG the anticipated indication of FDC as reflected in the draft SPC of D195 of the EMA regulatory process and as per CHMP opinion. The Company has also included in the original submission from pharmacokinetic studies to demonstrate bioequivalence. The ERG clinical experts in the report are mentioned that they would not expect separate single tablets to perform differently to a dual	This statement is recommended to be rephrased or removed.	The fixed dose combination (FDC) program has been developed by the applicant to be bridged together with the bempedoic acid program because the 2 drug components of bempedoic acid and ezetimibe were co-administered in a large number of patients both on maximally tolerated statin therapy and in patients intolerant to statins, including patients not adequately controlled on both a maximally tolerated dose of statin and ezetimibe. Table 1 below provides the tabular representation of how the proposed indications align with the EMA FDC Guideline (EMA/CHMP/158268/2017) (EMA, 2017), the European Union (EU) Standard of Care Guidelines, and the overall program that includes clinical data based on the studies conducted that directly or indirectly bridge the data together. In the Clinical Overview of the Original Marketing Authorisation Application (MAA; Module 2.5, Section 4.3.2) to EMA which has been provided as reference to the NICE submission, the clinical data that support each of the conditions of use included in the proposed indication statement discussed how they align with the	This is not a factual inaccuracy . The ERG notes that any decision would be based on pharmacokinetic studies as no patients had prior ezetimibe background therapy immediately before randomized study treatment

combination tablet and this is an agreement with expert opinion that the company has obtained.		therapeutic scenarios described in the EMA 2017 FDC Guideline (EMA/CHMP/158268/2017) (EMA, 2017). Namely these include: • The bempedoic acid and FDC programs achieving meaningful LDL-C reduction in patients insufficiently responding to maximally tolerated statins, including in subgroups also insufficiently controlled with ezetimibe or other lipid-modifying therapies • Demonstrating equivalent pharmaco-dynamic behavior of the FDC to its co-administered individual components • Establishing the clinical superiority of the FDC to ezetimibe alone or bempedoic acid alone in patients insufficiently responding to maximum tolerated statin therapy, meet the respective conditions of use for the proposed positioning. Should this had been raised at the clarification stage by ERG as a point of concern, the Company would have provided the relevant regulatory documents to further elaborate on this.	in Study 1002FDC-053.

Issue 4 Table 1. Trial data supporting the proposed positions and FDC anticipated indication

Proposed position and FDC anticipated indication	Data to support this position as submitted to the CHMP in original MAA submission and as part of the D120 responses	Relevant EMA Guidance
[redacted]	• Direct data: bempedoic acid as add-on to a maximum tolerated statin dose	This meets EMA 2017 FCMP Guideline (EMA/CHMP/158268/2017) and anticipated indication of the FDC as per CHMP opinion

		plus ezetimibe in subset of patients (Study 1002-040 and Study 1002-047) • Supported by comparison of FDC vs bempedoic acid alone and ezetimibe alone in patients on a maxim			

	um tolerated statin dose in Study 1002FDC-053		
[redacted]	• Direct evidence: bempedoic acid alone plus ezetimibe (Study 1002-048) • Direct evidence: patients on background ezetimibe in Study	This meets EMA 2017 FCMP Guideline (EMA/CHMP/158268/2017) and anticipated indication of the FDC as per CHMP opinion	

	1002-046 • Supportive data: FDC vs bempedoic acid alone and ezetimibe alone among subset of patients on no statin (Study 1002FDC-053)		

Issue 5 Inaccurate statement regarding the presentation of subgroups

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, section 1.1 states: "*None of the subgroups specified in the final scope (presence or risk of cardiovascular disease, people with heterozygous familial hypercholesterolaemia [HeFH], people with statin intolerance and severity of hypercholesterolaemia) are presented for bempedoic acid or FDC compared to the comparators specified in the NICE final scope.*" This statement, made in the general critique of the decision problem in the Company's submission, is incorrect.	This statement should be deleted.	Outcomes in the decision problem relate to presentation of both clinical and cost-effectiveness evidence. The NICE final scope specified that these subgroups will be considered if the evidence allows. Clinical efficacy for all available subgroups were presented in the Company evidence submission (Section B.2.7). In some trials (CLEAR Wisdom, CLEAR Harmony and 1002FDC-053, a separate subgroup analysis for HeFH patients was not feasible due to patient numbers (≤27 per arm), therefore, HeFH patients were included in the secondary prevention (presence of cardiovascular disease) subgroup. In CLEAR Tranquility, patients with no recent history of CVD were excluded, and HeFH was not recorded. Separate trials were performed in people with statin intolerance (CLEAR Serenity and CLEAR Tranquility). In all trials, subgroups with differing severity of hypercholesterolemia were presented by baseline LDL-C category. The treatment-effect for bempedoic acid and FDC was consistent across these subgroups with the exception of statin intolerant patients vs patients receiving maximally tolerated statin therapy. The NMA considered these two patient groups	The ERG has amended the text to highlight that the subgroup analyses from the clinical trials detailed by the company were not for the prior ezetimibe population.

		separately. The economic evaluation considered a range of clinically relevant subgroups within the patient population for which bempedoic acid and FDC are expected to be a therapy option. The subgroups were defined by a combination of these clinical features, and were aligned with the NICE recommendations for current therapy including alirocumab and evolocumab. These subgroups were labelled 2a, 2b, 4a and 4b in the Company evidence submission. In addition, subgroup analyses based on the individual clinical variables were available in the submitted economic model.	

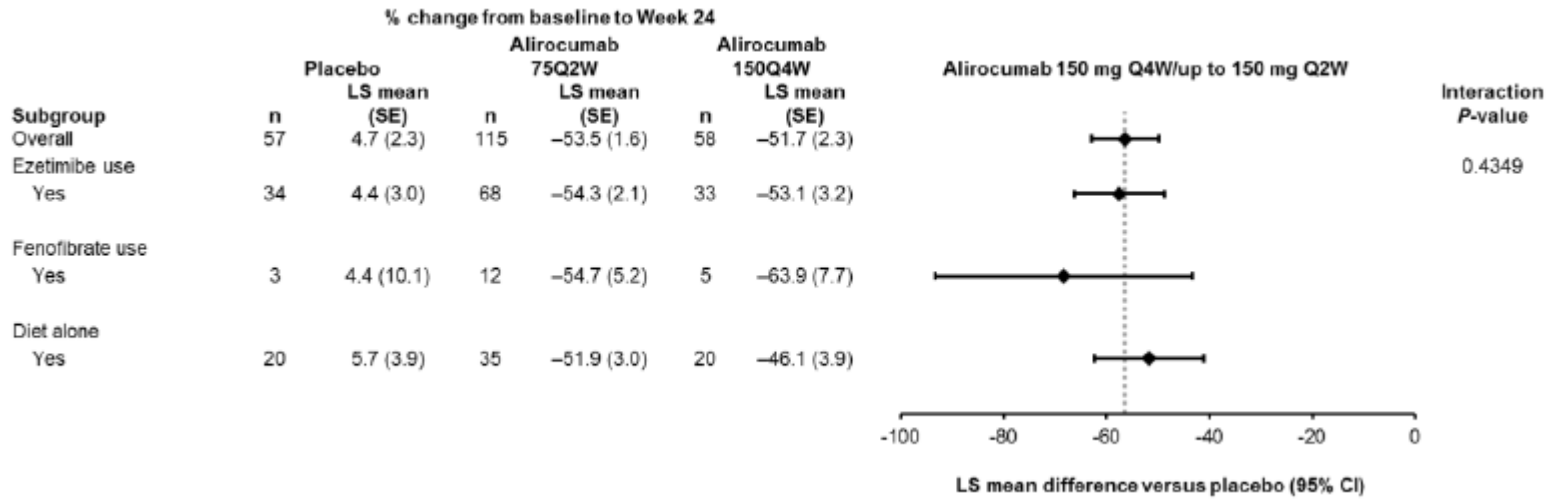
Issue 6 Inaccurate statement regarding use of efficacy data for patients populations with or without prior ezetimibe therapy in the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19, section 1.2 states: "*The use of incorrect populations in the NMAs to address the population in whom ezetimibe does not appropriately control LDL-C with studies included that have a mix or even no patients with prior ezetimibe therapy*". The ERG has not established that the use of efficacy data for patient populations with or without prior ezetimibe therapy to address the population in whom ezetimibe	This statement should be amended to read "*The use of* ***efficacy data for patient populations with or without prior ezetimibe therapy*** *in the NMAs to address the population in whom ezetimibe does not appropriately control LDL-C."*	As presented in the Company evidence submission (section B.2.8.2), for bempedoic acid trials in post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe use. This was the basis upon which the Company decided to conduct the NMA using all available evidence for the comparators of interest independently of prior ezetimibe use. Furthermore, no evidence was identified by	This is not a factual inaccuracy. On page 19 it is made clear that this is an ERG opinion.

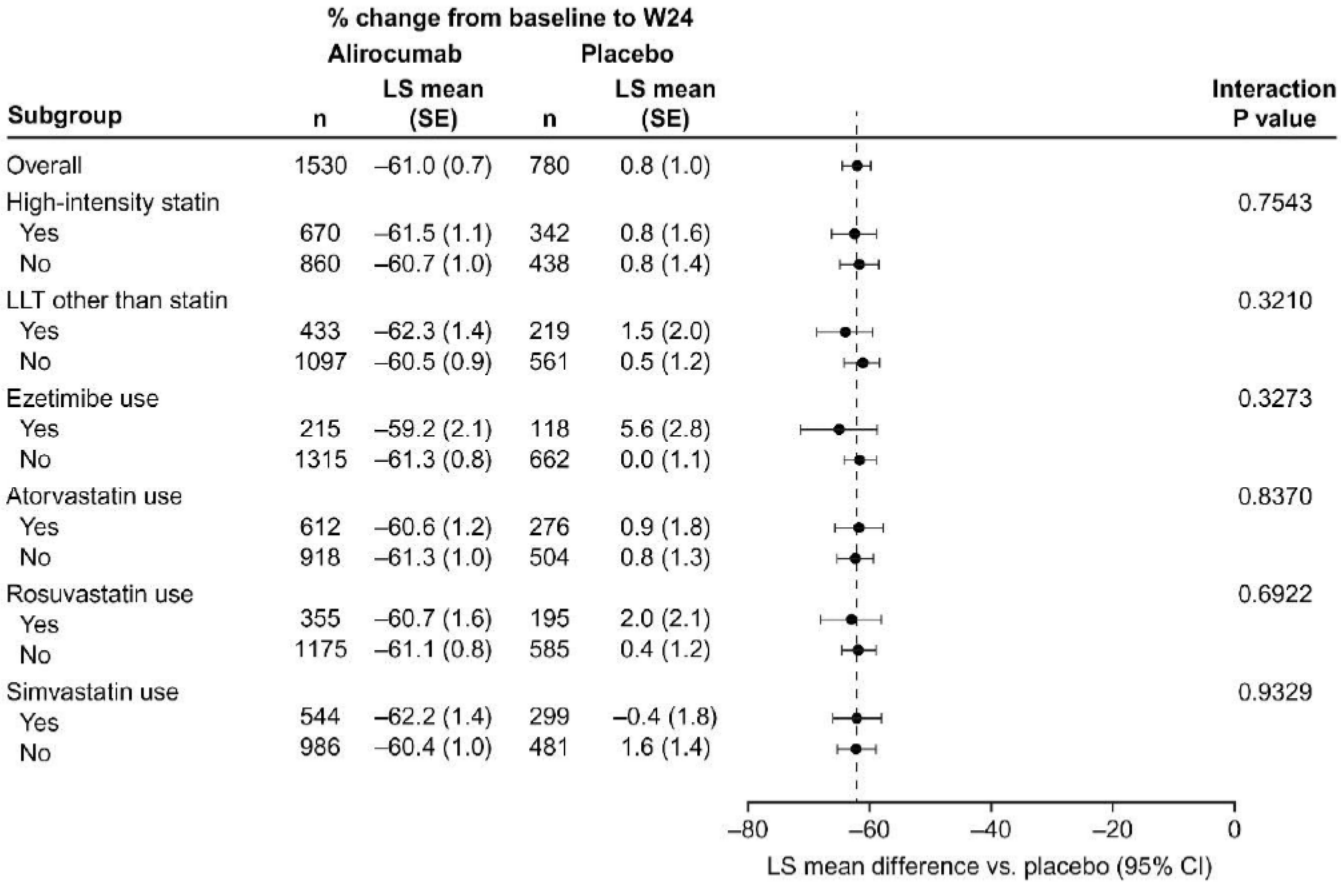
does not appropriately control LDL-C is indeed incorrect as mentioned above.		the ERG or the Company systematic reviews which suggest a difference in treatment effect the comparator interventions in patients with or without prior ezetimibe therapy. In the subgroup analyses for alirocumab in patients with and without ezetimibe identified by the ERG and used in the ERG's NMA, there was no evidence for a difference in treatment effect for alirocumab with and without ezetimibe. In statin intolerant patients, the ERG used ODYSSEY CHOICE II (Stroes et al., 2016). The treatment-effect for alirocumab was consistent for patients with ezetimibe use and in the overall population and the interaction *P*-value was not significant (*P*=0.4349) (Issue 6 Figure 1). In maximally tolerated statin patients, the ERG used ODYSSEY LONGTERM (Robinson et al., 2015). The treatment-effect for alirocumab was consistent for patients with and without ezetimibe use and the interaction *P*-value was not significant (P = 0.3273) (Issue 6 Figure 2). The ERG has not presented evidence to support the statement that use of efficacy data for patient populations with or without prior ezetimibe therapy to address the population in whom ezetimibe does not appropriately control LDL-C is incorrect. Clinical expert opinion has also verified that there is no expectation for difference in treatment effect by prior ezetimibe therapy. The evidence base in patients with prior ezetimibe use only is very limited, whilst	

		there is a wealth of evidence in the overall population of patients with or without ezetimibe use and background of other lipid lowering treatments. As no evidence was identified that the treatment-effect differs by prior ezetimibe use, the company included trial data, using all relevant evidence regardless of ezetimibe use. The ERG excluded the majority of the relevant evidence, and their NMAs were based on only 2 trials per NMA, with data being taken from subgroups based on very small patient numbers in each group (CLEAR Harmony, n = [redacted] and [redacted]; ODYSSEY CHOICE II, n = 34, 68 and 33) and in which it was unclear whether randomisation was stratified by prior ezetimibe therapy (ODYSSEY LONGTERM). Therefore, there is potential for imbalance in patient characteristics between arms. The selection of this very small subset of the available evidence may be expected to introduce bias.	

Issue 6 Figure 1. Subgroup analysis by ezetimibe use in ODYSSEY CHOICE II (Stroes et al., 2016)



Issue 6 Figure 2. Subgroup analysis by ezetimibe use in ODYSSEY LONG TERM (Robinson et al., 2015)



Issue 8 Inaccurate statement regarding the exclusion of ODYSSEY LONGTERM from the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19, Section 1.2 states: "*The company's updated NMAs may be missing studies of relevance; e.g. ODYSSEY Long Term is missing from the maximally tolerated statin NMA and yet the ERG considered it suitable for inclusion in the ERG's NMA*" Page 78, Section 3.4.1 states: "*In addition, the ERG is concerned that the company erroneously removed ODYSSEY Long Term from the maximally tolerated statin NMA for having an exclusive diabetic population when less than 50% of patients were diabetic*" The ERG has previously requested removal of ODYSSEY LONGTERM and thus the Company has removed the study during the Clarification stage to satisfy this.	These statements should be deleted.	Section A (page 4) of the ERG Clarification Questions included the following request from the ERG regarding the maximally tolerated statin NMA: "*b. Exclude studies that exclusively recruited populations with Type 1 diabetes or Type 2 diabetes (ODYSSEY-DM and DM-DYSLIPIDEMIA and DM-INSULIN, BANTING, ODYSSEY LONGTERM and BERSON*)"	This is not a factual inaccuracy although the ERG would like to apologise for erroneously suggesting the company consider removal of ODYSSEY LONGTERM in the clarification questions. However, the ERG considers it important to highlight that it only suggested changes to the NMA in the clarification questions and did not directly request the removal of set studies. The ERG considers the company should have thoroughly reviewed all studies prior to excluding any from their NMAs.

Issue 9 Misleading statement regarding double counting of patients in the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19, Section 1.2, point 1 states: "*it appears that there is double counting of patients in the NMA through the use of 12- and 24-week data for some of the alirocumab trials. The ERG notes that alirocumab patients who have received 75 mg and also been uptitrated to 150 mg at 12 weeks may have been included in both the 75 mg and 150mg analyses albeit using data from different timepoints (12 weeks and 24 weeks, respectively) (Section 3.4.2).*" Page 41, section 2.3.3 states: "*The ERG notes that the 24-week data uses the same baseline LDL-C values and thus considers it likely to be double-counting the 75mg patients by using a later data point to inform 150 mg*." The information regarding "double counting" is misleading with no clarification on the minimal impact of this.	The statement should be amended to: *"it appears that there is double counting of patients in the NMA through the use of 12- and 24-week data for some of the alirocumab trials. The ERG notes that alirocumab patients who have received 75 mg and also been uptitrated to 150 mg at 12 weeks may have been included in both the 75 mg and 150mg analyses albeit using data from different timepoints (12 weeks and 24 weeks, respectively).* ***This would not be anticipated to impact on the comparative efficacy estimates for alirocumab 150 or 75mg*** *(Section 3.4.2)."* *"The ERG notes that the 24-week data uses the same baseline LDL-C values (for the 150mg dose) as the 12-week data uses (for the* ***75mg dose), although the 12 week results for 75mg and the 24 week results for 150mg were used; therefore the change from baseline values differ. The inclusion of both 75mg and 150mg within the evidence base provided a method to consider both doses and would***	Without information on the anticipated impact of the inclusion of alirocumab 150 and 75mg data, the ERGs comment casts doubt on the validity of the Company's NMA. Whilst the same baseline values are used for alirocumab 150mg uptitrated from 75mg and alirocumab 75mg, different endpoint values were used and hence the change from baseline values considered within the analyses are different for the 75mg and 150mg doses. The incorporation of the 150mg and 75mg data within the evidence base provided an approach to provide comparative efficacy estimates for both alirocumab doses of interest. The ERG did not propose an alternative approach other than to exclude the 75mg dose, thus removing a comparator intervention recommended by NICE from the network. Within the analysis these were included as if they were two different trials, rather than as a further treatment arm within the trial. Given the large number of studies within the evidence base for the Company's NMA, and the limited amount of additional baseline data incorporated through "double counting" of baseline data for alirocumab	This is not a factual inaccuracy.

	***not be anticipated to impact on the estimates for 150mg or 75mg within the Company's NMA**."*	included within (see Tables 37 and 38 of the Company's response to ERG clarification questions), any impact on results would be expected to have been negligible. Further, alirocumab results from the Company's NMA have been shown to be comparable to those in previous NMAs in this disease area (Toth et al. 2017).	

Issue 10 Misleading statement regarding subgroup analyses presented in the Company's NMA and cost-effectiveness evaluation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19, Section 1.2 point 2 states: "*No subgroup analyses based on primary or secondary prevention (CV risk) or presence of HeFH were conducted by the company despite being specified in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively). In addition, patients from these subgroups are included in the economic model. There is limited information reported in the clinical studies in the NMAs on the*	These statements should be deleted.	All available subgroup analyses based on CV risk and presence of HeFH were provided by the company in the clinical evidence section. In all four phase 3 trials which included both primary prevention, secondary prevention and HeFH patients (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity and 1002FDC-053), the treatment effect was consistent in subgroup analyses (data presented in the Company evidence submission, Section B.2.7). The ERG does not provide a justification for the statement that it is unreliable to use treatment effectiveness estimates from a wider population with and without these characteristics. The economic evaluation considered a range of clinically relevant subgroups	This is not a factual inaccuracy.

proportion of patients who are primary or secondary prevention and who do or don't have HeFH. In the absence of suitable subgroup analyses, the ERG does not consider it appropriate to assume no difference in treatment effect across potentially important subgroups of relevance in the economic model" Page 21, section 1.3 states: *"An additional and related area of concern is that no subgroup analyses based on CV risk or presence of HeFH were conducted by the company despite being specified in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively). Moreover, given the high proportion of secondary prevention patients without HeFH entering the model, the ERG considers it unreliable to use treatment effectiveness estimates from a wider population with and without these characteristics. For these reasons, the ERG stresses its opinion that cost-effectiveness results by subgroup should be provided by the company in order to reflect the patients entering the*		within the patient population for which bempedoic acid and FDC are expected to be a therapy option. The subgroups were defined by a combination of prior cardiovascular disease, HeFH and baseline LDL-C in order to align with the NICE recommendations for current therapy, including alirocumab and evolocumab. This approach was adopted in order to provide consistency with previous NICE appraisals. These subgroups were labelled 2a, 2b, 4a and 4b in the Company evidence submission. In addition, subgroup analyses based on the individual clinical variables were available in the submitted economic model.	

model and in order to allow for consistent decision making with previous NICE appraisals" Page 162, section 6.5 states: *"Another key area of concern is that no subgroup analyses based on cardiovascular (CV) risk or presence of heterozygous familial hypercholesterolaemia (HeFH) were conducted by the company, despite being requested in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively)."*			

Issue 11 Misleading statement regarding waning of treatment-effect for bempedoic acid and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19-20, Section 1.2 point 2 states: "*Data are mostly limited to 12-weeks in the company's NMAs, although treatment is likely to be long-term depending on patient response and tolerance. The ERG considers that there may be a slight waning of treatment effect with bempedoic*	This statement should be amended to *"Data are mostly limited to 12-weeks in the company's NMAs, although treatment is likely to be long-term depending on patient response and tolerance. The ERG considers that there may be a slight waning of treatment effect with bempedoic acid beyond 12-weeks,* ***albeit non-meaningful. It is noted that a slight numerical waning of treatment***	The company has provided data on treatment effect of bempedoic acid expressed as reduction in LDL-C at week 12 from baseline and at later timepoints available (week 24 and week 52, where available) demonstrating the consistency of bempedoic acid effect. Furthermore, during the clarification stage, the Company has provided evidence form the CLEAR-OLE study presenting data up to 52 weeks on the persistence of effect of	This is not a factual inaccuracy.

acid beyond 12-weeks and is unable to comment as to whether similar waning would be seen for the comparators." It is unclear why the ERG is unable to comment as to whether waning of treatment-effect would be seen for comparators.	***effect also has been observed for comparators.**"*	bempedoic acid. In addition, pharmacokinetic and pharmacodynamic analyses available do not imply a mechanistic reason for loss of treatment effect for bempedoic acid. As such, any differences in LDL-C reduction in time is not considered to be statistically different, however the Company recognises that slight waning may be attributed to the inherent analyses of study regarding adherence and thus has been considered in the model as part of discontinuation rates. Similarly, waning of the numerical change in LDL-C from baseline over time for comparators was noted in the Company evidence submission (section B.2.9, page 126), and was also evident in one of the studies included by the ERG in their NMA (ODYSSEY LONGTERM, Robinson et al. 2015, Figure 2) as well as other studies identified by the systematic review presented in the Company evidence submission and provided to the ERG. The ERG should be aware of this evidence. See also Issue 17.	

Issue 12 Misleading statement regarding the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20, Section 1.2 point 3 states:	The ERG was unable to replicate the results obtained from the company's NMAs, ***despite provision of the***	The statement throws doubt on the validity of the Company NMA, without recognising that the company provided	This is not a factual inaccuracy. As the company notes in issue 21, the ERG acknowledges the company's

"The ERG was unable to replicate the results obtained from the company's NMAs and is unsure of the reason for this."	***code, supporting references, and validation of the results by the Company via independent analyses***, and is unsure of the reason for this."	the ERG with requested code and information (Company evidence submission, Document C, Section D.2.8 and in response to ERG requests), that the company performed validation of their results by an independent statistician, and that the Company performed validation of the Bayesian results via independent frequentist analyses (Company evidence submission, Document C, Section D.2.8). It is possible that the ERG did not centre baseline LDL-C when attempting to replicate the results, or did not use a sufficiently uninformative prior.	provision of the NMA code on page 73 of the ERG report.

Issue 13 Misleading statement regarding the methods to adjust for baseline LDL-C

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20, Section 1.2 states: *"The ERG also considers the company to have used incorrect methods to adjust for differences in baseline LDL-C in the NMAs which results in issues relating to the reliability of the results (Section 3.4.1)."*	*"The ERG also considers the company to have* ***used one approach to adjust for differences in baseline LDL-C, although other methods to adjust for differences in baseline LDL-C in the NMAs exist.*** (Section 3.4.1)."	The statement casts doubt on the reliability of the Company's NMA although methods used to adjust for differences in baseline LDL-C in the Company's NMAs were based on published methods and in line with the NICE DSU guidelines, NICE DSU TSD 3. Although published NMAs did not adjust for baseline LDL-C, the results from the Company's NMA were in line with a published NMA (Toth et al., 2017). Whilst different approaches exist to adjust for baseline LDL-C in NMAs, the	This is not a factual inaccuracy. The method employed by the company does not appropriately capture the correlation of the uncertainty around the treatment effect and the baseline LDL-C.

		selected approach used in the Company's NMA does not make its results unreliable. Convergence was reached in the Company's NMA, see (Figures 14 and 23 of Company evidence submission response to ERG clarification questions, Appendix A Section A.1.). The Company's results were replicated by an independent statistician and results were comparable to results from frequentist models (Company evidence submission, Document C, Section D.2.8). Further, the Company would like to draw attention to the large credible intervals presented by the ERG in their NMAs (Table 30 and 31 of the ERG report), which the Company considers to flag issues relating to the reliability of the results from these.	

Issue 14 Misleading statement regarding the exploratory NMAs conducted by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20, Section 1.2 point 3 states: *"The ERG conducted exploratory NMAs with data used only in the population of patients who have received prior ezetimibe and are assumed to continue ezetimibe*	The statement should be amended to read: *"The ERG conducted exploratory NMAs with data used only in the population of patients who have received prior ezetimibe and are assumed to continue ezetimibe throughout the study. However, the ERG was unable to include all the appropriate data from the bempedoic*	*See Issue 6.*	This is not a factual inaccuracy.

throughout the study. However, the ERG was unable to include all the appropriate data from the bempedoic acid studies and the ERG's appraisal of studies was limited. As such, the results of the ERG's analyses should be interpreted with caution."	*acid studies and the ERG's appraisal of studies was limited.* ***In addition, the ERG did not identify any evidence that the treatment-effect for bempedoic acid, FDC, or comparators may vary in patients with or without prior ezetimibe. The ERGs NMAs were based on 2 trials per NMA, subgroup analyses involving small patient numbers, and in which it was unclear whether randomisation was stratified by prior ezetimibe therapy. The selection of this very small subset of the available evidence may be expected to introduce bias.*** *As such, the results of the ERG's analyses should be interpreted with caution.*"		

Issue 15 Inaccurate statement about the NMAs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20-21, Section 1.3, point 1 states: "*The revised NMAs provided by the company at the clarification stage remain unfit for decision making, principally due to the extent of the clinical and statistical heterogeneity observed from the studies*	"*The revised NMAs provided by the company at the clarification stage* ***should be interpreted with caution****, principally due to the extent of the clinical and statistical heterogeneity observed from the studies included in the networks and* ***limited*** *evidence for bempedoic acid in patients with prior ezetimibe* ***on maximally tolerated statin therapy****.* ***The ERG performed***	The Company performed all revisions to the NMAs for LDL-C at 12 weeks requested by the ERG, and adopted this revised NMA as the Company base case. The ERG's NMAs are subject to substantial limitations and potential bias, and preclude comparison with evolocumab (see Issue 6 and Issue 14). The ERG has not demonstrated that the ERG's estimates are closer to a robust	This is not a factual inaccuracy. The ERG has explained why the ERG's estimates are closer to a robust analysis in Section 3.5 of the main ERG report.

included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. To address these issues, the ERG performed additional NMAs. Although the ERG's estimates are closer to a robust analysis they are still subject to limitations and should be interpreted with caution."	***additional NMAs which focus only on data in patients with prior ezetimibe therapy. The ERG's estimates also are subject to limitations, preclude comparison with evolocumab,*** *and should be interpreted with caution (Section 4.2.5.3)."*	analysis than the Company's NMAs. The ERG's NMA is based on a small number of studies and has used fixed effects models. The estimates therefore rely on the results from those limited studies being representative of all studies which is unlikely to be a robust assumption. Further, the fixed effects model used by the ERG assumes that the there is a single true effect size, which is unlikely to be correct and is typically not considered robust, the fixed effects were considered appropriate by the ERG because of the limited study numbers within their analysis. This does not mean that fixed effects models are more robust or appropriate, just that the size of the evidence base did not permit the appropriate method to be performed (without use of informative priors which was not considered by the ERG). Random effects models are widely recognised to be more robust where there is variation in effect sizes across studies, which is anticipated to be the case for the populations on which these evidence networks are based. The results presented for the Company's NMA used a broader evidence base, and are based on random effects models, therefore these may be considered to more accurately represent the true variation in effect sizes anticipated for these populations and to be a more robust analysis. Further the Company's NMA adjusted for baseline LDL-C, whilst	

		the NMAs presented by the ERG did not, despite evidence suggesting that the magnitude of LDL-C lowering is a function of both baseline LDL-C level and drug efficacy {Navarese, 2018 #45}. Clinical experts have indicated that inclusion of baseline LDL-C in the NMA should be considered and that the magnitude of change in LDL-C may be related to baseline LDL (which may be considered a marker of severity). It is misleading to state that there is a lack of evidence for bempedoic acid in patients with prior ezetimibe. The CLEAR Tranquility study investigated this population specifically. No trial in patients on maximally tolerated statin therapy focussed on patients with prior ezetimibe specifically. However, in CLEAR Harmony and CLEAR Wisdom (combined), 150 patients randomised to bempedoic acid and 76 patients randomised to placebo reported ezetimibe background therapy. The term “lack” may be interpreted as no data, which is misleading. The evidence for patients with prior ezetimibe was presented in the Company evidence submission (Document B, section B.2.8.2 and Figure 7). It is misleading to state “To address these issues, the ERG performed additional NMAs”. The ERG’s NMAs do not address the extent of the clinical and statistical heterogeneity observed from	

		the studies included in the networks (rather, they excluded relevant evidence). Nor do they address the limited evidence for bempedoic acid in patients with prior ezetimibe on maximally tolerated statin therapy.	

Issue 16 Misleading statement regarding subgroup analyses presented in the Company's cost-effectiveness evaluation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21, section 1.3 states: *"An additional and related area of concern is that no subgroup analyses based on CV risk or presence of HeFH were conducted by the company despite being specified in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively). Moreover, given the high proportion of secondary prevention patients without HeFH entering the model, the ERG considers it unreliable to use treatment effectiveness estimates from a wider population with and without these characteristics. For these reasons, the ERG stresses its opinion that cost-effectiveness*	These statements should be deleted.	All available subgroup analyses based on CV risk and presence of HeFH were provided by the company. The economic evaluation considered a range of clinically relevant subgroups within the patient population for which bempedoic acid and FDC are expected to be a therapy option. The subgroups were defined by a combination of prior cardiovascular disease, HeFH and baseline LDL-C in order to align with the NICE recommendations for current therapy, including alirocumab and evolocumab. This approach was adopted in order to provide consistency with previous NICE appraisals. These subgroups were labelled 2a, 2b, 4a and 4b in the Company evidence submission. In addition, subgroup analyses based on the individual clinical variables were available in the submitted economic model.	This is not a factual inaccuracy.

results by subgroup should be provided by the company in order to reflect the patients entering the model and in order to allow for consistent decision making with previous NICE appraisals" Page 162, section 6.5 states: *"Another key area of concern is that no subgroup analyses based on cardiovascular (CV) risk or presence of heterozygous familial hypercholesterolaemia (HeFH) were conducted by the company, despite being requested in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and alirocumab (TA393 and TA394, respectively)."*		In all four phase 3 trials which included both primary prevention, secondary prevention and HeFH patients (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity and 1002FDC-053), the treatment effect was consistent in subgroup analyses (data presented in the Company evidence submission, Section B.2.7). The ERG does not provide a justification for the statement that it is unreliable to use treatment effectiveness estimates from a wider population with and without these characteristics.	

Issue 17 Inaccurate statement on LDL-C reduction and sustained response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21, section 1.3 states: "*the ERG notes that the reductions in LDL-C recorded in the CLEAR trials at week 12 are not sustained at week 24 (CLEAR Serenity) or week 52 (CLEAR Harmony and CLEAR*	The statement should be deleted.	The Company has presented data in the original submission and the Clarification stage demonstrating that the treatment effect of bempedoic acid is maintained across the timepoints available in the analyses. The graphs with mean LDL-C levels and standard errors have been provided and further information is also	This is not a factual inaccuracy. Figures 4, 5 and 6 in the CS show the mean LDL-C or absolute change in LDL-C in the bempedoic acid arm converging towards the placebo arm.

Wisdom). Therefore, assuming 12-week results are maintained for the duration of the model's time horizon, or until treatment is discontinued is questionable. The ERG's clinical experts also affirmed that the response at week 12 would be larger than the sustained response. As such, it is the ERG's view that the dataset including the latest outcomes available is the preferred approach to addressing this important area of uncertainty." Page 115 states: *"The reductions in LDL-C recorded in the CLEAR trials at week 12 are not sustained at week 24 (CLEAR Serenity) or week 52 (CLEAR Harmony and CLEAR Wisdom), indicating treatment waning effects."*		available in the published manuscripts of the pivotal trials. The company has also provided data from the CLEAR-OLE study up to 52 weeks where treatment effect is sustained. In addition, the Company has provided data on the pooled analyses of trial data up to 52 weeks. In those, the median LDL-C value stays basically constant over time (week 12: [redacted] mg/dL, 24: [redacted]mg/dL, 36: [redacted] mg/dL, 52: [redacted] mg/dL for Pool 1). That means, in the median –which is the more robust measure than the mean- a difference of [redacted] mg/dL between week 12 and week 52. This is a minimal difference and also not statistically significant different. Also the other robust measures (Q1 and Q3) stay nearly constant over time. The Company has therefore used the LDL-C reduction at week 12 as this was available across all studies as primary efficacy outcome and in order to enable informative decision making. The Company has also considered discontinuation rates across treatments in the model in order to account for any uncertainty around treatment effect; this is in accordance with literature, previous HTA submissions and verified by expert opinion.	

Issue 18 Inaccurate statement regarding the baseline LDL-C levels for populations 2a and 4a

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22, section 1.3, point 5 states: "*In the non-PCSK9i eligible subpopulations, the ERG found that the company used the baseline LDL-C levels of all patients in the CLEAR trials (population 2: [redacted]; population 4: [redacted]) and that these levels are notably higher than the levels of non-PCSK9i eligible patients in the CLEAR trials (subpopulation 2a: [redacted]; subpopulation 4a: [redacted]). This approach contradicts the company's decision to separate populations according to PCSK9i eligibility using NICE recommendations."*	This statement should be removed.	A large proportion of patients that are eligible for alirocumab or evolocumab therapy do not receive such therapy. In an analysis for the Accelerated Access Collaborative (ABPI Webinar 27th January 2020), the NHS Innovation Scorecard showed uptake of these medicines was between 72% and 77% lower than expected. Therefore, the mean LDL-C for patients not receiving PSCK9i therapy is expected to be higher than that for non-PCSK9i eligible patients in the CLEAR studies. Therefore, the mean baseline LDL-C is better represented by all patients in the CLEAR studies, than only non-PCSK9i eligible patients. This rationale was presented in the Clarification questions response, Question 8.	This is not a factual inaccuracy. The Accelerated Access Collaborative is supporting PCSK9 inhibitors as a rapid uptake product and if the Accelerated Access Collaborative meets its key deliverables this will increase the uptake of this product.

Issue 19 Misleading statement regarding treatments included in NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40, section 2.2.3, states: "*The ERG also notes that alternative dosing schedules for evolocumab, namely 140 mg*	*"The ERG also notes that alternative dosing schedules for evolocumab, namely 140 mg every two weeks (Q2W) and 420 mg once monthly (QM), were combined in the NMA as*	This is factually incorrect. The company's NMA was amended following ERG comments to remove 420mg once monthly (QM) from the NMA.	Thank you for highlighting this inaccuracy. The text in the ERG report related to this issue has been amended.

every two weeks (Q2W) and 420 mg once monthly (QM), were combined in the NMA as a single intervention."	*a single intervention* ***within the original company submission, but 420mg once monthly QM doses for evolocumab were removed from the subsequent NMA performed by the company.****"*		

Issue 20 Misleading statement regarding analysis that should have been performed for NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73, section 3.4.1, states: "*The ERG considers that the impact of this will be to cause additional uncertainty in the analysis. In the opinion of the ERG, the company should have addressed this by using the IPD from the relevant CLEAR studies to establish the correlation between baseline LDL-C and treatment effect, and then assumed this correlation held across all studies included in the network. The required methods to adopt this approach are covered in NICE DSU TSD 20."*	"*The ERG considers that the impact of this will be to cause additional uncertainty in the analysis,* ***although there is no evidence in the submission to indicate that this is the case****. In the opinion of the ERG, the company should have addressed this by using the IPD from the relevant CLEAR studies to establish the correlation between baseline LDL-C and treatment effect, and then assumed this correlation held across all studies included in the network. The required methods to adopt this approach are covered in NICE DSU TSD 20.* ***Primary benefits of the multivariate NMA approach is the gain in precision through the extension of the evidence base, and the gaining of information through the analysis of two outcome variables. For the Company's NMA the evidence base***	It is misleading to state that the inclusion of baseline LDL-C within the models lead to additional uncertainty, there is no evidence to support this in the submission, and given that the magnitude of LDL-C lowering has been shown to be a function of both baseline LDL-C and efficacy (Navarese et al., 2018), the inclusion of baseline LDL-C would be expected to reduce the uncertainty in the NMA estimates. As baseline LDL-C was available for all studies, the use of the multivariate model would not have expanded the evidence base. Further, within NICE DSU TSD 20, the proposed uses of multivariate analysis are to jointly consider two outcome variables; this does not represent the data within this analysis, baseline LDL-C would not be considered an outcome variable within this analysis, nor a surrogate marker for change in LDL-C across treatments.	This is not a factual inaccuracy. While the focus of NICE DSU TSD 20 is the correlation between two outcomes, the ERG considers this approach to be analogous to appropriately accounting for the correlation between changing baseline LDL-C and a change in the magnitude of the treatment effect.

	would not have been expanded through the use of a multivariate NMA, and there is a only single outcome variable, change in LDL-C."		

Issue 21 Misleading statement about the Company's NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73, section 3.4.1, states: "At the request of the ERG, the company provided the code and the data set for its NMAs for the ERG to validate its analyses. The ERG started by attempting to validate the Statin Intolerant NMA. However, the ERG was unable to replicate the results presented by the company. This could be because: • Incomplete or inaccurate data were provided • The company incorrectly used standard deviations in the analyses that required the use of standard errors (although when the ERG estimated the standard errors the results obtained were still substantially different)	"*At the request of the ERG, the company provided the code and the data set for its NMAs for the ERG to validate its analyses. The ERG started by attempting to validate the Statin Intolerant NMA. However, the ERG was unable to replicate the results presented by the company* ***despite being provided with the full code and data used within the analysis***. *This could be because:* • Some unforeseen difference in the way the analysis is specified and run between the company's use of R and JAGS, and the ERG's use of OpenBUGS. *However, in attempting the validation the ERG became aware of the following issues:* • *The random effects NMA converges on the posterior distribution after a substantial*	The statement suggests that insufficient information or inaccurate information was provided to replicate the Company's NMA, although the company provided all code required to replicate the analysis and provided the full data required to run the analysis that was utilised in the Company's NMA. The data used for the Company's NMA, including study name, treatment arm, and the baseline LDL-C and change in LDL-C were presented in the Company's response to ERG clarification questions. Appendix section A.8, Tables 37 and 38). There were the exact tables used for the analysis. The correct use of standard errors were applied within the NMA, these were either taken directly from the publications for the included studies or calculated as required using published data. The Company is unsure of why the	This is not a factual inaccuracy.

• Some unforeseen difference in the way the analysis is specified and run between the company's use of R and JAGS, and the ERG's use of OpenBUGS However, in attempting the validation the ERG became aware of the following issues: • The random effects NMA converges on the posterior distribution after a substantial number of iterations (1.2 million in the company's base case) • The results appear to be sensitive both to the prior distributions specified and to the number iterations the model is run The ERG notes that these issues are not present when the company's NMA is run without the covariate adjustment for baseline LDL-C level. This further supports the view of the ERG that the correlation between treatment effect and baseline LDL-C would be more appropriately captured by following the recommendations in NICE DSU TSD 20."	*number of iterations (1.2 million in the company's base case);* ***however, within the Company's NMA the required number of simulations and burn-in were used.*** • *The results appear to be sensitive both to the prior distributions specified and to the number iterations the model is run.* ***Although the posterior probability plots and Company's reporting that comparability between frequentist and Bayesian results indicates that there was not an issue with the selection of the prior distribution.*** *The ERG notes that these issues are not present when the company's NMA is run without the covariate adjustment for baseline LDL-C level."*	ERG could not replicate the results as the JAGs code is comparable to the OpenBugs code, however, the application of the code is the only valid explanation for the ERG not being able to replicate the Company's NMA. Whilst we agree with the ERG that a large number of iterations were required to achieve convergence, as per the Company's response to ERG clarification questions, convergence was reached, See figures 14 and 23. Without the inclusion of this information, the text indicates that convergence was an issue in the Company's NMA, which it was not. It is correct that the use of different priors such as an informative prior, would provide a different set of results, this is known to be the case and is a feature of Bayesian analysis. However, without providing further context, this statement is misleading. The Company utilised a non-informative prior, and provided information about the prior used to the ERG. The fact that the ERG could not replicate the results with the covariate does not indicate that the inclusion of a covariate within the models was incorrect and does not support that a different method would have been more appropriate. The company performed frequentist results for validation and the Bayesian results were comparable,	

		(Company evidence submission, Document C, Section D.2.8). Further, the analysis performed by the company was validated by an independent statistician. Also see Issue 21.	

Issue 22 Misleading statement regarding subgroup analyses presented in the Company's cost-effectiveness evaluation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101, section 4.2.2 states "*An additional and related area of concern is that the company did not provide cost-effectiveness results for the subgroups specified in the NICE final scope (presence or risk of CVD, HeFH, statin intolerance and severity of HC).*"	The statement should be corrected to read: *"An additional and related area of concern is that the company did not provide cost-effectiveness* ***results for subgroups defined by the individual variables*** *specified in the NICE final scope (presence or risk of CVD, HeFH, statin intolerance and severity of HC)."*	See Issue 16.	This is not a factual inaccuracy.

Issue 23 Inaccurate statement regarding the Delphi Panel

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101, section 4.2.2 states: *"However, the ERG notes that the company is basing their information on a European panel while the eligibility criteria applied*	The ERG statement should be removed or amended to correctly reflect that this was a Delphi panel consisting of only UK clinicians.	Currently wording in the ERG report misrepresents the information available to the ERG in the model and Company evidence submission (for instance, Table in the Reference section page	Thank you for highlighting this inconsistency, we have made the suggested amendment. Please note that in response to clarification question B8, it was stated, "*clinical expert opinion from*

by the company aligns with NICE recommendations. Ideally, the company would have UK specific data to base this on." This statement is incorrect, it was a UK Delphi panel as stated in the Company evidence submission (for instance, Table in the Reference section page 212).		212).	*the Daiichi Sankyo Delphi panel (Daiichi Sankyo Europe data on file, 2019)*."

Issue 24 Misleading statement regarding the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102, section 4.2.2 states and Page 22 also states: *"This approach contradicts the company's decision to separate populations according to PCSK9i eligibility using NICE recommendations."* This is misleading. In the Company submission, the data used for positions 2b and 4b only include patients fulfilling the NICE PCSK9i criteria because (almost) no patients not fulfilling the criteria will receive treatment in clinical practice due to reimbursement restrictions. However, the UK Delphi panel used in the	The ERG statement should be removed or amended to correctly reflect that the statement that this contradicts the company approach is an ERG opinion.	The current wording is misleading.	This is not a factual inaccuracy. On page 102 it is made clear that this is an ERG opinion, "*the ERG considers that the company's rationale contradicts the company's separation of the populations into subpopulations according to PCSK9i eligibility*."

Company submission and real-world NHS data indicate that most patients fulfilling the criteria are currently not getting treatment. Hence, we believe there is no contradiction as these patients (fulfilling the criteria but not receiving PCK9i treatment) are also used to inform the baseline LDL-C level in the populations 2a and 4a.			

Issue 25 Misleading statement regarding the effect of bempedoic acid on triglyceride levels

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115, section 4.2.5.3 states: "*Furthermore, the ERG's clinical experts expressed concerns that bempedoic acid may increase triglyceride levels and reduces HDL levels (see Section 3.3.1).*"	This sentence should be removed	The Company believes that this statement is speculative and is not based on any factual evidence. Triglyceride (TG) results were presented in Table 27 and Table 28 of the Company evidence submission; TGs and HDL-C levels from baseline are presented among the lipid parameters as secondary outcomes in the CSRs and manuscripts of the pivotal trials. Overall, results of HDL-C and TGs in studies CLEAR-Harmony, CLEAR-Serenity, CLEAR-WISDOM and CLEAR-Tranquility as well as FDC-053 trial were consistent. The impact of bempedoic acid on HDL-C and TGs was minimal; no consistent, clinically meaningful changes in TGs were identified and an approximate 4 to 6% reduction in HDL-C (representing an	This is not a factual inaccuracy.

		absolute decrease in HDL-C of 2 to 3 mg/dL) is not likely to be clinically meaningful. • Changes from baseline in triglyceride levels were comparable between bempedoic acid and placebo in CLEAR-WISDOM (see Goldberg et al, 2019 supplementary material) • Changes in TG levels were modest and comparable between treatment groups (median change: -1.4% bempedoic acid vs +7.8% placebo) in CLEAR-Tranquility (see Ballantyne et al, 2018). HDL-C decreased from baseline to week 12 in both the bempedoic acid and placebo treatment groups, although to a large extent in the former (-7.3% vs -1.4%)(see Ballantyne et al, 2018) • Changes in TG were minimal and similar with bempedoic acid and placebo in CLEAR-Serenity. Effects on HDL-C were negligible (<6% change from baseline in both treatment groups) (see also Laufs et al, 2019) • Changes from baseline in HDL-cholesterol and TGs ere modest (<10%) in all treatment groups in the FDC trial (see also Ballantyne et al, 2019)	

Issue 26 Inaccurate statement regarding the reporting of the CV-related costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 135, section 4.2.10 states: *"The company used the mean 6-month acute event costs and the post-acute event costs from months 7 to 36 (i.e. over a period of 30 months) from Danese et al. 2017 to estimate acute costs in the model by summing the first 6 month acute costs and half of the 7-36-month post-event costs. Given that this cost is applied for the first year after the event in the model, this approach assumes that half of the total post-event costs estimated in Danese et al. 2017 (incurred over 15 months) would be accrued in the 6-12-month period after the event. This overestimates the costs of acute events in the analysis. Furthermore, given that the company did not adjust the post-event costs to remove the 6-12-month costs from the post-event estimate, the company's approach double counts CV-related costs in the analysis."* Page 23, section 1.3 also states: *"In addition, by using the estimates obtained from Danese*	The ERG statement should be removed or amended to correctly reflect that, in the Company submission, 6 months of the annualised (6-36 months) data is used to reflect the health state cost 6-12 months after a CV event. Further, as annualised data are used, adjustment of the long-term health state costs should not be considered relevant according to the stated rationale.	The current wording in the ERG report misrepresents the information available to the ERG in Danese et al. 2016 and in the Company submission (for instance, in the Economic model, Costs-sheet, cell P99:115).	Thank you for highlighting this inaccuracy. All text in the ERG report related to this issue has been amended. The calculations in the model reflect the amended text, therefore no changes are needed in the model.

et al. 2017 at different time points, the company's approach double counts CV-related costs in the analysis (Section 4.2.10.6).” Both the ERG and the company agree that a cost is need to be added to the short-term cost (6-months) to capture the full cost of the first year (12 months) after a CV event. The long-term cost reported in Danese is annualised. Hence using 6 months (50% of the annualised cost) of the long-term data (6-36 months) could be considered a reasonable approach as this will sum to 12 months. Both the ERG and the Company think it is valid to apply a constant monthly rate for the 6-36 months costs. It would not be valid to remove anything from the long-term cost because this in an annualised cost.			

References

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Toth PP, Worthy G, Gandra SR, Sattar N, Bray S, Cheng LI, et al. Systematic review and network meta-analysis on the efficacy of evolocumab and other therapies for the management of lipid levels in hyperlipidemia. J Am Heart Assoc. 2017 Oct 2;6(10).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Table 1. List of abbreviations and acronyms

ALI	Alirocumab
ASCVD	Atherosclerotic cardiovascular disease
BA	Bempedoic acid
BA/EZE FDC	Bempedoic acid / ezetimibe (180mg/10mg tablet) fixed dose combination pill
CG	Clinical guidance
CHMP	Committee for Medicinal Products for Human Use
CV	Cardiovascular
CVD	Cardiovascular disease
ERG	Evidence review group
EVO	Evolocumab
EZE	Ezetimibe
FDC	Fixed-dose combination
HDL-C	High-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HRQOL	Health-related quality of life
HsCRP	High-sensitivity C-reactive protein
ICER	Incremental cost-effectiveness ratio
IS	Ischemic stroke
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LLTs	Lipid lowering therapies
LS	Least squares
MI	Myocardial infarction
NA	Not applicable
NC	Not calculable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
QALY	Quality-adjusted life year
SA	Stable angina
TA	Technology appraisal
THIN	The Health Improvement Network
TIA	Transient ischemic attack
UK	United Kingdom
VLD	Very low dose
VLDL	Very low-density lipoprotein

Summary of the draft technical report

1.1 In summary, the technical team considered the following:

Issue 1 More information is needed to determine the treatment pathway in clinical practice.

Issue 2 The impact of previous ezetimibe therapy and concomitant therapy on the treatment effect of bempedoic acid (BA) is uncertain.

Issue 3 Baseline low-density lipoprotein cholesterol (LDL-C) in subpopulations 2a and 4a should be informed by patients not eligible for alirocumab (ALI) or evolocumab (EVO) in the CLEAR trials.

Issue 4 Subgroup analyses should be provided by cardiovascular (CV) risk and heterozygous familial hypercholesterolaemia (HeFH).

Issue 5 Subpopulation 2b, 4a and 4b should be evaluated as secondary prevention populations to reflect the data sources informing the analyses for these subpopulations. Relatedly, the information and the approach used to model CV events, inclusive of health-related quality of life (HRQoL), should be consistent with the definition of the modelled cohort.

Issue 6 There is methodological uncertainty in the company and evidence review group (ERG) network meta-analysis (NMA).

Issue 7 The latest data available should be used to inform decision making and give further information on whether a treatment waning effect is present.

Issue 8 Amendments made by the ERG to model HRQoL are preferred by the technical team. The information and the approach used to model health-related quality of life (HRQoL) should be consistent with the definition of the modelled cohort (see issue 5)

Issue 9 Amendments made by the ERG to model costs are preferred by the technical team.

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be fully resolved:

- The clinical evidence is based on small patient numbers and the model is based on indirect comparative evidence.
- The clinical trial evidence study populations may differ from the subpopulations of interest.
- The clinical trial evidence is not wholly reflective of bempedoic acid (BA) with ezetimibe (EZE) in combination with concomitant therapies which may be used in clinical practice, and therefore the safety profile of drugs used in combination is uncertain.

The economic analyses assume that bempedoic acid / ezetimibe (180mg/10mg tablet) fixed dose combination pill (BA/EZE FDC) is the same as BA plus concomitant EZE in terms of effectiveness and cost, and therefore the cost-effectiveness results for BA/EZE FDC and BA and concomitant EZE are equivalent.

1.3 The cost-effectiveness results presented in this report are based on list prices and do not include confidential commercial arrangements (patient access scheme/commercial access agreements) for ALI (ALI) and EVO (EVO).

1.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of:

- £29,856 per quality-adjusted life year (QALY) gained (see table 1) for BA plus ezetimibe fixed dose combination (BA/EZE FDC) versus EZE in subpopulation 2a;
- *£93,455 saved per QALY lost* (see table 2) for BA/EZE FDC versus ALI + EZE in subpopulation 2b, with BA/EZE FDC being less effective and less costly than the comparator;

- £75,437 per QALY gained (see table 3) for BA/EZE FDC versus EZE + statin in subpopulation 4a;
- *£54,250 saved per QALY lost* (see table 4) for BA/EZE FDC versus ALI + EZE + statin in subpopulation 4b. with BA/EZE FDC being less effective and less costly than the comparator.

BA/EZE FDC falls in the south-west quadrant of the cost-effectiveness plane in subpopulations 2b and 4b, meaning that BA/EZE FDC is less costly and less effective than comparator drugs. The ICER should be interpreted with caution as it represents cost savings per QALY lost. ICERs which fall in the South west plane are *represented with italics*.

These estimates do not include the commercial arrangements for ALI and EVO because these are confidential and cannot be reported here. Taking the commercial discounts into account for ALI and EVO, cost-effectiveness estimates for BA and BA/EZE FDC are within the range of what would be normally considered a cost-effective use of resources in certain scenarios, and are in the south-west quadrant of the cost effectiveness plane (BA and BA/EZE FDC being less costly and less effective than the comparators) in some subpopulations.

1.5 The end of life criteria does not apply for this technology.

1.6 The technology is not considered innovative.

1.7 No equality issues were identified by the company, consultees and their nominated clinical experts and patient experts. BA and BA/EZE FDC is an oral drug in the form of a tablet, and therefore it could be easier to administer than drugs which are injected (for example ALI and EVO).

2. Topic background

2.1 Disease background

- Mixed dyslipidaemia is characterised by elevated LDL-C and triglycerides and/or reduced or elevated high-density lipoprotein cholesterol (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.

- It is estimated that 6 in 10 adults in England have cholesterol levels above 5 mmol/litre. 15.4% of adults in the UK were estimated to have hypercholesterolaemia in 2018.

- It is estimated that approximately 7% of the population in England have been diagnosed with primary (familial and non-familial) hypercholesterolaemia, of whom about a third are receiving lipid-modifying treatment.

- Hypercholesterolaemia and mixed dyslipidaemia are associated with many comorbidities, including diabetes and cardiovascular disease (CVD) such as atherosclerotic cardiovascular disease (ASCVD).

- In addition to lifestyle changes, pharmacological lipid-lowering therapy is used in adults with raised LDL-C, with ASCVD, or those at risk of ASCVD or with presence of risk factors, such as age, diabetes and chronic kidney disease.

- Statins are the most common pharmacological treatments for lowering LDL-C levels in patients with hypercholesterolemia and mixed dyslipidaemia in the United Kingdom. These may be followed by the addition of EZE where required, and an option of either ALI or EVO for patients meeting criteria set out in TA393 and TA394 respectively. These are the only proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) currently indicated for this subpopulation.

- Statin intolerance ranges from complete intolerance of any statin at any dose or, more frequently, the inability to tolerate statins that provide optimal reductions of LDL-C.

2.2 Summary of BA authorization and action

Anticipated Mmarketing authorisation (CHMP positive opinion granted 30 January 2020)	BA is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, • alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. Bempedoic acid / ezetimibe (180mg/10mg tablet) fixed dose combination pill (BA/EZE FDC) is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe; • alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone; • in patients already being treated with the combination of BA and ezetimibe as separate tablets with or without statin. The anticipated marketing authorisation would permits use of the BA single agent tablet (but not the FDC tablet) previously to ezetimibe

Mechanism of action	BA that is a cholesterol synthesis inhibitor (inhibiting adenosine triphosphate citrate lyase). BA upregulates LDL receptors by suppression of cholesterol synthesis. It is activated by an enzyme largely found in the liver (and not in skeletal muscle). Unlike statins, it does not inhibit cholesterol biosynthesis in skeletal muscle (which can cause myotoxicity). It upregulates LDL receptors by suppression of cholesterol synthesis. The fixed-dose combination (FDC) pill contains 180 mg BA and 10 mg EZE. EZE is an NPC1L1 (sterol transporter) inhibitor, which inhibits gastrointestinal cholesterol absorption and upregulates LDL receptors.
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 ezetimibe.
Price	The list price of BA is [redacted] per pack of 28 tablets. The list price of FDC is [redacted] per pack of 28 tablets.
FDC = BA and ezetimibe fixed-dose combination; ; LDL = low-density lipoprotein Note: The economic model compares BA with concomitant EZE; which assumes the same price as FDC. The model therefore does not look at the costs of BA monotherapy.	

2.3 Treatment pathway

- The company did not anticipate BA would be used before EZE in the treatment pathway in the National Health Service (NHS) setting so therefore have not presented a case for use of BA in subpopulations 1 and 3.

- The company include the cost of BA in combination with EZE, and therefore does not consider the cost-effectiveness of BA monotherapy.

- The company positions BA and BA/EZE FDC for the treatment of hypercholesterolaemia or mixed dyslipidaemia in people with high risk of cardiovascular disease. The company defines people with high risk as people with:

    - Markedly elevated single-risk factors, in particular total cholesterol > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL), or blood pressure > 180/110 mmHg
    - Patients with FH without other major risk factors
    - Patients with DM without target organ damage, with DM duration ≥ 10 years or another additional risk factor
    - Moderate chronic kidney disease (eGFR 30-59 mL/min/1.73 m2)
    - A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD

- Of people who have high risk of cardiovascular disease, the company then positions BA and BA/EZE FDC in people previously treated with EZE who are either statin intolerant (population 2) or are maximally tolerating statins.

- A previous submission for EZE (TA385) suggested that 17.5% of people receiving statins do not achieve an adequately controlled cholesterol level and that statins are not tolerated in approximately 14.8% of people with hypercholesterolaemia.

- The company evaluates subpopulations according to their eligibility to be treated with EVO or ALI. Low-density lipoprotein cholesterol concentrations above which ALI and EVO are recommended in TA393 and TA394 are outlined below.

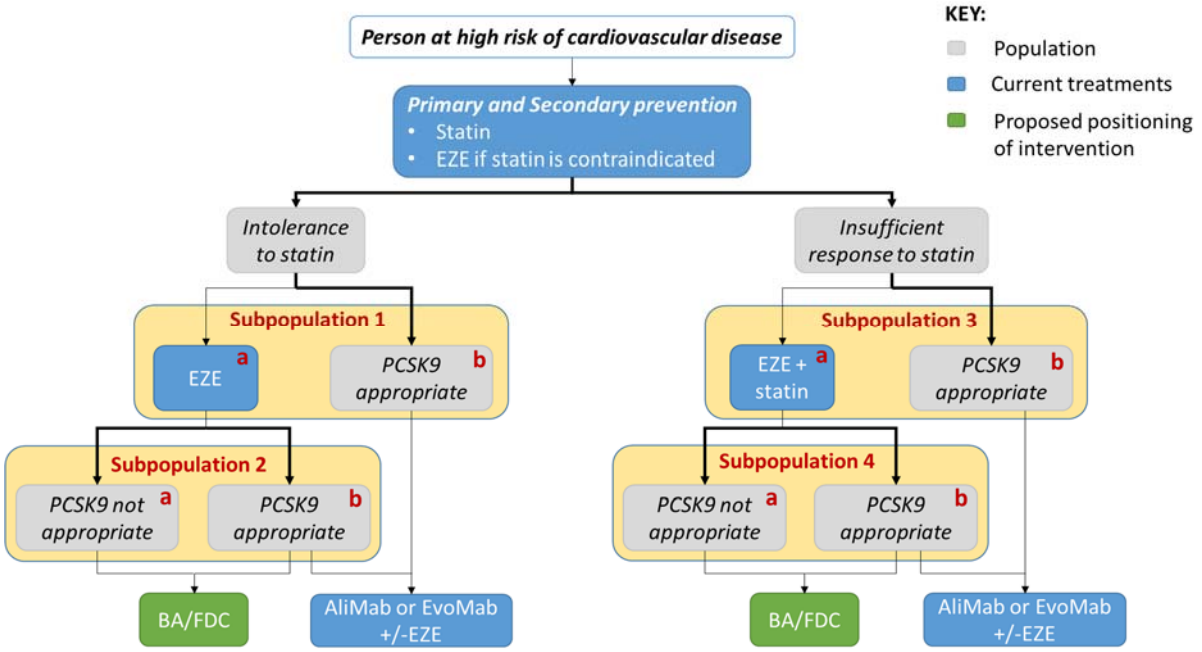
	Alirocumab and evolocumab		
	Without CVD (primary prevention)	**With CVD (secondary prevention)**	
		High risk of CVD (1)	**Very high risk of CVD (2)**
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
Primary HeFH	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 CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

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

- The figure and table below outline the treatment pathway, the subpopulations considered within the submission, the relevant comparators and summary of evidence.

Figure 1. NICE pathway and recommendations and proposed placement of BA and FDC (adapted from company submission figure 3, table 8 and table 62)



Subpopulation	Current treatment options	Previous therapy	Intervention	Study evidence for BA/FDC
2a - statin intolerant and not eligible for ALI and EVO [α]	EZE	EZE	BA +/- EZE FDC	**CLEAR Serenity:** BA versus placebo **1002-008:** BA/EZE FDC or BA alone versus EZE or placebo **CLEAR Tranquility**: BA+EZE versus placebo+EZE
2b - statin intolerant and eligible for ALI and EVO[β]	ALI or EVO +/- EZE	EZE	BA +/- EZE FDC	
4a – insufficient response to statin and not eligible for ALI and EVO[β]	EZE + statin	EZE + statin	BA +/- EZE FDC	All study populations had previous statin therapy +/- LLTs: **CLEAR Harmony:** BA versus placebo **CLEAR Wisdom** BA versus placebo **1002FDC-053:** BA/EZE FDC or BA alone versus EZE or placebo **1002-009:** BA versus placebo
4b - insufficient response to statin and eligible for ALI and EVO[β]	ALI or EVO + statin +/- EZE	EZE + statin	BA +/- EZE FDC	

ALI = alirocumab; BA = bempedoic acid 180 mg oral once daily; EVO = evolocumab; EZE = ezetimibe 10 mg once daily; FDC = bempedoic acid and ezetimibe fixed-dose combination; NICE = National Institute for Health and Care Excellence; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[α] Evidence for this subpopulation evaluates a predominately primary prevention population.
[β]Evidence for these subpopulations evaluates predominately secondary prevention populations.
Sources: TA393; CG181; TA394; CG71.

2.4 Clinical evidence

Study title (year of publication)	CLEAR Tranquility (2018)	CLEAR Harmony (2019)	CLEAR Serenity (2019)	CLEAR Wisdom (2019)	1002FDC-053 (2019)	1002-008 (2016)	1002-009 (2016)
Study design	RCT, phase 3	RCT, phase 3	RCT, phase 3	RCT, phase 3	RCT, phase 3	RCT, phase 2	RCT, phase 2
Population hypercholesterol-emic patients	Statin-intolerant	Maximally tolerated statin therapy either alone or in combination with other LLTs	Statin-intolerant.	Maximally tolerated statin therapy either alone or in combination with other LLTs	Maximally tolerated statin therapy either alone or in combination with other LLTs	Statin-intolerant	Patients on stable statin therapy
Intervention(s)	BA with ezetimibe (separate pills)	BA	BA	BA	BA/EZE FDC or BA alone	BA with ezetimibe (separate pills) or BA alone	BA
Comparator(s)	Placebo with ezetimibe	Placebo	Placebo	Placebo	Ezetimibe, placebo	Ezetimibe	Placebo
Background therapy	LMT including no/low dose statin and various others	LMT including moderate-/high-intensity statin, ezetimibe	LMT including no/low-dose statin or non-statin	LMT including moderate-/high-intensity statin, PCSK9i and various others	No/moderate-/high-intensity statin	No statin	Low-/moderate-intensity statin
Outcomes specified in the decision problem	LDL-C	LDL-C, non-HDL-C, TC, apolipoprotein B, and hsCRP from baseline; AE	LDL-C, non-HDL-C, HDL-C, TC, apolipoprotein B, triglycerides, and hsCRP from baseline; CV rates; AE	LDL-C, non-HDL-C, TC, apolipoprotein B, and hsCRP from baseline; CV event rates; AE	LDL-C	LDL-C, non-HDL-C, HDL-C, TC, triglycerides, VLDL, apolipoprotein B, triglycerides, and hsCRP from baseline; AE	LDL-C, non-HDL-C, HDL-C, TC, triglycerides, VLDL, apolipoprotein B, triglycerides, and hsCRP from baseline: AE

Abbreviations: AE, adverse events; Apo B, apolipoprotein B; CV, cardiovascular; BA/EZE FDC, bempedoic acid and ezetimibe fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapies; LMT, lipid modifying therapy; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor; RCT, randomised controlled trial; TC, total cholesterol; VLD, very low dose; VLDL, very low-density lipoprotein.

2.5 Key results

Table 2. Difference of least squares (LS) mean % change LDL-C, mg/dL (from baseline to week 12) for in statin intolerant subpopulation:

Efficacy parameter	CLEAR Serenity (1002-046)	CLEAR Tranquility (1002-048)	Study 1002-008		
	Difference of LS means (95% CI; P value)		LS mean % change from baseline to week 12 (SD)		
	BA vs Placebo	BA + EZE vs Placebo +EZE	BA + EZE	BA (n = 99)	EZE (n = 98)
LDL-C, mg/dL	-21.4 (−25.1 to −17.7; < 0.001)	−28.5 (−34.4 to −22.5); < 0.001	-49.61 (5.98)	−31.41 (12.90)	−19.82 (10.02)

Table 3. Difference of least squares mean % change LDL-C, mg/dL (from baseline to week 12) for in maximally tolerated statin subpopulation:

Efficacy parameter	CLEAR Harmony (1002-040)	CLEAR Wisdom (1002-047)	1002FDC-053	Study 1002-009		
	Difference of LS means (95% CI; *P* value)			LS mean % change from baseline to week 12 (SD)		
	BA vs Placebo	BA vs Placebo	FDC vs. BA	BA	Placebo	P value
LDL-C, mg/dL	−18.1 (−20.0 to −16.1; < 0.001)	−17.4 (−21 to −13.9; < 0.001)	−19.0 (−26.1, −11.9); < 0.001	−24.3 (4.2)	−4.2 −(4.2)	< 0.0001

Table 4. Company's updated NMA results in statin-intolerant patients

Treatment	Estimated difference in % change in LDL-C from baseline compared to ezetimibe		
	Mean	95% CrIs	*P* value
BA	[redacted]	[redacted]	[redacted]
BA+EZE	[redacted]	[redacted]	[redacted]
EVO	[redacted]	[redacted]	[redacted]
EVO+EZE [a]	[redacted]	[redacted]	[redacted]
ALI (75mg)	[redacted]	[redacted]	[redacted]
ALI (150mg)	[redacted]	[redacted]	[redacted]

CrI = credible interval; EVO = EVO; LDL-C = low-density lipoprotein cholesterol.
Note: Other treatments were included in the evidence network but were not reported in the table as they are not comparators. P value relates to the difference in percentage change from baseline in LDL-C compared with EZE. No trial data were identified for ALI + EZE.

[a] EVO + EZE estimates are based on data for 30 patients in GAUSS (Sullivan et al., 2012).
Results used in the cost-effectiveness analyses presented in the submission are highlighted in bolded text

Table 5. Company's updated NMA results in maximally tolerated statin patients

Treatment	Estimated difference in % change in LDL-C from baseline compared to ezetimibe		
	Mean	95% CrIs	*P* value
BA+statin	[redacted]	[redacted]	[redacted]
BA+ezetimibe FDC+ statin	[redacted]	[redacted]	[redacted]
EVO+statin	[redacted]	[redacted]	[redacted]
ALI (75mg) +statin	[redacted]	[redacted]	[redacted]
ALI (150mg) +statin	[redacted]	[redacted]	[redacted]
ALI (75mg) +statin+ezetimibe	[redacted]	[redacted]	[redacted]
ALI (150mg) +statin+ezetimibe	[redacted]	[redacted]	[redacted]

ALI = ALI; CrI = Credible interval; EVO = EVO; LDL-C = low-density lipoprotein cholesterol.

Note: Other treatments were included in the evidence network but were not reported in the table as they are not comparators. *P* value relates to the difference in percentage change from baseline in LDL-C compared with EZE. Results used in the cost-effectiveness analyses presented in the submission are highlighted in bolded text

2.6 Model structure

ASCVD = arteriosclerotic cardiovascular disease; CVD = cardiovascular disease; MI = myocardial infarction; TIA = transient ischaemic attack.

2.7 Key model assumptions

The model makes the following assumptions:

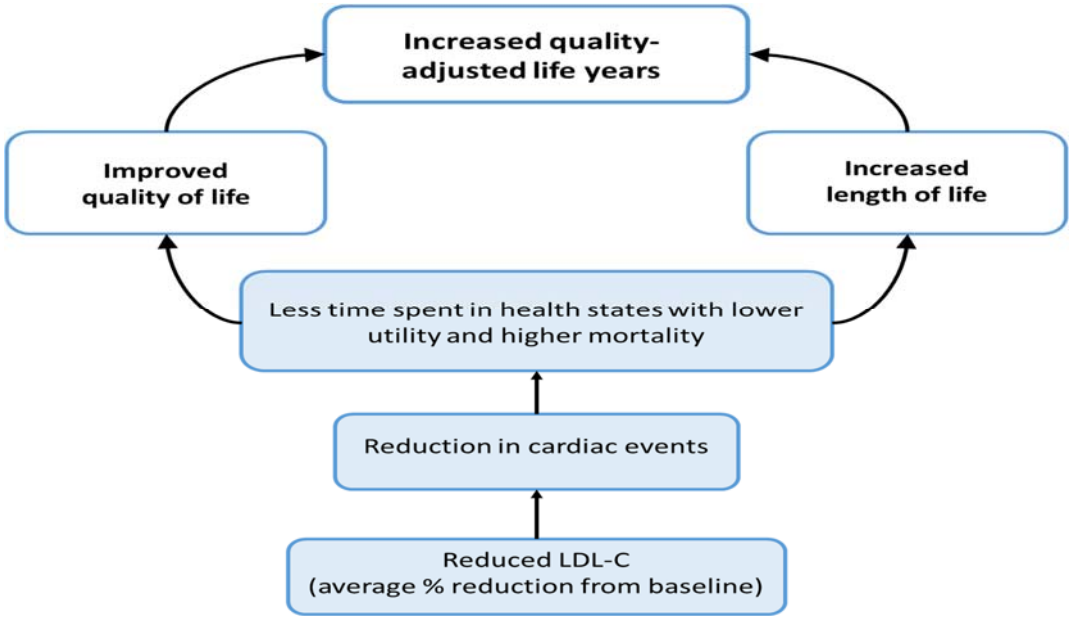
- The FDC price and treatment effect is assumed equivalent to that for BA with concomitant EZE.
- LDL-C is a surrogate outcome for CV events. LDL-C reduction is based on CLEAR studies and network meta-analysis of EZE, ALI, and EVO.

- CV risk based on The Health Improvement Network (THIN) UK data for secondary prevention and QRISK3 for primary prevention.
- Patients do not benefit from continuation of treatment effects after treatment discontinuation. Treatment discontinuation based on long-term data of EVO in the base case.
- A discontinuation rate of 6.7% was applied for all drugs.
- Oral drugs had an annual pharmacy prescription cost, whereas ALI and EVO had a one off £42 administration cost at the beginning of treatment.

2.8 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.

Figure 2. Quality-adjusted life years



1. Key issues for consideration

Issue 1 – The clinical pathway

Questions for engagement	1. What concomitant therapy would people having bempedoic acid or BA/EZE FDC receive in clinical practice for subpopulations who are: a) statin intolerant and have had previous EZE? b) in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin? 2. What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO? 3. Would ALI or EVO be used alone or in combination with EZE in clinical practice? 4. Would ALI or EVO be used after bempedoic acid if there is insufficient response? 5. If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with bempedoic acid? 6. If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO? 7. If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE? 8. Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or LDL therapy when commencing bempedoic acid? 9. Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO? 10. In which circumstances would BA be considered as monotherapy? 11. Under which circumstances would a patient treated with EZE discontinue treatment with EZE? 12. Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy? 13. Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have BA therapy? 14. Under which circumstances would a patient treated with a maximally tolerated statin discontinue treatment with a statin?

Background/description of issue	The ERG considered that the evidence included within the company submission was not reflective of the intended positioning of BA and BA/EZE FDC in clinical practice. To understand if the evidence is appropriate for decision making, the technical team would like to clarify the clinical pathway of BA for treating primary hypercholesterolaemia or mixed dyslipidaemia. The technical team would also like to clarify if the treatment pathway may change with the introduction of bempedoic acid and what treatments may be used after BA if there was insufficient response.
Why this issue is important	Determination of clinical practice relates to several of the key issues outlined in this report. For example, understanding the treatment pathway informs the discussion on whether the studies in the ERG or company NMA are generalisable to clinical practice (please see issue 6). Information on the treatment pathway may also be useful to understand which combinations of therapies are used and allow an assessment on whether safety data is available for all potential combinations of treatment. A professional organisation has commented that options for the secondary prevention of cardiovascular disease currently include statins, EZE and PCSK-9 inhibitors. For the primary prevention of cardiovascular disease current options include: statins; EZE; PCSK-9 inhibitors and plasma apheresis. The professional organisation also commented that the definition and field of statin intolerance is subjective and uncertain, however, BA and BA/EZE FDC may offer an alternative treatment for statin intolerant patients.
Technical team preliminary judgement and rationale	The technical team believes it is plausible that EZE and maximally tolerated statin treatment may be continued with the addition of a new therapy (for example, BA, EVO or ALI) but are unclear on whether this common practice and the characteristics of the patients who are likely to be offered each treatment option in isolation or in combination. If this is common-place within UK practice, studies which report high proportions of people on who have had previous and/or concomitant EZE therapy are therefore more likely to be generalisable to current clinical practice (see issue 2).

Issue 2 – Impact of previous and/or concomitant therapy on the treatment effect of BA

Questions for engagement	15. Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE? 16. To what extent does previous EZE therapy affect the treatment effect of BA? 17. To what extent does concomitant statin therapy affect the treatment effect of BA?

Background/description of issue	**The study populations differ from the proposed population of interest due to having limited previous therapy with EZE:** The company has positioned BA and FDC for people who were previously treated with EZE (EZE) (i.e. subpopulation 2 and 4). The marketing authorisation permits use of the BA single agent tablet (BA), but not the FDC tablet, previously to EZE. The ERG's clinical experts support the company's view that BA or FDC is unlikely to be used before EZE. With the exception of the CLEAR Tranquility study, the 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 (LLTs). The ERG's clinical experts reported that in clinical practice, patients would be expected to continue on LLTs alongside BA and therefore studies with washout periods or lacking concomitant EZE do not reflect how BA would be used in the company's proposed positioning in clinical practice. The company did not present the clinical data separately for subpopulations who were previously treated with EZE. The company considers that the full population of the BA trials, where there is a mix of patients who were and who were not treated with EZE at baseline, are representative of, and generalisable to, the subpopulation who were previously treated with EZE. The company provides data from a pooled analysis of the patients previously treated with EZE in CLEAR Harmony and CLEAR Wisdom (population 4) and CLEAR Tranquility and CLEAR Serenity (population 2) to support their argument that the BA treatment effect is unrelated to previous EZE therapy. The pooled analyses included BA patients and placebo patients who were treated with concomitant EZE. The company compared post-hoc subgroup results of mean percentage LDL-C reduction for the groups with and without previous treatment with EZE therapy, and the ERG acknowledged results were similar between the two subgroups. However, for analyses of subpopulation 2 and 4, the ERG does not consider the respective [redacted]% and [redacted]%difference between the presence and absence of EZE use at baseline to be clinically insignificant, given that the trials were not designed or powered sufficiently to detect a statistical difference for this comparison. The ERG comment that the pooled analyses had small patient numbers, had *post hoc* subgroup selection and lacked methodology detail, and therefore the ERG did not consider the results of the pooled analyses sufficiently supported the company's conclusion. The ERG consider that the full trial populations (with the exception of CLEAR Tranquility) that inform the NMA do not reflect people previously treated with EZE, (for whom the company is positioning BA and FDC). Because of this, the ERG considers the results of both the company's original or updated

	NMA, and therefore the cost-effectiveness analyses on which these are based, to not address the population of interest. Furthermore, the ERG consider the variability in the study populations exposure to baseline and/or concomitant therapy a potential cause of clinical and statistical heterogeneity in the NMA, which adds to uncertainty to the conclusions. The ERG therefore used a restricted set of studies to inform its own NMA (see issue 6). **Concomitant lipid lowering therapy** It is expected that subpopulation 2a would not have statin therapy, however, the ERG comment that the relevant study populations may have had concomitant LLT use for primary prevention and it is likely that subpopulations 2b, 4a and 4b were given LLTs for secondary prevention. For subpopulation 4, the ERG commented that over 30% of patients were on no statin at baseline in the FDC trial. The company presented subgroup analyses for CLEAR Harmony and CLEAR Wisdom based on intensity of statin therapy; both studies have non-significant p-values for tests of subgroup interaction based on intensity of statin therapy (p = 0.18, and p = 0.51, respectively). In CLEAR Harmony the mean difference for change from baseline LDL-C to week 12 in the low or moderate statin intensity subgroup was -20.0 (-22.8 to -17.3) and in the high statin intensity subgroup it was -17.5 (95% CI -20.0 to -14.7). The ERG does not consider these data sufficient to either prove or disprove a difference in treatment effect based on baseline statin intensity as the subgroups were not powered to detect treatment differences. However, the ERG agrees that the difference based on the underpowered subgroup analysis is statistically non-significant.
Why this issue is important	There is uncertainty about whether the clinical evidence is reflective of the subpopulations of interest. The impact of previous EZE therapy and concomitant statin therapy on the treatment effect of BA is uncertain. This introduces uncertainty in whether BA is a cost-effective option in people who have previously been treated, and/or continue treatment with EZE use or who have continued statin therapy.
Technical team preliminary judgement and rationale	The technical team acknowledge the potential for previous and concomitant therapy to have an impact on treatment effect, as well as recognise that differences in the study populations' treatment history and concomitant therapy could contribute to the heterogeneity within the company NMA.

	There is uncertainty about whether the findings of the analyses presented by the company are generalisable to the subpopulations of interest. This increases the uncertainty in the assessment of whether BA is a cost-effective option following EZE or if used with a statin (when maximally tolerated).

Issue 3 – Baseline LDL-C in subpopulations that are not eligible for ALI and EVO

Questions for engagement	18. In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it? 19. Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO)?
Background/description of issue	The CLEAR trials contained people who were and weren't eligible for ALI and EVO (subpopulations 2b/4b were eligible and 2a/4a were not). The company used the baseline LDL-C levels of all patients in the CLEAR trials in the model. However, baseline LDL-C levels in subpopulations 2a/4a were higher than the levels of patients from subpopulations 2b/4b in the CLEAR trials (subpopulation 2, [redacted]; subpopulation 4[redacted]; subpopulation 2a, [redacted]; subpopulation 4a, [redacted]). The company explained in their clarification response that their approach of using LDL-C levels from all patients in the CLEAR trails was appropriate because only limited numbers of patients eligible for ALI/EVO treatment actually receive ALI/EVO treatment (according to clinical expert opinion from a delphi panel). ERG clinical experts suggested that access to ALI/EVO treatments is variable across different centres and regions. However, if a centre had access to ALI/EVO treatments, the majority of patients eligible for ALI/EVO treatment from that centre would receive ALI/EVO treatment. The ERG notes that the eligibility criteria applied by the company aligns with NICE recommendations. However, it considers that the company's rationale contradicts the company's separation of the populations into subpopulations according to ALI/EVO eligibility. The ERG preferred a scenario whereby baseline LDL-C levels are taken from patients who were not eligible for ALI/EVO.
Why this issue is important	The assumption regarding the baseline LDL-C levels of a ALI/EVO treatment has a greater impact on the cost-effectiveness estimate for subpopulation 4a in comparison to 4b. However, changing the

	baseline LDL-C levels with ALI/EVO has potential to impact on whether BA is viewed as a cost-effective option.
Technical team preliminary judgement and rationale	The technical team agree with the ERG suggested amendments in the use of data specific to the subpopulation of interest in the estimation of baseline LDL-C levels. The technical team pose this as a key issue for technical engagement to understand if there is clinical opinion that concurs with that of the ERG experts.

Issue 4 – Subgroup analyses by CV risk and HeFH

Questions for engagement	20. Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)? 21. Is it appropriate to assume that treatment effect is similar in people with different CV risk? 22. Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?
Background/description of issue	**Overview** People with hypercholesterolaemia are at increased risk of CVD because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). The focus of primary prevention is on delaying or preventing the onset of CVD, whereas secondary prevention focuses on reducing the impact of the disease previously to any critical and permanent damage. CV risk algorithms suggest that once you have a CV event, you are at greater risk of having a second, and more severe, second event. The company defines CV risk according to number of risk factors, as outlined by The European Atherosclerosis Society (EAS)/ European Society of Cardiology (ESC) guidelines, where hypercholesterolemia and high levels of total cholesterol were reported to be closely linked to the level of CV risk. The final scope for this appraisal identified that the presence or risk of CVD and the subgroup of people with heterozygous familial hypercholesterolaemia were important. These subgroups also inform the basis of the recommendations for related technology appraisals for EVO and ALI (TA394 and TA3943 respectively). These subgroups are important because of expected different baseline risks of mortality and CV events, as well as HRQoL (see issue 5b). People with CVD have a higher

	risk of CV events, and so would be expected to gain more total QALYs from treatment than those without CVD for an intervention with a similar relative risk reduction. Furthermore, different resource use may be expected for these different subgroups. Primary prevention interventions, in comparison with secondary prevention measure, may have a greater long-term impact in reducing the health and cost burden associated with CV (and recurrent CV) events. **Subgrouping by HeFH** The ERG reports that clinical experts stressed that HeFH, non-familial hypercholesterolaemia (HC) and mixed dyslipidaemia each have distinct lipid profiles which may require different types and levels of treatment, and a common treatment effect (for LDL-C, non-HDL-C and CV outcomes) should not be assumed across them. The company did not present subgroup analyses based on presence of HeFH. In the economic model, the company modelled a high proportion of patients without HeFH [redacted] in each subpopulation. The company clarified that subgroups, such as patients with HeFH, were too small to be analysed separately. However, the company also used data from the subgroup analyses to demonstrate similar efficacy across groups such as patients with and without HeFH. The ERG considers many of the subgroup analyses provided by the company to be associated with low patient numbers and underpowered to detect between-subgroup differences in treatment effectiveness. The ERG report that the 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 the other four BA studies. The ERG summarise that it was generally unclear how many patients had HeFH in most of the statin intolerant subpopulation studies and in maximally tolerated statin population studies, and that the small number of HeFH patients recorded in the CLEAR studies does not substantiate the company's assumption that the overall reduction in LDL-C is equally relevant for all populations. The ERG note that a high proportion without HeFH 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. For these reasons, the ERG prefers to assume all subpopulations are representative of patients without HeFH. **Subgrouping by CV risk** The company did not present subgroup analyses based on CV risk. The ERG notes that all patients in CLEAR Harmony, CLEAR Wisdom and Study 1002FDC-053 were required to be at high risk of CVD but they were not all necessarily secondary CV prevention patients (considered high risk due to existing CVD or previous CV events). In CLEAR Wisdom 4% of patients were primary prevention and 96% were secondary prevention and/or HeFH. In CLEAR Serenity over 60% of patients were primary prevention. The ERG notes from the NCEP ATP-III risk category baseline data reported for the Phase 2 studies that approximately 40% of patients were low risk and approximately 20% were at high or very high risk of CV events. The company did not present any baseline CV risk data for CLEAR Tranquility. The ERG note that a 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. This issue links to issue 5b because the lack of clarity regarding CV risk links to the suitability of approach to modelling the subpopulations as primary prevention, secondary prevention or mixed prevention populations
Why this issue is important	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. It is also unclear how the ICER would be different for subgroups defined by these characteristics.
Technical team preliminary judgement and rationale	The technical team agree with the ERG that cost-effectiveness results by subgroup should be provided by the company in order to reflect the patients entering the model and to allow for consistent decision making with previous NICE appraisals.

Issue 5 – Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations

Questions for engagement	23. What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice? a) For people who are statin intolerant and not eligible for EVO or ALI (population 2a)?

	b) For people who are statin intolerant and eligible for EVO or ALI (population 2b)? c) For people who are treated with a maximally tolerated statin and eligible for EVO or ALI? d) For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI? 24. Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI? 25. Is it appropriate to generalise between primary and secondary prevention populations? 26. Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort? 27. How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?
Background/description of issue	The company present analyses for a mixed cohort of primary and secondary prevention patients for all the subpopulation groups. The ERG note that [redacted] , [redacted] and [redacted] of patients in subpopulations 2b, 4a and 4b, respectively, as well as the study population in in Luengo-Fernandez *et al*. 2013a (used to derive the utility values for TIAs) had a history of previous CV events and as such these three subpopulations reflect a secondary rather than a primary prevention population. The ERG considers there to be limited data for subpopulation 4 of patients on lipid lowering therapy for primary prevention or low risk of CV disease. The CLEAR Serenity statin intolerant subpopulation is known to be mixed with over 60% primary prevention. The ERG considers that including a small proportion of primary prevention patients in these subpopulations is of limited benefit as it causes unnecessary "noise" (due to the additional complexities required to model primary and secondary prevention patients in the same model) and potentially leads to inappropriate conclusions in a primary prevention population, for which there is little data. With this in mind, the ERG considers the structure of the company model in regard to baseline CV risks applied within the model, the approach of modelling subsequent events and HRQoL to not be reflective of a secondary prevention population. In the ERG scenario, secondary

	prevention patients would be allocated into a starting health state based on the proportions based on Ward *et al.* 2007. For subpopulation 2a, the majority (around [redacted]) of patients did not have a CV history at baseline and therefore the ERG's preference is to model subpopulation 2a as a primary prevention population. **Secondary prevention patient should enter the model in a different place to primary prevention patients** On the predication that subpopulation 2b, 4a and 4b are secondary prevention patients, the ERG disagrees with the company's approach of allocating secondary prevention patients to enter the model in one of the 0 to 1 year-post CV event health states, incurring the costs and benefits for an acute event. The ERG considers it more appropriate to allocate the secondary prevention cohort to enter the model in the 3-year+ post-event state, associated with post-event costs and benefits, until a new event occurs. An additional and related area of concern is that primary events and recurrent events (two or more CV events) are associated with the same impacts on costs and benefits in the model, despite clinical expert opinion that recurrent events have larger impacts compared with primary events. Therefore, the ERG's base-case and subsequent analyses assign subpopulations 2b, 4a and 4b to begin the model in the 3-year+ post-event state.
Why this issue is important	The appropriateness of using efficacy data from mainly a secondary prevention population to infer efficacy of the intervention in a primary prevention population is unclear. If treatment effect is derived for a secondary population, but applied to a primary prevention population, it may overestimate the absolute QALY gain and cost saved, which in turn may exaggerate the cost-effectiveness result over time, in part due to the prevention of recurrent events.
Technical team preliminary judgement and rationale	The technical team recognise that there is limited data to inform decision making regarding the primary prevention population (except for subpopulation 2a who are statin intolerant and when ALI and EVO are not appropriate). The ERG changes to the economic model mean that the results of analyses for 2b, 4a and 4b subpopulations reflect a secondary prevention population, and therefore committee will need to determine whether these ERG results are generalisable to the primary prevention population in their decision making.

	The technical team recognise the uncertainty associated with the lack of directly applicable efficacy data. On balance there is a preference for the ERG approach as it allows for cleaner definition of population, which is also useful when synthesising the evidence (i.e. in the NMA) for parameterising the model. The ERG approach also allows for transparency when considering generalisability of the model results to the population of interest in the decision problem, as well as consistency between the population informing treatment effect and those informing other model parameters. On this basis, the technical team feel it is appropriate that subpopulations 2b, 4a, and 4b are modelled as secondary prevention patients and agree that not all of these patients will have recently had an acute cardiac event. However, there is considerable uncertainty regarding the most appropriate approach in the absence of data informing the primary prevention cohort.

Issue 5a – CV event history and risk data are not consistent with the effectiveness data

Questions for engagement	No question posed, see key questions in Issue 5.
Background/description of issue	The ERG was concerned with the imbalance between the sources used to inform treatment effectiveness and the sources used to inform baseline characteristics and CV risks. As treatment effectiveness data were taken from the CLEAR trials, the ERG considers that CV event history and underlying CV risks in these trials may be more appropriate to use in the economic analyses. The company has responded to the ERG clarification question that this data is not yet available.
Why this issue is important	CV event history is a prognostic risk factors, and so is important in the estimation of future risk of a CV event. The baseline risk of a CV event is a key driver of the model, and may have particular relevance for population 2a which has a higher proportion of primary prevention patients An exploratory analysis undertaken by the company at clarification using a 10-year risk of 20% calculated by insertion of trial data into the QRISK2 increased the ICER from £28,521 to £35,009 in population 2a, whereas it had less impact for the other subpopulations The impact of using the QRISK3 with the CLEAR trial data on cost-effectiveness estimates is unknown.
Technical team preliminary judgement and rationale	If the company's approach is to model the primary prevention population then the CV event and risk data from the CLEAR trials, which have predominately a secondary prevention study population, may not be the most appropriate data to use. If committee preference is that these populations are

	modelled as secondary prevention populations then the ERG concerns stand and additional analyses incorporating this CV data from the clear trials would be useful. The technical team is unclear about the impact of using the baseline characteristics from the CLEAR trials on the economic model results and overall conclusions, although note that an exploratory analysis undertaken in clarification suggests that a modification in estimation of CV events is likely to have more impact on the results for subpopulation 2a than the other subpopulations. The technical team request that the company make available economic analyses which utilise the patient data from the CLEAR trials to inform CV risk in the economic model (calculated by the QRISK3 algorithm).

Issue 6 – Methodological uncertainty in the company and ERG network meta-analysis

Questions for engagement	28. Should the company's revised NMA or ERG's NMA be used for decision making?
Background/description of issue	The company included clinical effectiveness evidence from 7 RCTs of BA and/or FDC. Three of these studies (Study 1002-008, CLEAR Serenity and CLEAR Tranquility) were used in the statin intolerant NMA. The remaining 4 studies (Study 1002-009, 1002FDC-053, CLEAR Harmony and CLEAR Wisdom) were used in the maximally tolerated NMA. The company reported that the methods used for conducting the NMAs followed those recommended in the NICE decision support unit technical support documents and the ISPOR task force recommendations (Jansen *et al.* 2014). The outcome used in the company's NMAs was percentage change from baseline LDL-C at 12 weeks. **Clinical and statistical heterogeneity** The ERG considered that there was heterogeneity in the company's original NMA, and requested the company amend their NMAs during clarification. The company updated the NMA's criteria in line with the ERG's suggestions.

	The ERG and technical team note that substantial heterogeneity still remains within the company revised NMA. Clinical heterogeneity in the studies in the NMAs includes differences between studies in terms of baseline CV risk and proportions of patients with HeFH (see issue 4 and 5); as well as statin intensity and proportion of patients receiving lipid lowering therapy for primary prevention (see issue 2 and 5). In the absence of suitable subgroup analyses (for example on CV risk), the ERG considers it inappropriate to assume no difference in treatment effect across potentially important subgroups of relevance in the economic model (see issue 4 and issue 5).The ERG believe that both the company's NMAs provided by the company are unfit for decision making, due to the extent of clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for BA in patients with previous EZE use. **Other methodological uncertainties of note regarding the updated company NMAs** The ERG also noted further methodological concerns, including: • High levels of statistical heterogeneity in the results of the company's NMAs, suggesting results are unreliable. • The use of covariate adjustment for baseline LDL-C instead of using the individual patient data from the relevant CLEAR studies to establish the correlation between baseline LDL-C and treatment effect, as per the method outlined in NICE DSU TSD 20. • Further co-variate adjustments that may have reduced heterogeneity were not undertaken. The company reported the reason for this was because the variables of interest were not consistently reported across studies. • Missing studies of relevance; e.g. ODYSSEY Long Term is missing from the maximally tolerated statin NMA • Double counting of patients in the NMA through the use of 12- and 24-week data from the same study for some of the ALI trials.

	• Data are mostly limited to 12-weeks in the company's NMAs, although treatment is likely to be long-term depending on patient response and tolerance (also see issue 7). • The ERG was unable to replicate the results obtained from the company's NMAs and is unsure of the reason for this. **ERG alternative NMA** The ERG explored alternative networks to implement in the economic analyses, however, were unable to fully assess all potentially relevant studies for inclusion in the networks within the timeframe available. Additionally, the ERG did not have access to the relevant subgroup data from the BA studies. Therefore, the ERG advised that the findings of the ERG's NMAs, as well as the economic results which are informed by the NMAs, are interpreted with caution. To note, due to differences in study selection, the ERG's NMA evaluates a different comparator for subpopulation 2 than that evaluated by the company. The ERG included a study that compared BA/EZE FDC with ALI + EZE, whereas the company base case comparison was for ALI alone versus EZE. 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. This means that the results of the ERG NMA cannot be directly compared to the company NMA. The ERG included only two studies in the ERG statin intolerant NMA and they provided data only for placebo, BA and ALI 150mg. The ERG acknowledges that there are still sources of clinical heterogeneity as 12-week data are used for BA and 24-week data for ALI and 10% of patients in ODYSSEY CHOICE II may not have been statin intolerant or ineligible. However, the ERG considers the data in its NMA to more closely reflect a population with previous EZE therapy and to have substantially less clinical heterogeneity compared to the company's statin intolerant NMA. **Table A: ERG's statin intolerant NMA results and the company's updated NMA results (population 2).**

	ERG's NMA			Company's updated NMA		
Treatment	Estimated difference in % change in LDL-C from baseline compared with EZE			Estimated difference in % change in LDL-C from baseline compared with EZE		
	Mean	95% CrIs	*P* value	Mean	95% CrIs	*p*-value
BA + EZE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALI 150 mg + 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.						

The ERG included only two trials in the ERG's maximally tolerated statin NMA and they provide data for BA, placebo and ALI 150 mg Q2W in patients on concomitant EZE. The ERG notes there is a difference in outcome measurement with 12-week data used from CLEAR Harmony and 24-week data from ODYSSEY LONG TERM but the ERG considers the company should have 24-week data from CLEAR Harmony in addition to further data on BA from CLEAR Wisdom. Please also see table B.

Table B: ERGs maximally tolerated statin NMA results and the company's updated NMA results (population 4)

	ERG's NMA			Company's updated NMA		
Treatment	Estimated difference in % change in LDL-C from baseline compared with EZE			Estimated difference in % change in LDL-C from baseline compared with EZE		
	Mean	95% CrIs	*P* value	Mean	95% CrIs	*P* value
BA +EZE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALI 150 mg + 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.						

Why this issue is important	The NMAs inform the economic model. Without robust effectiveness data informing the economic model there is a high degree of uncertainty in the economic model results and conclusions. It is

	unclear how reduction of heterogenity or changes in the NMA study selection will impact on the direction of the ICER. Choice of NMA also influences the available comparisons for subpopulation 2b. The company's NMA informs comparisons of BA/FDC with ALI and EVO, whereas the ERG's NMA informs a comparison of BA/FDC with ALI+EZE. The ERG NMA did not include evidence for the comparison with EVO as it considered the evidence informing this comparison was not appropriate to include in its NMA.
Technical team preliminary judgement and rationale	The technical team are concerned that results from both the company updated NMA and the ERG NMA have considerable uncertainty. The 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. The technical team are mindful of these uncertainties and are aware that using indirect evidence introduces additional uncertainty to the clinical and cost effectiveness results. It is important to understand the extent the heterogeneity is stemming from the studies' populations' previous treatment with EZE and contaminant therapy (see issue 2). More information on the clinical pathway is required to assess which studies include the right comparators and may be generalisable to the population of interest (see issue 1, 2, 4 and 5). This in turn may assist the decision as to which of the NMAs may be most useful to decision making. On balance, until further information on the clinical pathway is obtained, the technical team prefer to use the NMA findings from the ERG in their preferred base-case due to the reduced heterogeneity within the study populations.

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

Questions for engagement	29. Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence? 30. Is it plausible that a treatment waning effect may occur with BA? 31. In clinical practice, would people stop treatment with BA after a certain time period?
Background/description of issue	**Data cut off at 12 weeks**

	The company's NMA primary efficacy outcome was percentage change from baseline LDL-C. In all the relevant BA and FDC trials, the outcome was assessed at 12 weeks. The ERG highlighted that there was data available on BA at 52 weeks in the maximally tolerated statin studies from CLEAR Wisdom and CLEAR Harmony, and 24 weeks for the statin intolerant analysis from CLEAR Serenity. However, the data analyses provided by the company, and therefore the economic results are based on a 12-week data cut. **Potential waning effect** The ERG highlight uncertainty about whether the 12-week timeframe is sufficient to inform decision making, given that primary hypercholesterolaemia and mixed dyslipidaemia are long term health conditions. Although patients in the model do not benefit from continuation of treatment effects after treatment discontinuation, there is uncertainty whether treatment effect seen at the start of treatment continues in the longer term. The economic model applied a 6.7% discontinuation rate for all drugs. The ERG considered that studies for both subpopulation 2 and 4 suggested a potential treatment waning effect. In regard to subpopulation 2, CLEAR Serenity showed that statistically significant reduction in LS mean percentage change in LDL-C with BA compared with placebo was maintained at 24-weeks ($p < 0.001$). However, reductions in LDL-C were observed at the first post-baseline study visit (week 4) and, while still showing a statistically significant reduction in LDL-C compared with placebo at 24-weeks, the ERG suggests that the mean reduction in LDL-C suggests a waning of treatment effect with BA between 4 and 24 weeks (CS, Figure 5). In addition, a similar treatment waning was seen in CLEAR Tranquility between 4 weeks and the trial endpoint at 12 weeks (CS, Figure 6). In regard to subpopulation 4, the ERG notes that the company have data on BA from the 52-week CLEAR Harmony and CLEAR Wisdom trials and therefore requested during clarification that a later 24-week time point be used for the analyses. As justification for not providing these analyses, the company noted that 12-weeks was the primary endpoint for the Phase 3 studies and the changes in efficacy for BA between weeks 12 and 24 were non-significant. The ERG also notes that Figure 1 in the clarification response demonstrates a slight waning of treatment effect with BA in terms of change in LDL-C from baseline at 24 weeks compared with at 12 weeks.

	The ERG recognise that comparators also may have different treatment waning effects and therefore it is not possible to predict the direction of any bias related to limiting the analyses to the earlier 12-week time point.
Why this issue is important	The impact on cost-effectiveness results of using a 24-week versus 12-week dataset is unclear. If a waning effect is present then the company may have overestimated the cost-effectiveness of BA. However, it is unclear whether comparators may also have treatment waning effects that could also affect cost-effectiveness. It is possible that non-significant changes in effectiveness once extrapolated over a longer time horizon may have greater than expected impact on cost-effectiveness conclusions. Any evidence of a waning treatment effect may also merit consideration of stopping rules.
Technical team preliminary judgement and rationale	The technical team and ERG agree that data from the latest time point is more reflective of its effectiveness in clinical practice given that BA is a long-term treatment. The use of data from a longer timeframe may assist committee in understanding any treatment waning effect. Therefore, technical team agree with the ERG that cost-effectiveness results utilising the 24-week data cut should be provided by the company to enable committee to compare findings against those utilising the 12-week data cut. The technical team would also be interested in understanding any stopping rules likely to be applied in clinical practice.

Issue 8 – Health related quality of life – across all populations

Questions for engagement	32. Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?
Background/description of issue	In addition to its consideration about capturing CV risk in utility values (see Issue 5b), the ERG disagreed with the company's approach to adjusting for the gender distribution. The ERG highlighted that the company adjusted for gender twice (once in the calculation of the adjusted multipliers and again in the baseline utilities) which it considered to be double counting. The ERG therefore removed the gender adjustment made by the company in the estimation of multipliers. The ERG also noted that the multipliers used in the model may not be appropriate, i.e. being above 1, for TIA events and used the baseline utility in Luengo-Fernandez *et al*. 2013a (0.86) to estimate the utility multipliers where this was the case.

	In conclusion, the ERG made the following adjustments for all of the modelled populations: • Removed the gender adjustment made by the company in the estimation of multipliers; • Used the 6 months-related utility value for acute TIAs (0.76) and the 12 months' estimate for post-TIA events (0.78) from Luengo-Fernandez et al. 2013; • Used the acute MI multiplier from Ara and Brazier in the analysis (reported in Table 24, page 127 ERG report, for subpopulations 4a, 4b and 2b, and in Table 25 for subpopulation 2a, respectively).
Why this issue is important	The adjustments made to estimation of HRQoL do not have a large impact on the cost-effectiveness estimates, however, alongside other amendments made under issue 5, they may have influential impact on whether BA is considered a cost-effective option. Please see issue 5 for a summary of how the ICER changes under different HRQoL assumptions.
Technical team preliminary judgement and rationale	The technical team agree with the ERG suggested amendments in the estimation of health related quality of life to avoid adjusting for gender twice and to reflect utilities after a CV event appropriately.

Issue 8a – Health related quality of life for secondary prevention populations and CV events

Questions for engagement	33. Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?
Background/description of issue:	*This issue is closely linked with issue 5, and whether it is appropriate to redefine the modelled populations as primary and secondary prevention patients based on the study populations informing effectiveness.* The company applied different age adjusted multipliers to baseline utilities in line with the Technical Support Document (TSD) 12. The ERG agreed with the use of the Ara and Brazier utility data but were concerned with the choice of utility multipliers and regression equation used to estimate the baseline adjusted utility. The ERG note that [redacted], [redacted] and [redacted] of patients in subpopulations 2b, 4a and 4b, respectively, as well as the study

population in Luengo-Fernandez *et al*. 2013 (used to derive the utility values for TIAs) had a history of previous CV events and as such these three subpopulations should not be considered as primary prevention populations in the model.

The ERG considers that the regression equation derived for a population with no history of CV disease does not accurately reflect the population underlying the effectiveness data used in the model. The ERG replaced the regression used by the company to estimate age-adjusted baseline utilities for subpopulation 4a, 4b, and 2b with a regression for a general population with a mixed history of CV events.

In conclusion, the ERG conducted the following scenarios (in combination with adjustments made as reported in issue 6):

- For subpopulation 2b, 4a and 4b:
    - Used the regression from Ara and Brazier for people with a mixed history of CV disease to estimate baseline utility and used the utility values reported in Ara and Brazier for patients experiencing multiple events.
- For subpopulation 2a:
    - Maintained the company's approach of using the Ara and Brazier regression for people with no history of CV events to estimate baseline utility. Nonetheless, the ERG notes that after patients in subpopulation 2a experience their first event, recurrent events should accrue the utilities for multiple events.

The following table summarises the various utilities and multipliers used by the company and ERG.

Health state	ERG								Company				
	Population 4a, 4b, 2b				Population 2a						Population		
	EQ-5D mean	Age	Multipliers		EQ-5D mean	Age	Multipliers		EQ-5D mean	Age	4	2	Age gender adjusted multiplier
			Male	Female			Male	Female					
SA < 1 yr	0.54	68	0.68	0.69	0.62	69	0.75	0.78	0.62	69	0.81	0.80	0.77

SA > 1 yr	0.72	69	0.90	0.93	0.78	68	0.95	0.98	0.78	68	0.81	0.80	0.96
UA < 1 yr	0.54	68	0.68	0.69	0.62	69	0.75	0.78	0.62	69	0.81	0.80	0.77
UA > 1 yr	0.72	69	0.90	0.93	0.78	68	0.95	0.98	0.78	68	0.81	0.80	0.96
MI < 1 yr	0.43	67	0.53	0.55	0.72	65	0.87	0.90	0.62	69	0.81	0.80	0.77
MI > 1 yr	0.69	69	0.86	0.89	0.74	65	0.89	0.92	0.74	65	0.83	0.82	0.91
IS < 1 yr	0.48	74	0.62	0.64	0.63	68	0.76	0.79	0.63	68	0.81	0.81	0.78
IS > 1 yr	0.64	70	0.81	0.84	0.67	67	0.81	0.84	0.67	67	0.82	0.81	0.82
TIA < 1 yr	0.76	73	0.98	**0.88***	0.76	73	0.95	0.98	0.76	73	0.79	0.78	0.97
TIA > 1 yr	0.78	73	**0.97***	**0.91***	0.78	73	0.98	**0.90***	0.76	73	0.79	0.78	0.97

*From literature rather than regression, as regression produced clinically implausible values

The below table are values used in the ERG analysis for the secondary prevention subpopulations (2b, 4a, and 4b).

Health state for secondary prevention patients	EQ-5D mean	Age	Utility multipliers for males	Utility multipliers for females
Previous history of SA	0.775	68	0.968	0.994
Previous history of UA	0.775	68	0.968	0.994
Previous history of MI	0.742	65.1	0.91	0.936
Previous history of IS	0.668	66.8	0.828	0.851

	Previous history of TIA | 0.76 | 73 | 0.979 | **0.884** *From literature rather than regression, as regression produced clinically implausible values
Why this issue is important	Changing assumptions regarding how HRQoL is modelled either increases or reduces the ICER depending on the subpopulation under evaluation.
Technical team preliminary judgement and rationale	If committee feel that the modelled subpopulations should be defined as primary or secondary prevention populations as outlined in issue 5, then it is also appropriate that HRQoL estimates reflect this definition. The technical team note that additional subgroup analyses that take CV risk into account should also consider the possible differences in HRQoL experienced by the cohort beyond

Issue 9 – Costing of ALI/EVO administration and CV events

Questions for engagement	34. In clinical practice, would you expect ALI/EVO to be administered in a hospital setting, with an annual follow up with a consultant?
Background/description of issue	A submission from NHS England suggests that treatment with bempedoic acid is expected to be managed predominantly in primary care, so funded via the prescribing budgets which CCGs agree with GP surgeries. It is not excluded from the Payment by Results tariff so where used in secondary care, costs would be within tariff. However, a key opinion leader for NHS England suggested that in some areas GPs are more likely to refer people with hypercholesterolaemia which is not adequately controlled on statins alone to secondary care; based on this a treatment such as BA may be more frequently initiated in secondary care in such areas. ALI and EVO are commissioned by CCGs for the treatment of primary hypercholesterolaemia. These agents are generally prescribed in secondary care and may be provided via homecare supply routes.

	ERG clinical experts, involved in the prescribing and monitoring of ALI/EVO, advised that patients on ALI and EVO are managed in the hospital setting and so would incur an annual cost of a hospital consultant visit. The ERG notes this is inconsistent with the monitoring schedules accepted in TA393 and TA394, which did not anticipate additional monitoring for ALI/EVO compared to current therapy. However, in line with clinical expert opinion, the ERG added the cost of an annual hospital appointment of £128 for follow-up treatments and a one-off initial cost of £163 for patients receiving ALI/EVO. The ERG also undertook various other amendments to the costing of CV events in the model within their base-case analysis, including: • Using first and second event incremental costs from Danese et al. 2017 separately, in the analysis; • Replacing the incremental cost of a CV-death (-£236) with the total cost estimate available in CG181 (£1,220 in 2019 prices) • Replacing the Danese et al. 2017 IS costs with the costs accepted in CG181 and TA393 (£8,959 for acute IS and £1,839 for post-IS in 2018 prices) The technical team agree with the ERG's proposed amendments and rationale as stated in the ERG report (section 4.2.10).
Why this issue is important	The adjustments made to the costing within the analysis do not have a large impact on the cost-effectiveness estimates, however, they may have influential impact on whether BA/EZE FDC is a cost-effective option.
Technical team preliminary judgement and rationale	The technical team agree with the ERG suggested amendments in the costing used in the base case analysis. The technical team pose this as a key issue for technical engagement to understand if there is clinical opinion that concurs with that of the ERG experts.

2. Issues for information

Tables 1 to 6 are provided to stakeholders for information only and not included in the technical report comments table provided. All analyses are deterministic and the results are presented for BA/EZE FDC only. This is because the results for BA with concomitant EZE are equivalent because of the underlying assumption that BA/EZE FDC and BA with concomitant EZE have equivalent costs and benefits. The cost-effectiveness results presented in this report are based on list prices and do not include confidential commercial arrangements (patient access scheme/commercial access agreements) for ALI and EVO. ICERs which fall in the South-West plane are *represented with italics*. These ICERs should be interpreted with caution as they represent cost savings per QALY lost.

Table 1.1: Technical team preferred assumptions for subpopulation 2a: BA/EZE FDC versus EZE

Alteration	Technical team rationale	ICER	Difference to base case
0. Company base case		£28,521	
1. ERG correction of minor errors (see table 6)	The technical team agreed with the ERG correction	£28,527	£6
2. ERG correction and ERG population: Primary prevention cohort without HeFH (scenario 1+2)	See issue 4 and 5	£31,504	£2,983
3. ERG correction, ERG population and ERG's NMA on LDL-C: Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe (scenario 1+2+3)	See issue 6	£30,504	£1,983
4a. Baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment (scenario 0+4)	See issue 3	£29,476	£955

Alteration	Technical team rationale	ICER	Difference to base case
4b. Baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment (scenario 1+2+3+4)	See issue 3	£31,484	£2,963
5a. ERG preferred assumptions regarding utility for subpopulation 2a (scenario 0+5)	See issue 8	£27,973	-£548
5b. ERG preferred assumptions regarding utility for subpopulation 2a (scenario 1+2+3+5)	See issue 8	£30,173	£1,652
6a. ERG preferred assumptions on health state costs (scenario 0+6)	See issue 9	£27,440	-£1,081
6b. ERG preferred assumptions on health state costs (scenario 1+2+3+6)	See issue 9	£29,197	£676
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate (scenarios 1+2+3+4+5+6)		£29,856	£1,335

In all scenarios BA/EZE FDC was more effective and more costly than EZE.
ICERs ran by technical team using ERG model for scenarios

Table 1.2: Technical team preferred assumptions for subpopulation 2a: BA/EZE FDC versus EZE

Alteration	Total costs	Total QALYs	Total life years	Inc. costs	Inc. QALYs	Inc. Life years	ICER
0. Company base case							
BA/EZE FDC	£14,125	8.71	11.76				
EZE	£8,277	8.51	11.51	£5,847	0.21	0.25	£28,521
1. ERG correction of minor errors							
BA/EZE FDC	£14,147	8.71	11.76				
EZE	£8,299	8.51	11.51	£5,848	0.21	0.25	£28,527

Alteration	Total costs	Total QALYs	Total life years	Inc. costs	Inc. QALYs	Inc. Life years	ICER
2. ERG correction and ERG population (scenario 1+2)							
BA/EZE FDC	£12,992	9.25	12.30				
EZE	£7,018	9.06	12.08	£5,973	0.19	0.22	£31,504
3. ERG correction, ERG population and ERG's NMA (scenario 1+2+3)							
BA/EZE FDC	£12,984	9.26	12.31				
EZE	£7,018	9.06	12.08	£5,966	0.20	0.23	£30,504
4a. Baseline LDL-C level from non-PCSK9i eligible patients (0+4)							
BA/EZE FDC	£14,128	8.72	11.77				
EZE	£8,270	8.52	11.53	£5,859	0.20	0.24	£29,476
4b. Baseline LDL-C level from non-PCSK9i eligible patients (1+2+3+4)							
BA/EZE FDC	£12,988	9.26	12.32				
EZE	£7,012	9.07	12.10	£5,976	0.19	0.22	£31,484
5a. ERG assumptions regarding utility (0+5)							
BA/EZE FDC	£14,125	8.67	11.76				
EZE	£8,277	8.47	11.51	£5,847	0.21	0.25	£27,973
5b. ERG assumptions regarding utility (1+2+3+5)							
BA/EZE FDC	£12,984	9.25	12.31				
EZE	£7,018	9.05	12.08	£5,966	0.20	0.23	£30,173
6a. ERG preferred assumptions on costs (0+6)							
BA/EZE FDC	£17,037	8.71	11.76				
EZE	£11,412	8.51	11.51	£5,626	0.21	0.25	£27,440
6b. ERG preferred assumptions on costs (1+2+3+6)							
BA/EZE FDC	£15,314	9.26	12.31				

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Alteration	Total costs	Total QALYs	Total life years	Inc. costs	Inc. QALYs	Inc. Life years	ICER
EZE	£9,604	9.06	12.08	£5,710	0.20	0.23	£29,197
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate							
BA/EZE FDC	£15,319	9.25	12.32				
EZE	£9,591	9.06	12.10	£5,727	0.19	0.22	£29,856

In all scenarios BA/EZE FDC was more effective and more costly than EZE.
ICERs ran by technical team using ERG model for scenarios

Table 2.1: Technical team preferred assumptions for subpopulation 2b: BA/EZE FDC versus ALI or EVO (company analysis) and BA/EZE FDC versus ALI+EZE (ERG analysis)

Alteration	ICER for BA/EZE FDC vs. ALI	ICER for BA/EZE FDC vs. EVO	ICER for BA/EZE FDC vs. ALI + EZE†
0. Company base case	*£342,008*	*£236,401*	NA
1. ERG correction of minor errors (see table 6)	*£342,008*	*£236,401*	NA
2. ERG correction and ERG population: Secondary prevention cohort without HeFH, allocated to begin the model in the 3-year+ post-event state (see issues 4 and 5) (scenario 1+2)	*£398,880*	*£275,430*	NA
3. ERG corrected model, population definition and ERG's NMA on LDL-C† Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe (see issue 6) (scenarios 1+2+3)	NA	NA	*£99,488*
4. ERG preferred assumptions regarding utility for subpopulation 2b, 4a and 4b (see issue 8) (vs. ALI or EVO = scenarios 0+4; vs. ALI + EZE† = scenarios 3+4)	*£200,121*	*£141,403*	*£89,677*

Alteration	ICER for BA/EZE FDC vs. ALI	ICER for BA/EZE FDC vs. EVO	ICER for BA/EZE FDC vs. ALI + EZE†
5. Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors (see issue 9) (vs. ALI or EVO = scenarios 0+5; vs. ALI + EZE† = scenarios 3+5)	*£356,887*	*£246,517*	*£103,738*
6. ERG preferred assumptions on health state costs) (see issue 9) (vs. ALI or EVO = scenarios 0+6; vs. ALI + EZE† = scenarios 3+6)	*£341,949*	*£236,344*	*£99,430*
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	*£286,306*	*£196,485*	*£93,455*

Note: ALI is extendedly dominated by EVO (i.e. the ICER for ALI is greater than that of a more effective intervention, EVO). The decision in subpopulation 2b reduces to a comparison with EVO. See appendix for fully incremental analysis of BA/EZE FDC compared with ALI and EVO.
ICERs ran by technical team using ERG model for scenarios
†This comparison is not in the company base case. All analyses for this comparison have been run using the ERG corrected model, population definition and ERG's NMA

Table 2.2: Technical team preferred assumptions for subpopulation 2b: BA/EZE FDC versus ALI or EVO (company analysis) and BA/EZE FDC versus ALI+EZE (ERG analysis)

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
Company base case							
BA/EZE FDC	£18,642	6.86	9.97				-

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
ALI	£41,337	6.93	9.57	-£22,695	-0.07	-0.39	*£342,008*
EVO	£41,776	6.96	9.57	-£23,134	-0.10	-0.39	*£236,401*
1. ERG correction of minor errors†							
BA/EZE FDC	£18,643	6.86	9.97				-
ALI	£41,338	6.93	9.57	-£22,695	-0.07	-0.39	*£342,008*
EVO	£41,777	6.96	9.57	-£23,134	-0.10	-0.39	*£236,401*
2. ERG correction and population (scenarios 1+2)							
BA/EZE FDC	£17,471	7.20	10.39				-
ALI	£40,817	7.25	10.04	-£23,346	-0.06	-0.35	*£398,880*
EVO	£41,256	7.28	10.04	-£23,785	-0.09	-0.35	*£275,430*
3. ERG NMA (scenarios 1+2+3)							
BA/EZE FDC	£17,429	7.09	10.24				
ALI + EZE†	£41,505	7.45	10.74	-£24,030	-0.24	-0.34	*£99,488*
4. ERG preferred assumptions regarding utility (scenarios 0+4)							
BA/EZE FDC	£18,642	12.38	9.97				-
ALI	£41,337	12.49	9.57	-£22,695	-0.11	-0.39	*£200,121*
EVO	£41,776	12.54	9.57	-£23,134	-0.16	-0.39	*£141,403*
4b. ERG preferred assumptions regarding utility (scenarios 3+4)							
BA/EZE FDC	£17,475	12.29	10.40				
ALI + EZE†	£41,505	12.56	10.74	-£24,030	-0.27	-0.34	*£89,677*

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
5a. Adding the costs for PCSK9 inhibitors (scenarios 0+5)							
BA/EZE FDC	£18,642	6.86	9.97				-
ALI	£42,325	6.93	9.57	-£23,683	-0.07	-0.39	*£356,887*
EVO	£42,766	6.96	9.57	-£24,124	-0.10	-0.39	*£246,517*
5b. Adding the costs for PCSK9 inhibitors (scenarios 3+5)							
BA/EZE FDC	£17,475	7.20	10.40				
ALI + EZE†	£42,532	7.45	10.74	-£25,057	-0.24	-0.34	*£103,738*
6b. ERG preferred assumptions on health state costs (scenarios 0+6)							
BA/EZE FDC	£24,853	6.86	9.97				-
ALI	£47,544	6.93	9.57	-£22,691	-0.07	-0.39	*£341,949*
EVO	£47,982	6.96	9.57	-£23,129	-0.10	-0.39	*£236,344*
6b. ERG preferred assumptions on health state costs (scenarios 3+6)							
BA/EZE FDC	£23,204	7.20	10.40				
ALI + EZE†	£47,221	7.45	10.74	-£24,016	-0.24	-0.34	*£99,430*
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate, without ERG NMA (scenarios 0+1+2+4+5+6)							
BA/EZE FDC	£23,201	12.28	10.39				-
ALI	£47,554	12.36	10.04	-£24,353	-0.09	-0.35	*£286,306*
EVO	£47,994	12.40	10.04	-£24,792	-0.13	-0.35	*£196,485*
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate (scenarios 3+4+5+6)							

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
BA/EZE FDC	£23,204	12.29	10.40				
ALI + EZE†	£48,247	12.56	10.74	-£25,043	-0.27	-0.34	*£93,455*

Table 3.1: Technical team preferred assumptions for subpopulation 4a: BA/EZE FDC versus EZE + statin

Alteration	Technical team rationale	ICER	Difference to base case
0. Company base case		£69,452	
1. ERG correction of minor errors: Inflating the costs of SA and post-SA health states to £8,042 and £250, respectively (as opposed to £7,907 and £245) - The technical team agreed with the ERG correction	The technical team agreed with the ERG correction	£69,453	£1
2. ERG correction and ERG population: Secondary prevention cohort without HeFH, allocated to begin the model in the 3-year+ post-event state (scenarios 1+2)	See issue 4 and 5	£82,286	£12,834
3. ERG corrected model, population definition and ERG's NMA on LDL-C: Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe (scenarios 1+2+3)	See issue 6	£66,343	-£3,109
4a. Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment (scenarios 0+4)	See issue 3	£82,275	£12,823
4b. Using the baseline LDL-C level from non-PCSK9i eligible patients in the subpopulations ineligible for PCSK9i treatment (scenarios 1+2+3+4)	See issue 3	£78,472	£9,020
5a. ERG preferred assumptions regarding utility for subpopulation 2b, 4a and 4b (scenarios 0+4)	See issue 8	£55,538	-£13,914

Alteration	Technical team rationale	ICER	Difference to base case
5b. ERG preferred assumptions regarding utility for subpopulation 2b, 4a and 4b (scenarios 1+2+3+5)	See issue 8	£55,309	-£14,143
6a. ERG preferred assumptions on health state costs (scenarios 0+4)	See issue 9	£69,345	-£107
6b. ERG preferred assumptions on health state costs (scenarios 1+2+3+6)	See issue 9	£66,243	-£3,209
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate		£75,437	£5,985

Note: In all scenarios BA/EZE FDC was more costly and more effective than EZE+statin.
ICERs ran by technical team using ERG model for scenarios

Table 3.2: Technical team preferred assumptions for subpopulation 4a: BA/EZE FDC versus EZE + statin

Alteration	Total costs	Total QALYs	Total life years	Inc. costs	Inc. QALYs	Inc. Life years	ICER
0. Company base case							
BA/EZE FDC	£18,110	6.89	9.91				
EZE	£12,690	6.81	9.80	£5,420	0.08	0.11	£69,452
1. ERG correction of minor errors							
BA/EZE FDC	£18,111	6.89	9.91				
EZE	£12,691	6.81	9.80	£5,420	0.08	0.11	£69,453
2. ERG correction and ERG population (scenario 1+2)							
BA/EZE FDC	£17,045	7.18	10.28				
EZE	£11,468	7.11	10.19	£5,577	0.07	0.10	£82,286

Alteration	Total costs	Total QALYs	Total life years	Inc. costs	Inc. QALYs	Inc. Life years	ICER
3. ERG correction, ERG population and ERG's NMA (scenario 1+2+3)							
BA/EZE FDC	£17,055	7.20	10.30				
EZE	£11,468	7.11	10.19	£5,587	0.08	0.12	£66,343
4a. Baseline LDL-C level from non-PCSK9i eligible patients (0+4)							
BA/EZE FDC	£18,147	6.98	10.03				
EZE	£12,680	6.91	9.94	£5,468	0.07	0.09	£82,275
4b. Baseline LDL-C level from non-PCSK9i eligible patients (1+2+3+4)							
BA/EZE FDC	£17,088	7.28	10.42				
EZE	£11,460	7.20	10.31	£5,628	0.07	0.10	£78,472
5a. ERG assumptions regarding utility (0+5)							
BA/EZE FDC	£18,110	9.24	9.91				
EZE	£12,690	9.14	9.80	£5,420	0.10	0.11	£55,538
5b. ERG assumptions regarding utility (1+2+3+5)							
BA/EZE FDC	£17,055	9.04	10.30				
EZE	£11,468	8.94	10.19	£5,587	0.10	0.12	£55,309
6a. ERG preferred assumptions on costs (0+6)							
BA/EZE FDC	£23,774	6.89	9.91				
EZE	£18,362	6.81	9.80	£5,412	0.08	0.11	£69,345
6b. ERG preferred assumptions on costs (1+2+3+6)							
BA/EZE FDC	£22,329	7.20	10.30				
EZE	£16,751	7.11	10.19	£5,578	0.08	0.12	£66,243
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate (scenarios 1+2+3+4+5+6)							

Alteration	Total costs	Total QALYs	Total life years	Inc. costs	Inc. QALYs	Inc. Life years	ICER
BA/EZE FDC	£22,352	9.14	10.42				
EZE	£16,731	9.06	10.31	£5,622	0.07	0.10	£75,437

Table 4.1: Technical team preferred assumptions and impact on the cost-effectiveness estimate for subpopulation 4b; when statins are maximally tolerated: ALI/EVO are appropriate.

Alteration	BA/EZE FDC versus ALI	BA/EZE FDC versus ALi + EZE	BA/EZE FDC versus EVO	BA/EZE FDC versus ALI + EZE + statin†
0. Company base case	£94,488	£121,686	£56,285	NA
1. ERG correction of minor errors (see table 6)	£94,488	£121,686	£56,285	NA
2. ERG correction and ERG population: Secondary prevention cohort without HeFH, allocated to begin the model in the 3-year+ post-event state (see issues 4 and 5) (scenario 1+2)	£111,482	£143,849	£65,992	NA
3. ERG corrected model, population definition and ERG's NMA on LDL-C† Using the ERG's estimated difference in % change in LDL-C from baseline compared with ezetimibe (see issue 6) (scenarios 1+2+3)	NA	NA	NA	£60,123
4. ERG preferred assumptions regarding utility for subpopulation 2b, 4a and 4b (see issue 8) (for comparison with ALI or EVO = scenarios 0+4; for comparison with ALI + EZE† = scenarios 3+4)	£85,090	£124,523	£49,497	£52,116

Alteration	BA/EZE FDC versus ALI	BA/EZE FDC versus ALi + EZE	BA/EZE FDC versus EVO	BA/EZE FDC versus ALI + EZE + statin†
5. Adding the cost of an annual hospital appointment (£128) and a one-off initial training cost (£163) for patients receiving PCSK9 inhibitors (see issue 9) (for comparison with ALI or EVO = scenarios 0+5; for comparison with ALI + EZE† = scenarios 3+5)	£98,604	£126,961	£58,683	£62,692
6. ERG preferred assumptions on health state costs) (for comparison with ALI or EVO = scenarios 0+6; for comparison with ALI + EZE† = scenarios 3+6)	£94,381	£121,577	£56,185	£60,016
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	£102,537	£135,858	£59,869	£54,250

Note: ALI plus ezetimibe is dominated by ALI (i.e. ALI plus ezetimibe is more expensive and less effective than ALI). Subsequently, ALI is extendedly dominated by EVO (i.e. the ICER for ALI is greater than that of a more effective intervention, EVO). Then, the decision in subpopulation 4b reduces to a comparison with EVO. See appendix for fully incremental analysis of BA/EZE FDC compared with ALI and EVO.
ICERs ran by technical team using ERG model for scenarios
†This comparison not in company base case. All analyses for this comparison have been run using the ERG corrected model, population definition and ERG's NMA

Table 4.2: Technical team preferred assumptions and impact on the cost-effectiveness estimate for subpopulation 4b; when statins are maximally tolerated: ALI/EVO are appropriate.

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
Company base case							
BA/EZE FDC	£18,090	6.48	9.35				
ALI	£40,289	6.72	9.67	-£22,200	-0.23	-0.32	*£94,488*
ALI + EZE	£40,298	6.67	9.60	-£22,208	-0.18	-0.25	*£121,686*
EVO	£41,126	6.89	9.91	-£23,037	-0.41	-0.57	*£56,285*
1. ERG correction of minor errors†							
BA/EZE FDC	£18,090	6.48	9.35				
ALI	£40,289	6.72	9.67	-£22,200	-0.23	-0.32	*£94,488*
ALI + EZE	£40,298	6.67	9.60	-£22,208	-0.18	-0.25	*£121,686*
EVO	£41,126	6.89	9.91	-£23,037	-0.41	-0.57	*£56,285*
2. ERG correction and population (scenarios 1+2)							
BA/EZE FDC	£16,955	6.83	9.78				
ALI	£39,810	7.03	10.07	-£22,855	-0.21	-0.29	*£111,482*
ALI + EZE	£39,842	6.99	10.00	-£22,887	-0.16	-0.22	*£143,849*
EVO	£40,595	7.18	10.28	-£23,640	-0.36	-0.50	*£65,992*
3. ERG NMA (scenarios 1+2+3)							
BA/EZE FDC	£16,965	6.85	9.82				
ALI + EZE†	£40,572	7.25	10.37	-£23,607	-0.39	-0.55	*£60,123*
4. ERG preferred assumptions regarding utility (scenarios 0+4)							
BA/EZE FDC	£18,089	8.85	9.35				

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
ALI	£40,289	9.11	9.67	-£22,200	-0.26	-0.32	*£85,090*
ALI + EZE	£40,297	9.03	9.60	-£22,208	-0.18	-0.25	*£124,523*
EVO	£41,126	9.32	9.91	-£23,037	-0.47	-0.57	*£49,497*
4b. ERG preferred assumptions regarding utility (scenarios 3+4)							
BA/EZE FDC	£16,965	8.69	9.82				
ALI + EZE†	£40,572	9.15	10.37	-£23,607	-0.45	-0.55	*£52,116*
5a. Adding the costs for PCSK9 inhibitors (scenarios 0+5)							
BA/EZE FDC	£18,089	6.48	9.35				
ALI	£41,256	6.72	9.67	-£23,167	-0.23	-0.32	*£98,604*
ALI + EZE	£41,260	6.67	9.60	-£23,171	-0.18	-0.25	*£126,961*
EVO	£42,107	6.89	9.91	-£24,018	-0.41	-0.57	*£58,683*
5b. Adding the costs for PCSK9 inhibitors (scenarios 3+5)							
BA/EZE FDC	£16,965	6.85	9.82				
ALI + EZE†	£41,580	7.25	10.37	-£24,615	-0.39	-0.55	*£62,692*
6b. ERG preferred assumptions on health state costs (scenarios 0+6)							
BA/EZE FDC	£23,842	6.48	9.35				
ALI	£46,017	6.72	9.67	-£22,174	-0.23	-0.32	*£94,381*
ALI + EZE	£46,031	6.67	9.60	-£22,188	-0.18	-0.25	*£121,577*
EVO	£46,838	6.89	9.91	-£22,996	-0.41	-0.57	*£56,185*
6b. ERG preferred assumptions on health state costs (scenarios 3+6)							

Alteration	Total costs	Total QALYs	Total life years	Inc. costs (versus BA/EZE FDC)	Inc. QALYs (versus BA/EZE FDC)	Inc. Life years (versus BA/EZE FDC)	ICER (versus BA/EZE FDC)
BA/EZE FDC	£22,296	6.85	9.82				
ALI + EZE†	£45,861	7.25	10.37	-£23,565	-0.39	-0.55	*£60,016*
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate, without ERG NMA (scenarios 0+1+2+4+5+6)							
BA/EZE FDC	£22,290	8.67	9.78				
ALI	£46,111	8.90	10.07	-£23,821	-0.23	-0.29	*£102,537*
ALI + EZE	£46,144	8.84	10.00	-£23,854	-0.18	-0.22	*£135,858*
EVO	£46,893	9.08	10.28	-£24,603	-0.41	-0.50	*£59,869*
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate (scenarios 3+4+5+6)							
BA/EZE FDC	£22,296	8.69	9.82				
ALI + EZE†	£46,869	9.15	10.37	-£24,573	-0.45	-0.55	*£54,250*

Table 5: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
The trial populations may not reflect the UK population	In terms of patient demographics, in comparison to the UK population likely to be eligible for BA, the ERG's clinical experts reported that the BA and FDC studies were broadly representative although they would expect a 50:50 gender split,	Unclear

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	higher proportion of non-white ethnicity patients, higher proportion of people with diabetes and statin therapy would most commonly be atorvastatin. In addition, more older patients would also be expected in clinical practice, but it is not uncommon for age to be lower in clinical trials.	
Using LDL-C as a surrogate for CV outcomes	The quality of life and life years are driven by cardiovascular event rates, which are in turn driven by the expected LDL-C level of the interventions. The CLEAR OUTCOMES trial, which investigates major adverse CV events as the primary outcome, is ongoing at this time and is not due to report until [redacted].The company has cited evidence to support their argument that it is reasonable to use LDL-C [for example, Cholesterol Treatment Trialists et al. (2010); Cholesterol Treatment Trialists et al. (2015); Navarese et al. (2015); Navarese et al. (2018)] and also argue that the assumption has been accepted by TA393 TA394 and TA385. The company state that the evidence base for other markers is not as established and were not considered. To note the evidence for LDL-C used in the model is for 12 weeks. In the economic model the reduction of LDL over time is estimated and the risk of CV events thus decreases with reduced LDL-C. However, uncertainty will remain in whether this short-term data can be used to extrapolate over a lifetime for a chronic disease area (see issue 7).	Unclear
The side effect profile of BA monotherapy may be different from BA with EZE	The proportion of patients who would be treated with BA as monotherapy is unclear. The side effect profile of BA monotherapy may be different to that of BA/EZE FDC or BA with EZE, which in turn may impact on HRQoL.	Unclear.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Methods on the pooled analysis for BA added to ezetimibe therapy were not sufficiently reported, and uncertainty may arise due to small numbers included	The company provide two pooled analyses of the subgroups of patients who had received ezetimibe as lipid lowering therapy at baseline and the subgroup of patients who had not received ezetimibe therapy: • CLEAR Harmony and CLEAR Wisdom comprised of a maximum of [redacted] patients with concomitant ezetimibe therapy from *post hoc* subgroups and all patients were also on maximally tolerated statins. • CLEAR Tranquility and CLEAR Serenity comprised of a maximum of [redacted] patients with concomitant ezetimibe therapy from *post hoc* subgroups and all patients were statin intolerant. The ERG was unable to critique the methods of the pooled analyses and advises results should be interpreted with caution given the small patient numbers, *post hoc* nature and lack of methodology detail.	The pooled analyses did not inform cost-effectiveness evidence. The PSA results of the ERG base case suggest that if uncertainty from this is taken into account the ICER rises slightly.
Safety considerations associated with the drugs in combination may have not been fully captured.	It is unclear if the safety profiles of the studies evaluated would be generalizable to the various different combinations of therapies and in each subpopulation. There may be additional safety considerations associated with the drugs in combination that have not been captured fully by the studies.	Unclear as this may impact both intervention and comparator.

Table 6: Other issues for information

Issue	Comments
End of Life	The company did not submit a case for end of life and the technical team and ERG agree with this decision.
Innovation	The company provided an overview of the mechanism of action for BA, and described it as a non-statin, first-in-class, adenosine triphosphate citrate lyase (ACL) inhibitor with a targeted mechanism of action. Unlike statins, BA does not inhibit cholesterol synthesis in skeletal muscle cells because the enzyme needed for its activation is not present in skeletal muscle cells (Pinkosky et al., 2016; Saeed and Ballantyne, 2018). In phase 3 clinical trials, the incidence of muscle-related side effects is similar between BA and placebo. BA may also provide additional benefits by reducing CV inflammation markers, as evidenced by consistent reductions in the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) (Bilen and Ballantyne, 2016; Ford et al., 2016; Gutierrez et al., 2014). The technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts. BA and BA/EZE FDC is an oral drug in the form of a tablet, and therefore it could be easier to administer than drugs which are injected (for example ALI and EVO). BA and BA/EZE FDC is expected to be initiated in secondary care, with further management in primary care.
Ongoing data collection and future studies	The company also highlighted that there was an ongoing open label extension (OLE) study (CLEAR-OLE [1002-050]) for safety that had enrolled patients who received BA 180 mg QD for 78 weeks after completion of the 52-week CLEAR-HARMONY study. The OLE study was expected to report in [redacted]. In addition, a further Phase 3 global, CV outcomes trial is ongoing (CLEAR CVOT, 1002-043) to investigate BA compared with placebo in patients with, or at high risk of, CVD who are statin intolerant. The CLEAR CVOT study is expected to report in [redacted].

Issue	Comments
PSA results	The probabilistic sensitivity analysis captures uncertainty in model parameter estimates but does not capture structural uncertainty or issues regarding generalisability of the data. The following give an overview of the results obtained by the ERG; further information is available in the ERG report. ERG results. • Subpopulation 2a: BA/EZE FDC vs EZE; deterministic ICER = £29,856; probabilistic ICER = £30,218 • Subpopulation 2b: BA/EZE FDC vs ALI + EZE; deterministic ICER = *£93,455*; probabilistic ICER could not be calculated • Subpopulation 4a: BA/EZE FDC vs EZE + statin; deterministic ICER = £75,437; probabilistic ICER = £73,723 • Subpopulation 4b: BA/EZE FDC vs ALI + EZE + statin; deterministic ICER = *£54,250*; probabilistic ICER = *£58,929* PSA results produced by ERG using company parameters and respective distributions. The following pairwise ICER with BA/EZE FDC was obtained. • Subpopulation 2a: BA/EZE FDC vs EZE; probabilistic ICER = £28,262 • Subpopulation 2b: BA/EZE FDC vs ALI; probabilistic ICER = *£340,370* • Subpopulation 2b: BA/EZE FDC vs Evo; probabilistic ICER = *£259,311* • Subpopulation 4a: BA/EZE FDC vs EZE + statin; probabilistic ICER = £69,657 • Subpopulation 4b: BA/EZE FDC vs ALI + EZE + statin; probabilistic ICER = *£118,617* • Subpopulation 4b: BA/EZE FDC vs ALI + statin; probabilistic ICER = *£93,373* • Subpopulation 4b: BA/EZE FDC vs Evo + statin; probabilistic ICER = *£55,817*
ERG correction of the economic model	The costs of SA and post-SA health states were incorrectly inflated in the company's base case, as these should have been inflated from 2014 to 2018 costs, resulting in £8,042 and £250, respectively (as opposed to £7,907 and £245).

Issue	Comments
Scenario analyses	The ERG conducted a range of scenario analyses, the results of which detailed in the ERG report (section 6.3). Further exploratory analyses included: • Using a lower proportion of recurrent/polyvascular events (7%) • Using previous IS events to inform the history of all secondary prevention patients • Using previous MI events to inform the history of all secondary prevention patients • Including transitions to the SA state from previous event states • Using all-cause mortality without subtracting the risk of CV death

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Appendix

Table A: Fully incremental analysis of company preferred assumptions for sub-population 2b using the company corrected base case

Treatment	Cost	QALYs	Inc. cost	Inc. QALY	ICER
BA/EZE FDC	£18,643	6.86	-	-	-
ALI	£41,338	6.93	-£22,695	-0.07	*£342,008**
EVO	£41,777	6.96	-£23,134	-0.10	*£236,401**

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

Table B: Fully incremental analysis of technical team preferred assumptions for sub-population 2b, using company NMA (and therefore ALI and EVO as comparators)

Treatment	Cost	QALYs	Inc. cost	Inc. QALY	ICER
BA/EZE FDC	£23,201	12.28	-	-	
ALI	£47,554	12.36	-£24,353	-0.09	*£286,306**
EVO	£47,994	12.40	-£24,792	-0.13	*£196,485**

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

Note: ALI is extendedly dominated by EVO (i.e. the ICER for ALI is greater than that of a more effective intervention, EVO). The decision in subpopulation 2b reduces to a comparison with EVO. ICERs ran by technical team using ERG model for scenarios

Table C: Fully incremental analysis of technical team preferred assumptions for sub-population 2b, using ERG NMA (and therefore ALI + EZE as comparator)

Treatment	Cost	QALYs	Inc. cost	Inc. QALY	ICER

BA/EZE FDC	£23,204	12.29	-	-	
ALI+ EZE	£48,247	12.56	-£25,043	-0.27	*£93,455**

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

Table D: Fully incremental analysis of company preferred assumptions for sub-population 4b

Treatment	Cost	QALYs	Inc. cost versus BA/EZE FDC	Inc. QALY versus BA/EZE FDC	ICER versus BA/EZE FDC
BA/EZE FDC	£18,090	6.48	-	-	-
ALI	£40,289	6.72	-£22,200	-0.23	*£94,488**
ALI + EZE	£40,289	6.67	-£22,208	-0.18	*£121,686**
EVO	£41,126	6.89	-£23,037	-0.41	*£56,285**

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

Note: ALI plus ezetimibe is dominated by ALI (i.e. ALI plus ezetimibe is more expensive and less effective than ALI). Subsequently, ALI is extendedly dominated by EVO (i.e. the ICER for ALI is greater than that of a more effective intervention, EVO). Then, the decision in subpopulation 4b reduces to a comparison with EVO.

Table E: Fully incremental analysis of technical team preferred assumptions for sub-population 4b, using company NMA (and therefore ALI/EVO as comparators)

Treatment	Cost	QALYs	Inc. cost	Inc. QALY	ICER
BA/EZE FDC	£22,290	8.67			
ALI	£46,111	8.90	-£23,821	-0.23	*£102,537**
ALI + EZE	£46,144	8.84	-£23,854	-0.18	*£135,858**
EVO	£46,893	9.08	-£24,603	-0.41	*£59,869**

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

Note: ALI plus ezetimibe is dominated by ALI (i.e. ALI plus ezetimibe is more expensive and less effective than ALI). Subsequently, ALI is extendedly dominated by EVO (i.e. the ICER for ALI is greater than that of a more effective intervention, EVO). Then, the decision in subpopulation 4b reduces to a comparison with EVO. ICERs ran by technical team using ERG model for scenarios

Table F: Fully incremental analysis of technical team preferred assumptions for sub-population 4b, using company NMA (and therefore Ali + EZE + statin as comparator)

Treatment	Cost	QALYs	Inc. cost	Inc. QALY	ICER
BA/EZE FDC	£22,296	8.69			
Ali + EZE + statin	£46,869	9.15	-£24,573	-0.45	*£54,250**

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

Table G: Summary of studies in the statin intolerant updated company NMA (ERG report, table 69)

Study	Relevant arms	Background EZE[a] (%)	N	Concomitant statin	Other permitted LMT	LDL-C inclusion (mg/dL)	Prior CV event (%)	HeFH (%)	% T2D
1002-008 (statin intolerant subgroup)	1) BA 2) BA + EZE 3) EZE	0%[c] 100%[c] 100%[c]	223	None (for statin intolerant subgroup)	Bile acid sequestrants, fibrates	≥130 or ≥100 (depending on LMT washout)	Excluded	NR	NR
CLEAR Serenity	1) BA 2) PBO	NR NR	345	Mixed very low	Bile acid sequestrants, fibrates, PCSK9i	≥130 (≥100 w/ HeFH or ASCVD)	NR	1.7% 2.7%	NR
CLEAR Tranquility	1) BA + EZE 2) EZE	100% 100%	269	Mixed low	EZE (given open-label) and others	>100	27.1% 25.0%	NR	NR
GAUSS-2	1) EVO 140 Q2W 2) EZE + Q2W PBO (SCI)	0% 100%	154	Mixed non-intensive	33% on lipid lowering therapies	≥100	NR (high, mod, low risk)	NR	19% 22%
ODYSSEY Alternative	1) ALI 75 Q2W[b] 2) EZE	0% 100%	251	Mixed low (lowest approved dose)	Bile acid sequestrants and others but EZE and fibrates prohibited	≥100 (high risk), ≥70 (very high)	NR (mod, high, very high risk)	NR	28.6% 19.2%

Study	Relevant arms	Background EZE[a] (%)	N	Concomitant statin	Other permitted LMT	LDL-C inclusion (mg/dL)	Prior CV event (%)	HeFH (%)	% T2D
ODYSSEY CHOICE I (statin intolerant subgroup)	1) ALI 75 Q2W[b] 2) PBO (SCI)	8.1% 15.1%	110	None	Stable LMT except fibrates	≥100 (high/mod risk) ≥70 (v. high risk)	NR (mod, high, very high risk)	0.0% 1.4%	10.3% 23.3%
ODYSSEY CHOICE II	1) ALI 75 Q2W[b] 2) PBO (SCI)	60.3% 60.3%	174	None	Two thirds receiving fenofibrate or EZE	≥100 (high/mod risk) ≥70 (v. high risk)	NR (mod, high, very high risk)	12.9% 8.6%	19.0% 15.5%

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ALI, alirocumab; BA, bempedoic acid 180 mg once daily; CV, cardiovascular; EVO, evolocumab; EZE, ezetimibe 10 mg once daily; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; mg/dL, milligrams per decilitre; NMA, network meta-analysis; NR, not reported; PBO, placebo; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q2W, once every two weeks; SCI, subcutaneous injection; T2D, type 2 diabetes mellitus.
a Proportion of patients on ezetimibe at baseline as background therapy or as part of trial intervention
b Escalation to 150 mg Q2W after 12 weeks if LDL-C still elevated; Some or all of the following background treatments were permitted that may impact plasma lipid levels, provided they were kept stable prior to screening/during the study: hormone replacement, thyroid replacement, obesity medication, Omega 3 fatty acids, and diabetes medications.
c Patients underwent a 5-week washout of all lipid-regulating drugs, including ezetimibe

Table H: Summary of studies in the statin intolerant updated company NMA (ERG report, table 70)

Study	Relevant arms	Background EZE* (%)	Total N	Concomitant statin	Other permitted LMT	LDL-C inclusion	Prior CV event	HeFH	% T2D
1002-009	1) BA 2) PBO	NR NR	90	Mixed (non-intensive)	None[e]	≥115 (after washout)	NR	NR	NR

Study	Relevant arms	Background EZE* (%)	Total N	Concomitant statin	Other permitted LMT	LDL-C inclusion	Prior CV event	HeFH	% T2D
1002FDC-053	1) BA 2) BA + EZE 3) EZE 4) PBOI	0%[d] 100%[d] 100%[d] 0%[d]	382	Mixed (high, other, none)	None[e]	≥130 (≥100 w/ HeFH or ASCVD)	NR	NR	NR
CLEAR Harmony	1) BA 2) PBO	7.8% 7.5%	2230	Mixed (high, mod, low)	EZE, bile acid sequestrants, fibrates, PCSK9i (w/ conditions).	≥70	NR	3.8% 3.1%	NR
CLEAR Wisdom	1) BA 2) PBO	7.3% 9.3%	779	Mixed (high, mod, low)		≥100 (screen), ≥70 (baseline)	82.8% 79.8%	5.2% 6.2%	NR
Dujovne 2002	1) EZE 2) PBO	100% 0%	892	NR	Stable CV regimens	≥130 to 250 (after washout)	NR	NR	NR
FOURIER	1) EVO[b] 2) PBO (SCI)	5.3% 5.2%	27564	All intensive (at least ator 20mg daily or equivalent)	Required optimised tx (statin +/-EZE)	≥70 on optimised tx	NR	NR	NR
Knopp 2003	1) EZE 2) PBO	100% 0%	827	None	None[e]	≥130 to 250 (after washout)	3% 8%	NR	NR
Krysiak 2011 (not statin intolerant subgroup)	1) EZE 2) PBO	100% 0%	66	None	NR	>130	NR	6% 3%	NR
LAPLACE-2 (atorv 80, rosu 40 and sim 40 groups)[a]	1) EVO 140 Q2W 2) EZE 3) PBO (SCI)	0% 100% 0%	NR	All intensive: ator 80, rosu 40 or sim 40 mg daily	None[e]	≥80 (intensive statin) ≥100 (non-intensive statin)	NR	NR	3.6–31.5% across statin groups
LAPLACE-TIMI-57	1) EVO 140 Q2W 2) PBO (SCI)	13% 9%	156	All (no details)	Statin +/- EZE required	>85	NR	NR	19.0% 12.0%

Study	Relevant arms	Background EZE* (%)	Total N	Concomitant statin	Other permitted LMT	LDL-C inclusion	Prior CV event	HeFH	% T2D
Masana 2005	1) EZE 2) PBO	100% 0%	433	Unclear	Unclear	50 to 160	NR	NR	NR
McKenney 2012	1) ALI 150 Q2W 2) PBO (SCI)	NR NR	62	All taking 10–40mg ator	None[e]	≥100 on stable statin	NR	NR	9.7% 0.0%
Melani 2003	1) EZE 2) PBO 3) EZE + statin 4) PBO + statin	100% 0% 100% 0%	538	All prav 10, 20 or 40 mg daily in groups 3) and 4)	NR	70–115 (converted from mmol)	NR	NR	NR
ODYSSEY Japan	1) ALI 75 Q2W[c] 2) PBO (SCI)	NR NR	108	Mixed (stable)	Required stable statin +/- other LMT	NR	NR	18.8% 19.4%	NR
ODYSSEY KT	1) ALI 75 Q2W[c] 2) PBO (SCI)	14.4% 11.8%	NR	All intensive	EZE and others	NR	NR	NR	NR
ODYSSEY OPTIONS I(ator 20 and 40 groups)[a]	1) ALI 75 Q2W[c] 2) EZE 3) PBO	0% 100% 0%	NR	All non-intensive (ator 20 or 40 mg)	Other statins and EZE prohibited	≥100 (high risk) ≥70 (v. high risk)	NR	NR	34.0–57.9% across statin groups
ODYSSEY OPTIONS II (rosu 10 and 20 groups)[a]	1) ALI 75 Q2W[c] 2) EZE 3) PBO	0% 100% 0%	NR	All non-intensive (rosu 10 or 20 mg)	Other statins and EZE prohibited	≥100 (high risk) ≥70 (v. high risk)	NR	13.6% 13.9% NR	33.3–47.6% across statin groups
ODYSSEY OUTCOMES	1) ALI 75 Q2W[c] 2) PBO (SCI)	NR NR	NR	All intensive	NR	Elevated atherogenic levels despite intensive statin	NR	NR	NR

Study	Relevant arms	Background EZE* (%)	Total N	Concomitant statin	Other permitted LMT	LDL-C inclusion	Prior CV event	HeFH	% T2D
ODYSSEY CHOICE I(max tolerated subgroup)	1) ALI 75 Q2W[c] 2) PBO (SCI)	11.5% 14.0%	235	All intensive (max tolerated rosu 20-40mg, ator 40-80mg, or simv 80mg)	All stable LMTs permitted except fibrates	NR	NR (mod, to v. high risk)	7.7% 7.6%	28.2% 31.8%
ODYSSEY COMBO I	1) ALI 75 Q2W[c] 2) PBO (SCI)	7.2% 10.3%	316	All intensive (max tolerated rosu 20-40mg, ator 40-80mg, or simv 80mg)	EZE, bile acid sequestrants and others permitted	≥100 (high risk) ≥70 (w/ CVD)	NR (high risk)	NR	45.0% 39.3%
ODYSSEY COMBO II	ALI 75 Q2W[c] 2) PBO	0% 100%	720	All intensive (max tolerated rosu 20-40mg, ator 40-80mg, or simv 80mg)	NR	≥100 (high risk) ≥70 (w/ CVD)	NR	NR	30.3% 31.5%
ODYSSEY MONO	1) ALI[c] + EZE 2) EZE	100% 100%	103	None	None for at least 4 weeks prior to screen	100–190	NR	NR	5.8% 2.0%
ODYSSEY NIPPON	1) ALI 150 Q2W 2) PBO (SCI)	26.4% 19.6%	109	Mixed low (ator 5 mg)	LMTs allowed but not specified	NR	NR	24.5% 25.0%	NR
YUKAWA-2	1) EVO 140 Q2W + statin 2) PBO (SCI)	NR NR	99	All low (ator 5 mg)	Stable LMT allowed	≥100 after statin + LMT (including EZE) run-in	NR	6% 5%	47% 51%
YUKAWA	1) EVO 140 Q2W 2) PBO (SCI)	NR NR	104	Mixed non-intensive (≤20mg ator, rosu, pita, prava)	Stable LMT allowed	≥100 after statin + LMT (including EZE) run-in	NR (high)	NR	40.4% 30.8%

Abbreviations: ator, atorvastatin; ASCVD, atherosclerotic cardiovascular disease; ALI, alirocumab; BA, bempedoic acid 180 mg once daily; CV/D, cardiovascular disease; EVO, evolocumab; EZE, ezetimibe 10 mg once daily; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density

lipoprotein cholesterol; mg/dL, milligrams per decilitre; NMA, network meta-analysis; NR, not reported; PBO, placebo; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; pita, pitavastatin; prav, pravastatin; Q2W, once every two weeks; rosu, rosuvastatin; simv, simvastatin SCI, subcutaneous injection; T2D, type 2 diabetes mellitus.
* Proportion of patients on ezetimibe at baseline as background therapy or as part of trial intervention
a Studies with multiple baseline subgroups according to background statin type and dose;
b 140 mg Q2W or 420 mg QM depending on patient preference;
c Escalation to 150 mg Q2W after 12 weeks if LDL-C still elevated;
d Patients underwent a 5-week washout of all lipid-regulating drugs, including ezetimibe
e Some or all of the following background treatments were permitted that may impact plasma lipid levels, provided they were kept stable prior to screening/during the study: hormone replacement, thyroid replacement, obesity medication, Omega 3 fatty acids, and diabetes medications.

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Technical engagement response form

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **3 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
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About you

Your name	Kyle Dunton
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Daiichi Sankyo
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Abbreviations: ALI = alirocumab; BA = Bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed dose combination pill; CrI = credible interval; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; CVD = cardiovascular disease; DIC = Deviance information criterion; DS = Daiichi Sankyo; EPAR = European public assessment report; ERG = evidence review group; EVO = evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; HES = Hospital Episode Statistics; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NA = not applicable; NHS = National Health Service; NMA = network meta-analysis; NMB = Net monetary benefit; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; pD = effective number of parameters.; QALY = quality-adjusted life-year; THIN = The Health Improvement Network; UK = United Kingdom.

Issue 1: The clinical pathway	
What concomitant therapy would people having BA or BA/EZE FDC receive in clinical practice for subpopulations who are: statin intolerant and have had previous EZE? in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin?	Daiichi Sankyo has followed the treatment flowchart in NICE recommendations[1] as the basis for the clinical pathway. In order for a patient's cholesterol level to be adequately controlled, it is anticipated that an additional LDL-C lowering therapy, such as BA, would be added to existing therapy. [2] As per marketing authorisation, BA is licensed for use in combination with a statin, with or without other lipid-lowering medicines, in patients whose LDL-C levels are not lowered enough by the maximum tolerated dose of a statin. BA can also be used alone or in combination with other lipid-lowering medicines in patients who cannot take statins.[3] BA/EZE FDC is licensed for use in combination with a statin in patients whose LDL-C levels are not lowered enough by the maximum tolerated dose of a statin taken together with EZE. BA/EZE FDC can also be used alone in patients who cannot take statins and whose cholesterol levels are not lowered enough by EZE. The medicine can be used to replace separate tablets of BA and EZE in patients already taking them.[4] For patients receiving BA or BA/EZE FDC, concomitant therapies for the subpopulations are expected to be as follows: a) EZE for position 2a and 4b b) Maximally tolerated statin and EZE for 4a and 4b A study of the CPRD-HES linked data has indicated that most patients that previously were

	treated with EZE will continue with EZE after receiving additional treatment.[5] It is a national policy priority in England to improve the prevention of CVD events over the course of the next decade. This is outlined within the NHS Long Term Plan, published in 2019, which outlines the ambition to prevent up to 150,000 CVD events over the next ten years. Additionally, the LTP also aims to reduce avoidable outpatient appointments and to strengthen the role of primary care professionals to keep patients out of hospital. [6] In the context of the burden of the COVID19 pandemic on NHS resources, the delivery of this priority is more important than ever. The recognition of the burden of raised cholesterol as a risk factor is also acknowledged by Public Health England, which similarly outlines a number of long-term ambitions to improve the detection and management (35% to 45%) of high cholesterol by 2029. [7] Daiichi Sankyo believes that the accessibility of oral bempedoic acid and bempedoic acid + ezetimibe FDC will provide healthcare professionals with an additional therapeutic option to help deliver upon these national ambitions, allowing more patient care outside of the hospital setting. The opportunities here are supplemented by the AHSN network's forthcoming work programme that aims to optimize the lipid management primary care pathway.[8] The availability of a therapeutic intervention with proven efficacy in reducing LDL-C, in addition to existing treatment regimens, can help improve patient outcomes and to deliver upon these national policy ambitions.
What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO?	DS acknowledges that there is uncertainty around this proportion. As presented in the company submission (Table 2, Budget impact document), this number in the CLEAR studies was commercial in confidence information removed in CLEAR Harmony and commercial in confidence information removed in CLEAR Tranquility. In the NICE resource impact template, 8% is estimated to require treatment with PCSK9i in the non-HeFH population based on clinical opinion in the ALI submission (TA393). Hence, the proportions from the CLEAR studies are in line with previous estimates. In a study by Elamin et al. (2019)[9] at least 2.17% of patients would be deemed eligible for PCSK9i post myocardial infarction according to the NICE lipid criteria but only 63.2% of the patients had full data available on their previous CV events. Elamin et al. (2019)[9] do not differentiate between statin-intolerant patients and those on maximum tolerated dose. However, Kohli et al. (2017)[10] found that 67% of the patients that were prescribed PCSK9i in two contrasting UK hospital centres were intolerant to statins.
Would ALI or EVO be used alone or in combination	Based on UK clinical opinion received by DS and in TA393, in most patients PCSK9i treatment will be used as an add-on to previous treatments. It is not anticipated that a patient would stop current

with EZE in clinical practice?	LDL-C lowering treatment when initiating a PCSK9i. A patient receiving EZE at the point of PCSK9i initiation is expected to be experiencing some level of cholesterol lowering, or would have discontinued treatment due to lack of efficacy. Approximately 50% of patients receiving ALI or EVO would be expected also to receive EZE. According to a UK clinical expert, in some patients EZE would be stopped if it is deemed that there is a sufficient response on PCSK9i, alternatively a clinician may maintain a patient on EZE. In the CPRD/HES study,[11] given little ALI- or EVO-use data were reported it is difficult to draw strong conclusions regarding concomitant EZE. However, where these were used, they were used together with EZE in the majority of cases. In a study of 105 patients who were prescribed a PCSK9i in two UK clinical centres (70 in a university hospital and 35 in a district general hospital), 54% were on EZE[10]). In a UK real-world study by Reynolds et al. (2019)[12] only 1.7% of the patients stopped their EZE treatment when ALI/EVO was initiated.
Would ALI or EVO be used after BA if there is insufficient response?	Until BA is used in clinical practice, no data are available to answer this question. The treatment goal in international and national clinical guidelines is not related to prior treatment.[2] Hence, if a patient does not reach their cholesterol lowering goal and is eligible for PCSK9i therapy, they may receive treatment. However, access to and uptake of PCSK9i treatment is limited within the NHS.[13]
If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with BA?	Until BA is used in clinical practice, no data are available to answer this question. As per marketing authorisation, BA and BA/EZE FDC are licensed as add-on therapies to existing LDL-C lowering therapy.[3,4] In a UK real-world study by Reynolds et al. (2019)[12] only 1.7% of the patients stopped their EZE treatment when ALI/EVO was initiated. Additionally, based on the CPRD/HES data analysis[11], when ALI/EVO was used, it was used together with EZE in all cases except for one. This might be a relevant proxy for how BA will be used.
If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO?	In the CPRD/HES study[11] few cases of ALI/EVO was reported. However, when it was used, it was used together with EZE in most cases. As mentioned above, in a UK real-world study by Reynolds et al. (2019)[12] only 1.7% of the patients stopped the EZE treatment when ALI/EVO was initiated.
If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE?	This will be dependent on whether a patient is deemed to have met their target LDL-C goal. [2] It is estimated that around 80% of patients on lipid-lowering therapy remain with elevated LDL-C and

	at increased ASCVD risk. [14]
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or LDL therapy when commencing BA?	BA or BA/EZE FDC should be used as an add-on treatment to tolerated statins and not as a replacement.[15] Data for PCSK9i may provide relevant evidence as a proxy, in the UK real-world study by Reynolds et al. (2019)[12] only 11.9% of the patients stopped the statin treatment when ALI/EVO was initiated. It is not reported whether another statin treatment was initiated at the same time, hence, this number could be an overestimate of the proportion of patients discontinuing statin when a new treatment is initiated.
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO?	In the UK real-world study by Reynolds et al. (2019)[12], only 11.9% of the patients stopped the statin treatment when ALI/EVO was initiated.[12] It is not reported whether another statin treatment were initiated at the same time, hence, this number could be an overestimate of the proportion of patients discontinuing statin when ALI/EVO is initiated.
In which circumstances would BA be considered as monotherapy?	BA would be considered as monotherapy in statin-intolerant patients that also cannot tolerate EZE. Based on clinical opinion, this is unlikely to be a common occurrence.
Under which circumstances would a patient treated with EZE discontinue treatment with EZE?	Reasons for EZE therapy discontinuation/dose change prior to initiation of PCSK9i were reported by Reynolds et al. (2019)[12]. Lack of efficacy and adverse events were the most common reasons. This was confirmed by a UK clinical expert.
Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy?	It is not anticipated that a patient would discontinue EZE when initiating BA. Rather, BA is intended as an add-on to existing therapy.[16]
Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have EZE therapy?	DS does not expect patients to discontinue EZE treatment in clinical practice. Further, no evidence was identified by the ERG or the company systematic reviews which suggest a difference in treatment effect for BA or comparators in patients with or without prior EZE therapy.
Under which circumstances would a patient treated with a maximally tolerated statin discontinue treatment with a statin?	Reasons for statin therapy discontinuation/dose change prior to initiation of PCSK9i were reported by Reynolds et al. (2019)[12]. Lack of efficacy and adverse events were the most common reasons.
Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA	
	The wording of Issue 2 on page 3 of the Technical Engagement Report is misleading: "*The impact*

	of previous ezetimibe therapy and concomitant therapy on the treatment effect of bempedoic acid (BA) is uncertain". The CLEAR Tranquility study provides randomised controlled trial evidence for the treatment effect of BA in statin-intolerant patients with previous and concomitant EZE therapy. The 1002FDC-053 study provides randomised controlled trial evidence for the treatment effect of BA with concomitant EZE therapy vs. BA and vs. EZE in patients receiving maximal tolerated statin therapy. It is not anticipated that BA will be used without concomitant EZE. Therefore, the impact of concomitant EZE on the treatment effect for BA (i.e. the difference in treatment effect with and without EZE) is not relevant, only the treatment effect for BA with concomitant EZE is relevant. We suggest that the statement is reworded as follows: "*The impact of previous ezetimibe therapy on the treatment effect of bempedoic acid (BA) in patients receiving maximal tolerated statin is uncertain".*
Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE?	The company believes that this is appropriate, based on data from the CLEAR studies presented in and published after[17] the submission, and also data from comparator studies. The pathways and mechanism of action for BA and EZE for cholesterol lowering are different and in the EPAR (page 35 and 48), the European Medicines Agency states that pharmacokinetics was not affected by EZE.[15] UK clinical expert opinion obtained during the assessment process has also verified that there is no expectation for a difference in treatment effect by prior EZE therapy. Experts expect that BA should have a similar effect with or without previous exposure to EZE. EZE has a long half-life and is excreted via the gastrointestinal tract so may be difficult to wash out in studies. However, EZE may not have a clinical effect for the whole amount of time it is present in body. In any case, EZE would not be stopped in clinical practice and the patient then "wait" to commence a new therapy. The company presented a pooled analysis of the patients previously treated with EZE in CLEAR Harmony and CLEAR Wisdom (population 4) and CLEAR Tranquility and CLEAR Serenity (population 2). The mean percentage LDL-C reduction for the groups with and without previous treatment with EZE therapy were presented, and the ERG acknowledged results were similar between the two subgroups. As the technical team note in the description of the issue, the ERG does not consider the respective commercial in confidence information removed and commercial in confidence information removed difference between the presence and absence of EZE use at baseline to be clinically insignificant, given that the studies were not designed or powered sufficiently to detect a statistical difference for this comparison. There is 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. Furthermore, in addition to the small

patient numbers and post-hoc subgroup selection noted by the ERG, the direction of the difference in effect was opposite in the two populations. For statin-intolerant patients, the treatment effect was numerically greater in patients with EZE than without, while for patients with maximum tolerated dose of statins, the treatment effect was numerically smaller in patients with EZE.

- In statin-intolerant patients (studies 1002-046 and 1002-048), the difference from placebo for the least square means of commercial in confidence information removed in patients taking EZE vs. commercial in confidence information removed with no EZE.
- In the maximum tolerated dose studies, (1002-040 and 1002-047), the difference from placebo for the least square means of commercial in confidence information removed in patients taking EZE and commercial in confidence information removed in patients not taking EZE.

The opposite direction of the numerical differences would be very difficult to explain mechanistically even if the differences were indeed clinically significant.

Furthermore, no evidence was identified by the ERG or the company systematic reviews which suggests a difference in treatment effect for the comparator interventions in patients with or without prior EZE therapy. In the subgroup analyses for ALI in patients with and without EZE identified by the ERG and used in the ERG's NMA, there was no evidence for a difference in treatment effect for ALI with and without EZE.

- In statin-intolerant patients, the ERG used ODYSSEY CHOICE II (Stroes et al. (2016)[18]). The treatment effect for ALI was consistent for patients with EZE use and in the overall population and the interaction *P*-value was not significant (*P* = 0.4349) (Clarification letter, Issue 7 Figure 1).
- In maximally tolerated statin patients, the ERG used ODYSSEY LONGTERM (Robinson et al. (2015)[19]). The treatment effect for ALI was consistent for patients with and without EZE use and the interaction *P*-value was not significant (*P* = 0.3273) (Clarification letter, Issue 7 Figure 2).

The lack of any evidence for a difference in treatment effect for BA or comparators with or without prior EZE use was the basis upon which the company decided to conduct the NMA using all available evidence for the comparators of interest independently of prior EZE use.

However, to examine the potential impact of EZE further, DS investigated the importance of baseline EZE treatment in an NMA (see Error! Reference source not found.**,** Error! Reference source not found. **and** Error! Reference source not found.**) which showed that the results were**

	consistent when considering EZE treatment at baseline as a covariate.
To what extent does previous EZE therapy affect the treatment effect of BA?	Previous EZE therapy is not expected to affect the treatment effect of BA. See the response in the previous row above. This was also confirmed through UK clinical expert opinion.
To what extent does concomitant statin therapy affect the treatment effect of BA?	As presented in the company evidence submission (section B.2.4.1.1), LDL-C lowering with BA was slightly greater in the absence of background statin therapy (in CLEAR Tranquility and CLEAR Serenity) than in the presence of background statin therapy (in CLEAR Harmony, CLEAR Wisdom, and study 1002FDC-053). However, within patients receiving background statin therapy in CLEAR Harmony, CLEAR Wisdom, and study 1002FDC-053, the treatment effect for BA was highly significant both for patient subgroups on high-dose statin and subgroups on low-to-moderate dose statin (presented in Figure 7, Figure 8, Figure 11, and Table 30 of the company evidence submission). Published pooled subgroup results from the CLEAR studies[17] and the comparator studies indicated that no statistical differences could be observed outside this differentiation. As LDL-C lowering with BA was slightly different in the presence and absence of background statin therapy, DS analysed the clinical evidence using two networks to cover the expected difference in treatment effect between patients that are statin intolerant and patients on maximum tolerated dose of statins. **DS also has investigated the importance of background statin in the maximal tolerated statin NMA by exploring the incorporation of baseline statin use as a covariate. The results of this scenario analysis are provided in** Error! Reference source not found. (Error! Reference source not found. **and** Error! Reference source not found.**). As shown in the results, the addition of the proportion of patients receiving statin at baseline as a covariate gave similar results to analyses excluding this covariate.**

Issue 3: Baseline LDL-C in subpopulations that are not eligible for ALI and EVO	
In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?	ERG clinical experts suggested that access to ALI/EVO treatments is varied across different centres and regions. A UK clinical expert confirmed this variation but stated that if a centre had access to ALI/EVO treatments, most patients eligible for ALI/EVO treatment from that centre would receive treatment. Data presented during the AAC webinar (27 January 2020) and provided in the clarification letter demonstrates that, overall, only a small proportion of patients eligible for PCSK9i actually receive such therapy: *"The NHS Innovation Scorecard showed uptake of these medicines [PCSK9i] was between 72% and 77% lower than expected".*[13] The ERG notes that the eligibility criteria applied by the company aligns with NICE recommendations. However, it considers that the company's rationale contradicts the company's separation of the populations into subpopulations according to ALI/EVO eligibility. The assumption that all patients who receive PCSK9i fulfil the NICE criteria does not contradict the assumption that most patients fulfilling the NICE criteria for PCSK9i therapy do not receive a PCSK9i in clinical practice, given they are not mutually exclusive. This assumption by DS has been confirmed by clinical experts as outlined in the clarification letter.
Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO)?	Yes, logically, and as shown in the CLEAR studies, baseline LDL-C levels are expected to be lower in patients not eligible for ALI/EVO than for patients eligible for ALI/EVO as the baseline LDL-C level is one of the criteria for eligibility. This is also the case in The Health Improvement Network (THIN) data presented in the ALI submission (Table 53 in TA393 company submission and Table 24 in TA393 ERG report. Mean baseline LDL-C data are also available in the company cost-effectiveness model) which is similar to the NICE criteria: • **Criteria 1: HeFH (primary prevention) and LDL-C threshold of >4.14:** 5.59 mmol/L in patients fulfilling the criteria compared with 3.6 mmol/L without LDL-C restrictions • **Criteria 2: HeFH (secondary prevention) and LDL-C threshold of > 3.35 mmol/L:** 4.80 mmol/L in patients fulfilling the criteria compared with 3.0 mmol/L without LDL-C restrictions • **Criteria 3: Prior CV event (13-24 months) and LDL-C threshold of >3.35 mmol/L:** 4.07 mmol/L in patients fulfilling the criteria compared with 2.2 mmol/L without LDL-C restrictions

	• **Criteria 4: Polyvascular and LDL-C threshold of > 2.58 mmol/L:** 3.31 mmol/L in patients fulfilling the criteria compared with 2.66 mmol/L with a > 1.80 LDL-C restriction Note that these comparisons are conservative as the reference values from the THIN population also includes those that meet the restrictions and the LDL-C thresholds are lower than in the NICE recommendations. However, DS does not consider that the baseline LDL-C levels for positions 2a and 4a are adequately reflected by the baseline LDL-C for patients not eligible for ALI/EVO. Most patients eligible for ALI/EVO do not receive these therapies in NHS clinical practice (as discussed in the previous row above). Therefore, the majority of patients eligible for ALI/EVO should be included in position 2a/4a to accurately reflect NHS patients, and the baseline LDL-C for analyses in these positions should also reflect this.
Issue 4: Subgroup analyses by CV risk and HeFH	
	The following statements in the technical engagement report is potentially misleading, *"The company did not present subgroup analyses based on presence of HeFH"; "The company did not present subgroup analyses based on CV risk".* These statements are true for the cost-effectiveness analysis, but not for the clinical evidence. We suggest that the statements are amended to read, "*"The company did not present cost-effectiveness analyses in subgroups based on presence of HeFH"; "The company did not present cost-effectiveness analyses in subgroups based on CV risk".*
Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)?	Consistent treatment effects across subgroups with different baseline characteristics and risks have been observed in studies of comparator treatments and also in the BA studies[17]. Furthermore, as outlined in the clarification letter, HeFH represents only a small proportion of patients with hypercholesterolaemia and, since there are no dedicated familial hypercholesterolaemia studies conducted for BA and BA/EZE FDC, the numbers of patients included in our global phase 3 studies are small (see Table 13 in the company evidence submission). CLEAR Harmony included the largest group of patients with HeFH, and subgroup analysis suggested that the treatment effect is consistent with the non-HeFH population (see Figure 7 in the company evidence submission). A subgroup analysis for the pooled data from CLEAR Harmony and CLEAR Wisdom provided similar findings (Figure 3 in the Clarification

	Response); the *P*-value for the treatment interaction by presence of the HeFH status (HeFH vs. non-HeFH) was not significant academic in confidence information removed; the treatment effect in terms of LDL-C reduction at 12 weeks was significant in both the HeFH group academic in confidence information removed and the non-HeFH group academic in confidence information removed and therefore the company considers that an NMA in this subgroup would not be informative. Furthermore, the appropriateness of assuming that the treatment effect would be similar in patients with and without HeFH has been confirmed through UK clinical expert opinion, the clinical expert expected that BA and BA/EZE FDC would be trialled in HeFH patients in clinical practice also. Clinical efficacy for all available subgroups were presented in the company evidence submission (section B.2.7): • In some studies (CLEAR Wisdom, CLEAR Harmony, and 1002FDC-053), a separate subgroup analysis for HeFH patients was not feasible due to patient numbers (academic in confidence information removed per arm), therefore, HeFH patients were included in the secondary prevention (presence of CVD) subgroup. • HeFH was not recorded in CLEAR Tranquility. **Cost-effectiveness results for patients with HeFH and non-HeFH are presented in** Error! Reference source not found. **(**Error! Reference source not found. **to** Error! Reference source not found.**). As in TA393, the cost-effectiveness results in HeFH and non-HeFH patients were similar in the secondary prevention patients. HeFH itself seems to not be an important parameter for the cost-effectiveness, the ICER is strongly correlated with the baseline LDL-C as it has an impact on the treatment effect but also the underlying risk for CV events.** For consistency and to align with the TA393 submission, we also provide the results in the secondary prevention patients with HeFH based on data from THIN.
Is it appropriate to assume that treatment effect is similar in people with different CV risk?	The treatment effect for BA and BA/EZE FDC was consistent for patients with and without prior atherosclerotic cardiovascular disease[17] (see also Figure 7, Figure 8, Figure 9, and Figure 11 of the company evidence submission; the *P*-values for the subgroup interaction were not significant). Note that CLEAR Tranquility only enrolled patients with no recent history of CVD (Table 14 of the company evidence submission). UK clinical expert opinion has verified that there is no reason to

	assume differential treatment effect dependent on risk. Consistent treatment effect across subgroups with different baseline characteristics and risks have also been observed in studies of comparator treatments. **Cost-effectiveness results for the primary and secondary prevention patients are presented in** Error! Reference source not found. **(**Error! Reference source not found. **to** Error! Reference source not found.**). As shown in the tables, BA is cost-effective in primary prevention, and secondary prevention using and LDL-C threshold of ≥2.5 mmol/L in the statin intolerant population. In patients with maximum tolerated dose of statins, bempedoic acid is cost-effective in secondary prevention populations where ALI and EVO are currently indicated.** The full set of variables required to reliably calculate risk using the QRISK3 algorithm is currently not available from the CLEAR studies and is unlikely to be available in the future. Previous NICE technology assessments of the comparators have not used the underlying regulatory studies to calculate the QRISK2/3, as complete patient data for the algorithm is rarely available. QRISK score was used based on assumptions without using the study data to estimate the risk in TA385[20] and CG181[21] (instead scenario analyses using different QRISK% were performed in these models similar to what DS provided in the clarification letter). In TA393, QRISK were not used as it was not a suitable algorithm for the population that was assessed in that technology assessment.[22] Complete information (such as committee papers) from TA394 is not publicly available. Further, QRISK3 is not typically used in clinical practice, given the large number of variables required for calculation.
Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?	DS believes the model to be reflective of UK clinical practice as costs, resource usage, quality-of-life measurements and baseline risks were based on UK patients in a real-world setting (as stated in B.7.2). Additionally: • The CLEAR trials included academic in confidence information removed UK study sites and the patient population in the trials and the economic analysis are likely to be reflective of patients with primary hypercholesterolaemia or mixed dyslipidaemia in the UK in terms of

	baseline characteristics and the treatment pathway. Post-hoc analysis of UK and English patients from the CLEAR trials showed that baseline characteristics and efficacy results did not differ when only UK or English patients were included in the analysis.[23] • All data sources have been validated by UK clinicians. **Cost-effectiveness results for the requested subgroups are presented in** Error! Reference source not found. **(**Error! Reference source not found. **to** Error! Reference source not found.**).**
Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations	
What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice? For people who are statin intolerant and not eligible for EVO or ALI (population 2a)? For people who are statin intolerant and eligible for EVO or ALI (population 2b)? For people who are treated with a maximally tolerated statin and eligible for EVO or ALI? For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI?	DS has presented the proportion from the CLEAR studies in each of the populations (2a, 2b, 4a, and 4b) in Table 63 in the company submission. Further: **a):** In the HES/CPRD study[11] conducted by DS, academic in confidence information removed of the patients that was statin intolerant had a previous atherosclerotic cardiovascular disease event. This is in line with the proportion reported in the CLEAR studies. **b) & d):** In the study by Reynolds et al. (2019)[12] only 23% of the PCSK9i population were primary prevention patients when PCKS9i treatment was initiated. It should be noted that this proportion represent patients who receive treatment and not patients eligible for treatment.
Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI?	If statin intolerant: As DS understands, statin intolerance is not related to history of prior CV events. However, DS believes this patient population to be one of very high unmet need, given ezetimibe is the only currently available treatment option in these patients. If suitable for EVO/ALI: Yes, given that EVO and ALI are only recommended by NICE in patients with previous events or HeFH, a difference in the proportion of primary versus secondary prevention patients would be expected between patients who are suitable for EVO/ALI and those who are not as “non-suitable” patients would also include patients that have a high risk of CVD for other reasons (e.g. diabetes, hypertension, chronic kidney disease.)
Is it appropriate to generalise between primary and secondary prevention populations?	Consistent treatment effect across subgroups with different baseline characteristics and risks have been observed in studies of comparator treatments and also in the BA studies[17] (for instance see

	Issue 2.2, 2.3, 2.4, 4.2 and 4.3). **In order to inform decision making, cost-effectiveness results for the primary and secondary prevention patients are presented in** Error! Reference source not found. **(**Error! Reference source not found. **to** Error! Reference source not found.**). As shown in the tables, BA is cost-effective in primary prevention, and secondary prevention using and LDL-C threshold of ≥2.5 mmol/L in the statin intolerant population. In patients with maximum tolerated dose of statins, bempedoic acid is cost-effective in secondary prevention populations where ALI and EVO are currently indicated.** **See Issue 4.2 for details.**
Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort?	**In order to inform decision making, cost-effectiveness results for the requested subgroups are presented in** Error! Reference source not found. **(**Error! Reference source not found. **to** Error! Reference source not found.**).**
How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?	There is a disconnect between this question and the ERG question about using the 3-year+ post-event states as starting health states. The question should probably read: *How much time would typically elapse between the first CV event and the time where treatment with BA/placebo/ALI/EVO is initiated given that treatment with statins and EZE is first trialled in patients?* Regardless, DS acknowledges that there is uncertainty around this assumption and accepts the ERG approach of using stable disease as the starting health state.
Issue 6: Methodological uncertainty in the company and ERG network meta-analysis	
Should the company's revised NMA or ERG's NMA be used for decision making?	The company NMAs included all relevant study evidence while the ERG NMAs were limited to evidence in patients with prior EZE. While there is a wealth of evidence in the overall population of patients with or without EZE use and other background LDL-C lowering treatments, the evidence base within patients with prior EZE use is very limited for all interventions. The ERG's NMAs were based on only two studies per NMA, with data being taken from subgroups based on very small patient numbers in each group (CLEAR Harmony, n = 112 and 53; ODYSSEY CHOICE II, n = 34,

	68 and 33) and in which it was unclear whether randomisation was stratified by prior EZE therapy (ODYSSEY LONGTERM). Therefore, there is potential for imbalance in patient characteristics between arms. The selection of this very small subset of the available evidence may be expected to introduce bias. Furthermore, the ERG's NMA was not able to provide comparative efficacy estimates vs. all relevant comparators. Specifically, no comparison with EVO was possible. The ERG has not presented evidence to support their assumption that use of efficacy data for patient populations with or without prior EZE therapy to address the population in whom EZE does not appropriately control LDL-C is incorrect. As described in Issue 2 above, no evidence was identified to suggest that the treatment effect for BA or comparators differs by prior EZE use. Therefore, we consider that use of the wider, more comprehensive evidence base, allowing inclusion of all relevant comparators, is more appropriate. DS acknowledges the uncertainty and heterogeneity in the NMAs and has therefore explored a wide range of sensitivity and scenario analyses. In response to the ERG's comments on the original NMAs included in the company evidence submission, DS provided updated NMAs for LDL-C reduction at 12 weeks which incorporated all of the ERGs suggestions. These updated NMAs were adopted as the new company base case. In response to the ERG report, DS has performed further sensitivity and scenario analyses for the updated NMAs. These further sensitivity and scenario analyses are presented in Appendix A. These analyses all used the updated NMAs provided including the ERG suggestions that were reported in the ERG Clarification Questions Response, 16 January 2020, as the base analysis. The following analyses were performed for the maximally tolerated statin NMA: 1. ODYSSEY LONGTERM included 2. ODYSSEY LONGTERM included and baseline LDL-C covariate removed (i.e. no covariates) 3. ODYSSEY LONGTERM included and baseline statin use as a covariate 4. ODYSSEY LONGTERM included and baseline EZE use as a covariate 5. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline LDL-C as a covariate **[new base case]** 6. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates 7. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline statin as a covariate 8. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline EZE as a covariate

	9. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 24-week data removed from the network where 12-week data for the same study was included 10. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 12-week data removed from the network where 24-week data for the same study was included The following analyses were performed for the statin-intolerant NMA: 11. Baseline LDL-C covariate removed (i.e. no covariates) 12. Baseline EZE use as a covariate As shown in the model fit tables (Appendix A, **Error! Reference source not found.** and **Error! Reference source not found.**), only addition of the baseline EZE covariate in the maximal tolerated network improved the model fit, and the improvement was small. As shown by the detailed results in Appendix A (**Error! Reference source not found.** to **Error! Reference source not found.**) all of these sensitivity analyses had a small impact on the NMA results and, in extension, the cost-effectiveness results. Analysis 9 and 10 was also tested with LDL-C baseline, statin use and EZE use as covariates with no substantial differences observed in the results. As suggested by the ERG, DS agrees that it is appropriate to include ODYSSEY LONGTERM and exclude ODYSSEY Mono, and proposes to adopt this NMA as the company base case (as indicated in the list above).
Issue 7: Use of 12-week study data cut off and evaluation of treatment waning	
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?	As reported in Table 21 in the EPAR report[15], in the open-label extension study (1002-050), improvements in LDL-C, other lipids, and hs-CRP with BA were durable through 52 weeks (−15.18 after 12 weeks and −15.82 after 52 weeks). commercial in confidence information removed [24,25] Additionally, a published, pooled analysis of all the CLEAR trials confirmed the 52 week results from the OLE study; this is consistent with what has been observed for other LDL-C lowering therapies.[17,26] DS considers percentage change in LDL-C at 24 weeks is not appropriate, given the primary endpoint for the phase 3 studies of BA and FDC was percentage change of LDL-C at 12 weeks. (Note that in studies where there was possible uptitration of the ALI dose at 12 weeks, with the

	primary measurement of the titrated dose at 24 weeks, the 24-week data were used in the NMA). The percentage LDL-C reduction has been shown to be consistent at 12 and 24 weeks with non-significant changes; this is shown in graphs also submitted to regulatory files[27] and in Figure 1 in the company response to the clarification questions. Sustained treatment effect has also been observed for the comparator studies. **Further, DS have been investigating the importance of excluding the 24-week ALI data and just using 12-week data (see** Error! Reference source not found.**). As shown in** Error! Reference source not found. **the impact is small for most treatment comparisons, but excluding some data for ALI, does have a modest impact on the ALI results. As removing that data arbitrarily reduces the size of the evidence base for those comparisons, DS proposes to retain all evidence.**
Is it plausible that a treatment waning effect may occur with BA?	**No waning of treatment effect is expected. See Issue 7.1 and the following further detail:** No reference is made to a potential waning of the treatment effect for BA within the marketing authorisation, and there is no mechanistic reason to expect a waning of the treatment effect.[3] Small numerical differences in LDL-C reduction over time are observed for BA and for comparator interventions, and these are expected to be related to treatment discontinuation rather than waning of the treatment effect in patients complying with and persisting on treatment. A treatment discontinuation rate of 6.7% was included in the cost-effectiveness model, and it was assumed that the treatment effect is immediately lost for patients discontinuing treatment. Addition of a putative waning of the treatment effect for patients continuing treatment would introduce a risk of double counting. Waning of treatment effects has not been explored in cost-effectiveness analyses in previous technology assessments for comparator treatments[20,22,28] despite observed small numerical differences in LDL-C reduction over time in the comparator studies.
In clinical practice, would people stop treatment with BA after a certain time period?	As with any therapy, some discontinuation of treatment over time may occur. However, there is no specific treatment time period for BA mentioned in assessment reports or in guidelines. Similarly, there is no specific time period for treatment with the comparator therapies mentioned in assessment reports or guidelines.[3,4,20,22,28]
Issue 8: Health related quality of life	

Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?	The ERG's approach to utility modelling is not consistent with previous technology assessments and NICE guidelines within the area, is more complex and has little impact on the cost-effectiveness results. However, DS is willing to accept the ERG's approach to modelling utilities as outlined in the ERG report.
Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?	DS is willing to accept the ERG's modelling of utilities.
Issue 9: Costing of ALI/EVO administration and CV events	
In clinical practice, would you expect ALI or EVO to be administered in a hospital setting, with an annual follow up with a consultant?	DS is willing to accept the ERG's approach to costing ALI/EVO administration.

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NICE National Institute for Health and Care Excellence

Technical engagement response form – Appendices [updated 14 July]

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **3 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Kyle Dunton
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Daiichi Sankyo
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Abbreviations: ALI = alirocumab; BA = Bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed dose combination pill; CrI = credible interval; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; CVD = cardiovascular disease; DIC = Deviance information criterion; DS = Daiichi Sankyo; EPAR = European public assessment report; ERG = evidence review group; EVO = evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; HES = Hospital Episode Statistics; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NA = not applicable; NHS = National Health Service; NMA = network meta-analysis; NMB = Net monetary benefit; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; pD = effective number of parameters.; QALY = quality-adjusted life-year; THIN = The Health Improvement Network; UK = United Kingdom.

Appendix A: Network meta-analyses sensitivity analyses

DS acknowledges the uncertainty and heterogeneity in the NMAs and has therefore explored a wide range of sensitivity and scenario analyses. In response to the ERG's comments on the original NMAs included in the company evidence submission, DS provided updated NMAs for LDL-C reduction at 12 weeks which incorporated all of the ERGs suggestions. These updated NMAs were adopted as the new company base case. In response to the ERG report, DS has performed further sensitivity and scenario analyses for the updated NMAs. These further sensitivity and scenario analyses are presented in Appendix A. These analyses all used the updated NMAs provided including the ERG suggestions that were reported in the ERG Clarification Questions Response, 16 January 2020, as the base analysis.

In response to comments from the ERG and Technical Team, DS proposes to adopt analysis 5 listed below as the new company basecase for the maximally tolerated statin NMA. This analysis includes ODYSSEY LONGTERM and excludes ODYSSEY Mono.

The following analyses were performed for the maximally tolerated statin NMA:

1) ODYSSEY LONGTERM included
2) ODYSSEY LONGTERM included and baseline LDL-C covariate removed (i.e. no covariates)
3) ODYSSEY LONGTERM included and baseline statin use as a covariate
4) ODYSSEY LONGTERM included and baseline EZE use as a covariate
5) ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline LDL-C as a covariate **[new base case]**
6) ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates
7) ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline EZE as a covariate
8) ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline statin as a covariate
9) ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 24-week data removed from the network where 12-week data for the same study were included
10) ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 12-week data removed from the network where 24-week data for the same study were included

The results and model fit information for these scenario and sensitivity analyses for the maximally tolerated statin network are summarised in Table A-1 to Table A-4**Error! Reference source not found.**. Table A-5 presents a comparison of the new company base case with the published NMA reported by Toth et al., 2017. The results and model fit information for these scenario and sensitivity analyses for the statin intolerant network are summarised in Table A-6 and Table A-7.

Table A-1. Maximally tolerated statin NMA – Including ODYSSEY MONO

Treatment	Estimated difference in % change in LDL−C from baseline compared with EZE		
	Mean	95% CrIs	*P* value
Revised results provided in Response to ERG Clarification Questions (16 January 2020)			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.6072
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1747
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0135
ALI (150 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0065
1.ODYSSEY LONGTERM included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.6083
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1700
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0097
ALI (150 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0033
2. ODYSSEY LONGTERM included and baseline LDL-C covariate removed (i.e. no covariates)			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.6647
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1293
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0133
ALI (150 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0070
3. ODYSSEY LONGTERM included and baseline statin use as a covariate			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.5563
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1267
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0143

ALI (150 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0037
4. ODYSSEY LONGTERM included and baseline EZE use as a covariate			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.8010
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1633
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0043
ALI (150 mg)+statin+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0023

Abbreviations: ALI = alirocumab; BA = bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed-dose combination pill; CrI = credible interval; EVO = evolocumab; EZE = ezetimibe; LDL = low-density lipoprotein; NMA = network meta-analysis.

Table A-2. Maximally tolerated statin NMA – Excluding ODYSSEY MONO

5. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline LDL-C as a covariate [new base case]			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.6290
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1733
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin+EZE	NA (only investigated in ODYSSEY Mono)		
ALI (150 mg)+statin+EZE	NA (only investigated in ODYSSEY Mono)		
6. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.6910
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1373
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
7. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline EZE as a covariate			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.7663
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1703
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
8. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline statin as a covariate			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.5353
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1387

EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
9a. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 24 week data removed from the network where 12-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.9117
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1233
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
9b. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline LDL-C covariate, and 24 week data removed from the network where 12-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.884
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1273
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
9c. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline ezetimibe covariate, and 24 week data removed from the network where 12-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.7647
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1440
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
9d. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline statin covariate, and 24 week data removed from the network where 12-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.8090
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1197
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
10a. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 12 week data removed from the network where 24-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.9183
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1370
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001

ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
10b. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline LDL-C covariate, and 12 week data removed from the network where 24-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.7897
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1383
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
10c. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline ezetimibe, and 12 week data removed from the network where 24-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.7110
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1413
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
10d. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline statin, and 12 week data removed from the network where 24-week data for the same study was included			
BA+statin	'academic in confidence information removed'	'academic in confidence information removed'	0.7607
FDC+statin[a]	'academic in confidence information removed'	'academic in confidence information removed'	0.1263
EVO+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (75 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001
ALI (150 mg)+statin	'academic in confidence information removed'	'academic in confidence information removed'	<0.0001

Abbreviations: ALI = alirocumab; BA = bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed-dose combination pill; CrI = credible interval; EVO = evolocumab; EZE = ezetimibe; LDL = low-density lipoprotein; NMA = network meta-analysis.

As observed in the previous NMAs, substantial heterogeneity was observed in the reduced (Odessey MONO excluded) maximally tolerated population (network 5 in Table A-2); with I2 of 86.8%. Cochran's Q was 324.7 with 43 degrees of freedom. The heterogeneity did not appear to be accounted for by the addition of covariates, based on the model fit statistics. The deviance information criterion for the fixed-effects model with covariate was 703.7 compared with 494.8 for the random-effects model and 719.3 compared with 498.1 for the models without baseline LDL-C included as a covariate. The total residual deviance for the random-effects model was 394.3 compared with 657.9 for the fixed-effects model. For some treatment comparisons, a difference was observed in the direct and indirect evidence. An explanatory variable that has not been included in the analysis may account for some of the underlying heterogeneity, however, results observed were similar for sensitivity analysis which considered the level of baseline statin use and ezetimibe as covariates (models fits were also similar to those with baseline LDL-C included as a covariate, DIC 496.2; total residual deviance 394.0 and DIC 491.3, total residual deviance 393.8 for the two sensitivity analysis respectively). As shown in Table A-3, the model fit was not substantially improved through the addition of baseline LDL-C as a covariate, nor by the addition of baseline statin or ezetimibe use. The level of heterogeneity observed is not in line with the assumptions underlying NMA, hence caution should be taken when interpreting the results and credible intervals.

Table A-3. Model fit parameters – maximum tolerated NMA – Original network

Model	Covariate	Total residual deviance	pD	DIC	Between-study standard deviation (s) (95% CrI)	Baseline covariate (95% CrI)
Random effects*	-	415.117	105.1	520.2	9.837 (7.264-13.016)	-
	Baseline LDL-C	414.52	103.6	518.1	9.93 (7.32-13.14)	0.07 (−0.02 to 0.068)
	EZE	413.951	97.8	511.7	8.325 (1.264-11.097)	-1.204 (−1.841 to −0.602)
	Statin	414.0189	105.0	519.0	9.950 (8.898-10.876)	0.083 (−0.056 to 0.130)

Abbreviations: CrI = credible interval; DIC = Deviance information criterion; EZE = ezetimibe; LDL-C = Low-density lipoprotein cholesterol; NMA = network meta-analysis; pD = effective number of parameters.

Table A-4. Model fit parameters – maximum tolerated NMA - Models 5 to 10

Model		Analysis Number	Covariate	Total residual deviance	pD	DIC	Between study standard deviation (s) (95% CrI)	Baseline covariate (95% CrI)
Random effects*		6	-	394.71	103.4	498.1	9.885 (7.280, 13.023)	-
		5	**Baseline LDL-C**	**394.292**	**100.5**	**494.8**	**9.946 (7.338, 13.179)**	**-0.072 (−0.208, 0.059)**
		7	Ezetimibe	393.8	97.5	491.3	8.217 (6.020, 10.926)	-1.224 (-1.842, -0.615)
		8	Statin	394.0	102.2	496.2	9.941 (7.335, 13.204)	0.081 (-0.052, 0.223)
	24 week adalimumab data removed from the network where 12-week data for the same study was included	9a	-	281.944	76.3	358.2	7.808 (5.259, 11.013)	-
		9b	Baseline LDL-C	281.510	77.1	358.6	8.011 (5.329, 11.514)	-0.002 (-0.129, 0.123)
		9c	Ezetimibe	280.472	74.2	354.7	7.524 (5.146, 10.767)	-0.779 (-1.553, -0.016)
		9d	Statin	281.601	78.8	360.4	8.031 (5.479, 11.641)	0.124 (-0.097, 1.50)
	12 week adalimumab data removed from the network where 24-week data for the same study was included	10a	-	286.4	82.5	368.8	8.200 (5.4505, 11.892)	-
		10b	Baseline LDL-C	285.302	78.1	363.4	8.414 (5.569, 12.071)	-0.054 (-0.186, 0.075)
		10c	Ezetimibe	284.852	75.1	360.0	7.180 (4.659, 10.375)	-0.943 (-1.6920, -0.294)
		10d	Statin	285.002	80.0	365.0	8.486 (5.665, 12.218)	0.048 (-0.077, 0.180)

CrI = credible interval; DIC = deviance information criterion; LDL-C = low-density lipoprotein cholesterol; pD = effective number of parameters.
Bolded text indicates the new Company basecase model.
Total residual deviance is the measure of the error in the model (the lower the better).
For the effective number of parameters, the lower the better. The number of parameters in a fixed-effects model = n studies (30) + n treatments (7) − 1 + number of covariates (1) =37. If a random-effects model gives a value close to 37, then it suggests a fixed-effects model is likely to be adequate.
The deviance information criterion is the model error penalised by model complexity (the lower the better; a difference of > 5 is typically considered to be meaningful).

High statistical heterogeneity also has been reported by other researchers in NMA of maximally tolerated statin studies.[1] Also consistent with our findings, the authors reported that sensitivity analyses investigating heterogeneity did not substantially change their results. Table A-5 compares the new company basecase NMA results with those from a published NMA of evolocumab, alirocumab, and ezetimibe trials in patients requiring further LDL-C reduction while on maximally tolerated medium- or high-intensity statin.[2]

Table A-5. Comparison of the new company base-case NMA results in maximally tolerated statin studies with those reported by Toth et al. (2017)[2]

	Estimated difference in % change in LDL-C from baseline compared with ezetimibe			
	NMA		Toth et al. (2017)[2]	
Treatment	Mean	95% CrIs	Mean	95% CrIs
Evolocumab + statin	'academic in confidence information removed'	'academic in confidence information removed'	−45.3[a]	−50.9 to −39.8
Alirocumab (75 mg) + statin	'academic in confidence information removed'	'academic in confidence information removed'	−26.1	−31.2 to −20.8
Alirocumab (150 mg) + statin	'academic in confidence information removed'	'academic in confidence information removed'	−32.5	−40.8 to −23.9

CrI = credible interval; FDC = bempedoic acid and ezetimibe fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; NR = not reported.

[a] Post-hoc analysis combining evolocumab 140 mg and evolocumab 420 mg. The estimate for evolocumab 140 mg was 'academic in confidence information removed'.

The following analyses were performed for the statin-intolerant NMA:

1. Baseline LDL-C covariate removed (i.e. no covariates)
2. Baseline EZE use as a covariate

Scenario and sensitivity analyses of the statin intolerant network is presented in Table A-6 and Table A-7. No improvement in model fit was observed in comparison with the previous company base case NMA for statin intolerant studies; the company therefore proposes not to change the base-case NMA for the statin intolerant population.

Table A-6. Statin intolerant NMA

Treatment	Mean	95% CrIs	*P* value
Revised NMA results provided in Response to ERG Clarification Questions, 16 Jan 2020			
BA	'academic in confidence information removed'	'academic in confidence information removed'	0.0985
BA+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0024
EVO	'academic in confidence information removed'	'academic in confidence information removed'	0.0015
EVO+EZE[a]	'academic in confidence information removed'	'academic in confidence information removed'	—
ALI (75 mg)	'academic in confidence information removed'	'academic in confidence information removed'	0.0004
ALI (150 mg)	'academic in confidence information removed'	'academic in confidence information removed'	0.0004
1. Baseline LDL-C covariate removed (i.e. no covariates)			
BA	'academic in confidence information removed'	'academic in confidence information removed'	0.0647
BA+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0012
EVO	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
EVO+EZE[a]	'academic in confidence information removed'	'academic in confidence information removed'	—
ALI (75 mg)	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
2. Baseline EZE use as a covariate			
BA	'academic in confidence information removed'	'academic in confidence information removed'	0.0985
BA+EZE	'academic in confidence information removed'	'academic in confidence information removed'	0.0023
EVO	'academic in confidence information removed'	'academic in confidence information removed'	0.0020
EVO+EZE[a]	'academic in confidence information removed'	'academic in confidence information removed'	—
ALI (75 mg)	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001
ALI (150 mg)	'academic in confidence information removed'	'academic in confidence information removed'	< 0.0001

Abbreviations: ALI = alirocumab; BA = bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed-dose combination pill; CrI = credible interval; ERG = evidence review group; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis.

Table A-7. Model fit – statin intolerant NMA

Model	Covariate	Total residual deviance	pD	DIC	Between study standard deviation (s) (95% CrI)	Baseline covariate (95% CrI)
Random effects	-	89.937	21.4	111.3	5.383 (1.163-13.338)	-
	Baseline LDL-C	90.053	22.1	112.2	6.177 (1.470-15.344)	-0.159 (−1.130 to 0.947)

	EZE	89.985	21.6	111.6	6.289 (1.456-15.784)	0.056 (−0.382 to 0.283)

Abbreviations: CrI = credible interval; DIC = Deviance information criterion; EZE = ezetimibe; LDL-C = Low-density lipoprotein cholesterol; NMA = network meta-analysis; pD = effective number of parameters..

Appendix B. Updated Cost-effectiveness Results

Formal agreement from the Department of Health for the new proposed prices for bempedoic acid and FDC was received 30/06/2020. The new prices are as follows:

- 28-pack BA: £55.44 (£1.98 per day)
- 28-pack FDC BA/EZE: £55.44 (£1.98 per day)

DS agrees with the following changes to the original submission model and these settings have been adopted for all analyses presented in this appendix, unless stated otherwise:

- ERG's correction of minor errors
- ERG's assumption regarding the characteristics of the starting population: % in primary prevention and % without HeFH
- ERG's preferred assumptions regarding utility for subpopulations
- ERG' preferred assumptions on health-state costs
- ERG' preferred assumption that 0% of patients have recurrent CV events at baseline in position 2a

Please see Issue 2 and Issue 6 for the rationale of the rejection of Change 3, and see Issue 3 for the rationale of the rejection of Change 4a-b.

Furthermore, based on the ERG feedback the updated NMA including ODYSSEY LONGTERM and excluding ODYSSEY Mono (scenario analysis 5) was selected as the new company base case.

Finally, the following errors was corrected in the ERG model:

- QALYs in position 2b, 4a and 4b in MI3+ were calculated based on patient numbers in the MI2 health state rather than the MI3+ state
- QALY calculations in position 2b, 4a and 4b in UA3+ were not linked to the number of patients alive and in the UA3+ health state. The utility weight was just applied for the remainder of the model time horizon.

Table B-1. Cost-effectiveness Results[a] – BA – new base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£/QALY)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	9,603.52	12.08	9.05								
BA	14,375.64	12.30	9.24	4,772.12	0.22	0.19	-938.29	-938.29	978.62	978.62	24,895
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
BA	22,350.50	10.39	7.02								
Alirocumab	47,554.22	10.47	7.08	25,203.72	0.08	0.06	-23,998.17	-23,998.17	-23,395.40	-23,395.40	418,128
Evolocumab	47,993.83	10.51	7.11	25,643.34	0.12	0.09	-23,865.11	133.06	-22,976.00	419.40	15,353
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	16,751.31	10.18	6.88								
BA	21,476.08	10.28	6.95	4,724.78	0.10	0.07	-3,326.13	-3,326.13	-2,626.80	-2,626.80	67,562
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
BA	21,471.21	9.78	6.59								
Alirocumab	46,120.19	10.07	6.80	24,648.98	0.29	0.21	-20,364.63	-20,364.63	-18,222.46	-18,222.46	115,065
Evolocumab	46,885.52	10.28	6.95	25,414.31	0.50	0.36	-18,127.70	2,236.93	-14,484.39	3,738.06	5,098

Abbreviations: ALI = Alirocumab; BA = bempedoic acid; ERG = evidence review group; EVO = Evolocumab; EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life year; NMB = Net monetary benefit; QALY = quality-adjusted life-year.

[a] See settings on first page in Appendix B.

Table B-2. Cost-effectiveness Results[a] –BA/EZE FDC – new base-case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£/QALY)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	9,603.52	12.08	9.05								
BA/EZE FDC	14,196.48	12.30	9.24	4,592.96	0.22	0.19	-759.13	-759.13	1,157.78	1,157.78	23,960
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
BA/EZE FDC	22,191	10.39	7.02								
Alirocumab	47,554	10.47	7.08	25,364	0.08	0.06	-24,158	-24,158.05	-23,555.28	-23,555	420,781
Evolocumab	47,994	10.51	7.11	25,803	0.12	0.09	-24,025	133.06	-23,135.88	419	15,353
Position 4a. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	16,751.31	10.18	6.88								
BA/EZE FDC	21,317.39	10.28	6.95	4,566.09	0.10	0.07	-3,167.44	-3,167.44	-2,468.11	-2,468.11	65,293
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate											
BA/EZE FDC	21,317	9.78	6.59								
Alirocumab	46,120	10.07	6.80	24,803	0.29	0.21	-20,518	-20,518	-18,376	-18,376	115,783
Evolocumab	46,886	10.28	6.95	25,568	0.50	0.36	-18,281	2,237	-14,638	3,738	5,098

Abbreviations: ALI = Alirocumab; BA = bempedoic acid; ERG = evidence review group; EVO = Evolocumab; EZE = ezetimibe; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life year; NMB = Net monetary benefit; QALY = quality-adjusted life-year.

[a] See settings on first page in Appendix B.

Appendix C: Cost-effectiveness in subgroups specified by NICE recommendations

Cost-effectiveness results in specific subgroups defined by the NICE recommendations for alirocumab and evolocumab are shown in **Error! Reference source not found.** to **Error! Reference source not found.**. Baseline LDL-C was estimated for each population segment based on analyses of the phase 3 BA and BA/EZE FDC study patient-level data. Additionally, Figure C-1 displays cost-effectiveness results dependent on baseline LDL-C for position 2 and 4. DS requests that these are taken into account for committee decision making purposes.

Table C-1. BA: Subgroup results - Statin intolerant population

	Population	LDL-C (based on threshold for PCSK9i)	PCSK9 appropriate	Recurrent CV at model baseline	Mean LDL-C at model baseline[a] (CLEAR-studies)	Deterministic ICER[b]	Probabilistic ICER[b]
1	Without CVD	Non-HeFH or HeFH <5	No	0%	'commercial in confidence information removed'	EZE: £24,209	EZE: £23,706
2	Without CVD, HeFH[f]	>5.0	Yes	0%	'academic/commercial in confidence information removed'	ALI: £383,561 EVO: £265,075	ALI: £386,895 EVO: £281,461
3[c]	With CVD (high risk or very high risk)	High risk <4.0 Very high risk < 3.5	No	'commercial in confidence information removed' [a]	'commercial in confidence information removed'	EZE: £31,446	EZE: £30,957
					'commercial in confidence information removed'	EZE: £21,837	EZE: £21,227
					'commercial in confidence information removed'	EZE: £19,860	EZE: £19,348
					'commercial in confidence information removed'	EZE: £15,580	EZE: £15,134
4	With CVD, high risk, Non-HeFH	>4.0	Yes	0%	'commercial in confidence information removed'	ALI: £370,259 EVO: £255,665	ALI: £366,608 EVO: £258,794
5	With CVD, very high risk, Non-HeFH	>3.5	Yes	100%	'commercial in confidence information removed'	ALI: £412,059 EVO: £284,017	ALI: £407,435 EVO: £297,321
6	With CVD, high or very high risk, HeFH[d]	<3.5	No	0%	'commercial in confidence information removed'	EZE: £41,875	EZE: £41,267
7	With CVD, high or very high risk, HeFH[d]	>3.5	Yes	'commercial in confidence information removed' [a]	'commercial in confidence information removed'	ALI: £430,614 EVO: £296,949	ALI: £417,634 EVO: £306,343

Abbreviations: ALI = Alirocumab; BA = bempedoic acid; CV = cardiovascular; CVD = cardiovascular disease; EVO = Evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; ICER = incremental cost-effectiveness ratio; LDL-C = Low-density lipoprotein cholesterol PSCK9i = proprotein convertase subtilisin/kexin type 9 inhibitors.

[a]Estimated from BA and FDC Phase 3 trials. [b]ICERs versus ALI and EVO is cost saving per QALY lost. [c]See Figure C-1 for details. [d]Using THIN data reported in TA393 to align with previous TAs.[e]LDL-C threshold. [f]No risk multiplier for HeFH applied, as risk in the primary prevention in the model is based on an assumed CV risk and not on baseline patient characteristics as in the secondary prevention population.

Table C-2. BA: Subgroup results - Maximum tolerated statin population

	Population	LDL-C (based on threshold for PCSK9i)	PCSK9 appropriate	Recurrent CV at model baseline	Mean LDL-C at model baseline[a] (CLEAR-studies)	Deterministic ICER[b]	Probabilistic ICER[b]
8	Without CVD	Non-HeFH or HeFH <5	No	0%	'commercial in confidence information removed'	EZE: £55,145	EZE: £55,475
9	Without CVD, HeFH[f]	>5.0	Yes	0	'commercial in confidence information removed'	ALI: £99,242 EVO: £61,067	ALI: £97,534 EVO: £60,652
10[c]	With CVD (high risk or very high risk)	High risk <4.0 Very high risk < 3.5	No	'commercial in confidence information removed' [a]	'commercial in confidence information removed'	EZE: £81,389	EZE: £82,084
					'commercial in confidence information removed'	EZE: £57,019	EZE: £56,264
					'commercial in confidence information removed'	EZE: £46,962	EZE: £46,949
					'commercial in confidence information removed'	EZE: £32,674	EZE: £32,563
11	With CVD, high risk, Non-HeFH	>4.0	Yes	0%	'commercial in confidence information removed'	ALI: £101,786 EVO: £62,066	ALI: £98,065 EVO: £60,290
12	With CVD, very high risk, Non-HeFH	>3.5	Yes	100%	'commercial in confidence information removed'	ALI: £116,231 EVO: £70,166	ALI: £114,537 EVO: £69,293
13	With CVD, high or very high risk, HeFH[d]	<3.5	No	0%	'commercial in confidence information removed'	EZE: £111,723	EZE: £114,466
14	With CVD, high or very high risk, HeFH[d]	>3.5	Yes	'commercial in confidence information removed' [a]	'commercial in confidence information removed'	ALI: £115,770 EVO: £70,131	ALI: £109,093 EVO: £66,858

Abbreviations: ALI = Alirocumab; BA = bempedoic acid; CV = cardiovascular; CVD = cardiovascular disease; EVO = Evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; ICER = incremental cost-effectiveness ratio; LDL-C = Low-density lipoprotein cholesterol PSCK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; THIN = The Health Improvement Network. *ICERs versus ALI and EVO is cost saving per QALY lost

[a]Estimated from BA and FDC Phase 3 trials. [b]ICERs versus ALI and EVO is cost saving per QALY lost. [c]See Figure C-1 for details. [d]Using THIN data reported in TA393 to align with previous TAs.[e]LDL-C threshold. [f]No risk multiplier for HeFH applied, as risk in the primary prevention in the model is based on an assumed CV risk and not on baseline patient characteristics as in the secondary prevention population.

Table C-3. FDC: Subgroup results - Statin intolerant population

	Population	LDL-C (based on threshold for PCSK9i)	PCSK9 appropriate	Recurrent CV at model baseline	Mean LDL-C at model baseline[a] (CLEAR-studies)	Deterministic ICER[b]	Probabilistic ICER[b]
1	Without CVD	Non-HeFH or HeFH <5	No	0%	'commercial in confidence information removed'	EZE: £23,298	EZE: £22,795
2	Without CVD, HeFH[f]	>5.0	Yes	0	'commercial in confidence information removed'	ALI: £386,017 EVO: £266,750	ALI: £389,351 EVO: £283,136
3[c]	With CVD (high risk or very high risk)	High risk <4.0 Very high risk < 3.5	No	'commercial in confidence information removed' [a]	'commercial in confidence information removed'	EZE: £30,376	EZE: £29,887
					'commercial in confidence information removed'	EZE: £21,084	EZE: £20,474
					'commercial in confidence information removed'	EZE: £19,172	EZE: £18,660
					'commercial in confidence information removed'	EZE: £15,031	EZE: £14,585
4	With CVD, high risk, Non-HeFH	>4.0	Yes	0%	'commercial in confidence information removed'	ALI: £372,607 EVO: £257,259	ALI: £368,956 EVO: £260,388
5	With CVD, very high risk, Non-HeFH	>3.5	Yes	100%	'commercial in confidence information removed'	ALI: £414,669 EVO: £285,785	ALI: £410,045 EVO: £299,089
6	With CVD, high or very high risk, HeFH[d]	<3.5	No	0%	'commercial in confidence information removed'	EZE: £40,392	EZE: £39,784
7	With CVD, high or very high risk, HeFH[d]	>3.5	Yes	'commercial in confidence information removed' [a]	'commercial in confidence information removed'removed'	ALI: £433,366 EVO: £298,820	ALI: £420,386 EVO: £308,214

Abbreviations: ALI = Alirocumab; BA = bempedoic acid; CV = cardiovascular; CVD = cardiovascular disease; EVO = Evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; ICER = incremental cost-effectiveness ratio; LDL-C = Low-density lipoprotein cholesterol PSCK9i = . proprotein convertase subtilisin/kexin type 9 inhibitors; THIN = The Health Improvement Network.

[a]Estimated from BA and FDC Phase 3 trials. [b]ICERs versus ALI and EVO is cost saving per QALY lost. [c]See Figure C-1 for details. [d]Using THIN data reported in TA393 to align with previous TAs.[e]LDL-C threshold. [f]No risk multiplier for HeFH applied, as risk in the primary prevention in the model is based on an assumed CV risk and not on baseline patient characteristics as in the secondary prevention population.

Table C-4. FDC: Subgroup results - Maximum tolerated statin population

	Population	LDL-C (based on threshold for PCSK9i)	PCSK9 appropriate	Recurrent CV at model baseline	Mean LDL-C at model baseline[a] (CLEAR-studies)	Deterministic ICER[b]	Probabilistic ICER[b]
8	Without CVD	Non-HeFH or HeFH <5	No	0%	'commercial in confidence information	EZE: £53,197	EZE: £53,527
9	Without CVD, HeFH[f]	>5.0	Yes	0	'commercial in confidence information	ALI: £99,881 EVO: £61,456	ALI: £98,173 EVO: £61,041
10[c]	With CVD (high risk or very high risk)	High risk <4.0 Very high risk < 3.5	No	'commercial in confidence information removed' [a]	'commercial in confidence information	EZE: £78,658	EZE: £79,353
					'commercial in confidence information	EZE: £55,101	EZE: £54,346
					'commercial in confidence information	EZE: £45,378	EZE: £45,365
					'commercial in confidence information	EZE: £31,561	EZE: £31,450
11	With CVD, high risk, Non-HeFH	>4.0	Yes	0%	'commercial in confidence information	ALI: £102,420 EVO: £62,441	ALI: £98,699 EVO: £60,665
12	With CVD, very high risk, Non-HeFH	>3.5	Yes	100%	'commercial in confidence information	ALI: £116,954 EVO: £70,588	ALI: £115,260 EVO: £69,715
13	With CVD, high or very high risk, HeFH[d]	<3.5	No	0%	'commercial in confidence information	EZE: £107,894	EZE: £110,637
14	With CVD, high or very high risk, HeFH[d]	>3.5	Yes	'commercial in confidence information removed' [a]	'commercial in confidence information	ALI: £116,510 EVO: £70,573	ALI: £109,833 EVO: £67,300

Abbreviations: ALI = Alirocumab; BA = bempedoic acid; CV = cardiovascular; CVD = cardiovascular disease; EVO = Evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; ICER = incremental cost-effectiveness ratio; LDL-C = Low-density lipoprotein cholesterol PSCK9i = . proprotein convertase subtilisin/kexin type 9 inhibitors; THIN = The Health Improvement Network.

[a]Estimated from BA and FDC Phase 3 trials. [b]ICERs versus ALI and EVO is cost saving per QALY lost. [c]See Figure C-1 for details. [d]Using THIN data reported in TA393 to align with previous TAs.[e]LDL-C threshold. [f]No risk multiplier for HeFH applied, as risk in the primary prevention in the model is based on an assumed CV risk and not on baseline patient characteristics as in the secondary prevention population.

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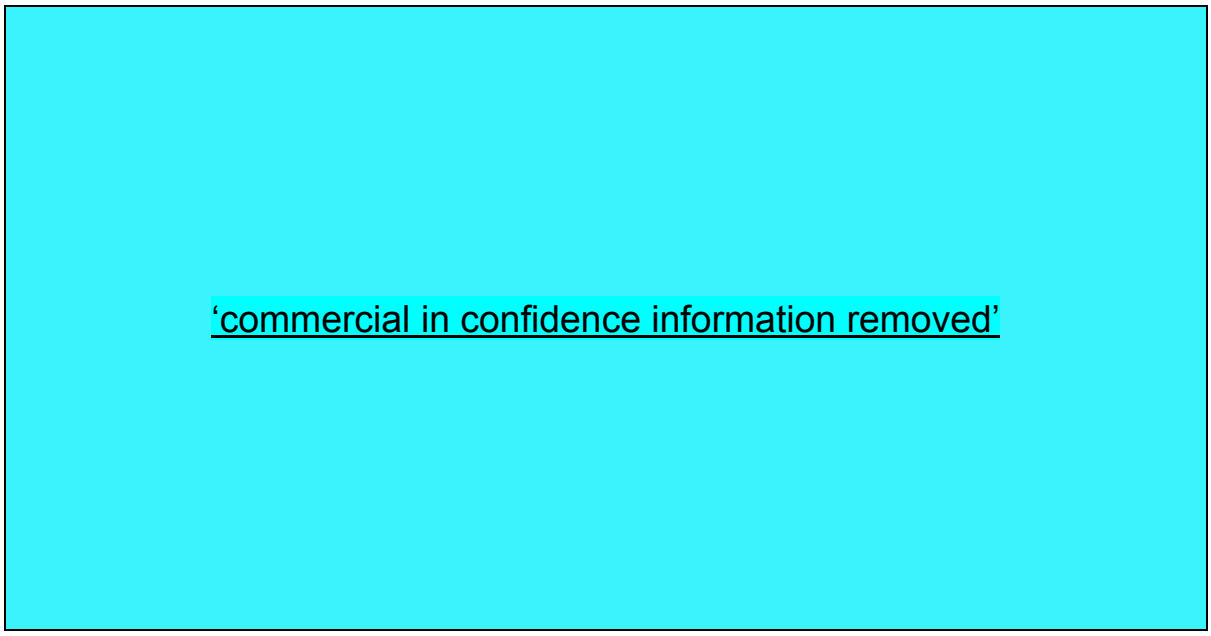
Figure C-1. BA – Subgroup 3* (Position 2) and Subgroup 10 (Position 4)**



see Table C-1, **Table C-2

Probabilistic results – cost-effectiveness planes:

Figure C-2. Subgroup/Analysis 1 - BA (see Table C-1)

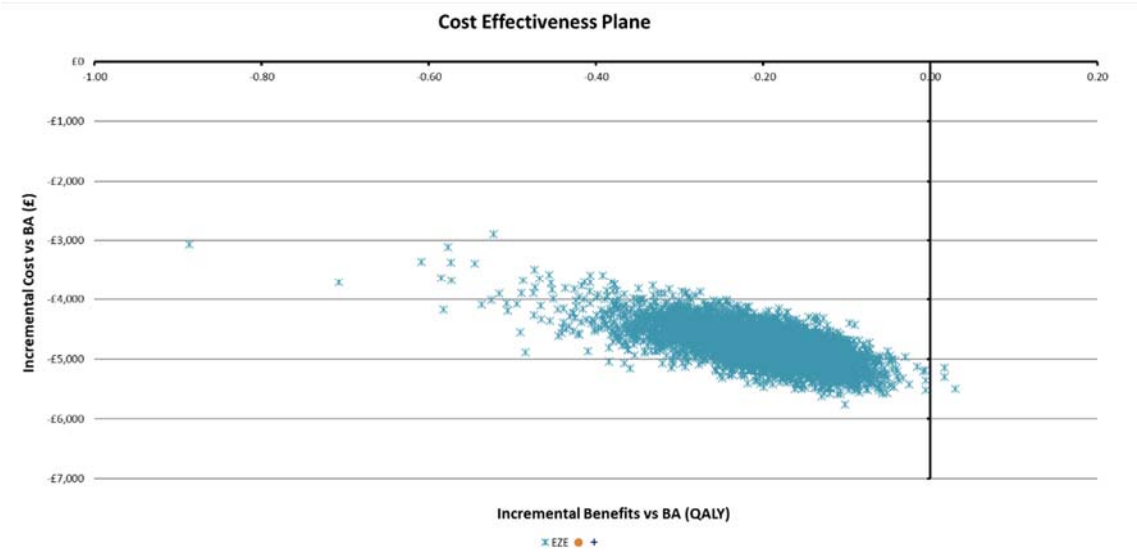


Figure C-3. Subgroup/Analysis 2 - BA (see Table C-1)

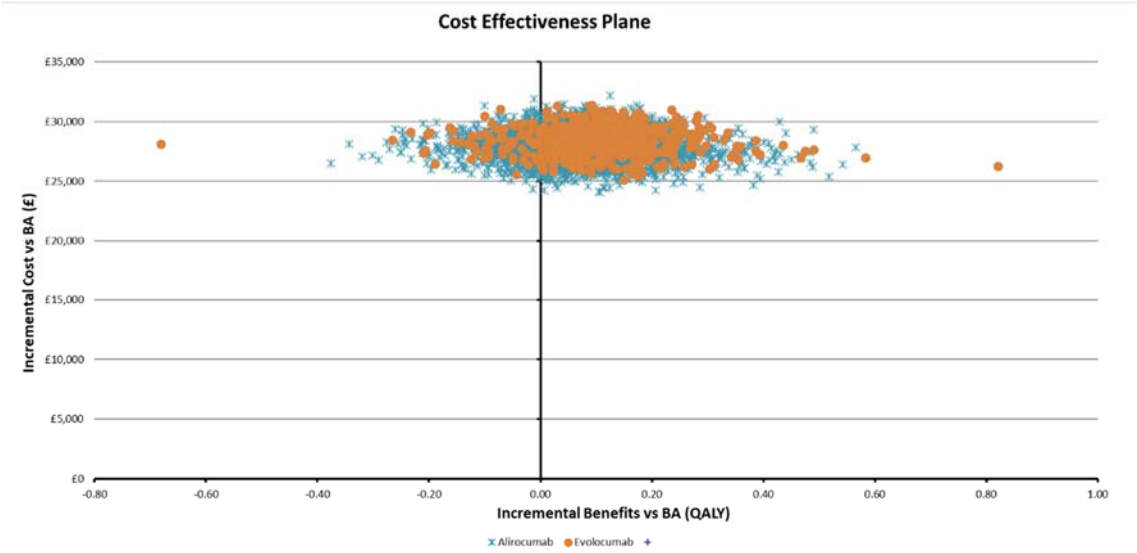


Figure C-4. Subgroup/Analysis 3a – BA (see Table C-1)

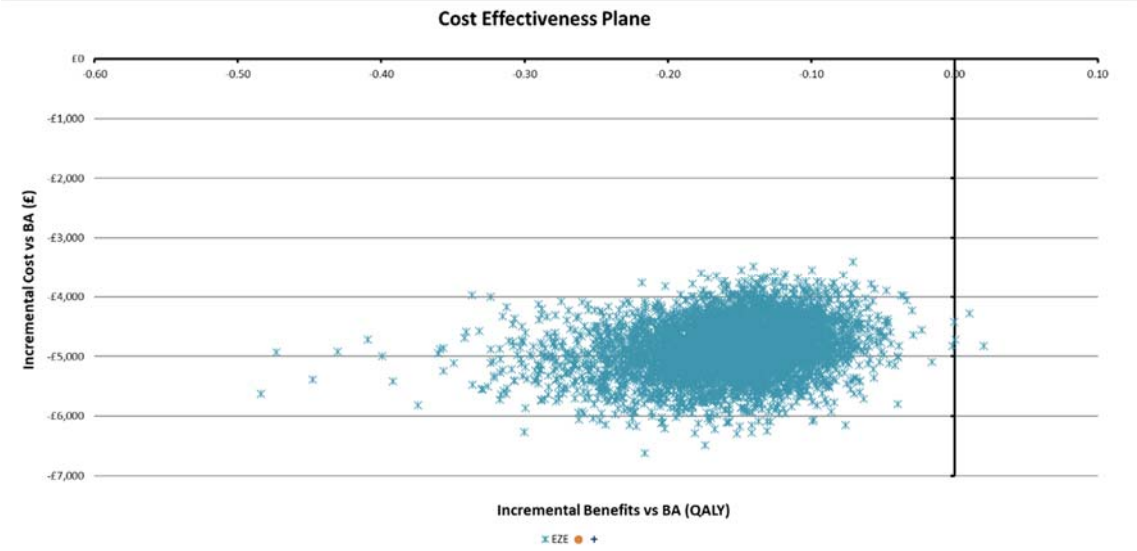


Figure C-5. Subgroup/Analysis 3b – BA (see Table C-1)

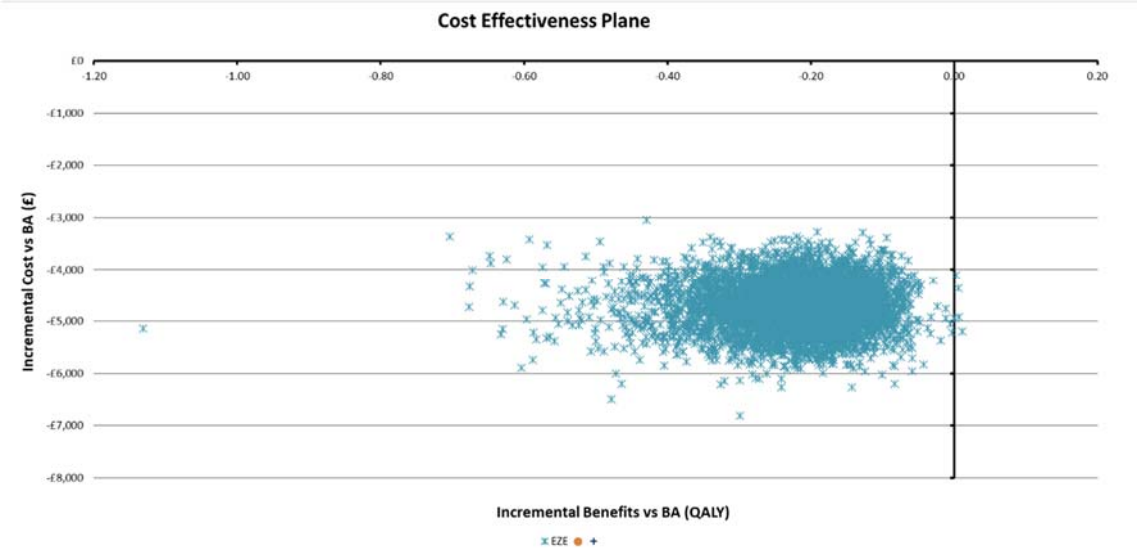


Figure C-6. Subgroup/Analysis 3c - BA (see Table C-1)

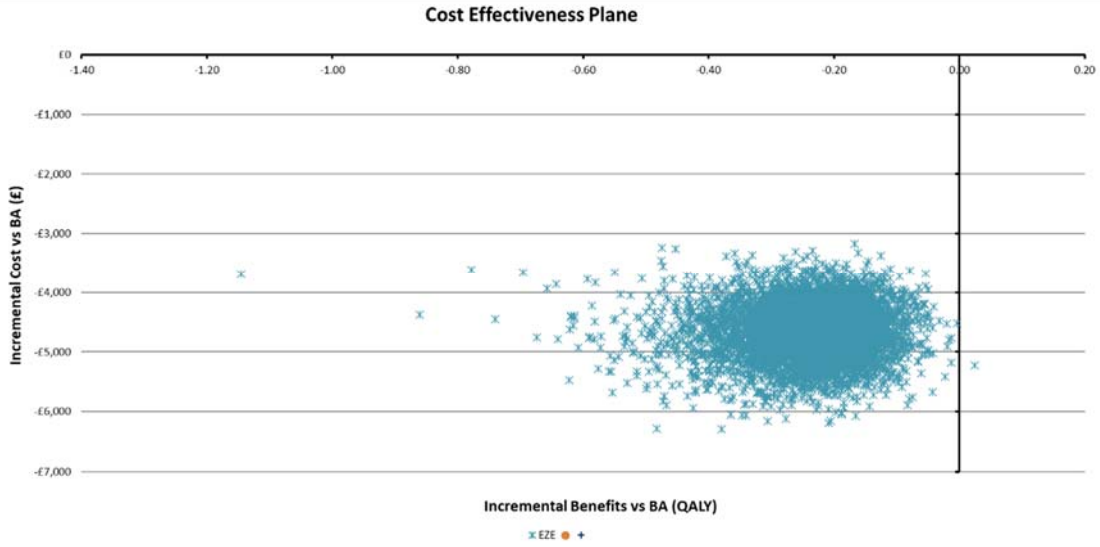


Figure C-7. Subgroup/Analysis 3d - BA (see Table C-1)

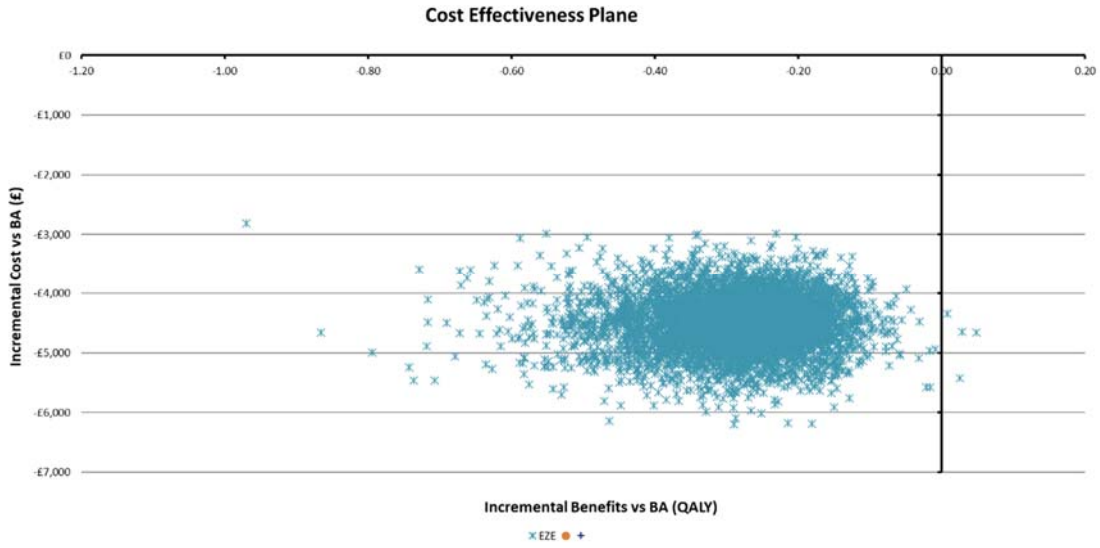


Figure C-8. Subgroup/Analysis 4 - BA (see Table C-1)

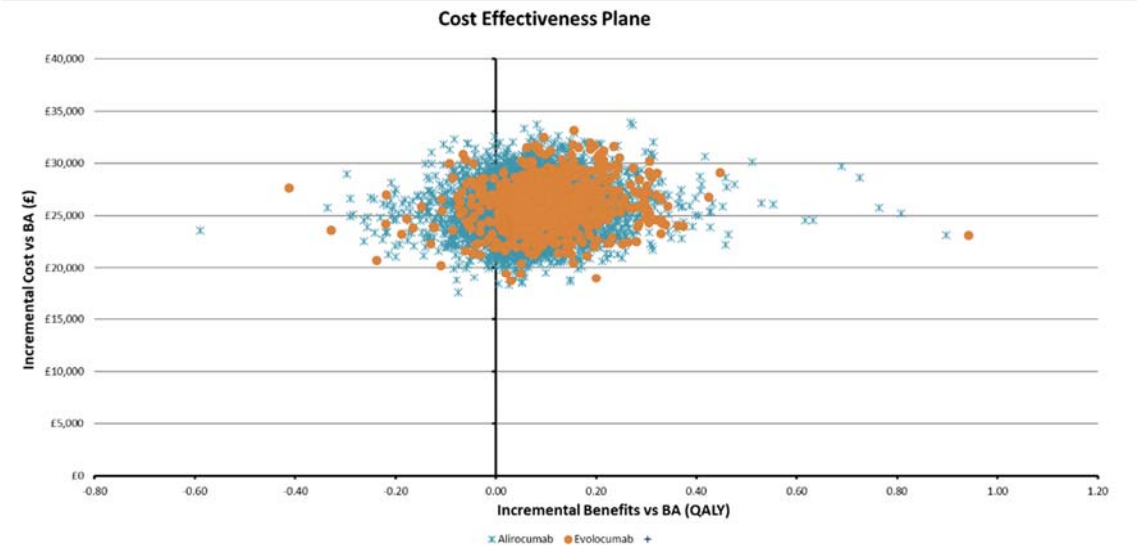


Figure C-9. Subgroup/Analysis 5 - BA (see Table C-1)

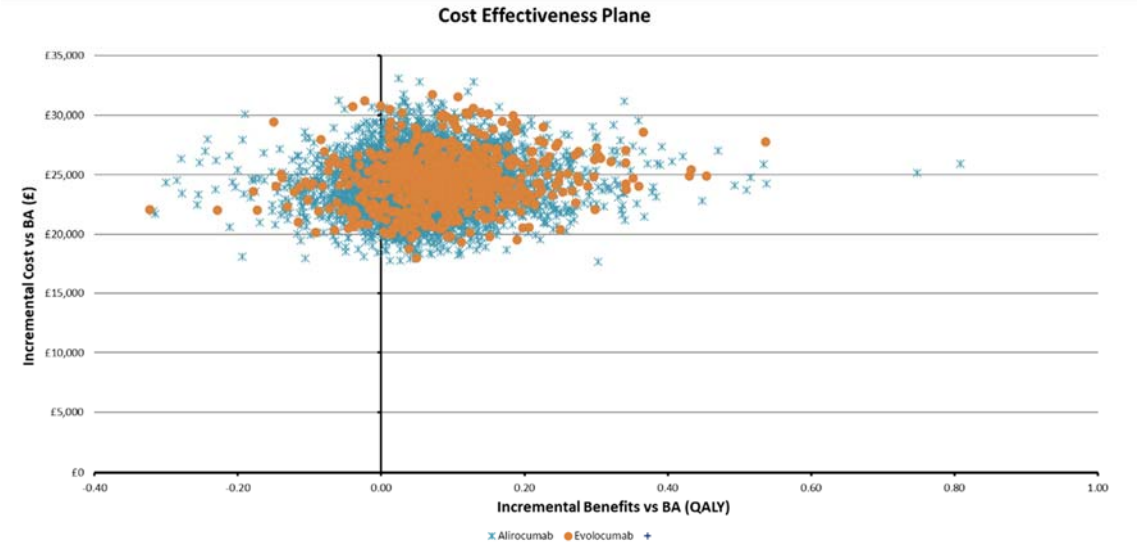


Figure C-10. Subgroup/Analysis 6 - BA (see Table C-1)

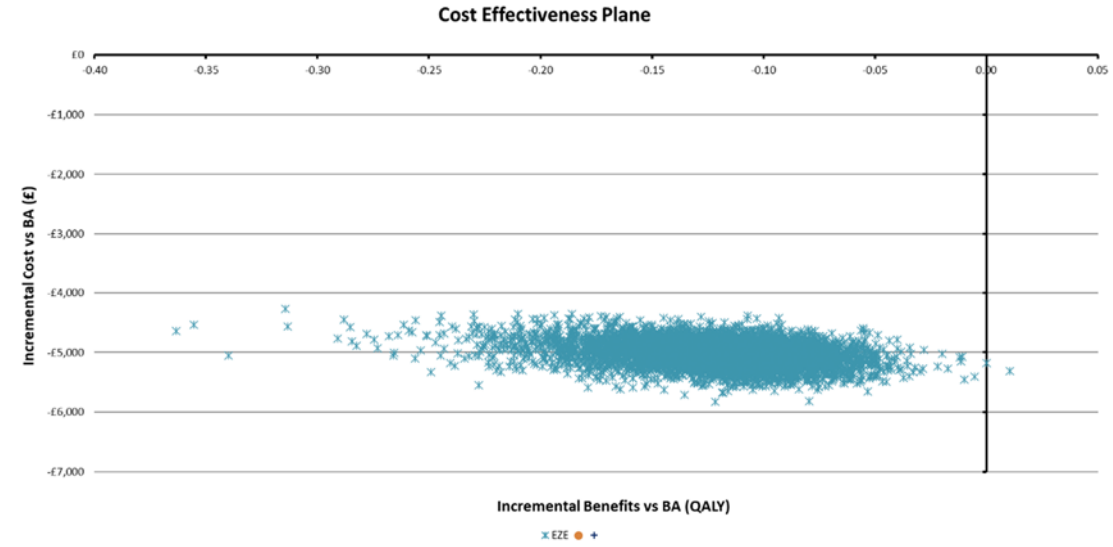


Figure C-11. Subgroup/Analysis 7 - BA (see Table C-1)

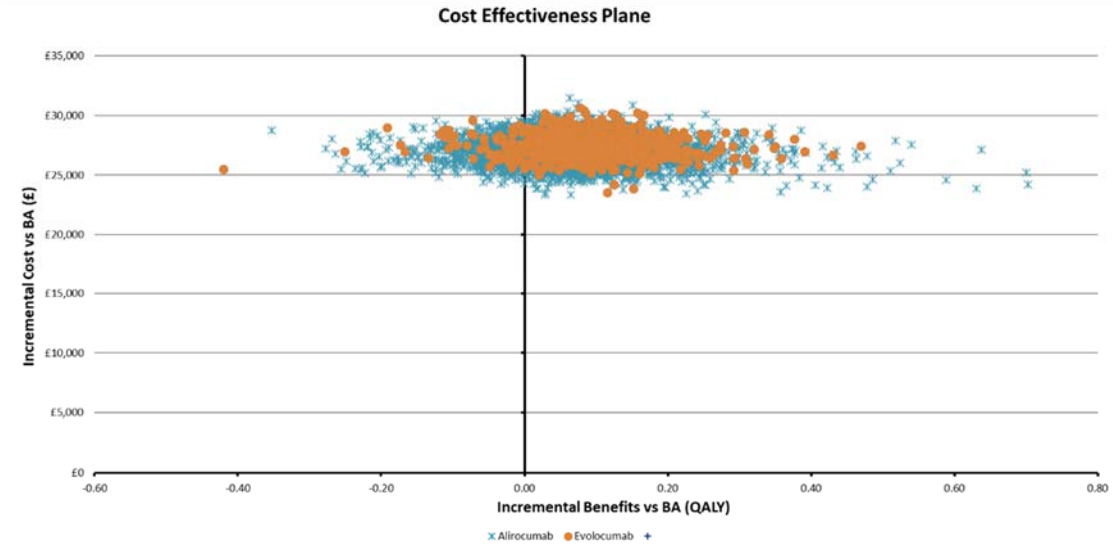


Figure C-12. Subgroup/Analysis 8 – BA (see Table C-2)

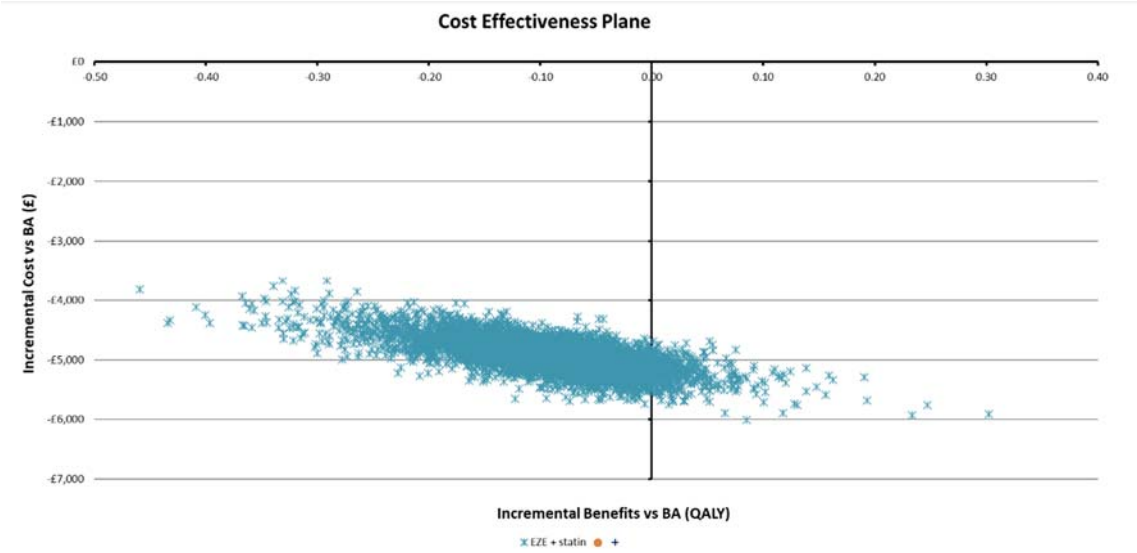


Figure C-13. Subgroup/Analysis 9 - BA (see Table C-2)

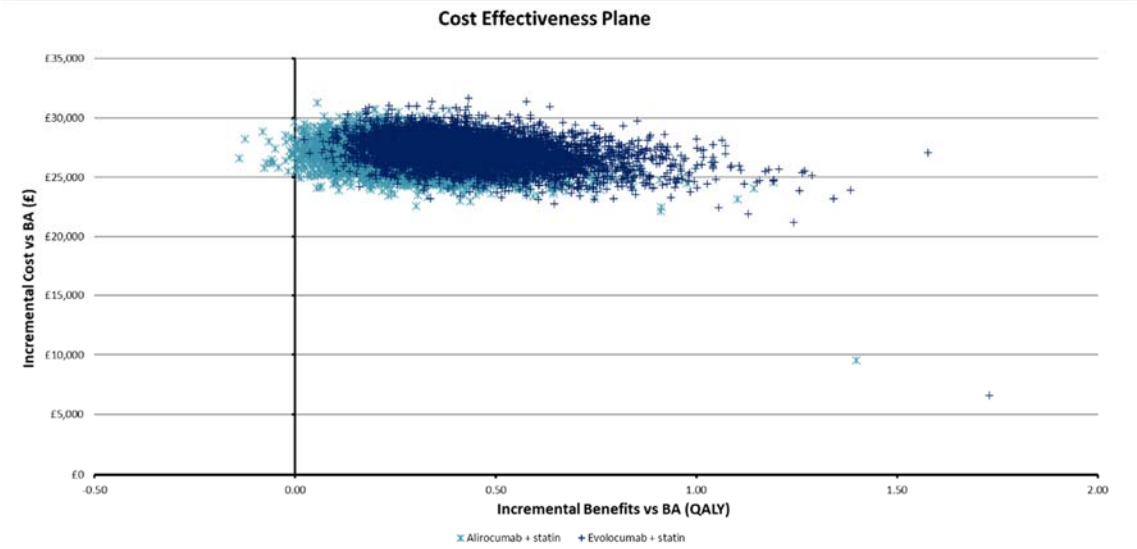


Figure C-14. Subgroup/Analysis 10a- BA (see Table C-2)

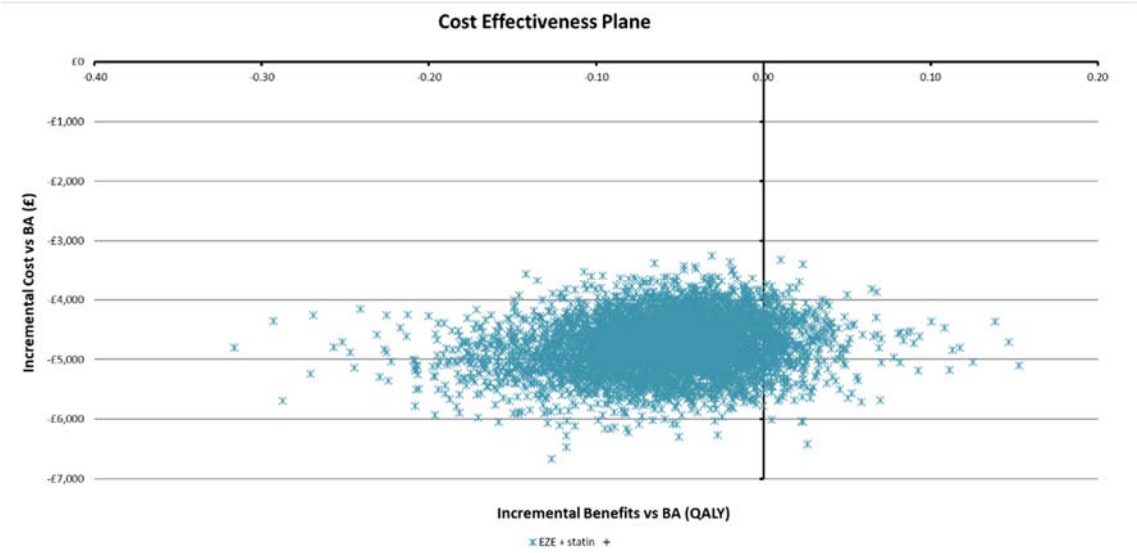


Figure C-15. Subgroup/Analysis 10b- BA (see Table C-2)

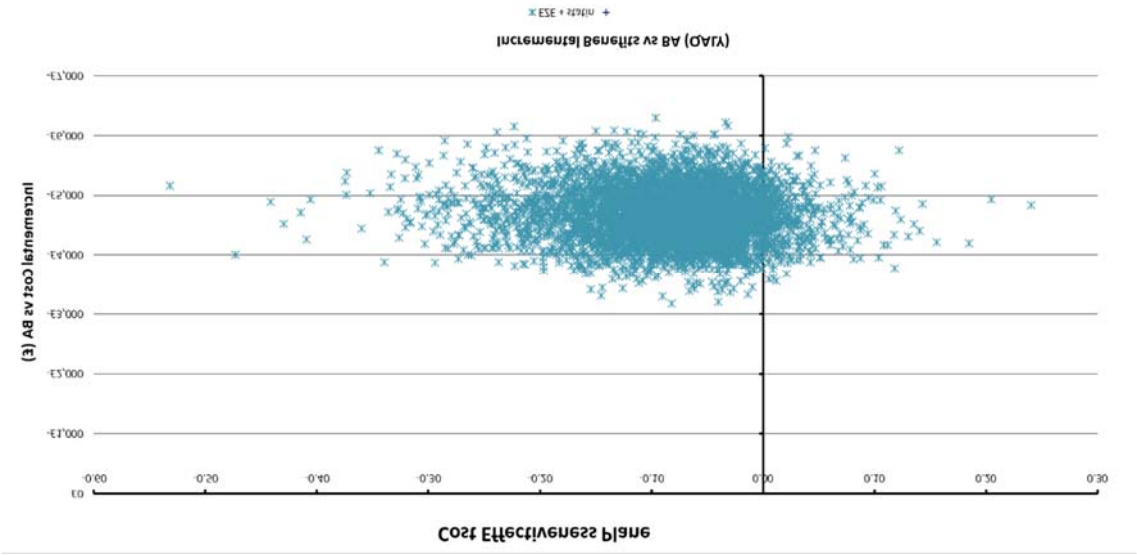


Figure C-16. Subgroup/Analysis 10c - BA (see Table C-2)

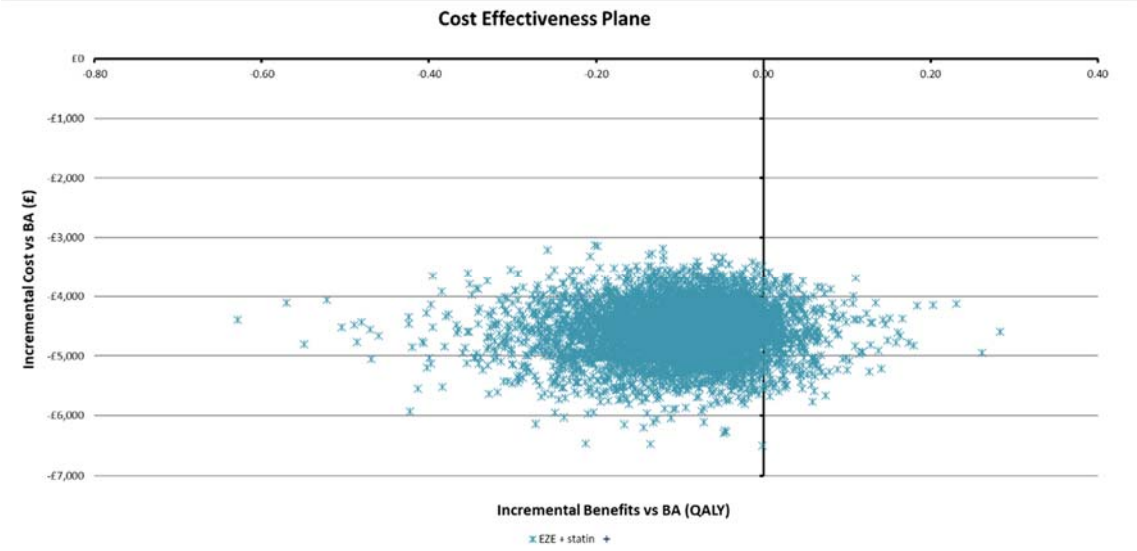


Figure C-17. Subgroup/Analysis 10d - BA (see Table C-2)

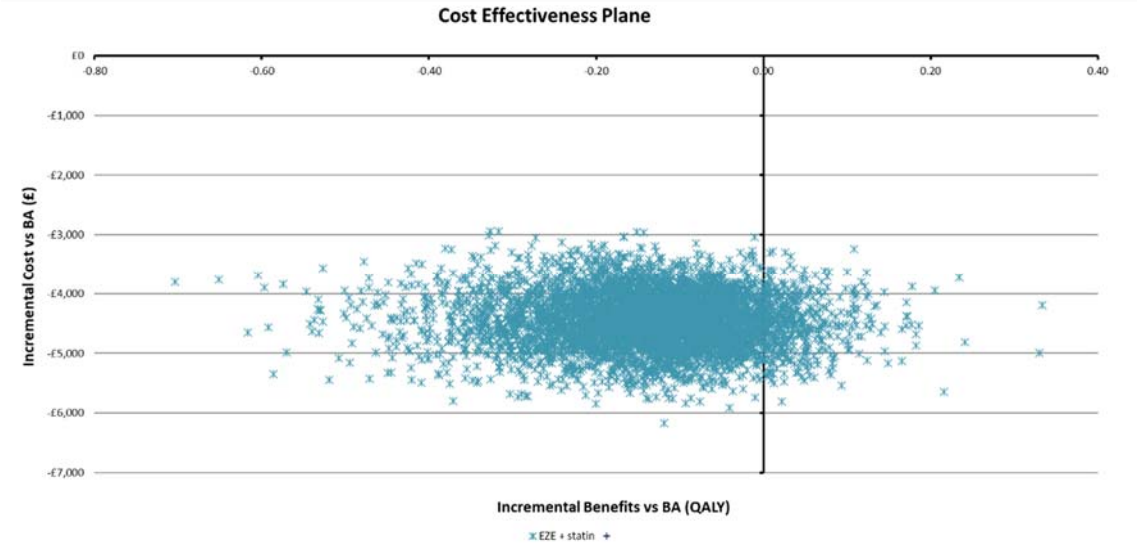


Figure C-18. Subgroup/Analysis 11- BA (see Table C-2)

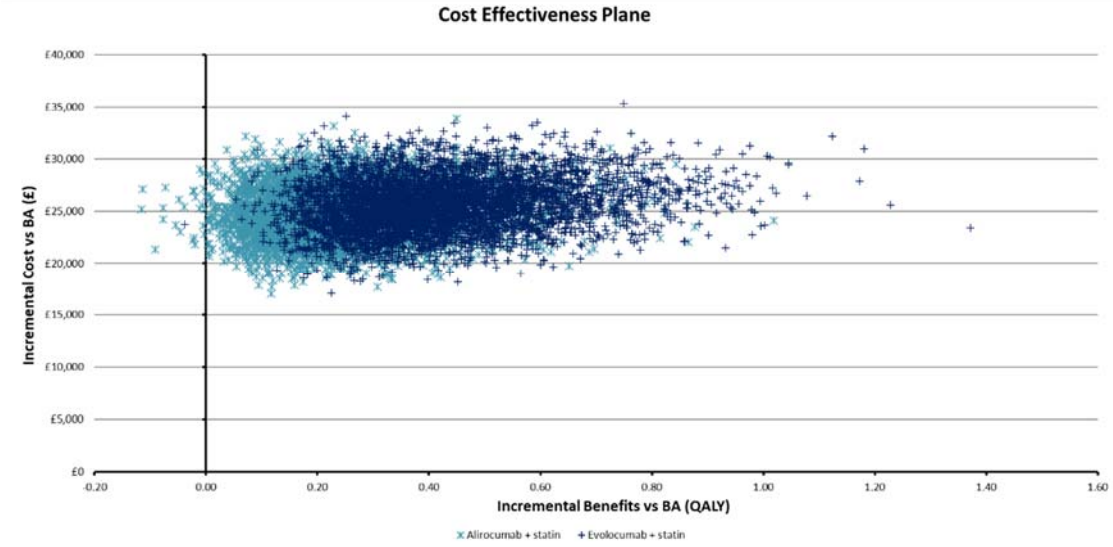


Figure C-19. Subgroup/Analysis 12- BA (see Table C-2)

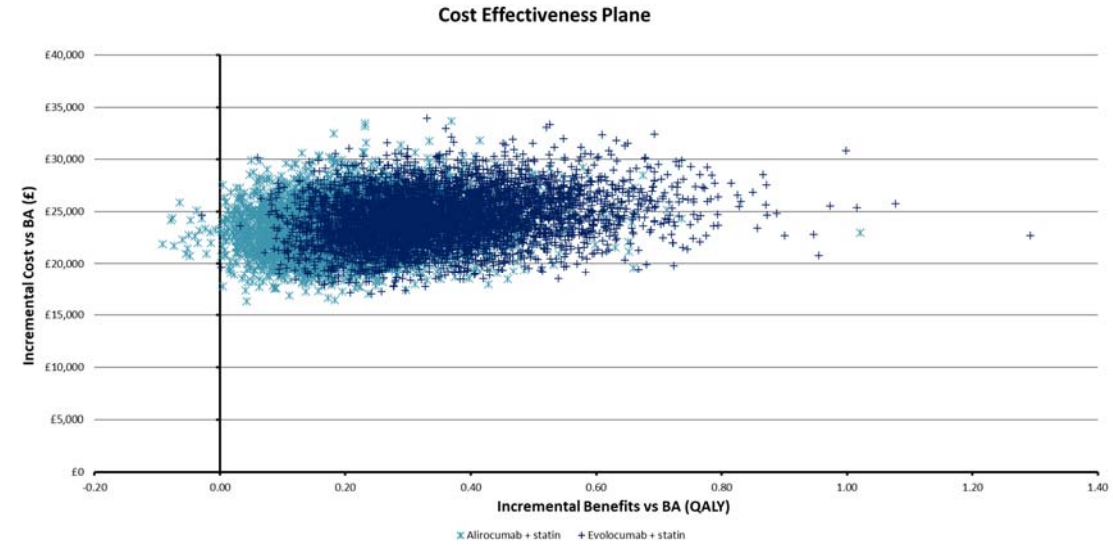


Figure C-20. Subgroup/Analysis 13 - BA (see Table C-2)

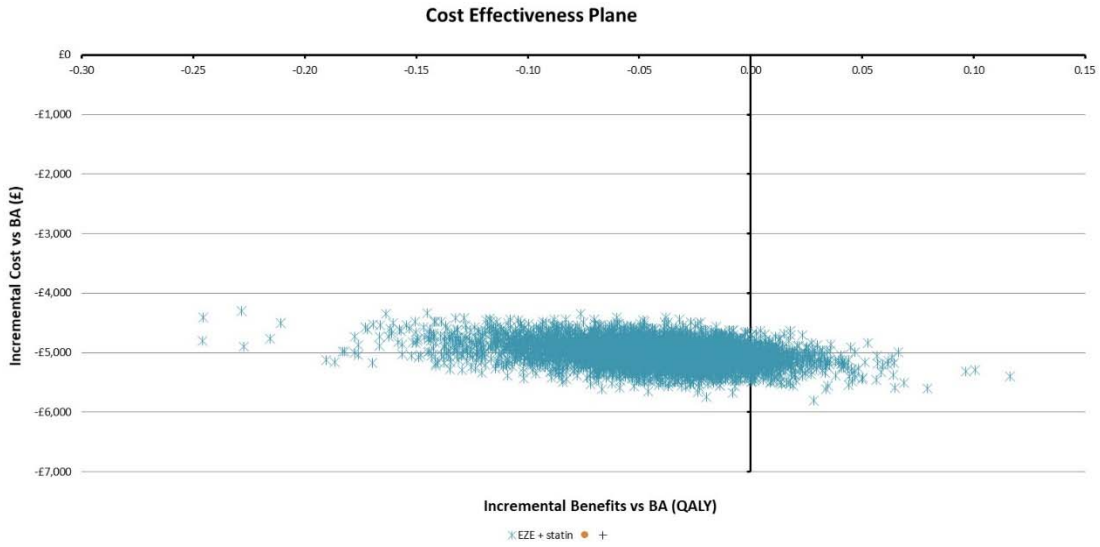
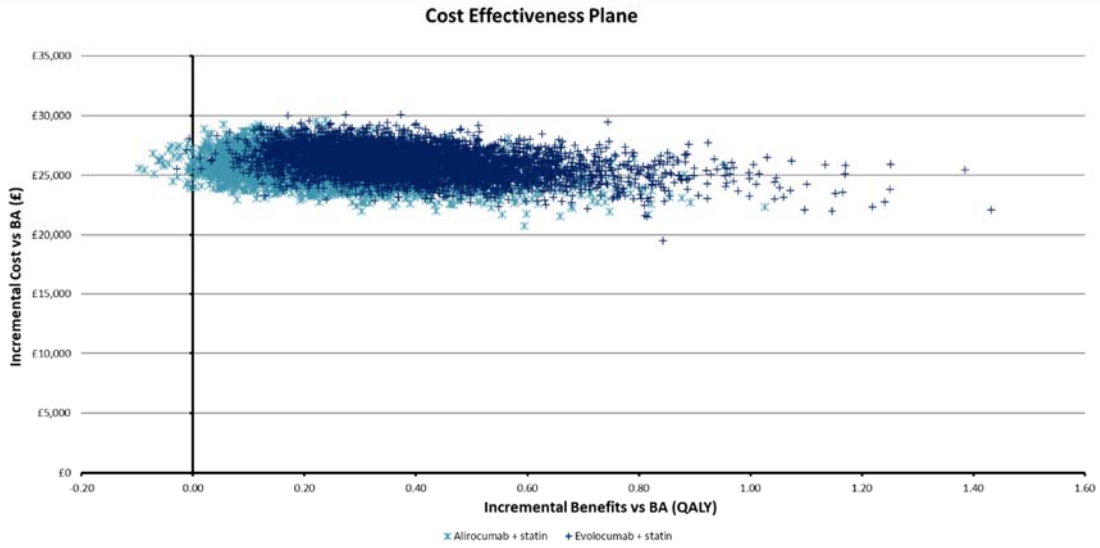


Figure C-21. Subgroup/Analysis 14- BA (see Table C-2)



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1. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. JAMA. 2012;308(23):2497-506.
2. Toth PP, Worthy G, Gandra SR, Sattar N, Bray S, Cheng LI, et al. Systematic review and network meta-analysis on the efficacy of evolocumab and other therapies for the management of lipid levels in hyperlipidemia. J Am Heart Assoc. 2017 Oct 2;6(10).

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xTechnical engagement response form

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **3 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Clinical Diabetologists (ABCD)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Abbreviations: ALI = Alirocumab; BA = Bempedoic acid; BA/EZE FDC = Bempedoic acid / ezetimibe fixed dose combination pill; CV = Cardiovascular; ERG = Evidence review group; EVO = Evolocumab; EZE = Ezetimibe; LDL = Low-density lipoprotein; NMA = Network meta-analysis

Issue 1: The clinical pathway	
What concomitant therapy would people having BA or BA/EZE FDC receive in clinical practice for subpopulations who are: a) statin intolerant and have had previous EZE? b) in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin?	**a) Ezetimibe; Alirocumab or Evolocumab** **b) Statin; Ezetimibe; Alirocumab or Evolocumab**
What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO?	**Based on local data approximately 10% would be eligible**
Would ALI or EVO be used alone or in combination with EZE in clinical practice?	**Depends on the response. If statin intolerant or on max tolerated dose of statin but eligible for Alirocumab / Evolocumab then most patients would go onto PCSK9i therapy first with addition of Ezetimibe if lipid profile still suboptimal.**
Would ALI or EVO be used after BA if there is insufficient response?	**If patients eligible for Alirocumab / Evolocumab then they would go onto this therapy first with addition of BA if insufficient response. Use of Alirocumab / Evolocumab after BA would only occur if significant deterioration of lipid profile.**
If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with BA?	**Yes**
If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO?	**If Ezetimibe is tolerated – yes.**

If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE?	**If lipid profile suboptimal - yes**
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or LDL therapy when commencing BA?	**Patients on maximal tolerated statin may still have muscle aches. Like Ezetimibe, BA may have a role as a statin sparing agent, allowing patients to achieve Non HDL or LDL targets with a lower dose of statin therapy. Patients are likely to continue on statin but may be at a lower dose. Patients on statin + ALI / EVO + Ezetimibe with suboptimal lipid profile are likely to continue on all previous agents following addition of BA**
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO?	**Depends on whether patient asymptomatic or managing tolerable symptoms on maximal tolerated dose of statin. If asymptomatic then likely to continue to get maximal lipid lowering effect. If ALI / EVO therapy highly effective (as is often the case) then statin / LDL lowering therapy dose may be reduced if LDL / NonHDL target achieved but patient still symptomatic.**
In which circumstances would BA be considered as monotherapy?	**Statin / Ezetimibe intolerant/ contraindicated but ALI /EVO not indicated** **Statin / Ezetimibe intolerant / contraindicated and ALI /EVO indicated but not tolerated**
Under which circumstances would a patient treated with EZE discontinue treatment with EZE?	**If Ezetimibe intolerant** **If patient on Ezetimibe is ineligible for ALI / EVO but would meet the LDL criteria for ALI / EVO if discontinued**
Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy?	**If patients tolerating Ezetimibe I would only consider adding in BA as adjunct, not as a replacement.**
Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have BA therapy?	**If you are suggesting** **a) Prior Ezetimibe switched to BA versus b) Placebo then YES**
Under which circumstances would a patient treated with a maximally tolerated statin discontinue	**As indicated previously, patients on statins may still have some side effects that are bearable. Use of "statin sparing agents" such as Ezetimibe may allow these patients to**

treatment with a statin?	**achieve their LDL or NonHDL targets. Some patients may be on low doses on statins such as Rosuvastatin 5 mg once a week, with on-going symptoms that are manageable. Current NICE advice is that some statin is better than no statin. However if patients can be commenced on an additional / alternative agent such as ALI or EVO which allows then to drop significantly below their LDL / NonHDL target then they may wish to stop their statin therapy to resolve their symptoms. It most circumstances however we would try to continue statin therapy in combination with other agents to achieve maximal lipid lowering effect.**
Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA	
Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE?	**Short answer – NO** **Longer answer – depends of the length of time treated with Ezetimibe and time since discontinued. Someone who has been on Ezetimibe for 10 years may have a lower CVD risk than an Ezetimibe naïve patient. Patients who have stopped Ezetimebe 1 week ago may have better starting lipid profile than Ezetimobe naïve patients ot those who have been off therapy for over 6 months.**
To what extent does previous EZE therapy affect the treatment effect of BA?	**Again – depends on length of previous Ezetimibe therapy (in terms of outcomes) and length of time off Ezetimibe (in terms of impact on Lipid profile). If adequate wash out period before BA therapy then this effect may be mitigated.**
To what extent does concomitant statin therapy affect the treatment effect of BA?	**I would expect that concomitant statin therapy may attenuate the treatment effect of BA compared to the use of BA monotherapy. A signal of marked benefit from the addition of BA to statin therapy would be significant.**
Issue 3: Baseline LDL-C in subpopulations that are not eligible for ALI and EVO	
In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?	**Yes – unless they decide they do not want it**
Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO)	**YES**

and 2b/4b (eligible for ALI/EVO)?	
Issue 4: Subgroup analyses by CV risk and HeFH	
Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)?	**No – patients with HeFH have a far greater risk of CVD (especially IHD) and would therefore expect to have a far greater benefit from lipid lowering therapy. This is why trials into new lipid lowering therapies often have studies in HeFH – as they have greater risk and it is easier to see if the intervention has a clear benefit.**
Is it appropriate to assume that treatment effect is similar in people with different CV risk?	**No. Recent PCSK9i trials have shown greater benefit in populations with Diabetes Melliltus and PAD and less benefit in stroke patients. Treatment effect is likely to be higher in high risk populations and lower in low risk populations.**
Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?	**Don't know.**
Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations	
What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice? a) For people who are statin intolerant and not eligible for EVO or ALI (population 2a)? b) For people who are statin intolerant and eligible for EVO or ALI (population 2b)? c) For people who are treated with a maximally tolerated statin and eligible for EVO or ALI? d) For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI?	**Don't know** **a) Most statin intolerant patients are not eligible for primary prevention unless they have FH. FH affects 1 in 250; statin intolerance affects 1 in 10 – suggests that only 4 in 10,000 would be eligible** **b) I suspect this compromises a significant number of FH patients but only a small number of secondary prevention patients** **c) These would be mainly patients with FH** **d) I think these may represent a significant number of patients although I don't have any data to refer to. In my experience there are several secondary prevention patients who do not achieve a non-HDL < 2.5 mmol/L but do have a LDL of < 4.0 or 3.5 mmo/L and therefore have suboptimal response to maximal dose statin +/- Ezetimibe but do not qualify for ALI / EVO therapy**

Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI?	**Yes** **Treatment targets are different for primary and secondary populations** **More FH patients (with higher risk of CVD) are likely to be eligible for primary prevention on grounds of statin intolerance. These patients are also more likely to be eligible for ALI / EVO therapy.**
Is it appropriate to generalise between primary and secondary prevention populations?	**No**
Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort?	**Yes**
How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?	**Don't know**
Issue 6: Methodological uncertainty in the company and ERG network meta-analysis	
Should the company's revised NMA or ERG's NMA be used for decision making?	**ERG NMAs**
Issue 7: Use of 12-week study data cut off and evaluation of treatment waning	
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?	**Most mature available evidence**
Is it plausible that a treatment waning effect may occur with BA?	**Yes**

In clinical practice, would people stop treatment with BA after a certain time period?	**Not routinely**
Issue 8: Health related quality of life	
Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?	**Yes**
Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?	**Yes**
Issue 9: Costing of ALI/EVO administration and CV events	
In clinical practice, would you expect ALI or EVO to be administered in a hospital setting, with an annual follow up with a consultant?	**Yes**

NICE National Institute for Health and Care Excellence

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Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

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Deadline for comments **3 July 2020**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**ABCD**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Abbreviations: ALI = Alirocumab; BA = Bempedoic acid; BA/EZE FDC = Bempedoic acid / ezetimibe fixed dose combination pill; CV = Cardiovascular; ERG = Evidence review group; EVO = Evolocumab; EZE = Ezetimibe; LDL = Low-density lipoprotein; NMA = Network meta-analysis

Issue 1: The clinical pathway	
What concomitant therapy would people having BA or BA/EZE FDC receive in clinical practice for subpopulations who are: a) statin intolerant and have had previous EZE? b) in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin?	**a) BA/EZE or ALI or EVO** **b) BA/EZE or ALI or EVO**
What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO?	**20%**
Would ALI or EVO be used alone or in combination with EZE in clinical practice?	**Alone**
Would ALI or EVO be used after BA if there is insufficient response?	**Yes**
If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with BA?	**Yes**
If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO?	**Not initially**
If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE?	**Yes**
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or	**Yes**

LDL therapy when commencing BA?	
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO?	**Yes**
In which circumstances would BA be considered as monotherapy?	**Intolerance to statin, EZE and patients not fulfilling ALI or EVO prescribing criteria**
Under which circumstances would a patient treated with EZE discontinue treatment with EZE?	**Probably wouldn't unless BA alone controls the lipids to target (seems unlikely from data)**
Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy?	**<10%**
Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have BA therapy?	**No**
Under which circumstances would a patient treated with a maximally tolerated statin discontinue treatment with a statin?	**Shouldn't really**
Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA	
Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE?	**No**
To what extent does previous EZE therapy affect the treatment effect of BA?	**Shouldn't if there has been enough of a wash out phase**
To what extent does concomitant statin therapy affect the treatment effect of BA?	**Potentiates action**

Issue 3: Baseline LDL-C in subpopulations that are not eligible for ALI and EVO	
In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?	**Depends largely on primary care doctors and secondary care clinicians recognising it is an issue and referring to a lipidologist. Probably less than half the time.**
Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO)?	**The 4a/4b group are likely to have lower LDL-C levels in view of the fact that they are on at least a small (tolerable) dose of statin.**
Issue 4: Subgroup analyses by CV risk and HeFH	
Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)?	**I would imagine it would largely depend on what the underlying genetic issue is causing the familial hypercholesterolaemia. If related to gene defect in the synthesis pathway for cholesterol then it may well do.**
Is it appropriate to assume that treatment effect is similar in people with different CV risk?	**We would have to assume this, as we have done so in the past.**
Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?	**The modelled population was largely a middle aged, white male population, so not very generalizable for that of the UK.**
Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations	
What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice? a) For people who are statin intolerant and not eligible for EVO or ALI (population 2a)? b) For people who are statin intolerant and eligible for EVO or ALI (population 2b)? c) For people who are treated with a maximally	**a) 5%** **b) 70%** **c) 20%**

tolerated statin and eligible for EVO or ALI? d) For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI?	d) **5%**
Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI?	**I would expect there to be more patients in primary care that have not been picked up rather than in secondary care. The treatment of these individuals should be the same though.**
Is it appropriate to generalise between primary and secondary prevention populations?	**Yes. The secondary care population is likely to have had an acute event that would precipitate the conversation about their lipids.**
Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort?	**Not really. The outcome measures are likely to be the same.**
How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?	**Not sure**
Issue 6: Methodological uncertainty in the company and ERG network meta-analysis	
Should the company's revised NMA or ERG's NMA be used for decision making?	**An independent NMA should be carried out, although the bulk of the available data is going to be company sponsored.**
Issue 7: Use of 12-week study data cut off and evaluation of treatment waning	
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?	**The longer the duration the better.**
Is it plausible that a treatment waning effect may occur with BA?	**Possible that tachyphylaxis could occur over time, although from the wealth of statin data**

	and the fact that BA works further down the same pathway, it seems less likely.
In clinical practice, would people stop treatment with BA after a certain time period?	**Unlikely to as that would defeat the objective of maintaining a low LDL-C level.**
Issue 8: Health related quality of life	
Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?	**Depends on how the modelling was conducted, but I am more inclined to accept the rigour and standardised approach of NICE.**
Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?	**Depends on how the modelling was conducted, but I am more inclined to accept the rigour and standardised approach of NICE.**
Issue 9: Costing of ALI/EVO administration and CV events	
In clinical practice, would you expect ALI or EVO to be administered in a hospital setting, with an annual follow up with a consultant?	**Yes**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society (BCS)** **This form should be read in conjunction with the BCS response to an earlier round of this technology appraisal which was submitted on 19 11 2019**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

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Issue 1: The clinical pathway	
What concomitant therapy would people having BA or BA/EZE FDC receive in clinical practice for subpopulations who are: a) statin intolerant and have had previous EZE? b) in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin?	**a) Depends on clinical context and cholesterol level** **b) Depends on clinical context and cholesterol level**
What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO?	**Depends on clinical context and cholesterol level**
Would ALI or EVO be used alone or in combination with EZE in clinical practice?	**Depends on clinical context and cholesterol level**
Would ALI or EVO be used after BA if there is insufficient response?	**Depends on clinical context and cholesterol level**
If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with BA?	**Yes**
If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO?	**Depends on clinical context and cholesterol level**
If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE?	**Depends on clinical context and cholesterol level, but, potentially, yes.**
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or	**Yes, because the outcome data relate primarily to statins**

LDL therapy when commencing BA?	
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO?	**Yes**
In which circumstances would BA be considered as monotherapy?	**Where there are outcome data to show it has benefit. In the absence of outcome data, it might be used as ezetimibe is currently…for statin intolerant patients with relatively modest elevation in cholesterol.**
Under which circumstances would a patient treated with EZE discontinue treatment with EZE?	**Intolerance. Lack of efficacy.**
Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy?	**Unable to provide any informed answer.**
Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have BA therapy?	**No**
Under which circumstances would a patient treated with a maximally tolerated statin discontinue treatment with a statin?	**Intolerance.**
Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA	
Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE?	**Yes, depending on what 'clinical effectiveness' is being referenced here.**
To what extent does previous EZE therapy affect the treatment effect of BA?	**Unknown to me – but I would not expect any 'hangover' effect.**
To what extent does concomitant statin therapy affect the treatment effect of BA?	**Unknown to me – but I would not expect any 'hangover' effect.**

Issue 3: Baseline LDL-C in subpopulations that are not eligible for ALI and EVO	
In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?	**I don't know, but I suspect that these drugs are underutilised compared with notional optimal NICE guideline implementation**
Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO)?	**Patients eligible for ALI/EVO are presumably likely to have higher cholesterol on average, since elevation is an eligibility criterion**
Issue 4: Subgroup analyses by CV risk and HeFH	
Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)?	**Depends what 'effect' is being sought. I would not make assumptions, but rather seek data.**
Is it appropriate to assume that treatment effect is similar in people with different CV risk?	**Not if the 'effect' sought is a reduction in cardiovascular risk. In general patients with the highest risk derive the greatest benefit.** **But this is a complex issue that should properly incorporate considerations of long term vs short / medium term risk.**
Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?	**I am not qualified to answer this question**
Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations	
What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice?	**I do not have the data required to answer these questions**

a) For people who are statin intolerant and not eligible for EVO or ALI (population 2a)? b) For people who are statin intolerant and eligible for EVO or ALI (population 2b)? c) For people who are treated with a maximally tolerated statin and eligible for EVO or ALI? d) For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI?	
Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI?	**This question is not sufficiently precise.**
Is it appropriate to generalise between primary and secondary prevention populations?	**Not generally.**
Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort?	**Probably not.**
How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?	**Highly variable**
Issue 6: Methodological uncertainty in the company and ERG network meta-analysis	
Should the company's revised NMA or ERG's NMA be used for decision making?	**I am not qualified to answer this question**
Issue 7: Use of 12-week study data cut off and evaluation of treatment waning	
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?	**I am not qualified to answer this question**

Is it plausible that a treatment waning effect may occur with BA?	**Plausible but not especially likely.**
In clinical practice, would people stop treatment with BA after a certain time period?	**Would depend on clinical trial data.** **Would depend on the indication for use.** **Most lipid-lowering drugs are used in the long term**
Issue 8: Health related quality of life	
Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?	**I am not qualified to answer this question**
Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?	**I am not qualified to answer this question**
Issue 9: Costing of ALI/EVO administration and CV events	
In clinical practice, would you expect ALI or EVO to be administered in a hospital setting, with an annual follow up with a consultant?	**Yes**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Amgen Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

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Issue 1: The clinical pathway	
What concomitant therapy would people having BA or BA/EZE FDC receive in clinical practice for subpopulations who are: a) statin intolerant and have had previous EZE? b) in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin?	-
What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO?	**There are known challenges in defining the proportion of patients eligible for therapy. However, despite these challenges, NICE should ensure any guidance for BA takes a consistent approach and is compatible with existing recommendations for EVO and ALI to enable patients to be optimally managed on the most appropriate and effective treatment for their CV risk profile.** All patients meeting the criteria specified in NICE TA393[i] and TA 394[ii] are potentially eligible to receive ALI or EVO; however, quantifying the proportion of patients who would receive ALI or EVO, or indeed the proportion of patients who could potentially receive BA, due to statin intolerance or those on maximally tolerated statins due to BA presents a number of challenges. NICE TA394 recommends the use of EVO (Repatha®) in patients with LDL-C concentrations above specific thresholds despite maximally tolerated lipid-lowering therapy, either because the maximum dose has been reached, or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia [FH], CG71[iii] *— the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy*).[iv] NICE CG 181 on cardiovascular disease (CVD) suggests that if a patient is unable to tolerate a high-intensity statin the aim should be to treat with the maximum

	tolerated dose; referral for specialist advice is suggested for patients who are high risk of CVD and those with CVD who are intolerant to 3 different statins.[v] We note that that the clinical trials provided in the submission for BA adopt various definitions of intolerance, including: • discontinuation of *≥1 statin* at any dose because of *muscle-related symptoms*; • the inability to tolerate *≥2 statins* because of *muscle-related symptoms* such as pain, weakness, or cramping that began or increased during statin therapy and resolved on statin discontinuation • inability to tolerate *≥two statins, one at a low dose*, owing to *a prior adverse event* that started or increased during statin therapy and resolved or improved when statin therapy was discontinued.[vi] There are clearly differences in the definition of statin intolerance adopted by NICE (in the FH guideline, the CVD guideline, and EVO and ALI recommendations) and the variable definitions adopted across the BA trials. There are also challenges in consistently applying a definition in practice. It is therefore uncertain how reflective of statin intolerant patients in clinical practice the "statin intolerant" populations enrolled in the BA trials would be. Furthermore, this lack of consistency in defining patients who are statin intolerant would be expected to lead to uncertainty in whether therapy is optimally targeted to patients who are in most need, and the size of that population.
Would ALI or EVO be used alone or in combination with EZE in clinical practice?	**Based on the large-scale FOURIER and ODYSSEY trials, and NICE TA394 and 393, in patients clinically eligible for EVO or ALI there is no requirement to use EZE in combination with EVO or ALI, nor to have used EZE before initiation, to achieve the significant lipid lowering and CV event reductions observed with EVO or ALI. This is reflected in the pathway schematic in the Technical Engage report – subpopulations 1b and 3b. However, in practice patients may experience delayed access to optimal therapy with EVO or ALI due to initiation firstly of less effective EZE. The proposed positioning of BA+EZE in patients who are clinically eligible for EVO and ALI under existing NICE guidance represents a proposed change in the existing treatment pathway for these patients towards less effective and sub-optimal therapy. This would leave these patients exposed to significant residual risk and could potentially preclude their access to optimal treatment with EVO and**

	ALI. We do not believe the clinical and economic evidence currently presented for BA+EZE is sufficient to allow robust consideration of its use as an alternative to EVO and ALI at any point in the pathway, and the potential consequences for patients and the health system. • NICE TA385 recommends EZE as an option for use as monotherapy in patients who cannot tolerate statin therapy or for whom statins are contraindicated. Use in combination with a statin is recommended as an option in patients who have started statin therapy but serum total cholesterol or LDL-C concentration is not appropriately controlled, or when a change to an alternative statin is being considered. • NICE TA394 recommends EVO and NICE TA393 recommends ALI as options for secondary prevention of CVD when, despite maximally tolerated lipid-lowering therapy, LDL-C concentrations are persistently above 4.0mmol/L in patients at high risk of CVD and above 3.5mmol/L in patients at very high risk of CVD. Both are recommended as options in primary prevention of CVD in patients with HeFH when LDL-C concentration is persistently above 5.0mmol/L, or in secondary prevention of CVD in patients with HeFH when LDL-C concentration is persistently above 3.5mmol/L. • The use of EZE at baseline in the pivotal FOURIER trial of EVO was minimal at 5.2%,[vii] and in the ODYSSEY trial of ALI was low at around 15%.[viii] Therefore, based on these data and NICE TA394 and 393, in patients clinically eligible for EVO or ALI there is no requirement to use EZE in combination with EVO or ALI, nor to have used EZE before initiation, to achieve the significant lipid lowering and CV event reductions observed with EVO or ALI. However, in practice patients may have experienced delayed access to EVO or ALI due to initiation firstly of less effective EZE. • Whilst NICE has not set specific LDL-C goals, the Joint British Societies for Prevention of Cardiovascular Disease (JBS) 3 Report recommends a 'lower is better' approach to achieve LDL-C values <1.8mmol/L[ix]. This is consistent with the recent guidelines from ESC/EAS, which recommend a targeted approach to lipid management, primarily aimed at reducing LDL-C as quickly as possible to levels that have been achieved in the large-scale trials of EVO (FOURIER trial) and ALI (ODYSSEY trial).[x] In the high or very high risk patients eligible for EVO and ALI under existing NICE guidance, ESC/EAS guidelines recommend an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L or <1.4 mmol/L.

	• EVO and ALI are included in the NHS England Accelerated Access Collaborative programme, which aims to remove barriers and accelerate the introduction of ground-breaking, cost-effective new treatments which can transform care in the NHS.[xi] The *Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD*, issued by NHS England as part of this programme, indicates that the expected further reduction in LDL-C with addition of EZE to statin therapy is <10%.[xii] In contrast addition of EVO to statin therapy or EZE provides a further reduction > 50%.[xiii] • We note that the submitting company is proposing to position BA in combination with EZE in patients who have previously been treated with EZE, as an alternative to EVO or ALI. Whilst BA+EZE is more effective than EZE, the reductions in LDL-C with BA+EZE are still significantly less than is achieved with EVO or ALI, meaning patients are significantly less likely to achieve the ESC/EAS guideline-recommended targets,[xiv] particularly in patients on maximally tolerated statins. If used in patients who are otherwise eligible for EVO and ALI, the reductions in LDL-C expected with BA+EZE would be sub-optimal and leave patients exposed to significant residual risks of CV events. • Furthermore, whilst leaving patients exposed to significant residual risks of CV events, BA+EZE may reduce LDL-C levels to below the threshold at which patients would otherwise have been eligible for EVO or ALI under existing NICE guidance. The use of sub-optimal BA+EZE could therefore preclude their access to optimal therapy with EVO or ALI, leaving them permanently exposed to significant residual risks. • The proposed positioning of BA+EZE in patients who are clinically eligible for EVO and ALI under existing NICE guidance therefore represents a proposed change in the existing treatment pathway for these patients towards less effective and sub-optimal therapy. Given the potential consequences for patients and the health system it is imperative that the evidence of clinical and cost effectiveness for BA+EZE is robust and transparent, and compatible with the evidence supporting EVO and ALI so that those consequences can be fully understood. • We concur with the ERG's concerns in the technical report that the clinical evidence base may not adequately reflect the proposed positioning of BA+EZE, and does not sufficiently explore efficacy in important subgroups based on CV risk that determine the current use of EVO and ALI (i.e. primary and secondary prevention, HeFH and no-HeFH). The economic model reflects a blended analysis of patients with different risk profiles and precludes

	transparent assessment of the cost effectiveness of BA+EZE in these important subgroups. This is in direct contrast to the evidence supporting the clinical and cost effectiveness of, and NICE recommendations for, EVO and ALI in TA394 and TA393. • On this basis we do not believe the clinical and economic evidence currently presented for BA+EZE is sufficient to allow robust consideration of its use as an alternative to EVO and ALI, and the potential consequences for patients and the health system.
Would ALI or EVO be used after BA if there is insufficient response?	Given that BA is less likely than EVO and ALI to achieve ESC/EAS guideline-recommended LDL-C targets, EVO or ALI would be necessary for patients with insufficient response to BA. However, as noted above: • **We do not believe there is sufficient robust and consistent clinical and cost effectiveness evidence currently presented in this appraisal to justify the use of BA+EZE before EVO or ALI.** • **Such use of BA+EZE in patients who are clinically eligible for EVO or ALI under existing NICE guidance would represent sub-optimal therapy that would leave patients at high residual risk of future CV events.** • **Such use of BA+EZE in patients who are clinically eligible for EVO or ALI under existing NICE guidance could lower LDL-C to levels below the thresholds at which EVO and ALI are recommended for use by NICE, but still insufficiently to achieve the LDL-C targets recommended in the ESC/EAS guidelines. Not only would this delay patients' access to EVO or ALI; it has potential to then preclude patients' access to these significantly more effective and optimal therapies, which would risk leaving those patients permanently exposed to the high risks of CV events**.
If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with BA?	-
If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO?	EVO and ALI were assessed in their large clinical trials as add-on therapy to lipid lowering therapy. It is possible that statin intolerant patients already receiving EZE would continue EZE when initiating EVO or ALI.

If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE?	This depends on patient characteristics, their LDL-C concentration and risk of CV events. If further reduction in LDL-C is required, then EZE may be added to maximally tolerated stain therapy. However, EZE use in current practice is limited; the latest available Prescription Cost Analysis data (2019) demonstrate that EZE accounts for <2.5% of all lipid regulating therapies dispensed in the community setting in England.[xv]
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or LDL therapy when commencing BA?	Unless the patient develops intolerance or a contraindication, we expect patients would continue receiving their statin and/or other lipid lowering therapy when commencing BA.
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO?	The pivotal trial of EVO (FOURIER trial) assessed addition of EVO to background lipid lowering therapy, which was primarily statin therapy. Few patients were receiving EZE on entry into the trial. It is therefore expected that patients receiving EVO will continue with their tolerated statin therapy.
In which circumstances would BA be considered as monotherapy?	-
Under which circumstances would a patient treated with EZE discontinue treatment with EZE?	-
Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy?	-
Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have BA therapy?	Based on the company's updated NMAs, BA without EZE seems to offer little, if any, benefit over EZE in terms of LDL-C reduction, particularly in patients on maximally tolerated statin. We therefore would not expect meaningful differences in outcomes.
Under which circumstances would a patient treated with a maximally tolerated statin discontinue treatment with a statin?	Possibly if the patient subsequently develops adverse events or intolerance, or develops a condition that make statin therapy contraindicated (e.g. liver disease, or pregnancy in a patient with HeFH).

Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA	
Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE?	We concur with the ERG view that there is uncertainty in whether the clinical evidence is reflective of the intended use of BA following previous EZE. We also note that there are other important subgroups defined by CV risks that have not been explored fully in terms of clinical and cost effectiveness, including primary vs secondary prevention, HeFH vs non HeFH.
To what extent does previous EZE therapy affect the treatment effect of BA?	We note that the company's updated NMAs demonstrate a minimal and non-significant reduction in LDL-C for BA without EZE compared with EZE, in both statin intolerant and maximally tolerated statin patients. A significant reduction in LDL-C is only apparent in these analyses when BA is combined with EZE, and only in statin intolerant patients.
To what extent does concomitant statin therapy affect the treatment effect of BA?	We agree with the ERG that there is uncertainty in the impact of concomitant statin therapy on the treatment effect of BA. We note that the company's updated NMAs demonstrate no significant difference in LDL-C reduction with BA+EZE vs in patients on maximally tolerated statin, but a significant difference in patients who are statin intolerant. We also note that the SmPC for BA reports pharmacokinetic interactions between BA and statins, resulting in elevations of statin concentrations and active metabolites. The SmPC notes that BA may potentially increase the risk of myopathy and that concomitant use of BA is contraindicated in patients taking >40mg simvastatin.[xvi]
Issue 3: Baseline LDL-C in subpopulations that are not eligible for ALI and EVO	
In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?	NICE TA394 and NICE TA393 clearly define the clinical circumstances in which EVO or ALI are treatment options. Use in clinical practice should be aligned with these NICE recommendations. Uptake in some areas is good, with eligible patients accessing EVO in line with NICE TA394; however, in some areas there have been local barriers to access since NICE issued its positive guidance. In recognition of the need to improve access to EVO and ALI, as ground-breaking, cost-effective new treatments, both are included in the NHS England Accelerated Access Collaborative programme. We therefore anticipate that patient access to EVO will continue to increase across areas in line with their clearly defined recommendations for use outlined in its NICE TA394.

Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO)?	**EVO and ALI eligibility is defined by previous CV events, HeFH status and LDL-C. By definition, the baseline LDL-C levels – and CV risks – will differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO). The company's implementation of baseline LDL-C levels for comparison against EVO and ALI is inconsistent with the threshold LDL-C levels at which EVO and ALI are recommended. Furthermore, the company's blanket modelling approach fails to account for differential cost effectiveness among the important subgroups defined by CV risk. Consistency of approach with the appraisals of EVO and ALI is required to fully understand the cost effectiveness of BA+EZE, and the potential consequences of recommending this less effective therapy**. NICE TA394 and TA393 recommend EVO and ALI as options only in: • Primary prevention: Patients with HeFH and LDL-C >5 mmol/L • Secondary prevention – High risk: LDL-C >4 mmol/L • Secondary prevention – Very high risk: LDL-C >3.5 mmol/L. LDL-C levels by definition are therefore different between subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO). We note that the implementation of the LDL-C thresholds in the company's economic model is based on mean LDL-C levels for different thresholds of LDL-C level (Table 50 of the company submission). For patients who are eligible for EVO or ALI (subpopulations 2b and 4b) the company has adopted a mean LDL-C level of approximately 4.4 mmol/L (Table 63 of the company submission). The recommendations for EVO and ALI specify an LDL-C threshold of >3.5mmol/L in very high risk secondary prevention patients and >4mmol/L in high risk secondary prevention patients. No analyses have been provided by the company for LDL-C levels at these actual thresholds, which is in contrast to the analyses that were required by NICE in the appraisal of EVO and ALI, and has potential to significantly impact on the ICER. A mean LDL-C is employed in other subpopulations and we believe appropriate threshold values should be thoroughly explored to determine the impact on the estimated cost effectiveness of BA+EZE.

	We also note that the company has not provided any analyses of cost effectiveness in the important subgroups defined by CV risk and which define the specific clinical circumstances in which EVO and ALI are recommended for use (i.e. primary prevention and secondary prevention, HeFH and non-HeFH). The risk profiles of patients within and between these subpopulations differs, which would influence the incidence of CV events and deaths, quality of life, and resource use and costs. The cost effectiveness of therapies is therefore likely to differ among these subpopulations. The blurring of these populations in the company's blanket approach to modelling the cost effectiveness of BA+EZE is therefore inappropriate and is inconsistent with the approach taken by NICE when considering the cost effectiveness of EVO and ALI and making recommendations within specific subpopulations. We therefore believe that cost effectiveness of BA+EZE should be modelled based on the appropriate LDL-C thresholds for the appropriate subpopulations, and within the important subpopulations that have distinct CV risk profiles and define the use of EVO and ALI. Only if there is this consistency of approach will it be possible to fully understand the cost effectiveness of BA+EZE, and the potential consequences of recommending a less effective therapy than EVO or ALI.
Issue 4: Subgroup analyses by CV risk and HeFH	
Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)?	It may be possible that the relative treatment effect is similar in people with or without HeFH; however, the underlying risk of CV events is different, which would mean that the absolute treatment effect observed would be different among these subgroups. We concur with the view of the ERG, that the overall reduction in LDL-C observed in a mixed population is not equally relevant for all patients in that population. As noted in our response to Issue 3, **in order to fully understand the cost effectiveness of BA+EZE, and the potential consequences of recommending this less effective therapy than EVO or ALI, consistency of approach with previous appraisals of EVO and ALI are required, in which the cost effectiveness of BA+EZE in the different subpopulations in which EVO and ALI are recommended is transparent. A blended approach as adopted by the submitting company has the potential to mask differential cost effectiveness across these important subpopulations.**
Is it appropriate to assume that treatment effect is similar in people with different CV risk?	As above and in our responses to Issues 3 & 5, as the underlying risk of CV events is different, the absolute treatment effect observed would be different among the different risk profiles. The

Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?	submitting company has not provided subgroup analyses based on CV risk, and we concur with the ERG view that **it is unclear how the cost effectiveness of BA+EZE may differ amongst the different subgroups defined as primary and secondary prevention, and with or without HeFH. It is essential to explore the impact of different subgroups with different CV risk profiles in order to inform decision-making.**
Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations	
What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice? a) For people who are statin intolerant and not eligible for EVO or ALI (population 2a)? b) For people who are statin intolerant and eligible for EVO or ALI (population 2b)? c) For people who are treated with a maximally tolerated statin and eligible for EVO or ALI? d) For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI?	-
Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI?	In the absence of evidence to the contrary, we believe statin intolerance is likely to be independent of whether a patient is receiving lipid lowering therapy for primary or secondary prevention. In terms of suitability of EVO in primary or secondary prevention patients, NICE TA394 recommends use of EVO in primary prevention patients only in those with HeFH and LDL-C >5mmol/L. In contrast, for secondary prevention patients EVO is recommended for use in patients at very high risk (multiple prior CV events) and with LDL-C>3.5mmol/L, and in patients at high risk (one prior CV event) and with LDL-C>4mmol/L. It is reasonable to assume a higher proportion of patients eligible for EVO will be secondary prevention patients rather than primary prevention patients; however, access to EVO in primary prevention is still important, given the high risk of events patients with HeFH face.

Is it appropriate to generalise between primary and secondary prevention populations?	**We do not believe it is possible to generalise between primary and secondary prevention populations. As discussed in responses to Issue 3 and 4, the risk profile of primary and secondary prevention patients is likely to differ in meaningful ways, which would impact on the incidence of CV events, deaths, quality of life and costs. It is not appropriate to assume that data derived largely in secondary prevention patients will reflect the efficacy of BA+EZE in a primary prevention population, and it is not appropriate to consider the blended cost effectiveness of BA+EZE in primary and secondary prevention populations when they have distinctly different baseline risks. We concur with the ERG view that to make this assumption could potentially lead to inappropriate conclusions on the efficacy and cost effectiveness of BA+EZE in the primary prevention population.** In further support of these concerns, we note: 1. The approach to modelling primary prevention risk appears to lack validity and may result in inflation of underlying risk in the primary prevention population. • In the company's model background CV risks were calculated by converting the SCORE risk algorithm in European Society of Cardiology (ESC) guidelines for a high-risk population into a QRISK3 risk. This has required a number of arbitrary adjustments, which are unnecessary when QRISK3 could have been used directly. • The company's approach using these adjustments estimates a baseline risk of around 30%, equivalent to the lower bound threshold risk for very-high risk secondary prevention population as per the ESC guidelines. This approach may overestimate risk by up to 50% versus that predicted by the QRISK3 tool directly. • We therefore agree with the views of the ERG that the QRISK3 algorithm be used directly to inform baseline risk in primary prevention population 2. The secondary prevention risks used in the submission are approximately 1.5-2.5 times greater than the primary prevention risks, depending on time since a previous CV event. This underlines the importance and need to transparently assess cost effectiveness in the primary and secondary prevention populations independently.
Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort?	We note that efficacy data for BA+EZE are limited in the primary prevention population, and concur with the ERG's conclusions that as data supporting subpopulations 2b, 4a and 4b are derived from trial populations in which the vast majority had previously experienced CV events these reflect secondary prevention populations and are unlikely to reflect primary prevention

	populations. However, we do not believe that redefining the populations in the model will, alone, address all of the issues we have raised above regarding the modelling approach taken by the company. We note that redefining the 2b, 4a and 4b subpopulations as secondary prevention would imply that the company's model does not provide a comparison of the cost effectiveness of BA+EZE vs EVO or ALI in any primary prevention patients. Furthermore, data supporting the positioning of BA+EZE in secondary prevention and primary prevention should be derived specifically in those populations; not all patients in the trials providing data to support use in subpopulations 2b, 4a and 4b were secondary prevention patients, and any assumption therefore that subpopulation 2a adequately reflects a primary prevention population is less compelling giving that a substantial proportion of patients (~20%) were secondary prevention patients. Subgroup analyses based on efficacy data directly relevant to the intended positioning should be conducted to avoid biasing the estimates of cost effectiveness. We also note from the company's updated NMAs that BA+EZE provides significantly inferior LDL-C reduction compared with EVO, and that EVO is the most effective of all therapies. From the ERG's NMAs the relative effects of BA+EZE vs ALI are lower than in the company's updated NMAs, and no comparisons against EVO have been made. It should also be noted that, although the relationship between LDL-C reduction and CV events is well established, it remains the case that, in contrast to EVO and ALI, BA+EZE has not yet been demonstrated to significantly reduce CV events. **Collectively, there are clearly deficiencies and significant uncertainties in the evidence supporting the company's economic modelling approach, which in our view will not be adequately addressed by simply assuming that the data supporting subpopulations 2b, 4a and 4b better reflects a secondary prevention population. The remaining uncertainties still preclude full, robust consideration of the cost effectiveness of BA+EZE, and the potential consequences of recommending this less effective therapy.**
How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?	-

Issue 6: Methodological uncertainty in the company and ERG network meta-analysis	
Should the company's revised NMA or ERG's NMA be used for decision making?	-
Issue 7: Use of 12-week study data cut off and evaluation of treatment waning	
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?	-
Is it plausible that a treatment waning effect may occur with BA?	We believe the long-term efficacy and safety of BA remain uncertain at this time. We note that efficacy and safety data presented by the company are limited to 1 year of follow-up. Furthermore, efficacy data for BA are limited to LDL-C reductions and there are no CV outcomes data currently available. In contrast, EVO is confirmed to provide long-term, sustained LDL-C reductions, that are superior to those achieved with BA, through 5 years of follow-up (OSLER-1 study)1. In addition, robust data from the FOURIER trial confirm that EVO reduces CV events.
In clinical practice, would people stop treatment with BA after a certain time period?	Our understanding is that patients would remain on lipid lowering therapy where possible to reduce their risks of CV events in the long term. In patients who would have otherwise been eligible for EVO and ALI, the use of BA+EZE instead would leave patients who are at high risk of CV events exposed to ongoing residual risks, and may preclude their access to optimal therapy. We note that the company has not explored subsequent therapies, and so **the full consequences of using sub-optimal BA+EZE in patients who would otherwise be eligible for EVO or ALI are not fully understood.**
Issue 8: Health related quality of life	

Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?	We believe that, as with the clinical data (see Issue 5) the utility estimates should reflect the populations being modelled and the approach taken should be as consistent as possible with the approaches taken for the appraisal of EVO and ALI.
Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?	
Issue 9: Costing of ALI/EVO administration and CV events	
In clinical practice, would you expect ALI or EVO to be administered in a hospital setting, with an annual follow up with a consultant?	EVO is initiated in secondary care but is generally administered via homecare services that are provided free of charge to the NHS. We expect that all patients identified as high risk or very high risk will have a routine periodic follow-up with a consultant or their primary care physician, irrespective of whether they are treated with EVO or ALI or some other therapy, i.e. there is no additional follow-up resource use or cost expected due to patients receiving EVO or ALI.

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Technical engagement response form

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **3 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
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information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Sanofi**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Abbreviations: ALI = Alirocumab; BA = Bempedoic acid; BA/EZE FDC = Bempedoic acid / ezetimibe fixed dose combination pill; CV = Cardiovascular; ERG = Evidence review group; EVO = Evolocumab; EZE = Ezetimibe; LDL = Low-density lipoprotein; NMA = Network meta-analysis

Issue 1: The clinical pathway	
What concomitant therapy would people having BA or BA/EZE FDC receive in clinical practice for subpopulations who are: a) statin intolerant and have had previous EZE? b) in subpopulations who have maximally tolerated statins who previously were treated with EZE with a statin?	
What proportion of patients who are statin intolerant or have maximally tolerated statins are eligible for ALI or EVO?	
Would ALI or EVO be used alone or in combination with EZE in clinical practice?	**Yes – Sanofi RWE suggests this occurs for ALI in statin-intolerant patients. Tai et al, 2018 UK RWE data for PCSK9i used in combination with Eze in 58% (54% on top of statins)**
Would ALI or EVO be used after BA if there is insufficient response?	**Depends on LDL thresholds and NICE cutoffs for PCSK9i – risk of the patient being taken below PCSK9i threshold with BA but still not at target according to local or ESC guideline recommendations**
If a person with statin intolerance is treated with EZE for primary hypercholesterolaemia or mixed dyslipidaemia, are they likely to continue EZE with BA?	
If a person with statin intolerance is treated with EZE, are they likely to continue EZE with ALI and/or EVO?	**Yes - Sanofi RWE suggests this occurs for ALI in statin-intolerant patients**

If a person is treated with a maximally tolerated statin, are they likely to be also treated with EZE?	**Depends on clinicians and centres, some yes, some no. Clinicians more likely to add in EZE on a background of low-moderate intensity statin dose**
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin and/or LDL therapy when commencing BA?	**Yes potentially – with the weight of evidence on the backdrop of statin use.**
Is it likely that a person on a maximally tolerated statin will continue having concomitant statin or LDL therapy when commencing therapy with ALI and/or EVO?	**Likely – RWE data suggest majority of PCSK9i patients commence on maximally tolerated statins, yet this may drop off through duration of treatment Tai et al, 2018**
In which circumstances would BA be considered as monotherapy?	**Potentially in patients unable to tolerate any dose of statin or EZE?**
Under which circumstances would a patient treated with EZE discontinue treatment with EZE?	**Adverse Events according to SPC – myopathy particularly with concomitant statin, lack of LDL lowering response**
Of people previously treated with EZE, approximately what proportion of people would be expected to discontinue EZE and be treated with BA monotherapy?	**Secondary prevention setting adherence (medication possession ratio of≥0.8) ranged from 68% to 72% in patients taking ezetimibe – Danese et al 2018. It is not clear to us if these patients would be eligible for BA use**
Is it plausible that there would be a large difference in outcomes between those who discontinued EZE who had BA monotherapy and those which did not have BA therapy?	
Under which circumstances would a patient treated with a maximally tolerated statin discontinue treatment with a statin?	**Newly developed contraindication or contraindicated use of other medicines**
Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA	
Is it appropriate to generalise clinical effectiveness results that are based on people who may or may not have had previous EZE to people who have had previous EZE?	

To what extent does previous EZE therapy affect the treatment effect of BA?	
To what extent does concomitant statin therapy affect the treatment effect of BA?	**Not Clear – MOA suggest compensatory mechanism in the absence of highest HMG CoA inhibition - data suggests no difference when statin use is grouped by intensity however no data for individual statins and doses**
Issue 3: Baseline LDL-C in subpopulations that are not eligible for ALI and EVO	
In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?	**We agree with the ERGs suggestion that access to ALI is variable across different centres and regions. However, what we have noticed is that even in areas where PCSK9i prescribing is allowed there are long waiting lists for lipid clinics and slow throughput**
Would baseline LDL-C levels differ between patients in subpopulations 2a/4a (not eligible for ALI/EVO) and 2b/4b (eligible for ALI/EVO)?	**Difficult to compare because patients who are completely intolerant to statins (and therefore not on one) will likely have a higher baseline LDL-C to those who can tolerate them and achieve a degree of LDL-lowering. In addition, we also need to account for primary and secondary prevention profile of patients.**
Issue 4: Subgroup analyses by CV risk and HeFH	
Is it appropriate to assume that treatment effect is similar in people with and without heterozygous familial hypercholesterolaemia (HeFH)?	**No – we agree with the ERG's comments. No potentially distinct and variable pathophysiology impacted by differing atherosclerotic burden related to cumulative LDL-C exposure.**
Is it appropriate to assume that treatment effect is similar in people with different CV risk?	**No – we agree with the ERG's comments**

	similar to above
Is the modelled population generalisable to the primary hypercholesterolaemia or mixed dyslipidaemia population treated in clinical practice?	**No – we agree with the ERG's comments**
Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations	
What proportion of patients with primary hypercholesterolaemia or mixed dyslipidaemia would be expected to be primary or secondary prevention patients in clinical practice? a) For people who are statin intolerant and not eligible for EVO or ALI (population 2a)? b) For people who are statin intolerant and eligible for EVO or ALI (population 2b)? c) For people who are treated with a maximally tolerated statin and eligible for EVO or ALI? d) For people who are treated with a maximally tolerated statin and not eligible for EVO or ALI?	
Is the proportion of primary and secondary prevention patients expected to be different dependent on whether the patient is statin intolerant or not, and whether the patient is suitable for EVO/ALI?	
Is it appropriate to generalise between primary and secondary prevention populations?	**No Secondary prevention makes up the majority of the model and potentially reflects the patients most likely to have lipids managed beyond statins (other than HeFH patients).**
Is it appropriate to redefine the subpopulations in the model according to whether the majority of the study population is either a primary prevention cohort or a secondary prevention cohort?	

How much time would typically elapse between the first and subsequent CV events in secondary prevention patients with primary hypercholesterolaemia or mixed dyslipidaemia?	
Issue 6: Methodological uncertainty in the company and ERG network meta-analysis	
Should the company's revised NMA or ERG's NMA be used for decision making?	**ERG's NMA if ODYSSEY LONG-TERM data is included. Although LONG-TERM did include ~18% HeFH whereas the BA studies only included ~5% so it is unclear how valid the comparisons would be.**
Issue 7: Use of 12-week study data cut off and evaluation of treatment waning	
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?	**The 12 week data was collected in controlled environments of RCTs whereas extension data may not be.**
Is it plausible that a treatment waning effect may occur with BA?	**Yes. Could be due to organic changes in liver metabolism or patient non-adherence to treatment.** **Yes- potential compensatory mechanisms of several metabolic pathways may impact BA MOA.**
In clinical practice, would people stop treatment with BA after a certain time period?	**Yes if they experience AEs** **Yes – potentially also poor compliance with another tablet if already on statin and EZE?** **Also potential lack of response.**

Issue 8: Health related quality of life	
Are the ERG's modifications to estimation of utility preferred over the company's approach to modelling?	
Are the methods and multipliers to estimate utilities proposed by the ERG more appropriate than those proposed by the company?	
Issue 9: Costing of ALI/EVO administration and CV events	
In clinical practice, would you expect ALI or EVO to be administered in a hospital setting, with an annual follow up with a consultant?	**Yes for ALI. Sanofi RWE shows that follow-up may occur more frequently than annually.**

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

ERG review of company's response to technical engagement

July 2020

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1 Summary

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement (TE) report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]. Each of the issues outlined in the technical report are discussed in further detail in Section **Error! Reference source not found.**. The company's updated base case analyses are outlined in Section 2 while the ERG's updated base case analyses are given in Section 4.

2 Updated company base case analyses

In response to the TE report, the company presented updated base case analyses. The changes that have been made to the company's base case analyses include the model corrections suggested by the ERG (including using stable disease as the starting health state for secondary prevention patients) and some of the ERG's preferred assumptions related to:

- the characteristics of the starting population: % in primary prevention and % without heterozygous familial hypercholesterolaemia (HeFH) (Issue 5);
- including ODYSSEY LONGTERM and excluding ODYSSEY Mono from the maximally tolerated statin network meta-analysis (NMA) (population 4) (Issue 6);
- the estimation of health-related quality of life (HRQoL) (Issue 8);
- the estimation of health state costs and inclusion of administration costs for alirocumab (ALI) and evolocumab (EVO) (Issue 9).

Additionally, the company agreed new prices with the Department of Health and Social Care for bempedoic acid and the bempedoic acid and ezetimibe fixed-dose combination (FDC). The new prices included in the company's revised base case analyses are given in Table 1.

Table 1. Intervention and comparator acquisition costs

Treatment	Dose	Pack size	Pack price	Cost per day	Annual Cost
FDC	180 mg with 10 mg daily	28	[redacted]	[redacted]	[redacted]
Bempedoic acid plus ezetimibe (separate tables)	180 mg with 10 mg daily	28	[redacted]	[redacted]	[redacted]
Bempedoic acid	180 mg daily	28	[redacted]	[redacted]	[redacted]
Ezetimibe	10 mg daily	28	£1.86	£0.07	£24.26

Abbreviations: FDC, bempedoic acid and ezetimibe a fixed-dose combination

In the company's original submission, the results did not differ between bempedoic acid plus ezetimibe (separate tablets) and the FDC because the price and efficacy were equivalent. Given that the prices of these preparations now differ, results are presented for each preparation. Table 2 to Table 5 provide the company's pairwise incremental cost-effectiveness ratios (ICERs). The company did not provide probabilistic ICERs in their report, so these have been generated (using 5,000 iterations) and added by the ERG for comparisons with the FDC (the least expensive preparation).

In subpopulations 2b and 4b bempedoic acid generates less quality-adjusted life years (QALYs) and less costs compared to its comparators, resulting in ICERs in the south-west quadrant of the cost-effectiveness plane. Table 6 and Table 7 provide the fully incremental results in subpopulations 2b

and 4b, respectively. In these two subpopulations, ALI is extendedly dominated by EVO (i.e. the ICER for ALI is greater than that of a more effective intervention, EVO). Thus, the decision reduces to a comparison with EVO.

Table 2. Company's revised base case results, subpopulation 2a

Results per patient	BA/EZE FDC	EZE	Incremental value
BA/EZE (separate tables)			
Total costs	£14,376	£9,604	£4,772
QALYs	9.24	9.05	0.19
Lys	12.08	12.30	0.22
ICER (cost per QALY)	-	-	£24,895
FDC			
Total costs	£14,196	£9,604	£4,593
QALYs	9.24	9.05	0.19
Lys	12.08	12.30	0.22
ICER (cost per QALY)	-	-	£23,960
Probabilistic ICER generated by the ERG	-	-	£23,969

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

Table 3. Company's revised base case results, subpopulation 2b

Results per patient	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
				(1-2)	(1-3)
BA/EZE (separate tables)					
Total costs	£22,350	£47,554	£47,994	-£25,204	-£25,643
QALYs	7.02	7.08	7.11	-0.06	-0.09
Lys	10.39	10.47	10.51	-0.08	-0.12
ICER (cost per QALY)	-	-	-	£418,128*	£288,415*
FDC					
Total costs	£22,191	£47,554	£47,994	-£25,364	-£25,803
QALYs	7.02	7.08	7.11	-0.06	-0.09
Lys	10.39	10.47	10.51	-0.08	-0.12
ICER (cost per QALY)	-	-	-	£420,781*	£290,213*
Probabilistic ICER generated by the ERG	-	-	-	£416,292*	£290,094*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

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

Table 4. Company's revised base case results, subpopulation 4a

Results per patient	BA/EZE FDC	EZE	Incremental value
BA/EZE (separate tables)			
Total costs	£21,476	£16,751	£4,725
QALYs	6.95	6.88	0.07
Lys	10.28	10.18	0.10
ICER (cost per QALY)	-	-	£67,562

FDC			
Total costs	£21,317	£16,751	£4,566
QALYs	6.95	6.88	0.07
Lys	10.28	10.18	0.10
ICER (cost per QALY)	-	-	£65,293
Probabilistic ICER generated by the ERG	-	-	£63,138

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

Table 5. Company's revised base case results, subpopulation 4b

Results per patient	BA/EZE FDC (1)	Ali (2)	Evo (3)	Incremental value	
				(1-2)	(1-3)
BA/EZE (separate tables)					
Total costs	£21,471	£46,120	£46,886	-£24,649	-£25,414
QALYs	6.59	6.80	6.95	-0.21	-0.36
LYs	9.78	10.07	10.28	-0.29	-0.59
ICER (cost per QALY)	-	-	-	£115,065*	£69,756*
FDC					
Total costs	£21,317	£46,120	£46,886	-£24,803	-£25,568
QALYs	6.59	6.80	6.95	-0.21	-0.36
LYs	9.78	10.07	10.28	-0.29	-0.59
ICER (cost per QALY)	-	-	-	£115,783*	£70,178*
Probabilistic ICER generated by the ERG	-	-	-	£114,181*	£69,088*

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; QALYs, quality-adjusted life years

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

Table 6. Company's revised base case results, subpopulation 2b, fully incremental

Treatment	Cost	QALYs	Inc cost	Inc QALY	ICER
BA/EZE (separate tables)					
BA/EZE FDC	£22,350	7.02	-	-	-
Ali	£47,554	7.08	£25,204	0.06	£418,128
Evo	£47,994	7.11	£440	0.03	£15,353
FDC					
BA/EZE FDC	£22,191	7.02	-	-	-
Ali	£47,554	7.08	£25,364	0.06	£420,781
Evo	£47,994	7.11	£440	0.03	£15,353

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 7. Company's revised base case results, subpopulation 4b, fully incremental

Treatment	Cost	QALYs	Inc cost	Inc QALY	ICER
BA/EZE (separate tables)					
BA/EZE FDC	£21,471	6.59	-	-	-
Ali	£46,120	6.80	£24,649	0.21	£115,065
Evo	£46,886	6.95	£765	0.15	£5,098

FDC					
BA/EZE FDC	£21,317	6.59	-	-	-
Ali	£46,120	6.80	£24,803	0.21	£115,783
Evo	£46,886	6.95	£765	0.15	£5,098

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

As touched upon earlier, ICERs in the south-west quadrant of the cost effectiveness plane represent the cost saving per QALY lost. If these ICERs are above the NICE willingness to pay (WTP) threshold they could be considered cost effective if the committee is willing to sacrifice small health gains in order to make large cost savings.

An alternative summary statistic to the ICER is the incremental net monetary benefit (NMB). The incremental NMB is calculated as:

(incremental QALYs * WTP) – incremental costs

It assigns a monetary value to the incremental QALYs achieved. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at a given WTP threshold (£20,000 or £30,000 per QALY).

Table 8 and Table 9 provide the incremental NMB in subpopulations 2b and 4b, respectively. The intervention EVO resulted in a positive NMB compared with ALI in subpopulations 2b and 4b. The interventions ALI and EVO resulted in a negative NMB compared with bempedoic acid in subpopulations 2b and 4b. Therefore, bempedoic acid would be considered cost-saving (and a cost-effective option) compared to ALI and EVO.

Table 8. NMB, subpopulation 2b

Technologies	Incremental costs	Incremental QALYs	NMB: £20,000/QALY		NMB: £30,000/QALY	
			Versus baseline	Fully incremental	Versus baseline	Fully incremental
BA/EZE (separate tablets)						
BA/EZE	-	-	-	-	-	-
Ali	£25,204	0.06	-£23,998	-£23,998	-£23,395	-£23,395
Evo	£25,643	0.09	-£23,865	£133	-£22,976	£419
FDC						
FDC	-	-	-	-	-	-
Ali	£25,364	0.06	-£24,158	-£24,158	-£23,555	-£23,555
Evo	£25,803	0.09	-£24,025	£133	-£23,136	£419

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

Table 9. NMB, subpopulation 4b

Technologies	Incremental costs	Incremental QALYs	NMB: £20,000/QALY		NMB: £30,000/QALY	
			Versus baseline	Fully incremental	Versus baseline	Fully incremental
BA/EZE (separate tablets)						
BA/EZE	-	-	-	-	-	-
Ali	£24,649	0.21	-£20,365	-£20,365	-£18,222	-£18,222
Evo	£25,414	0.36	-£18,128	£2,237	-£14,484	£3,738
FDC						
FDC	-	-	-	-	-	-
Ali	£24,803	0.21	-£20,518	-£20,518	-£18,376	-£18,376
Evo	£25,568	0.36	-£18,281	£2,237	-£14,638	£3,738

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

3 ERG review of issues

3.1 Issue 1: The clinical pathway

As discussed in the ERG report, the company has only considered four subpopulations for the economic analysis and these are:

- Subpopulation 2a: When statins are contraindicated or not tolerated and ezetimibe (EZE) does not appropriately control LDL-C and ALI and EVO are not appropriate;
- Subpopulation 2b: When statins are contraindicated or not tolerated and EZE does not appropriately control LDL-C and ALI and EVO are appropriate;
- Subpopulation 4a: When maximally tolerated statin dose with EZE does not appropriately control LDL-C and ALI and EVO are not appropriate; and,
- Subpopulation 4b: When maximally tolerated statin dose with EZE does not appropriately control LDL-C and ALI and EVO are appropriate.

In their response to TE, the company reported that for patients receiving bempedoic acid (BA) or BA + EZE fixed dose combination (BA/EZE FDC) concomitant therapies for the subpopulations are expected to be as follows:

a) EZE for subpopulations 2a and 4b; and
b) Maximally tolerated statin and EZE for subpopulations 4a and 4b.

The ERG considers that EZE would also be used in subpopulation 2b but otherwise the ERGs clinical experts agree with the company's proposed concomitant treatments for the company's proposed positioning of BA and BA/EZE FDC.

The ERG considers it important to highlight that the cost-effectiveness data presented by the company relates only to patients in whom EZE does not appropriately control LDL-C despite the broader anticipated marketing authorisation for BA. In addition, the ERG is concerned that the impact of the use of clinical data in the company's NMAs where there is a mix of patients with and without prior EZE therapy is unknown and that the impact of prior EZE therapy on LDL-C with subsequent BA is uncertain (See Section 3.2 Issue 2 for further detail).

3.2 Issue 2: Impact of previous and/or concomitant therapy on the treatment effect of BA

As highlighted by the company, the ERG considers the CLEAR studies subgroup data suggest similar results in terms of mean percentage LDL-C reduction regardless of background EZE therapy. However, the ERG also notes that there is still a difference in the results of the analyses and as such the ERG does not consider a [redacted] difference (statin intolerant population) or a [redacted] difference (maximally tolerated statin population) between the presence and absence of background EZE use at baseline to be clinically insignificant given that the trials were not designed (and so not powered) to detect a statistical difference for this comparison. In addition, it is important to note that the background EZE analyses are based on *post-hoc* subgroups.

The ERG agrees with the company that the direction of the difference in effect with background EZE was opposite in the two populations:

- For statin-intolerant patients, the treatment effect was numerically greater in patients with EZE than without; and
- For patients with maximum tolerated dose of statins, the treatment effect was numerically smaller in patients with EZE.

The ERG is unsure as to whether or not there is any plausible clinical rationale to explain this difference in direction of treatment effect, although the ERG considers it could just be an artefact of the subgroup analyses being based on small patient numbers and so underpowered.

The ERG did not have time to examine the impact of prior EZE therapy for the comparator treatments in the NMA and therefore is unable to comment on whether or not they are impacted by prior therapy. However, the ERG does not consider it appropriate to extrapolate the findings from background EZE subgroup analyses of ALI to BA, given that they have different mechanisms of action and that there may be other baseline differences between the studies which could impact on the subgroup results.

The ERG notes that the company presented new NMA analyses in their response to TE and that some of these new NMAs explored the impact of including covariate adjustment for baseline EZE use and baseline statin use (see Section 3.7 Issue 6 for further detail). The 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; the ERG instead considers subgroup data would be more appropriate.

The ERG is unclear as to how the company have applied the covariate adjustment for baseline statin use but the ERG acknowledges this covariate adjustment has minimal impact on the results of any of

the analyses compared to the analyses where there are no covariate adjustments. In addition, the ERG notes that the subgroup analyses for baseline statin intensity reported by the company are likely to be underpowered to detect differences between subgroups due to the small patient numbers in the analyses.

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

The ERG maintains that the cost effectiveness of bempedoic acid should be modelled based on the appropriate LDL-C levels for the appropriate subpopulations. Baseline LDL-C levels are by definition different between subpopulations 2a and 4a (not eligible for ALI/EVO), and 2b and 4b (eligible for ALI/EVO). NICE TA394 and TA393 recommend EVO and ALI as options only in:

- Primary prevention: Patients with HeFH and LDL-C >5 mmol/L;
- Secondary prevention – High risk: LDL-C >4 mmol/L;
- Secondary prevention – Very high risk: LDL-C >3.5 mmol/L.

The mean baseline LDL-C levels obtained from patients in the CLEAR trials are summarised in Table 10. The ERG is concerned that the company is overestimating the baseline LDL-C level in subpopulations 2a and 4a (not eligible for ALI/EVO) by using the mean baseline LDL-C from all patients. As a result, the company is potentially overestimating the cost-effectiveness of bempedoic acid compared to ezetimibe: a higher baseline LDL-C leads to larger absolute reductions in LDL-C and therefore lower CV event risks, favouring more effective treatments.

Table 10. Baseline LDL-C

Subpopulation	Population 2* (no or low dose statin)	Population 4^ (max dose statin)
Subpopulation a (not eligible for ALI/EVO)	[redacted]	[redacted]
Subpopulation b (eligible for ALI/EVO)	[redacted]	[redacted]
All patients (used to inform subpopulation a in the company's base case analysis)	[redacted]	[redacted]

Abbreviations: ALI, alirocumab; EVO, evolocumab; LDL-C, low-density lipoprotein cholesterol.
*CLEAR Tranquility and CLEAR Serenity
^CLEAR Wisdom and CLEAR Harmony

The company's main argument for using the baseline LDL-C from all patients is that most patients eligible for ALI/EVO do not receive ALI/EVO in clinical practice. Stakeholder responses to this issue were variable (Table 11). To account for this uncertainty, the ERG presents its preferred base analysis using the appropriate LDL-C levels in the relevant subpopulations ([redacted] and [redacted] in subpopulations 2a and 4a, respectively) and an alternative base case analysis using LDL-C levels from all patients in subpopulations 2a and 4a ([redacted] and [redacted], respectively).

Table 11. Summary of stakeholder responses to Issue 3

Organisation	In clinical practice, if a person is eligible for ALI/EVO, are they likely to receive it?
ABCD, part 1	Yes - unless they decide they do not want it.
ABCD, part 2	Depends largely on primary care doctors and secondary care clinicians recognising it is an issue and referring to a lipidologist. Probably less than half the time.
BSC	I don't know, but I suspect that these drugs are underutilised compared with notional optimal NICE guideline implementation.
Sanofi	We agree with the ERGs suggestion that access to ALI is variable across different centres and regions. However, what we have noticed is that even in areas where PCSK9i prescribing is allowed there are long waiting lists for lipid clinics and slow throughput.
Amgen Ltd	NICE TA394 and NICE TA393 clearly define the clinical circumstances in which EVO or ALI are treatment options. Use in clinical practice should be aligned with these NICE recommendations. Uptake in some areas is good, with eligible patients accessing EVO in line with NICE TA394; however, in some areas there have been local barriers to access since NICE issued its positive guidance. In recognition of the need to improve access to EVO and ALI, as ground-breaking, cost-effective new treatments, both are included in the NHS England Accelerated Access Collaborative programme. We therefore anticipate that patient access to EVO will continue to increase across areas in line with their clearly defined recommendations for use outlined in its NICE TA394.

Abbreviations: ABCD, Association of British Clinical Diabetologists; ALI, alirocumab; BSC, British Cardiovascular Society; ERG, Evidence Review Group; EVO, evolocumab; NICE, The National Institute for Health and Care Excellence; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors

Finally, to address stakeholder concerns on how the actual LDL-C thresholds for ALI/EVO impact on the cost effectiveness of bempedoic acid, the ERG has explored scenarios using baseline LDL-C levels of 3.5 mmol/L and 4 mmol/L in subpopulations 2b and 4b (eligible for ALI/EVO) for the FDC (Table 12). These scenarios have been performed in the company's model, changing the baseline LDL-C input only. As mentioned earlier, higher baseline LDL-C levels favour more effective treatments, but in subpopulations 2b and 4b, bempedoic acid is the least effective treatment included in the comparison.

Table 12. ERG scenario using the actual LDL-C threshold for ALI/EVO

Results per patient	FDC (1)	Ali (2)	Evo (3)	Incremental value	
				(1)-(2)	(1)-(3)
Subpopulation 2b, 3.5 mmol/L (very high risk)					
Total costs	£22,199	£47,936	£48,365	-£25,737	-£26,166
QALYs	7.22	7.27	7.29	-0.05	-0.07
ICER	-	-	-	£566,317	£389,886
Subpopulation 2b, 4.0 mmol/L (high risk)					
Total costs	£22,190	£47,720	£48,155	-£25,530	-£25,965
QALYs	7.11	7.16	7.19	-0.05	-0.08
ICER	-	-	-	£476,432	£328,319
Subpopulation 4b, 3.5 mmol/L (very high risk)					
Total costs	£21,303	£46,462	£47,149	-£25,159	-£25,845
QALYs	6.81	6.97	7.09	-0.16	-0.28
ICER	-	-	-	£155,896	£93,558
Subpopulation 4b, 4.0 mmol/L (high risk)					

Total costs	£21,306	£46,266	£46,997	-£24,960	-£25,691
QALYs	6.69	6.88	7.01	-0.19	-0.33
ICER	-	-	-	£130,740	£78,909

Abbreviations: Ali, alirocumab; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALYs, quality-adjusted life years

3.4 Issue 4: Subgroup analyses by CV risk and HeFH

The ERG notes that the company reported in their clarification responses that subgroups such as patients with HeFH are too small to be analysed separately, but the company also used the data from the subgroup analyses to demonstrate similar efficacy across groups such as patients with and without HeFH, which the ERG considers to be contradictory. The ERG considers many of the subgroup analyses presented for the BA and BA/EZE FDC trials in the company submission were associated with low patient numbers and so underpowered to detect between subgroup differences in treatment effectiveness. Additionally, the company report in their TE response that *post-hoc* analysis of UK and English patients from the CLEAR trials showed that baseline characteristics and efficacy results did not differ when only UK or English patients were included in the analysis. However, no numerical data are presented in support of this statement and therefore the ERG is also unsure as to how robust this subgroup analysis is.

In Appendix C of the company's response to TE, the company presented cost-effectiveness results in seven subgroups according to CV risk and HeFH:

1. Without CVD;
2. Without CVD, HeFH;
3. With CVD (high risk or very high risk);
4. With CVD, high risk, Non-HeFH;
5. With CVD, very high risk, Non-HeFH;
6. With CVD, high or very high risk, HeFH;
7. With CVD, high or very high risk, HeFH.

Baseline LDL-C levels were estimated for each subgroup based on analyses of the patient-level data in the CLEAR trials. However, the same treatment effect was employed in each subgroup based on the assumption that the treatment effect would be similar in patients with and without HeFH and with and without prior ASCVD. Therefore, the company's results only serve the purpose of demonstrating that the ICER is correlated with the baseline LDL-C level.

3.5 Issue 5: Consideration of subpopulation 2b, 4a and 4b as secondary (not primary or mixed) prevention populations

One of the ERG's major concerns with the modelled subpopulations is that the efficacy data for bempedoic acid are limited in HeFH and primary prevention. In consequence, modelling a mixed cohort could lead to inappropriate conclusions for these populations. Most stakeholders responding to the TE report also agreed that it is inappropriate to generalise between primary and secondary prevention populations. As a result, the company accepted the ERG's suggestion to redefine the subpopulations according to the vast majority of the study population in the CLEAR trials ([redacted] in most cases):

- Subpopulation 2a, primary prevention without HeFH;
- Subpopulation 2b, secondary prevention without HeFH;
- Subpopulation 4a, secondary prevention without HeFH;
- Subpopulation 4b, secondary prevention without HeFH.

However, the ERG notes that redefining the subpopulations in the model is only one step closer to a robust analysis. Not all patients in the trials included in the NMA supporting the data for subpopulations 2b, 4a and 4b are derived from trial populations without HeFH in secondary prevention. Additionally, not all patients in the NMA supporting that data for subpopulation 2a are derived from trial populations without HeFH in primary prevention. Analyses based on efficacy data directly relevant to the intended subpopulation should be conducted in order to provide reliable cost effectiveness estimates. However, as discussed under Issue 4, the ERG considers many of the subgroup analyses presented by the company to be associated with low patient numbers and so underpowered to detect between subgroup differences in treatment effectiveness.

Finally, another concern of the ERG's was related to the starting health state of secondary prevention patients in the model. However, in the company's response to TE, the company acknowledged that there is uncertainty around this assumption and accepted the ERG's approach of using stable disease as the starting health state instead of a 3-year+ post-event health state.

3.6 Issue 5a: CV event history and risk data are not consistent with the effectiveness data

As treatment effectiveness data were taken from the CLEAR trials, the ERG considers that primary CV risks and CV event history in these trials may be more appropriate to use in the economic analysis than other sources. In the company's response to TE it was explained that the full set of variables

required to reliably calculate primary CV risks using the QRISK3 algorithm is not available from the CLEAR studies.

In consequence, the ERG considers that the true risk for primary CV events would lie somewhere in between the company's base case analysis (a 10-year risk of around 30% for myocardial infarction [MI], ischemic stroke [IS] or CV death estimated using the SCORE risk algorithm in European Society of Cardiology [ESC] guidelines) and the company's scenario analysis provided during the clarification stage (a 10-year risk of 20% for MI, IS or CV death to reflect CG181 and TA385). The ERG has provided the results of this scenario analysis using the company's revised base case assumptions in Table 13 for subpopulation 2a (the only subpopulation in primary prevention). These results should be viewed as conservative.

Table 13. Scenario analysis on primary CV risks, subpopulation 2a

Results per patient	FDC	EZE	Incremental value
Total costs	£12,434	£7,580	£4,854
QALYs	9.82	9.67	0.15
ICER (cost per QALY)	-	-	£31,806

Abbreviations: CV, cardiovascular; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Finally, the company did not mention in their response if CV event history from the CLEAR trials was available. Therefore, the ERG would like to pose this question to the company again.

3.7 Issue 6: Methodological uncertainty in the company and ERG network meta-analysis

In their response to TE the company presented 10 different NMAs for the maximally tolerated statin population (NMA 1 to NMA 10). In summary these ten NMAs are as follows:

- NMA 1: ODYSSEY LONGTERM included and baseline LDL-C covariate included;
- NMA2: ODYSSEY LONGTERM included and baseline LDL-C covariate removed (i.e. no covariates);
- NMA 3: ODYSSEY LONGTERM included and baseline statin use as a covariate;
- NMA 4: ODYSSEY LONGTERM included and baseline EZE use as a covariate;
- NMA 5 [**new base case**]: ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline LDL-C as a covariate;
- NMA 6: ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates;
- NMA 7: ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline EZE as a covariate;

- NMA 8: ODYSSEY LONGTERM included, ODYSSEY Mono excluded, baseline statin as a covariate;
- NMA 9a: ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 24-week data removed from the network where 12-week data for the same study was included;
- NMA 10a: ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 12-week data removed from the network where 24-week data for the same study was included.

In the company's maximally tolerated statin NMA post-clarification questions, ODYSSEY LONGTERM was excluded, ODYSSEY MONO was included and baseline LDL-C covariate adjustment was included.

The ERG considers that ODYSSEY MONO, a study where no one had received prior lipid lowering therapy (LLT) should be excluded from the maximally tolerated statin NMA and ODYSSEY LONGTERM should be included as less than 50% of patients were diabetic (rather than the whole study population being diabetic). The ERG therefore considers the company's new NMAs numbered 5 to 10 in Appendix A of the company response to TE are the most relevant to the decision problem and therefore does not discuss NMAs 1-4 or the NMA from post-clarification questions any further.

The ERG notes that a maximum of one covariate (baseline LDL-C, baseline EZE use and baseline statin) is applied in each of the company's NMAs, whereas the ERG would prefer that all three covariates were applied in a single analysis. In the absence of an appropriate multivariate analysis, the ERG considers that of the three covariates baseline LDL-C is likely to be the most appropriate single covariate to use as it is likely to be linked to baseline use of LLTs such as statins and EZE. The ERG therefore considers NMA 5 (LDL-C covariate) to be more relevant than NMA 6 (no covariates), NMA 7 (EZE covariate) or NMA 8 (statin covariate). However, the ERG notes that the application of the covariate adjustment for baseline EZE use in the maximally tolerated NMA did have an impact on the results of the NMA (NMA 7) compared to when no covariate adjustment was applied (NMA 6): the covariate adjustment resulted in [redacted] benefit in terms of LDL-C reduction (Table 14). In addition, interestingly only inclusion of the baseline EZE covariate in the maximally tolerated statin NMA improved the model fit suggesting that baseline EZE use is an important aspect of the analysis.

Table 14. Results of NMA 5, 6, 7 and 8.

Treatment	NMA 5 [a]	NMA 6 [b]	NMA 7 [c]	NMA 8 [d]
	Estimated mean difference in % change in LDL−C from baseline compared with EZE (95% Credible Interval)			
BA+statin	[redacted]	[redacted]	[redacted]	[redacted]
FDC+statin	[redacted]	[redacted]	[redacted]	[redacted]
EVO+statin	[redacted]	[redacted]	[redacted]	[redacted]

ALI (75 mg)+statin	[redacted]	[redacted]	[redacted]	[redacted]
ALI (150 mg)+statin	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; NMA, network meta-analysis

Note: greyed data not used in the economic analysis

*Mean % change in LDL-C with baseline ezetimibe: a[redacted] b[redacted] c[redacted] d[redacted]

The company argues that the ERG has presented no evidence to support its decision to focus only on studies where patients have received prior EZE in the ERG NMAs. The ERG considers that given the population in which the company is positioning bempedoic acid (BA) is one where patients have received prior EZE and that there are data available from this population, it is most appropriate to use these data albeit that they comprise data from small subgroups.

Finally, the ERG notes that the company has also conducted NMAs where either the 24-week data (NMA 9) or 12-week data (NMA 10) are excluded, where data from both timepoints from the same study were previously included (NMA 1-8). The ERG agrees with this exclusion of data in NMA 9 and NMA 10 as patients may otherwise be double counted in the analyses.

The ERG also notes that in NMA 9 patients are all randomised directly to ALI 150mg and that the data for all comparators in the NMA are assessed at 12 weeks. In contrast, in NMA 10, some studies for ALI 150mg are included with 24-week data rather than 12-week data , although the ERG acknowledges that the data the company is using is based on LDL-C change from week 12 to week 24. In addition, in NMA 10 there is a mix of studies where patients were directly randomised to treatment with ALI 150mg and studies where patients have been up titrated from 75mg following an in adequate response at 12 weeks. In NMA 10, not all patients have thus been randomised to ALI 150mg and not all data are based on outcomes assessed at 12-weeks post randomised study drug commencement.

The ERG notes that in clinical practice patients can either be directly commenced on ALI 150mg or be up titrated from 75mg to 150mg if they are deemed to have an inadequate response to ALI 75mg. The ERG considers that based on the results of NMA 9 and NMA 10, there may be a difference in the results for change in LDL-C from baseline for ALI 150mg depending on whether or not patients have been up titrated from 75mg. In NMA 10, the ERG is uncertain whether the proportion of patients who have been randomised to 150mg and the proportion who have been up titrated from 75mg accurately reflect UK clinical practice. The ERG is therefore unsure of how applicable the results of NMA 10 are to UK clinical practice. In contrast, the ERG acknowledges that NMA 9 is likely to favour ALI 150mg as it does not include the patients who would have been up titrated from 75mg and thus

may derive less benefit from further treatment with ALI than those patients randomised directly to the 150mg dose. The ERG also considers it important to highlight that the inclusion criteria for treatment with ALI 150mg in the trials included in the company's NMAs may not align with the strict eligibility criteria for treatment with ALI 150mg in UK clinical practice. However, the ERG is unable to predict the likely direction of potential bias relating to the applicability of the trials to UK clinical practice. The ERG also notes that NMA 9 more closely reflects how ALI is currently modelled in the company's cost-effectiveness analysis with all patients starting directly on 150 mg ALI.

The company's NMA 9a and NMA 10a do not include covariate adjustment for baseline LDL-C but the company also provided results of these NMAs with covariate adjustment for baseline LDL-C (NMA 9b and 10b), baseline ezetimibe (NMA 9c and 10c) and baseline statin (NMA 9d and 10d). The company reported in their response to TE appendix A that they did not consider any of their proposed covariate adjustments in NMAs 9 and 10 to result in any substantial differences in the results. The ERG considers the baseline EZE covariate to have a small impact on the results although the ERG considers the inclusion of covariate adjustment for LDL-C to be the key covariate for inclusion in the company's NMAs. The ERG therefore discusses only the results of NMA 9b and 10b in further detail as these are the NMAs with LDL-C covariate adjustment.

The results of NMA 9b and 10b are reported alongside the results of the NMA informing the company's revised base case (NMA 5) in Table 15. The mean change in LDL-C with FDC (i.e. BA +EZE) suggest [redacted] NMA 9b and 10b compared to in NMA 5. The results for ALI 150mg are [redacted] which, as discussed above, is likely to be reflective of the exclusion of the patients who have been up titrated from 75mg to 150mg and so have likely already had some response to ALI.

Table 15. Results of NMA 5, NMA 9b and NMA 10b.

Treatment	NMA 5 (company revised base case)*	NMA 9b^	NMA 10b~
	Estimated mean difference in % change in LDL−C from baseline compared with EZE (95% Credible Interval)		
BA+statin	[redacted]	[redacted]	[redacted]
FDC+statin	[redacted]	[redacted]	[redacted]
EVO+statin	[redacted]	[redacted]	[redacted]
ALI (75 mg)+statin	[redacted]	[redacted]	[redacted]
ALI (150 mg)+statin	[redacted]	[redacted]	[redacted]

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; NMA, network meta-analysis

Note: greyed data not used in the economic analysis

Mean % change in LDL-C with baseline ezetimibe:* [redacted]; ^ [redacted]; [redacted]

The ERG notes that for NMA 5, that is used in the company's revised base case for the maximally tolerated statin population, there is poor model fit and high levels of statistical (I^2 86.8%) and clinical heterogeneity present (e.g. differences between studies in terms of baseline cardiovascular risk, statin intensity, proportion of patients receiving LLT for primary prevention, and proportions of patients with HeFH as detailed in the ERG report). The ERG has reviewed the total residual deviance reported for NMA 5 in comparison to the number of data points included in the analysis, although due to time constraints the ERG has used the effective number of parameters (pD) reported by the company as an estimate of the number of data points. The ERG notes that the total residual deviance (394.292) is approximately four times higher than the pD (100.5), which implies that the company's NMA would poorly predict the data from the trials used in the analysis. The ERG considers this to be further evidence of the unreliability of the NMA results. The ERG notes that the total residual deviance for the company's other NMAs in the maximally tolerated statin population are similarly at least three times the value of their respective pD.

The ERG prefers NMA 9b presented by the company over NMA 5, because NMA 9b includes covariate adjustment for LDL-C and removes the double counting issue discussed above. However, the ERG would have preferred an NMA with all covariate adjustments applied and for the NMA to use only the prior EZE subgroup. The ERG therefore still considers the ERG's NMA to be the most appropriate in terms of addressing the correct population and minimising clinical and statistical heterogeneity (as detailed in Section 3.5 of the ERG report). In addition, the issues identified with the reliability of the company's NMA were not present in the ERG's NMA as the residual deviance and number of data points were similar (1.995 and 2, respectively).

The results from the company's NMA 9b are given in Table 16 alongside the results of NMA 5 and the ERG's NMA. The ERG considers it important to highlight that the ERG's results for FDC+statin are exclusively in patients who have received prior ezetimibe, whereas the company's NMAs also include patients with no prior history of ezetimibe.

Table 16. Results of NMA 5, NMA 9b and the results of the ERG's NMA

Treatment	NMA 5			NMA 9b			ERG NMA		
	Mean*	95% CI	P value	Mean*	95% CI	P value	Mean*	95% CI	P value
BA+statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE	NE	NE
FDC+statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE
EVO+statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE	NE	NE
ALI (75 mg) +statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE	NE	NE
ALI (150 mg) +statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE	NE	NE

ALI (150 mg) +statin+EZE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CI, credible interval; ERG, evidence review group; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination, NE, not estimable; NMA, network meta-analysis.

* Estimated difference in % change in LDL−C from baseline compared with EZE

Note: greyed data not used in the economic analysis

Due to time constraints, the company did not provide cost effectiveness results for the new NMAs. Therefore, the ERG requested that the company provided the mean percentage change in the EZE arm (the baseline treatment) obtained from each NMA in order for the ERG to run the analyses themselves. These data have been added to Table 14 and Table 15. In response to ERG, the company also provided deterministic cost-effectiveness results for the ERG's preferred new NMA (NMA 9b). Using the results from NMA9b in the economics analysis led to notable changes in the company's base case ICER in favour of ALI and EZE. The changes in the ICER for the FDC preparation using NMA9b are as follows:

- Subpopulation 4a:
    - ICER increased from £65,293 to £70,144 for FDC vs EZE.
- Subpopulation 4b:
    - ICER reduced from £115,783 to £85,081 for ALI vs FDC;
    - ICER increased from £5,098 to £10,668 for EVO vs ALI;
    - ICER increased from £70,178 to £75,124 for EVO vs FDC.

As part of their response to TE, the company also provided two further NMAs in the statin intolerant population to supplement their NMA in supplied at the clarification stage of using baseline LDL-C as a covariate:

- Baseline LDL-C covariate removed (i.e. no covariates);
- Baseline EZE used as a covariate.

The ERG notes that in the NMA with baseline EZE covariate adjustment there is little change in the results for change in LDL-C from baseline compared to in the NMA with no covariate adjustment; the inclusion of covariate adjustment for baseline LDL-C also has minimal impact on the NMA results for change in LDL-C from baseline at 12 weeks (Table 17). The ERG also notes that all three of these NMAs are associated with similar model fit statistics and have similar DIC values (range 111.3-112.2). Due to time constraints, the ERG used the pD reported by the company as an estimate of the number of data points in the company's NMAs and compared this with the total residual deviance. The ERG notes that the total residual deviance (range from 89.937 to 90.053) is approximately four times higher than the pD (range from 21.4 to 22.1) in each of the NMAs in Table 17, which implies

that the company's NMA would poorly predict the data from the trials used in the analysis. The ERG considers this to be further evidence of the unreliability of the company's NMA results.

Table 17. Results of company statin intolerant NMAs and ERG NMA

Treatment	Mean*	95% CI	P value
NMA results provided in Response to ERG Clarification Questions, 16 Jan 2020			
BA	[redacted]	[redacted]	0.0985
BA+EZE	[redacted]	[redacted]	0.0024
EVO	[redacted]	[redacted]	0.0015
EVO+EZE	[redacted]	[redacted]	—
ALI (75 mg)	[redacted]	[redacted]	0.0004
ALI (150 mg)	[redacted]	[redacted]	0.0004
1. Baseline LDL-C covariate removed (i.e. no covariates)			
BA	[redacted]	[redacted]	0.0647
BA+EZE	[redacted]	[redacted]	0.0012
EVO	[redacted]	[redacted]	< 0.0001
EVO+EZE	[redacted]	[redacted]	—
ALI (75 mg)	[redacted]	[redacted]	< 0.0001
ALI (150 mg)	[redacted]	[redacted]	< 0.0001
2. Baseline EZE use as a covariate			
BA	[redacted]	[redacted]	0.0985
BA+EZE	[redacted]	[redacted]	0.0023
EVO	[redacted]	[redacted]	0.0020
EVO+EZE	[redacted]	[redacted]	—
ALI (75 mg)	[redacted]	[redacted]	< 0.0001
ALI (150 mg)	[redacted]	[redacted]	< 0.0001
ERG's NMA			
Bempedoic acid + ezetimibe	[redacted]	[redacted]	[redacted]
AliMab 150 mg + ezetimibe	[redacted]	[redacted]	[redacted]

Abbreviations: Ali, alirocumab; BA, bempedoic acid; CrI, credible interval; ERG, evidence review group; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; LDL C, low-density lipoprotein cholesterol; NA, not applicable; NMA, network meta-analysis.

* Estimated difference in % change in LDL−C from baseline compared with EZE

The company NMA with LDL-C covariate adjustment remains as reported in the response to clarification questions (16 January 2020) and the ERG agrees that out of the NMAs presented by the company in the statin intolerant population, this is reasonable. However, the ERG's concern about the company's NMA still remains given the high levels of statistical heterogeneity (I^2 of 66.1%) and clinical heterogeneity in the studies included in the NMAs (e.g. differences between studies in terms of baseline cardiovascular risk, statin intensity, proportion of patients receiving LLT for primary prevention, and proportions of patients with HeFH as discussed in the ERG report Section 3). In addition, as discussed in Issue 1, the company has used an incorrect population in its NMAs to address the population in whom EZE does not appropriately control LDL-C with studies included that have some patients who have not received prior EZE therapy.

Given all the issues detailed above with the company's NMA, the ERG still considers the ERG's NMA is the most appropriate analysis in the statin intolerant population. The ERG also considers that the issues identified with the reliability of the company's NMA were not present in the ERG's NMA as the residual deviance and number of data points were similar (2.005 and 3, respectively). However, as discussed in the ERG report, the ERG's NMA is subject to uncertainty and may be missing data. The ERG's NMA uses data only in the population of patients who have received prior EZE and patients are assumed to continue EZE throughout the study. Nevertheless, the ERG was unable to include all the appropriate data from the bempedoic acid studies as the data were not reported in the CS and the ERG's appraisal of other studies potentially relevant to the analysis was limited. As such, the results of the ERG's analyses should be interpreted with caution.

In summary, the ERG considers clinical, methodological, and statistical heterogeneity in the clinical effectiveness evidence remains despite the new NMAs presented by the company. The ERG considers the key outstanding issues in the clinical effectiveness evidence to be:

1. **Clinical studies:**
    - The use of incorrect populations in the NMAs to address the population in whom ezetimibe does not appropriately control LDL-C with studies included that have a mix or even no patients with prior ezetimibe therapy;
    - Other sources of clinical heterogeneity in the studies included in the NMAs which includes differences between studies in terms of baseline cardiovascular risk, statin intensity, proportion of patients receiving lipid lowering therapy (LLT) for primary prevention, and proportions of patients with HeFH;
    - The company's updated NMAs do not have all the appropriate covariates applied. In addition, it appears that there is double counting of patients in NMAs 1 to 7 through the use of 12- and 24-week data for some of the alirocumab trials. The ERG notes that alirocumab patients who have received 75 mg and also been uptitrated to 150 mg at 12 weeks may have been included in both the 75 mg and 150mg analyses albeit using data from different timepoints (12 weeks and 24 weeks, respectively).
2. **Data and analyses:**
    - No subgroup analyses based on primary or secondary prevention (CV risk) or presence of HeFH were conducted by the company for the NMAs despite being specified in the NICE final scope and deemed important subgroups in the recommendations made in the related technology appraisals for evolocumab and

alirocumab (TA393 and TA394, respectively). In addition, patients from these subgroups are included in the economic model. There is limited information reported in the clinical studies in the NMAs on the proportion of patients who are primary or secondary prevention and who do or don't have HeFH. In the absence of suitable subgroup analyses, the ERG does not consider it appropriate to assume no difference in treatment effect across potentially important subgroups of relevance in the economic model.

- Data are mostly limited to 12-weeks in the company's NMAs, although treatment is likely to be long-term depending on patient response and tolerance. The ERG considers that there may be a slight waning of treatment effect with bempedoic acid beyond 12-weeks and is unable to comment as to whether similar waning would be seen for the comparators.

3. **NMA methodology:**
   - The ERG considers the main problem with the company's NMAs is the clinical heterogeneity as detailed above (1. Clinical studies).
   - The ERG was unable to replicate the results obtained from the company's NMAs due to time constraints. However, the ERG considers that the company has used a method to adjust for differences in baseline LDL-C that has introduced additional uncertainty into an already heterogeneous analysis. In the ERG's opinion, the company could have used individual patient data (IPD) from the relevant CLEAR studies to establish the correlation between baseline LDL-C and treatment effect, and then assumed this correlation held across all studies included in the network
   - In addition, there were high levels of statistical heterogeneity in the results of the company's NMAs despite the inclusion of covariate adjustment for baseline LDL-C differences and updates to the NMAs during the clarification stage suggesting that the results of the company's NMAs are unreliable:
     - for the company's statin intolerant NMA the I^2 is 66.1%;
     - for the company's maximally tolerated statin NMA the I^2 for the new analysis is not reported but the previous is I^2 was 86.6%.

- **ERG NMAs:**
  - The exploratory ERG NMAs use data only in the population of patients who have received prior ezetimibe and are assumed to continue ezetimibe throughout the study. However, the ERG was unable to include all the appropriate data from the bempedoic acid studies and the ERG's appraisal of studies was limited. As such, the

results of the ERG's analyses are also subject to uncertainty and should be interpreted with caution.

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

The ERG considers that the data for mean reduction in LDL-C suggest a waning of treatment effect with BA beyond 4 weeks in CLEAR Harmony, CLEAR Wisdom, CLEAR Tranquillity and CLEAR Serenity and that this continues beyond 12 weeks. In addition, in their response to TE the company reported that, in the CLEAR Harmony open-label extension study (1002-050), improvements in LDL-C with BA were durable through 52 weeks [redacted]. The company also acknowledges that small numerical differences in LDL-C reduction over time are observed for BA but considers these are likely to be related to treatment discontinuation rather than waning of the treatment effect in patients complying with and persisting on treatment. However, the ERG considers that treatment discontinuation is also likely to be an issue in clinical practice and that the current statistical analyses and data for BA are not suitable to confirm or refute the presence of treatment waning. In addition, the ERG notes that the stakeholder technical engagement comments also suggest there is no evidence to refute the presence of a potential treatment waning effect with BA.

The ERG considers the latest timepoint (24 weeks for statin intolerant NMA and 52 weeks for maximally tolerated statin NMA) to be the most informative to the decision problem as patients in clinical practice would be expected to potentially take bempedoic acid for the rest of their lives and well beyond 12 weeks. The ERG's clinical experts also reported that treatment with BA would be expected to be life-long assuming it was effective and there was no clinical rationale for otherwise discontinuing treatment which is in keeping with the view of the company. The ERG notes that technical engagement feedback from other stakeholders is also in agreement with the use of the latest available data and supported the ERG's view that BA treatment would be expected to be long-term rather than limited to 12 weeks (Table 18).

The ERG notes that the company further argues to use 12-week data in the NMAs because 12-weeks was the primary outcome assessment in the BA studies of relevance, but the ERG sees no rationale why data from non-primary outcomes could not be used in the NMAs. The ERG would therefore prefer to see data from the latest timepoints with data given the possible treatment waning effect with BA and the long-term nature of expected treatment with BA in clinical practice. The ERG's clinical experts also affirmed that the response at week 12 would be expected to be larger than the sustained response in terms of reduction in LDL-C.

Table 18. Summary of stakeholder comments in relation to Issue 7

ABCD, part 1	ABCD, part 2	BCS	Amgen	SANOFI
Should the outcome in the NMAs be measurements at 12 weeks, or the most mature available evidence?				
Most mature available evidence	The longer the duration the better.	I am not qualified to answer this question	-	The 12 week data was collected in controlled environments of RCTs whereas extension data may not be.
Is it plausible that a treatment waning effect may occur with BA?				
Yes	Possible that tachyphylaxis could occur over time, although from the wealth of statin data and the fact that BA works further down the same pathway, it seems less likely.	Plausible but not especially likely.	We believe the long-term efficacy and safety of BA remain uncertain at this time. We note that efficacy and safety data presented by the company are limited to 1 year of follow-up. Furthermore, efficacy data for BA are limited to LDL-C reductions and there are no CV outcomes data currently available. In contrast, EVO is confirmed to provide long-term, sustained LDL-C reductions, that are superior to those achieved with BA, through 5 years of follow-up (OSLER-1 study) . In addition, robust data from the FOURIER trial confirm that EVO reduces CV events.	Yes. Could be due to organic changes in liver metabolism or patient non-adherence to treatment.
In clinical practice, would people stop treatment with BA after a certain time period?				
Not routinely	Unlikely to as that would defeat the objective of maintaining a low LDL-C level.	Would depend on clinical trial data.	Our understanding is that patients would remain on lipid lowering therapy where possible to reduce their risks of CV events in the long term. In patients who would have otherwise been eligible for EVO and ALI, the use of BA+EZE instead would leave patients who are at high risk of CV events exposed to ongoing residual risks, and may preclude their access to optimal therapy. We note that the company has not explored subsequent therapies, and so the full consequences of using sub-optimal BA+EZE in patients who would otherwise be eligible for EVO or ALI are not fully understood.	Yes- potential compensatory mechanisms of several metabolic pathways may impact BA MOA.

Abbreviations: ABCD, Association of British Clinical Diabetologists; ALI, alirocumab; BA, bempedoic acid; BSC, British Cardiovascular Society; CV, cardiovascular; EVO, evolocumab; LDL-C, low-density lipoprotein cholesterol RCT, randomised controlled trial

The ERG notes that a treatment discontinuation rate of 6.7% was included in the cost-effectiveness model, and that it was assumed that the treatment effect is immediately lost for patients discontinuing treatment. The ERG considers this to be a reasonable assumption. However, the ERG notes that treatment waning effects are different to treatment discontinuation rules: 12-week results are still maintained for the duration of the model's time horizon in patients on-treatment.

Finally, as discussed in relation to Issue 6, the ERG considers the inclusion of both 12-week and 24-week ALI data from the same study's in the company's maximally tolerated stain NMA to be inappropriate as there is double counting of patients. The ERG notes that only 12-week data are included for the other comparators in the company's NMA.

3.9 Issue 8: Health related quality of life

The company has resolved this issue using the ERG's approach outlined in the ERG report.

3.10 Issue 9: Costing of ALI/EVO administration and CV events

The company has resolved this issue using the ERG's approach outlined in the ERG report. Most stakeholders responding to the TE report also agreed with the ERG that ALI or EVO would be administered in a hospital setting, with an annual follow up with a consultant.

4 ERG base case analyses

The company was generally in support of the ERG's preferred assumptions related to the starting population, and the estimation of costs and QALYs.

However, the company rejected the ERG's suggestion to use LDL-C levels from patients not eligible for ALI/EVO in subpopulations 2a and 4a (see Section 3.3 Issue 3). Stakeholder responses to this issue were also variable. To account for this uncertainty, the ERG presents two base case analysis: the ERG's preferred base case analysis employs LDL-C levels from patients not eligible for ALI/EVO in subpopulations 2a and 4a, while the ERG's alternative base case employs the LDL-C levels from all patients in the subpopulation not eligible for ALI/EVO in subpopulations 2a and 4a (i.e. the company's base case assumption).

Furthermore, the ERG still considers that the ERG's NMA is the most appropriate NMA in the statin intolerant population (see Section 3.7 Issue 6). However, as discussed in the ERG report, this NMA is

subject to uncertainty and may not include all appropriate data. The ERG is also unable to produce PSA results for subpopulation 2b given that inputs for the CODA for ALI+EZE are not included in the model.

As for the maximally tolerated statin NMA, the ERG would have preferred to have seen the results of NMA 9 with all three covariates applied (baseline LDL-C, statin use and EZE use). Unfortunately, the company did not provide this analysis, and therefore out of the NMAs currently presented by the company, NMA 9b is the ERG's preferred NMA. However, as concluded in Issue 6, the ERG still considers the ERG's NMA to be the most appropriate in terms of addressing the correct population (patients have received prior EZE) and minimising clinical and statistical heterogeneity. As noted in the ERG report, the ERG NMA did not include a comparison of prior EZE with continued EZE. Additionally, it was not known how many prior EZE patients continued on EZE. Therefore, in order to inform the mean percentage change in LDL-C with EZE in the model, the ERG made the pragmatic decision to employ the estimate from the company's base case analysis. The ERG has updated this estimate from [redacted] to [redacted] to reflect the estimate in NMA9b. The ERG notes that the impact of changing this estimate in the model has a minimal impact on the results, but still acknowledges that this is still a limitation of the ERG's analysis. Furthermore, as the ERG does not have access to the CODA for EZE obtained from NMA9b, the ERG does not provide probabilistic results for subpopulations 4a and 4b.

The ERG presents its base case analyses for comparisons with the FDC (the least expensive preparation) in Table 19 to Table 22. In subpopulations 2b and 4b, the FDC resulted in a positive NMB compared to ALI+EZE at a WTP threshold of £20,000 per QALY (£21,088 and £17,491, respectively) and £30,000 per QALY (£18,605 and £13,470, respectively).

Table 19. ERG's base case analysis, subpopulation 2a

Results per patient	FDC	EZE	Incremental value
Company's revised base case			
Total costs	£14,196	£9,604	£4,593
QALYs	9.24	9.05	0.19
ICER (cost per QALY)	-	-	£23,960
Probabilistic ICER	-	-	£23,969
ERG's preferred base case (ERG's NMA and LDL-C levels from patients not eligible for ALI/EVO)			
Total costs	£14,185	£9,591	£4,594
QALYs	9.25	9.06	0.19
ICER (cost per QALY)	-	-	£23,948
Probabilistic ICER	-	-	£24,641
ERG's alternative base case (ERG's NMA and LDL-C levels from all patients)			
Total costs	£14,181	£9,604	£4,577

QALYs	9.25	9.05	0.20
ICER (cost per QALY)	-	-	£23,150
Probabilistic ICER	-	-	£24,264

Abbreviations: Ali, alirocumab; Evo, evolocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; QALYs, quality-adjusted life years

Table 20. ERG's base case analysis, subpopulation 2b

Results per patient	FDC (1)	Ali (2)~	Evo (3)^	Incremental value	
				(1-2)	(1-3)
Company's revised base case					
Total costs	£22,191	£47,554	£47,994	-£25,364	-£25,803
QALYs	7.02	7.08	7.11	-0.06	-0.09
ICER (cost per QALY)	-	-	-	£420,781*	£290,213*
ERG's base case (company's revised assumptions with the ERG's NMA)					
Total costs	£22,193	£48,247	NC	-£26,054	NC
QALYs	7.03	7.28	NC	-0.25	NC
ICER (cost per QALY)	-	-	-	£104,930*	NC

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; NC, not calculable; NMA, network meta-analysis; QALYs, quality-adjusted life years

~ in the ERG's NMA, ALI is in addition to ezetimibe

^ no evidence on EVO was identified by the ERG in order to include this treatment as a comparator

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

Table 21. ERG's base case analysis, subpopulation 4a

Results per patient	FDC	EZE	Incremental value
Company's revised base case			
Total costs	£21,317	£16,751	£4,566
QALYs	6.95	6.88	0.07
ICER (cost per QALY)	-	-	£65,293
ERG's preferred base case (ERG's NMA and LDL-C levels from patients not eligible for ALI/EVO)			
Total costs	£21,339	£16,731	£4,608
QALYs	7.04	6.97	0.07
ICER (cost per QALY)	-	-	£62,874
ERG's alternative base case (ERG's NMA and LDL-C levels from all patients)			
Total costs	£21,324	£16,751	£4,572
QALYs	6.97	6.88	0.09
ICER (cost per QALY)	-	-	£53,056

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; QALYs, quality-adjusted life years

Table 22. ERG's base case analysis, subpopulation 4b

Results per patient	FDC (1)	Ali (2)~	Evo (3)^	Incremental value	
				(1-2)	(1-3)
Company's revised base case					
Total costs	£21,317	£46,120	£46,886	-£24,803	-£25,568
QALYs	6.59	6.80	6.95	-0.21	-0.36
ICER (cost per QALY)	-	-	-	£115,783*	£70,178*
ERG's base case (company's revised assumptions with the ERG's NMA)					

Total costs	£21,320	£46,854	NC	-£25,534	NC
QALYs	6.61	7.0`	NC	-0.40	NC
ICER (cost per QALY)	-	-	-	£63,495*	NC

Abbreviations: Ali, alirocumab; BA, bempedoic acid; Evo, evolocumab; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life yeas; NC, not calculable; QALYs, quality-adjusted life years

~ in the ERG's NMA, ALI is in addition to ezetimibe

^ no evidence on EVO was identified by the ERG in order to include this treatment as a comparator

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

Date: 19 August 2020

Dear [redacted]

At the first meeting for this topic on 4th August 2020 the appraisal committee were unable to come to a decision. The committee were concerned with the volume of network meta analyses (NMAs) that were submitted for consideration, which resulted in uncertainties in the relative effectiveness of bempedoic acid. There was considerable heterogeneity in the groups included which further undermined the credibility of the NMAs. In addition (and of course this is not uncommon in technology appraisals) the data are immature and as yet there is no evidence to assess what, if any, impact bempedoic acid may have on longer term cardiovascular events and morbidity/mortality and the evidence on the lipid lowering effect is also short term. These considerations led the committee to conclude that the body of evidence submitted was inadequate for decision making.

The appraisal committee expressed a preference for the approach taken by the Evidence Review Group (ERG) for conducting the NMAs for bempedoic acid compared to the treatments identified in the NICE final scope. The committee is particularly keen to see analyses that eliminate heterogeneity as far as possible. However, the committee is also mindful of the limitations of the analyses raised by the ERG and would welcome further thought and a revised submission from the company. The company consider the analyses outlined in this letter to reduce the limitations of the ERG's NMAs. The committee will consider these new analyses again in due course.

The appraisal committee has also indicated that increasing the number of scenario analyses would not be welcomed, and instead, prefer a focussed effort on improving the quality of small number of analyses. Therefore, the evidence submission should be succinct as outlined below.

Yours sincerely,

Jasdeep Hayre, Associate Director, Technology Appraisals & HST

Professor Stephen O'Brien, Chair, Technology Appraisal Committee C

Analyses to consider following ACM1

Primary analysis

- Building upon the NMAs conducted by the ERG, identify any additional studies in the wider group of trials included in the company's NMAs that:
    - Have use of ezetimibe prior to randomisation (ideally this would be for all patients, or from subgroup data from the trial wherein all patients had received prior ezetimibe; however, consider also including trials where most patients have had ezetimibe (80% or more);
    - If possible, please select trials where unadjusted baseline low-density lipoprotein cholesterol (LDL-C) levels would be considered similar;
    - Use appropriate trials to inform treatment efficacy for primary prevention (population 2a) and secondary prevention (populations 2b, 4a, and 4b);
    - Consider using trials where the following baseline characteristics are similar to each other:
        - Cardiovascular disease (CVD) risk;
        - Heterozygous Familial Hypercholesterolemia (HeFH);
        - Type of statin;
        - Sex;
        - Ethnicity.
- To inform the efficacy of bempedoic acid, please use those subgroups of the relevant CLEAR trials that received prior ezetimibe for both the statin intolerant (CLEAR Serenity and CLEAR Tranquility) and max tolerated statin populations (CLEAR Harmony and CLEAR Wisdom).
- If it is not possible to include trials for evolocumab in a network (but where alirocumab has been included as in the ERG's NMAs), please assume a "class effect" for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and use the same efficacy in the economic model for both PCSK9 inhibitors.

Scenario analyses

- As a scenario analysis in subpopulations 2b and 4b (situations when alirocumab or evolocumab are appropriate), please provide a network of studies that reflects the eligibility criteria for PCSK9 inhibitors, using the requirements for trial inclusion as for the primary analysis.

- As a scenario analysis in subpopulations 2a and 4a (situations when alirocumab or evolocumab are not appropriate), please provide a network of studies that reflects the ineligibility criteria for PCSK9 inhibitors, using the requirements for trial inclusion as for the primary analysis.

Sensitivity analyses

- As a sensitivity analysis, please consider relaxing the assumptions used in the primary analysis to enable a larger network of studies but still apply restrictions to provide a more homogenous network compared to those previously presented by the company; e.g. if focusing on only studies with prior ezetimibe use produces a population of studies which is not considered representative of the population of studies available then relax the prior ezetimibe use criterion.
- As a sensitivity analysis in subpopulations 2b and 4b (situations when alirocumab or evolocumab are appropriate), please consider relaxing the assumptions used in the primary analysis to enable a larger network of studies in patients eligible for PCSK9 inhibitors; e.g. if focusing on only studies with prior ezetimibe use produces a population of studies which is not considered representative of the population of studies available then relax the prior ezetimibe use criterion.
- As a sensitivity analysis in subpopulations 2a and 4a (situations when alirocumab or evolocumab are not appropriate) please consider relaxing the assumptions used in the primary analysis to enable a larger network of studies in patients ineligible for PCSK9 inhibitors; e.g. if focusing on only studies with prior ezetimibe use produces a population of studies which is not considered representative of the population of studies available then relax the prior ezetimibe use criterion.

For all analyses

- Please provide model fit statistics and measures of statistical heterogeneity including the between study standard deviations and associated 95% confidence intervals.
- Implement the results from the NMAs requested for the primary analysis, scenario analyses and sensitivity analyses in the economic model, providing pairwise and fully incremental results. Please provide deterministic and probabilistic results. In addition, when the incremental cost-effectiveness ratio (ICER) falls in the south-west quadrant of the cost-effectiveness plane, please also provide results as net monetary benefit (NMB) using the values of £20,000 per quality-adjusted life year (QALY) and £30,000 per QALY.

Additional considerations for the cost-effectiveness analyses

- Please use the patient characteristics from the CLEAR trials providing data for the primary prevention analysis (population 2a) for the estimation of baseline risk in the economic model (using QRISK3). For cardiovascular (CV) events not included in QRISK3, please calculate these proportionately using the prior CV events from the CLEAR trials.
- For the secondary prevention analysis (populations 2b, 4a, and 4b), please use the prior CV events from the CLEAR trials to estimate what prior events have occurred in the model.
- Please provide the baseline LDL-C levels from the CLEAR trials in patients with prior ezetimibe use (i.e. data equivalent to Table 50 of the CS, Document B). If there is any evidence of a statistically significant difference between the baseline LDL-C levels derived from patients with prior ezetimibe use and baseline LDL-C levels derived from all patients (the values used in the company's base case analysis), please use the baseline LDL-C levels derived from patients with prior ezetimibe use to inform the economic model.
- As a sensitivity analysis in subpopulations 2a and 4a (situations when alirocumab or evolocumab are not appropriate), please use baseline LDL-C levels from patients ineligible for PCSK9 inhibitors. Please consider the appropriateness of using baseline LDL-C levels derived from patients with prior ezetimibe as per the previous point.
- Please explain why the FDC-1002-053 trial has been used to inform the baseline LDL-C level in all patients in population 4 (i.e. [redacted] mmol/L) and not the baseline LDL-C levels according to PCSK9i eligibility (subpopulations 4a and 4b).

NICE National Institute for Health and Care Excellence

Response to Request for Additional Information of 19 August 2020 Post ACM1

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Document date: 15 September, 2020

About you

Your name	Kyle Dunton
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Daiichi Sankyo
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Abbreviations: ALI = alirocumab; BA = Bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed dose combination pill; CrI = credible interval; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; CVD = cardiovascular disease; DIC = Deviance information criterion; DS = Daiichi Sankyo; EPAR = European public assessment report; ERG = evidence review group; EVO = evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; HES = Hospital Episode Statistics; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NA = not applicable; NHS = National Health Service; NMA = network meta-analysis; NMB = Net monetary benefit; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; pD = effective number of parameters.; QALY = quality-adjusted life-year; THIN = The Health Improvement Network; UK = United Kingdom.

Re: Clarification Letter following the 1st Appraisal Committee meeting: Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Company response

Thank you for providing us the background on the appraisal committee concerns around decision making regarding our submission, we welcome the opportunity to address those during this process. Daiichi Sankyo is committed to working collaboratively with NICE to support timely access for patients to bempedoic acid in England and Wales.

Positioning of bempedoic acid

The SmPCs for Nilemdo and Nustendi are now published (Available at: https://www.medicines.org.uk/emc/search?q=bempedoic+acid)

Daiichi Sankyo proposes that bempedoic acid (BA) and bempedoic acid plus ezetimibe fixed dose combination (BA+EZE FDC) should be considered as add-on treatment options on top of existing lipid lowering therapies (statin and ezetimibe), in line with clinical expert opinion. The availability of additional first-in-class and low cost therapeutic interventions with proven efficacy in reducing LDL-C, in addition to existing treatment regimens, can help improve patient outcomes and help to deliver upon the national policy priority in England to improve the prevention of CVD events over the course of the next decade supporting objectives outlined in the NHS Long Term Plan.

A recent EU wide observational study (DA VINCI, Ray et al., 2020) has demonstrated low ezetimibe use in combination with moderate- or high-intensity statins (only 9% of patients) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors use in combination with statins and/or ezetimibe in 1% of patients. This verifies previously reported studies such as the EUROASPIRE and CPRD studies. Recently the ESC 2020 congress experts called upon the need for intensifying treatment combinations as there is a large proportion of patients (more than 70%) who are not at their recommended LDL-C goals.

Treatment with BA as demonstrated in a large pooled analysis of 3623 adults with hypercholesterolaemia/mixed dyslipidaemia enrolled in four phase 3 randomized clinical trials (Banach et al., 2020)was associated with significantly decreased LDL-C levels compared with placebo (maximally tolerated lipid lowering therapies including statins). The decreased LDL-C levels were maintained throughout the treatment period, and were observed on a background of stable LLT, including statins, ezetimibe, or other non-statin agents. In general, a decrease in the LDL-C level associated with BA vs placebo was consistent in all individual clinical trial subgroup analyses. The results of the present pooled analysis suggested the consistency of the effect associated with BA treatment across the majority of demographic and disease-related subgroups.

It is appropriate to assume based on available data, and verified through clinical expert opinion, that the treatment effect of BA (in terms of relative % LDL-C reduction) is consistent in patients regardless of whether they have received prior ezetimibe. BA inhibits cholesterol synthesis through HMG-CoA reductase inhibition in the liver, unlike ezetimibe which blocks reabsorption of cholesterol in the small intestine. The European Medicines Agency states that pharmacokinetics of BA was not affected by ezetimibe. The company presented a pooled analysis of the patients previously treated with ezetimibe in CLEAR Harmony and CLEAR

Wisdom (population 4) and CLEAR Tranquility and CLEAR Serenity (population 2). The mean percentage LDL-C reduction for the groups with and without previous treatment with ezetimibe therapy were presented, and the ERG acknowledged results were similar between the two subgroups. Further, no evidence was identified by the ERG or the company systematic reviews which suggests a difference in treatment effect for the comparator interventions in patients with or without prior ezetimibe therapy.

With regards to background statin therapy, as presented in the company evidence submission (section B.2.4.1.1), LDL-C lowering with BA was slightly greater in the absence of background statin therapy such as in statin intolerance (CLEAR Tranquility and CLEAR Serenity) than in the presence of background statin therapy (CLEAR Harmony, CLEAR Wisdom, and study 1002FDC-053). However, within patients receiving background statin therapy in CLEAR Harmony, CLEAR Wisdom, and study 1002FDC-053, the treatment effect for BA was highly significant both for patient subgroups on high-dose statin and subgroups on low-to-moderate dose statin (presented in Figure 7, Figure 8, Figure 11, and Table 30 of the company evidence submission). Published pooled subgroup results from the CLEAR studies (Banach et al., 2020) and the comparator studies indicated that no statistical differences could be observed outside this differentiation. As discussed in the pooled analysis (Banach et al., 2020), a greater treatment effect was observed among patients in the pool of patients with statin intolerance who were receiving no dose, low-dose, or very low-dose background statin therapy (82% were receiving no background statin), as evidenced by the greater magnitude of the LDL-C level decrease compared with the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, 91% of whom were receiving a moderate- or high-intensity statin regimen. Attenuation of the magnitude of LDL-C level decrease for patients receiving a statin regimen was not unexpected based on the shared mechanism of inhibition of hepatic cholesterol synthesis by both statins and BA. Nonetheless, the additional LDL-C level decrease achieved when BA was added to background statin therapy was greater than the anticipated LDL-C level decrease of 5% to 6% that would be achieved by doubling the statin dose.

The treatment effect for BA and BA/EZE FDC was consistent for patients with and without prior atherosclerotic cardiovascular disease (Banach et al., 2020; see also Figure 7, Figure 8, Figure 9, and Figure 11 of the company evidence submission). UK clinical expert opinion has verified that there is no reason to assume differential treatment effect dependent on ASCVD risk.

These conclusions support the assumptions which fed into the originally submitted Company network meta-analyses. However, in order to inform decision making, Daiichi Sankyo has aimed to address the analyses requested by the NICE Appraisal Committee following the ACM1 on 4th August 2020.

In consideration of the cost effectiveness results using the current analyses in position 4a (when maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate), Daiichi Sankyo is not seeking a recommendation for use of BA in this position. As such, cost-effectiveness results for position 4a will not be presented in this response.

Revised NMA approach

Based on the NICE appraisal committee requested clarifications detailed under *"Analyses to*

consider following ACM1" in the Clarification Letter received on 19th August 2020, we have reviewed the data inputting into the two main network meta-analyses (NMAs). The below outlines the Company approach to the additional information request which aims to build upon and reduce the limitations of the ERG NMAs and limit heterogeneity in the networks to support decision-making for this appraisal. These are referred to as the "**Company additional analyses post ACM1**."

Following further clarification from NICE on the requested primary analyses following ACM1, we have also performed NMAs in which the ERGs networks were expanded only to include all available data for BA in patients receiving ezetimibe at baseline from the CLEAR studies. These are referred to as the "**expanded ERG analyses post ACM1"**. As all patients in these networks were on background ezetimibe, the interventions are referred to accordingly (BA+EZE, alirocumab+EZE, and EZE). As evolocumab is not represented in these networks, the efficacy of evolocumab+EZE was assumed to be the same as alirocumab+EZE in the cost-effectiveness model – i.e. a 'class-effect' is assumed as recommended in the letter received on 19th August 2020 from NICE.

It should be noted that the expanded ERG NMAs provide estimates for alirocumab+EZE (as all alirocumab patients were also receiving EZE), while the company analyses provide estimates for alirocumab (as full trial data were used rather than EZE subgroup data). Whilst we understand the request for one primary analysis for decision-making, it is important to be able to provide estimates for alirocumab without co-administered EZE as this is an important intervention in routine clinical practice. As outlined in the company response to Technical Engagement, based on UK clinical expert opinion not all patients receiving alirocumab or evolocumab would be expected to also receive ezetimibe. In a study of 105 patients who were prescribed a PCSK9i in two UK clinical centres (70 in a university hospital and 35 in a district general hospital), 54% were also receiving ezetimibe (Kohli et al., 2010). Therefore, the company proposes that both analyses should be considered for decision-making purposes.

Daiichi Sankyo maintains that the Company NMA submitted as part of the Technical Engagement (also presented in this response document for completeness) is the most robust source for decision-making and makes most use of the available data.

Expanded ERG analysis post ACM1

The trial data included in the expanded ERG analyses post ACM1 are summarized in Table 1

Table 1. Trial data included in the expanded ERG analyses post ACM1

Maximally tolerated statin NMA[a]	Statin intolerant NMA[b]
CLEAR Harmony EZE subgroup	CLEAR Tranquility
CLEAR Wisdom EZE subgroup	CLEAR Serenity EZE subgroup
ODYSSEY Longterm EZE subgroup	ODYSSEY Choice II EZE subgroup

[a] Study 1002FDC-053 is not included as only 4 patients were receiving ezetimibe at baseline, spread across the 4 study arms. Phase 2 trial 1002-009 is not included as ezetimibe treatment was not permitted.

[b] Phase 2 trial 1002-008 was not included because few patients received ezetimibe at baseline (3 patients in the BA180+EZE arm and 13 patients in the BA180 arm).

Company additional analysis post ACM1

The Company additional analysis post ACM1 aimed to address the considerations laid out in

the NICE Request for Additional Information, 19th August 2020. Each of the points raised are considered in turn below. The trials included in the Company additional analysis post ACM1 are presented in Appendix A, along with the rationale for inclusion and exclusion of studies from the analysis.

Trials with use of ezetimibe to randomisation or at baseline

An analysis in which the network is dedicated to trials with high background ezetimibe use (80% or more) is not feasible in the maximally tolerated statin dose (MTD) network, as all trials reported less than 20% of patients on ezetimibe at baseline (or data were not reported).

In the statin intolerant (SI) network, although ODYSSEY CHOICE II could be added to the ERG's NMA if the ezetimibe threshold were relaxed to 60%, this results in a disconnected network. All other trials had less than 20% of patients on ezetimibe at baseline (or data were not reported).

*Limiting studies on the basis of b*aseline LDL-C

Baseline LDL-C is often a parameter reflecting baseline characteristics and background therapy which in turn reflect trial entry criteria. Therefore, we have revisited studies to ensure they are in similar patient populations with similar background therapy and/or comparable LDL at baseline. The following studies were removed from the MTD NMA as patients were not receiving maximally tolerated statin at baseline: Dujovne, Knopp, Krysiak, Melani. The GAUSS-2 and ODYSSEY ALTERNATIVE studies were removed from the SI NMA because the entry criteria (for example high cardiovascular risk) are skewed in comparison with current guidelines and resulted in very high baseline LDL-C; clinical expert opinion was sought on these two studies, verifying rationale for their exclusion, and confirming baseline LDL-C in SI patients is expected to be ~140mg/dL (as in line with BA and comparator studies, and analysis of patients within the EUROASPIRE registry [data on file]).

Primary/secondary prevention

Limiting to primary prevention and secondary prevention trials in order to inform relevant positions is challenging. Most of the trials in dyslipidaemia have been conducted in mixed populations, as there are primary prevention patients with CV risk factors who are at high CV risk and were therefore deemed eligible for further lipid-lowering treatment; many studies excluded patients with a recent cardiovascular event but do not report information about prior events, it is therefore unclear if these patients can be considered secondary or primary prevention and in some trials reporting is unclear. Because of these limitations (and because the percentage reduction in LDL-C has been observed to be consistent among primary and secondary prevention patients as long as other characteristics remain the same such as background therapy, baseline LDL-C), we planned to limit trials by primary/secondary prevention in scenario analyses rather than the main analysis. However, recognising the request from NICE to restrict the number of analyses to aid in decision-making, we have not presented these scenario analyses.

Other baseline characteristics

It is difficult to include studies in which all of the suggested baseline characteristics are similar. However, we are able to remove studies that were conducted in a particular ethnicity such as trials strictly in Asian populations. This removed ODYSSEY NIPPON, ODYSSEY Japan,

ODYSSEY KT, Yakawa and Yakawa-2 (which were conducted in Asia) from the MTD NMA.

We also made the following changes to explore whether heterogeneity is further reduced.

- Remove all of the Alirocumab 75mg data, as this dose is not required (the model uses data for the 150mg dose)
- Remove the ODYSSEY OPTIONS I and II statin control arms from the MTD network as patients randomised to these arms did not just continue the baseline statin, but the baseline statin dose was doubled.

The trials selected for inclusion in the Company additional analyses post ACM1 are presented in Table 2. Details of the trials and the rationale for inclusion/exclusion are provided in Appendix A.

Table 2. Trial data included in the Company additional analyses post ACM1

Maximally tolerated statin NMA	Statin intolerant NMA
CLEAR Harmony EZE subgroup	CLEAR Tranquility
CLEAR Wisdom EZE subgroup	CLEAR Serenity EZE subgroup
ODYSSEY Longterm	ODYSSEY Choice I
ODYSSEY Choice I	ODYSSEY Choice II
ODYSSEY Options I	1002-008
ODYSSEY Options II	
ODYSSEY Combo I	
ODYSSEY Combo II	
FOURIER	
LAPLACE-2	
LAPLACE-TIMI	
McKenney 2012	
Masana 2005	

Note: trial arm labelling in the Company additional analysis post ACM1 was consistent with that in the previous analyses presented by the Company (see Appendix A).

Requested scenario analyses

The NICE Request for Additional Information, 19th August 2020, requested scenario analyses according to eligibility for PCSK9i therapy. The NICE recommendations for PSCK9is use a combination of baseline LDL-C thresholds, cardiovascular history categories, and presence of HeFH. The baseline characteristics and efficacy data for these particular patient subpopulations are not available from the PCSK9i NICE appraisals or any other published sources for use in the company NMAs.

The most informative analysis we are able to provide for decision-making uses a similar approach, i.e., cost-effectiveness analyses for populations with baseline LDL-C and cardiovascular history which reflect the PCSK9i eligible populations. Results from these analyses were provided in the Technical Engagement response.

The percentage reduction in LDL-C for patients in the BA studies meeting the criteria for PCSK9i treatment are presented in Table 3. Across the trials, the percentage reduction was similar in patients meeting the criteria for PCSK9i therapy and those who do not.

Table 3. **Percentage reduction in LDL-C for BA in patients meeting PCSK9i criteria**

Study	PSCK9i non-eligible		PSCK9i 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	596	[redacted]	183	[redacted]
Clear Harmony	2030	[redacted]	200	[redacted]
1002-FDC	192	[redacted]	190	[redacted]
Clear Tranquility	251	[redacted]	18	[redacted]
Clear Serenity	278	[redacted]	67	[redacted]

Patients with the following characteristics are eligible for PCSK9i therapy: patients at high risk for CVD and LDL-C persistently above 4.0 mmol/l; patients at very high risk for CVD and LDL-C persistently above 3.5 mmol/l; patients with HeFH and LDL-C persistently above 5.0 mmol/l; and patients with HeFH at high or very high risk for CVD and LDL-C persistently above 3.5 mmol/l. 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. 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). Note that the identification of patients in the BA trials meeting these criteria was somewhat limited by the cardiovascular history available in the trial datasets.

Sensitivity analyses

The NICE Request for Additional Information, 19th August 2020, requested sensitivity analyses in which the criteria for trial selection suggested in the document are relaxed. We have relaxed the criteria for the Company additional analyses post ACM1 in order to build additional studies into the ERGs NMAs. Therefore, the sensitivity analyses requested have been incorporated in the Company additional analysis post ACM1.

Results

MTD Network

The results of the MTD NMA are presented in Table 4, alongside the most recent results provided at Technical Engagement. The following notation is used in the tables:

- **Expanded ERG analysis post ACM1:** relates to the ERG NMA expanded only to include all BA data in patients with ezetimibe at baseline.
- **Company additional analysis post ACM1:** relates to the analysis to address the request from NICE (19th August 2020).

Table 4. Post ACM 1 Analysis Results: MTD Network

Treatment	Estimated difference in % change in LDL−C from baseline compared with EZE		
	Mean	**95% CrIs**	**P value**
Technical Engagement analysis 10a. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 12 week data removed from the network where 24-week data for the same study was included			
BA+statin	[redacted]	[redacted]	0.9183
FDC+statin	[redacted]	[redacted]	0.1370
EVO+statin	[redacted]	[redacted]	< 0.0001
ALI (75 mg)+statin	[redacted]	[redacted]	< 0.0001
ALI (150 mg)+statin	[redacted]	[redacted]	< 0.0001
Expanded ERG analysis post ACM1			
BA+EZE+statin	[redacted]	[redacted]	0.1417
ALI (150 mg)+EZE+statin	[redacted]	[redacted]	<0.0001
Company additional analysis post ACM1[a]			
EVO+statin	[redacted]	[redacted]	<0.0001
ALI (150 mg)+statin	[redacted]	[redacted]	<0.0001

[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 (see Appendix A)

Table 5. Heterogeneity and model fit parameters – maximum tolerated NMA

Analysis	Total residual deviance	pD	DIC	I2	Between-study standard deviation (s) (95% CrI)
Technical Engagement analysis 10a	286.4	82.5	368.8	80.8%	8.20 (5.4505, 11.892)
Expanded ERG analysis post ACM1	31.4	5.7	37.1	4.8%	8.83 (0.40, 19.31)
Company additional analysis post ACM1	162.6	34	196.6	56.5%	4.58 (1.76, 8.61)

SI Network

Table 6. Post ACM 1 Analysis Results: SI Network

Treatment	Estimated difference in % change in LDL−C from baseline compared with EZE		
	Mean	**95% CrIs**	***P* value**
Technical Engagement Analysis 1. Baseline LDL-C covariate removed (i.e. no covariates)			
BA	[redacted]	[redacted]	0.0647
BA+EZE	[redacted]	[redacted]	0.0012

EVO	[redacted]	[redacted]	< 0.0001
EVO+EZE[a]	[redacted]	[redacted]	—
ALI (75 mg)	[redacted]	[redacted]	< 0.0001
ALI (150 mg)	[redacted]	[redacted]	< 0.0001
Expanded ERG NMA post ACM1			
BA+EZE	[redacted]	[redacted]	0.0157
ALI (150mg)+EZE	[redacted]	[redacted]	<0.0001
Company additional analysis post ACM1			
BA	[redacted]	[redacted]	0.0640
BA+EZE	[redacted]	[redacted]	0.0037
ALI (150 mg)	[redacted]	[redacted]	0.0030

Abbreviations: AC = appraisal committee; ALI = alirocumab; BA = bempedoic acid; CrI = credible interval; EVO = evolocumab; EZE = ezetimibe; ITT = intention-to-treat; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; SI = statin intolerant.

Table 7. Heterogeneity and model fit parameters – statin intolerant NMA

Analysis	Total residual deviance	pD	DIC	I^2 (95% CrI)	Between-study standard deviation (s) (95% CrI)
Technical Engagement Analysis 1	89.9	21.4	111.3	66.1%	5.38 (1.16-13.34)
Expanded ERG analysis post AMC1	29.0	6.4	35.4	65.9%	9.22 (0.62, 19.25)
Company additional analysis post ACM1	49.5	10.4	60.0	20.3%	5.57 (0.20-17.64)

Abbreviations: CrI = credible interval; DIC = deviance information criterion; NMA = network meta-analysis; pD = effective number of parameters.

Updated cost-effectiveness analyses

Cost-effectiveness results in positions 2a, 2b and 4b using the additional NMAs are provided in Appendix B, are summarised in Table 8.

Statin intolerant patients (position 2a and 2b)

- Cost-effectiveness results are provided using the expanded ERG analysis post ACM1. As described above, this network is limited as it does not provide estimates for the treatment effect of ezetimibe versus placebo at baseline. The ezetimibe treatment effect versus placebo was set to zero in the cost-effectiveness model since all patients are receiving background ezetimibe treatment. Also, this network provides estimates for alirocumab + EZE, but not for alirocumab (without co-administered ezetimibe) or evolocumab (with or without ezetimibe). A class effect is assumed for alirocumab and evolocumab.
- Cost-effectiveness results also are provided using the Company additional analysis

post ACM1.

- As head-to-head trial data are available for position 2a from CLEAR Tranquility, we have also provided cost-effectiveness results for this position based on the head-to-head data. Cost-effectiveness estimates are consistent with the expanded ERG analysis post ACM1, the Company additional analyses post ACM1, and those provided at Technical Engagement (Table 8). Note that all but 1 patient received prior ezetimibe at baseline in CLEAR Tranquility (see Table 9).

Patients receiving maximally tolerated statin (position 4b)

- Cost-effectiveness results are provided using the expanded ERG analysis post ACM1. It should be noted that this network is limited as it does not provide estimates for the effect of ezetimibe versus placebo at baseline. The ezetimibe effect versus placebo was set to zero in the cost-effectiveness model since all patients are on background ezetimibe treatment. Additionally, this network provides estimates for alirocumab+EZE, but not for alirocumab (without co-administered ezetimibe) or evolocumab (with or without ezetimibe). A class effect is assumed for alirocumab and evolocumab.

- It is not possible to provide cost-effectiveness results using the Company additional analysis post ACM1 as no estimates for BA+EZE are available (because trial 1002FDC-053 was not included in the network due to very few patients on ezetimibe at baseline). However, the analysis provides supporting evidence for the treatment effects of alirocumab and evolocumab based on an NMA with substantially reduced heterogeneity. The treatment effects estimated for alirocumab and evolocumab by the Company additional analysis post ACM1 ([redacted] and [redacted], respectively) are lower than those estimated at Technical Engagement ([redacted] and [redacted], respectively).

- As neither the expanded ERG analysis post ACM1 or the Company additional analyses post ACM1 are able to provide cost-effectiveness estimates versus alirocumab without co-administered ezetimibe, and this is an important intervention in routine practice, Daiichi Sankyo proposes that the company results submitted at Technical Engagement provide the most robust basis for decision-making.

Table 8. Summary of ICER Estimates for bempedoic acid (£/QALY)

	When statins are contraindicated or not tolerated		**Patients receiving maximally tolerated statin** (Position 4b)
	Position 2a	Position 2b	
Technical Engagement (company submitted ICERs)	£24,895 (BA+EZE vs EZE)	£418,128 (ALI vs BA+EZE)	£115,065 (ALI vs BA+EZE)
Expanded ERG analysis post ACM1	£25,600 (BA+EZE vs EZE)	£84,533 (ALI+EZE vs BA+EZE)	£55,196 (ALI+EZE vs BA+EZE)
Company additional analysis post ACM1	£22,357 (BA+EZE vs EZE)	£152,424 (ALI vs BA+EZE)	-[a]

Post ACM1 response
Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

CLEAR Tranquility head-to-head data	£25,720 (BA+EZE vs EZE)	-	-

ACM1 = Appraisal Committee Meeting 1; ALI = alirocumab; BA = bempedoic acid; ERG = Evidence Review Group; EZE = ezetimibe

[a] A cost-effectiveness analysis in position 4b using the Company Additional Analysis Post ACM1 is not feasible because no estimates are available for BA+EZE (as study 1002FDC-053 was not included in the network due to only 4 patients receiving ezetimibe at baseline, spread across the 4 study arms).

Additional considerations for the cost-effectiveness analyses

Regarding the QRISK3 estimation using the patient characteristics from the CLEAR trials for the primary prevention analysis, we have analyzed the CLEAR trial data in order to identify the characteristics needed for the QRISK3 calculation. However, the algorithm requires parameters (such as family history, deprivation score or extensive medical history) which have not been captured in the trial datasets and cannot be obtained from published data. Therefore, we have been unable to provide these QRISK3 estimates. Limited if any data exist for QRISK3 in the UK population and NICE CG181 does not recommend use of QRISK3 as a tool for use in UK clinical practice.

Additionally, we are unable to use prior CV events from the CLEAR trials to estimate what prior events have occurred in the model. Data would be needed for prior unstable angina, stable angina, myocardial infarction, transient ischemic attack, and stroke. These data are not available from the CLEAR studies.

The mean baseline LDL-C for patients in the CLEAR trials with and without ezetimibe at baseline are presented in Table 9. Statistical tests for differences between the baseline LDL-C levels derived from patients with prior ezetimibe use and baseline LDL-C levels derived from all patients (the values used in the company's base case analysis) have not been performed.

Table 9. Mean (SD) baseline LDL-C levels (mmol/L) in patients by ezetimibe use at baseline in the CLEAR trials

	STUDY	**Wisdom 1002-047**		**Harmony 1002-040**		**Tranquility 1002-048**		**Serenity 1002-046**	
	Ezetimibe Use	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
All patients	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=2 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=3 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=4 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=5 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	STUDY	Wisdom 1002-047		Harmony 1002-040		Tranquility 1002-048		Serenity 1002-046	
	Ezetimibe Use	No	Yes	No	Yes	No	Yes	No	Yes
	(SD)	[redacted]							
PCSK9i eligible	N	[redacted]							
	Mean (SD)	[redacted]							
Not PCSK9i eligible**	N	[redacted]							
	Mean (SD)	[redacted]							

* There was one patient in the placebo group of Tranquility who didn't take any IMP, so there is one patient without baseline Ezetimibe

** Includes all patient not assigned to "PCSK9i eligible" and may also include patients with insufficient information

As a sensitivity analysis in subpopulations 2a and 4a (situations when alirocumab or evolocumab are not appropriate), please use baseline LDL-C levels from patients ineligible for PCSK9 inhibitors. Please consider the appropriateness of using baseline LDL-C levels derived from patients with prior ezetimibe as per the previous point.

The requested analysis in position 2a is presented in Table 10. Analyses for position 4a are not presented in this response as stated previously.

Table 10. Position 2a: only patients with prior ezetimibe and PSCK9 ineligible (Mean LDL-C: 3.29 mmol/L)

	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)	NMB (£20,000)	NMB (£30,000)
BA	14,398	9.26					
No further treatment/placebo with background ezetimibe	9,552	9.09	4,846	0.17	29,120	-1,518	146

Please explain why the FDC-1002-053 trial has been used to inform the baseline LDL-C level in all patients in population 4 (i.e. 2.91 mmol/L) and not the baseline LDL-C levels according to PCSK9i eligibility (subpopulations 4a and 4b).

The PCSK9i eligibility criteria use a combination of cardiovascular history, presence of HeFH and LDL-C thresholds. The reporting/coding of previous cardiovascular events is not consistent and differs slightly in the study databases among the three BA studies in patients on maximum tolerated dose of statins. In particular, the definition/coding of the complex parameter “polyvascular/recurrent events” varies.

The selection of patients that are PCSK9 eligible is of relevance for the calculation of baseline LDL-C in position 4b. To ensure consistency in how patients eligible for PCSK9i were identified across the studies, the FDC-053 study was not included in the base case calculation of LDL-

C for position 4b as the reporting in this trial differed from CLEAR Harmony and CLEAR Wisdom.

However, when analyzing the baseline LDL-C without any PCSK9i restrictions (position 4), DS used the data set with the largest sample size (i.e. including FDC-053). Removing the FDC-053 trial from the calculation, the baseline LDL-C would be 2.79 mmol/L.

Using the full trial population from FDC-053 was considered appropriate in position 4a given that the majority of patients eligible for PCSK9i therapy in UK clinical practice do not receive these. Further analyses in position 4a are not presented as discussed previously.

Appendix A. Study Listings with Rationale for Inclusion/Exclusion in the Company NMAs

Table A-1 presents details of the studies included in the NMAs most recently provided to NICE during Technical Engagement, the studies that were included in the Company additional analyses post ACM1, and the rationale for removal of trials. The studies included in the Expanded ERG analyses post ACM1 also are indicated. The indicator labels within the tables are as follows.

Indicator label	Meaning
1	Included in the statin intolerant NMA
2	Included in the maximum tolerated statin NMA
0	Not included in the proposed NMA
Rationale for removal of study arms from the proposed NMA	
A	ITT data replaced with prior ezetimibe subgroup (see end of table)
B	alirocumab 75mg data removed
C	Ethnicity
D	Entry criteria misaligned with guidelines, high baseline LDL-C
E	Statin control arm was double baseline statin dose
F	Not maximally tolerated dose at baseline
G	Insufficient patients with prior/baseline ezetimibe

The columns in the tables below relate to the following analyses:

- **Tech Eng**: relates to the NMA that was provided most recently during Technical Engagement This is Analysis 10 of the MTD NMA which included ODYSSEY Longterm, excluded ODYSSEY Mono, included adalimumab data at week 24, but excluded adalimumab data at week 12 for those studies reporting both adalimumab 75mg data at week 12 and data at week 24 from those uptitrated from 75mg to 150mg. For the SI network, this represents analysis 1 presented at Technical Engagement. Details of these analyses and the results are provided in Appendix B for reference.
- **Company additional analysis post ACM1:** relates to the Company additional analysis post ACM1 designed to address the request from NICE (19th August 2020). Trials have been removed due to reasons A-G.
- **Expanded ERG analysis post ACM1:** relates to the ERG analysis with ezetimibe subgroup data also included for the bempedoic acid trials.

Table A-1. Trial arms included in the Technical Engagement NMA, Expanded ERG analysis post ACM1, and the Company Additional (CA) Analysis Post ACM1

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
5	CLEAR.Harmony	BA	12	-16.5	20.1	1488	103.6	7.8	99.8	>75% prior CVE	2	0	A	0
5	CLEAR.Harmony	Placebo	12	1.6	23.4	742	102.3	7.5	100.0	>75% prior CVE	2	0	A	0
82	ODYSSEY OUTCOMES	AliMab_75mg	12	-55.8	29.2	9462	92.0			Removed	2	0	B	0
82	ODYSSEY OUTCOMES	Placebo	12	4.4	29.2	9462	92.0			Removed	2	0	B	0
36	ODYSSEY.NIPPON	AliMab_150mg	12	-70.1	16.7	53	149.2	19.6	34.6	Removed	2	0	C	0
36	ODYSSEY.NIPPON	Placebo	12	-4.3	16.5	56	149.4	19.6	33.9	Removed	2	0	C	0
6	CLEAR.Serenity	BA	12	-22.6	19.7	234	158.5		7.7	Mixed	1	0	A	0
6	CLEAR.Serenity	Placebo	12	-1.2	15.0	111	155.6		9.9	Mixed	1	0	A	0
4	CLEAR.Tranquility	BA_EZE	12	[redacted]	[redacted]	175	[redacted]	100.0	32.6	No recent CVE	1	1		1
4	CLEAR.Tranquility	EZE	12	5.0	21.6	82	123.0	100.0	28.4	No recent CVE	1	1		1
3	ODYSSEY KT.24w	AliMab_150mg	24	-57.1	29.5	97	97.0	14.4	100.0	Removed	2	0	C	0
3	ODYSSEY KT.24w	Placebo	24	6.3	29.3	102	99.3	11.8	100.0	Removed	2	0	C	0
11	FOURIER	EvoMab	12	-69.6	14.1	13784	92.0	5.0	100.0	>75% prior CVE	2	2		0
11	FOURIER	Placebo	12	-4.5	14.1	13780	92.0	5.2	100.0	>75% prior CVE	2	2		0
45	ODYSSEY.CHOICE.	AliMab_150m	24	-51.6	28.8	76	114.9	13.8	99.4	No recent CVE	2	2		0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
	l.24w	g												
45	ODYSSEY.CHOICE. I.24w	Placebo	24	-0.1	28.7	156	112.1	14.0	100.0	No recent CVE	2	2		0
43	ODYSSEY.CHOICE. I.24wSI	AliMab_150m g	24	-50.2	22.5	37	154.7	6.8	1.4	No recent CVE	1	1		0
43	ODYSSEY.CHOICE. I.24wSI	Placebo	24	-0.3	22.8	71	134.1	15.1	0.0	No recent CVE	1	1		0
47	ODYSSEY.CHOICE. II.24w	AliMab_150m g	24	-53.5	12.2	58	167.5	59.3	0.0	Unclear	1	1		0
47	ODYSSEY.CHOICE. II.24w	Placebo	24	4.7	17.4	57	156.6	60.3	0.0	Unclear	1	1		0
10	1002-009	BA	12	-24.3	27.8	45	141.7		100.0	No recent CVE	2	0	G	0
10	1002-009	Placebo	12	-4.2	28.1	45	130.9		100.0	No recent CVE	2	0	G	0
1	1002-008	BA	12	-31.4	12.9	50	170.5	0.0	100.0	No recent CVE	1	1		0
1	1002-008	BA_EZE	12	-49.6	6.0	10	164.2	100.0	100.0	No recent CVE	1	1		0
1	1002-008	EZE	12	-19.8	10.0	51	169.5	100.0	100.0	No recent CVE	1	1		0
67	YUKAWA-2 (Kiyosue 2016 hs)	EvoMab	12	-75.2	27.9	51	97.0		100.0		2	0	C	0
67	YUKAWA-2 (Kiyosue 2016 hs)	Placebo	12	0.7	9.0	51	91.0		100.0		2	0	C	0
62	ODYSSEY Japan (Teramoto 2016) 24w	AliMab_150m g	24	-62.5	15.6	144	143.1		100.0		2	0	C	0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
62	ODYSSEY Japan (Teramoto 2016) 24w	Placebo	24	1.6	15.3	72	143.1		100.0		2	0	C	0
23	ODYSSEY.alternative.24	AliMab_150mg	24	-45.0	24.7	126	191.1		0.0		1	0	D	0
23	ODYSSEY.alternative.24	EZE	24	-14.6	24.6	125	193.5		0.0		1	0	D	0
25	ODYSSEY.COMBO.I.24	AliMab_150mg	24	-47.9	29.1	205	100.3	7.2	99.5	>75% prior CVE	2	2		0
25	ODYSSEY.COMBO.I.24	Placebo	24	-2.5	24.9	106	104.6	10.3	100.0	>75% prior CVE	2	2		0
49	ODYSSEY OPTIONS I (Bays 2015.hs) 24wk	AliMab_150mg	24	-54.0	29.5	47	116.4	0.0	100.0	Mixed	2	2		0
49	ODYSSEY OPTIONS I (Bays 2015.hs) 24wk	EZE	24	-22.6	29.5	47	98.9	0.0	100.0	Mixed	2	2		0
49	ODYSSEY OPTIONS I (Bays 2015.hs) 24wk	Placebo	24	-4.8	28.8	47	108.6	0.0	100.0	Mixed	2	0	E	0
48	ODYSSEY OPTIONS I (Bays 2015.ls) 24wk	AliMab_150mg	24	-44.1	34.0	57	103.9	0.0	100.0	Mixed	2	2		0
48	ODYSSEY OPTIONS I (Bays	EZE	24	-20.5	34.9	55	100.4	0.0	100.0	Mixed	2	2		0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
	2015.ls) 24wk													
48	ODYSSEY OPTIONS I (Bays 2015.ls) 24wk	Placebo	24	-5.0	34.7	57	100.3	0.0	100.0	Mixed	2	0	E	0
27	ODYSSEY.COMBO. II.24	AliMab_150mg	24	-50.6	30.6	479	108.3		99.8	Mixed	2	2		0
27	ODYSSEY.COMBO. II.24	EZE	24	-20.7	29.5	241	104.4		100.0	Mixed	2	2		0
13	GAUSS-2Q2W	EvoMab	12	-56.1	19.4	103	192.0		18.4		1	0	D	0
13	GAUSS-2Q2W	EZE	12	-18.1	18.2	51	195.0		17.6		1	0	D	0
87	YUKAWA.Q2W	EvoMab	12	-71.3	15.9	52	139.2		100.0		2	0	C	0
87	YUKAWA.Q2W	Placebo	12	-2.7	15.9	52	143.1		100.0		2	0	C	0
68	LAPLACE-2 (Robinson 2014 hs1) Q2W	EvoMab	11	-61.8	29.3	109	94.2	0.0	100.0	Mixed	2	2		0
68	LAPLACE-2 (Robinson 2014 hs1) Q2W	EZE	11	-16.9	28.9	55	98.7	0.0	100.0	Mixed	2	2		0
68	LAPLACE-2 (Robinson 2014 hs1) Q2W	Placebo	11	13.1	30.0	56	100.3	0.0	100.0	Mixed	2	2		0
70	LAPLACE-2 (Robinson 2014 hs2) Q2W	EvoMab	11	-59.1	23.7	111	88.5	0.0	100.0	Mixed	2	2		0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
70	LAPLACE-2 (Robinson 2014 hs2) Q2W	Placebo	11	6.6	23.5	56	77.4	0.0	100.0	Mixed	2	2		0
74	LAPLACE-2 (Robinson 2014 ms2) Q2W	EvoMab	11	-66.2	31.5	113	114.9	0.0	100.0	Mixed	2	2		0
74	LAPLACE-2 (Robinson 2014 ms2) Q2W	Placebo	11	3.3	26.0	58	110.3	0.0	100.0	Mixed	2	2		0
78	LAPLACE-TIMI-57aQ2W	EvoMab	12	-68.0	31.4	78	119.9	8.9	99.2	<25% prior CVE	2	2		0
78	LAPLACE-TIMI-57aQ2W	Placebo	12	1.2	30.4	78	123.7	9.0	100.0	<25% prior CVE	2	2		0
83	McKenney 2012	AliMab_150mg	12	-72.4	17.8	31	123.9		100.0	<25% prior CVE	2	2		0
83	McKenney 2012	Placebo	12	-5.1	17.3	31	130.2		100.0	<25% prior CVE	2	2		0
81	Krysiak 2011.s	EZE	12	-46.0	8.9	35	183.0			Removed	2	0	F	0
81	Krysiak 2011.s	Placebo	12	-34.0	9.5	33	182.0			Removed	2	0	F	0
65	Masana 2005	EZE	12	-23.7	33.9	355	136.6	0.0	100.0	Unclear	2	2		0
65	Masana 2005	Placebo	12	3.3	23.0	78	131.4	0.0	100.0	Unclear	2	2		0
18	Melani 2003.ns	EZE	12	-18.7	12.8	64	177.9		21.9	Removed	2	0	F	0
18	Melani 2003.ns	Placebo	12	1.3	12.9	65	177.9		23.1	Removed	2	0	F	0
19	Melani 2003.s	EZE	12	-37.7	12.9	204	177.9		30.9	Removed	2	0	F	0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
19	Melani 2003.s	Placebo	12	-24.3	22.9	205	177.9		23.1	Removed	2	0	F	0
17	Knopp 2003	EZE	12	-17.7	14.7	621	165.1		21.7	Removed	2	0	F	0
17	Knopp 2003	Placebo	12	0.8	12.4	204	164.3		18.5	Removed	2	0	F	0
8	Dujovne 2002	EZE	12	-16.9	14.2	666	167.8		22.4	Removed	2	0	F	0
8	Dujovne 2002	Placebo	12	0.4	12.5	226	168.0		23.0	Removed	2	0	F	0
53	ODYSSEY OPTIONS II (Farnier 2016.hs) 24wk	AliMab_150mg	24	-36.3	31.6	54	118.3	0.0	100.0		2	2		0
53	ODYSSEY OPTIONS II (Farnier 2016.hs) 24wk	EZE	24	-11.0	32.0	53	119.0	0.0	100.0		2	2		0
53	ODYSSEY OPTIONS II (Farnier 2016.hs) 24wk	Placebo	24	-15.9	31.3	53	112.9	0.0	100.0		2	0	E	0
52	ODYSSEY OPTIONS II (Farnier 2016.ls) 24wk	AliMab_150mg	24	-50.6	30.1	49	107.3	0.0	100.0		2	2		0
52	ODYSSEY OPTIONS II (Farnier 2016.ls) 24wk	EZE	24	-14.4	30.5	48	102.4	0.0	100.0		2	2		0
52	ODYSSEY OPTIONS II (Farnier 2016.ls) 24wk	Placebo	24	-16.3	29.8	48	105.9	0.0	100.0		2	0	E	0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
33	ODYSSEY.LONGTERM	AliMab_150mg	12	-60.2	26.5	1436	122.8	13.9	100.0	<25% prior CVE	2	2		0
33	ODYSSEY.LONGTERM	Placebo	12	-1.6	27.3	746	122.0	15.0	100.0	<25% prior CVE	2	2		0
9	1002FDC-053	BA	12	-17.7	23.9	110	146.4			Mixed	2	0	G	0
9	1002FDC-053	BA_EZE_FDC	12	-31.5	26.0	108	152.0			Mixed	2	0	G	0
9	1002FDC-053	EZE	12	-21.0	21.3	109	147.5			Mixed	2	0	G	0
9	1002FDC-053	Placebo	12	-2.5	22.8	55	152.6			Mixed	2	0	G	0
7	CLEAR.Wisdom	BA	12	-15.1	24.5	522	119.4			>75% prior CVE	2	0	A	0
7	CLEAR.Wisdom	Placebo	12	2.4	23.2	257	122.4			>75% prior CVE	2	0	A	0
5	CLEAR.Harmony.e	BA	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
5	CLEAR.Harmony.e	Placebo	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
7	CLEAR.Wisdom.e	BA	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
7	CLEAR.Wisdom.e	Placebo	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
6	CLEAR.Serenity.e	BA	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	1		1
6	CLEAR.Serenity.e	Placebo	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	1		1
330	ODYSSEY.LONGTERM.e	AliMab_150mg_EZE	24	-59.2	30.8	215		100			0	0		2
330	ODYSSEY.LONGTERM.e	EZE	24	5.6	30.4	118		100			0	0		2
470	ODYSSEY.CHOICE.	AliMab_150m	24	-54.3	17.3	68		100			0	0		1

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
	II.24w.e	g_EZE												
470	ODYSSEY.CHOICE. II.24w.e	EZE	24	4.4	17.5	34		100			0	0		1

CVE = cardiovascular events; * labelling of treatment arms in the ERG expanded analysis was as we understand was performed in the ERG analysis.

Appendix B. Updated Cost-effectiveness Results

Updated cost-effectiveness results using the NMA results from the Expanded ERG analysis post ACM1 and the Company additional analysis post ACM1 are presented below.

For Table 11 and Table 12 , the NMA results from the ***Expanded ERG analysis post ACM1*** were used to generate cost-effectiveness results. As additional supportive evidence for position 2a, results using the treatment effect (versus baseline ezetimibe) and baseline LDL-C directly from CLEAR Tranquility is provided in Table 15 and Table 16. This trial provides head-to-head data for the patient population in position 2a.

For Table 13 and Table 14, the NMA results from the ***Company additional analysis post ACM1*** were used to generate cost-effectiveness results.

Table 11. BA: Cost-effectiveness results using the *Expanded ERG analysis post ACM1*

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		Deterministic ICER (£/QALYs)	Probabilistic ICER (£/QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental		
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate												
No further treatment/placebo with background ezetimibe	9,989	11.94	8.92									
BA	14,735	12.15	9.10	4,745.91	0.21	0.19	-1,038	-1,038	816	816	25,600	25,846
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate												
BA	22,312	10.14	6.84									
Alirocumab + EZE + statin	47,875	10.55	7.14	25,563.43	0.41	0.30	-19,515	-19,515	-16,491	-16,491	84,533	83,477
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate												
BA	21,464	9.56	6.43									
Alirocumab + EZE + statin	46,490	10.18	6.88	25,025.85	0.62	0.45	-15,958	-15,958	-11,424	-11,424	55,196	53,342

Table 12. BA/EZE FDC: Cost-effectiveness results using the *Expanded ERG analysis post ACM1*

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		Deterministic ICER (£/QALYs)	Probabilistic ICER (£/QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental		
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate												
No further treatment/placebo with background ezetimibe	9,989	11.94	8.92									
BA/EZE FDC	14,558	12.15	9.10	4,568	0.21	0.19	-860	-860	994	993.51	24,641	24,887
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate												
BA/EZE FDC	22,155	10.14	6.84									
Alirocumab + EZE + statin	47,875	10.55	7.14	25,721	0.41	0.30	-19,672	-19,672	-16,648	-16,648	85,053	83,997
Position 4b. When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate												
BA/EZE FDC	21,312	9.56	6.43									
Alirocumab + EZE + statin	46,490	10.18	6.88	25,177	0.62	0.45	-16,109	-16,109	-11,575	-11,575	55,530	53,676

Table 13. BA: Cost-effectiveness results using the *Company additional analysis post ACM1*

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		Deterministic ICER (£/QALYs)	Probabilistic ICER (£/QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental		
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate												
No further treatment/placebo with background ezetimibe	9,800	12.01	8.98									
BA	14,501	12.25	9.19	4,701	0.24	0.21	-496	-496	1,607	1,607	22,357	22,303
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate												
BA	22,334	10.30	6.96									
Alirocumab	47,665	10.53	7.12	25,331	0.23	0.17	-22,008	-22,008	-20,346	-20,346	152,424	151,428

Please note that BA+EZE is not connected to the network in the MTD network (see Table 4).

Table 14. BA/EZE FDC: Cost-effectiveness results using the *Company additional analysis post ACM1*

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		Deterministic ICER (£/QALYs)	Probabilistic ICER (£/QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental		
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate												
No further treatment/placebo with background ezetimibe	9,800	12.01	8.98									
BA/EZE FDC	14,322	12.25	9.19	4,522	0.24	0.21	-317	-317	1,786	1,786	21,507	21,453
Position 2b. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are appropriate												
BA/EZE FDC	22,175	10.30	6.96									
Alirocumab	47,665	10.53	7.12	25,490	0.23	0.17	-22,167	-22,167	-20,505	-20,505	153,380	154,376

Please note that BA+EZE FDC is not connected to the network in the MTD network (see Table 4).

Table 15. **BA: Cost-effectiveness results using the *CLEAR Tranquility data directly in the model for baseline LDL-C and treatment effect versus baseline ezetimibe***

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£/QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	9,889.08	12.02	8.98								
BA	14,648.46	12.23	9.16	4,759.38	0.21	0.19	-1,058.44	-1,058.44	792.03	792.03	25,720

Table 16. **BA/EZE FDC: Cost-effectiveness results using the *CLEAR Tranquility data directly in the model for baseline LDL-C and treatment effect versus baseline ezetimibe***

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			NMB: £20,000/QALY (£)		NMB: £30,000/QALY (£)		ICER (£/QALYs)
				Costs (£)	LYs	QALYs	Versus baseline	Fully incremental	Versus baseline	Fully incremental	
Position 2a. When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate											
No further treatment/placebo with background ezetimibe	9,889.08	12.02	8.98								
BA/EZE FDC	14,470.14	12.23	9.16	4,581.06	0.21	0.19	-880.12	-880.12	970.34	970.34	24,756

Figure 1. Probabilistic results: Expanded ERG analysis post ACM1: Position 2a: EZE versus BA + EZE

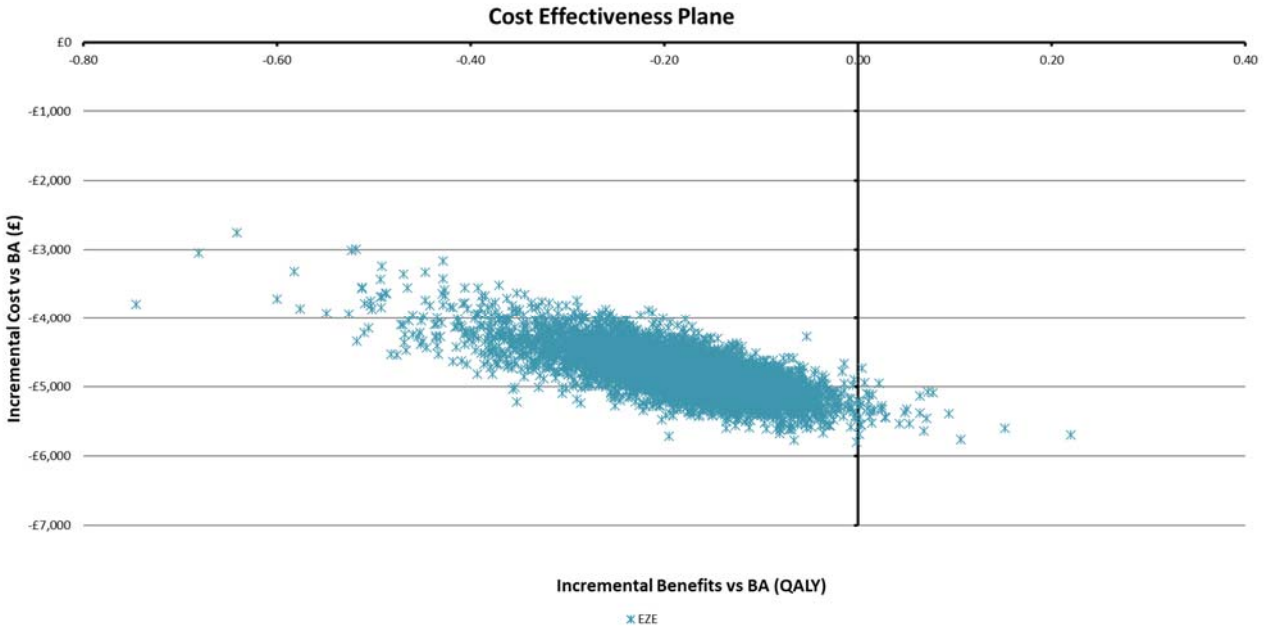


Figure 2. Probabilistic results: Expanded ERG analysis post ACM1: Position 2b: Alirocumab + EZE versus BA + EZE

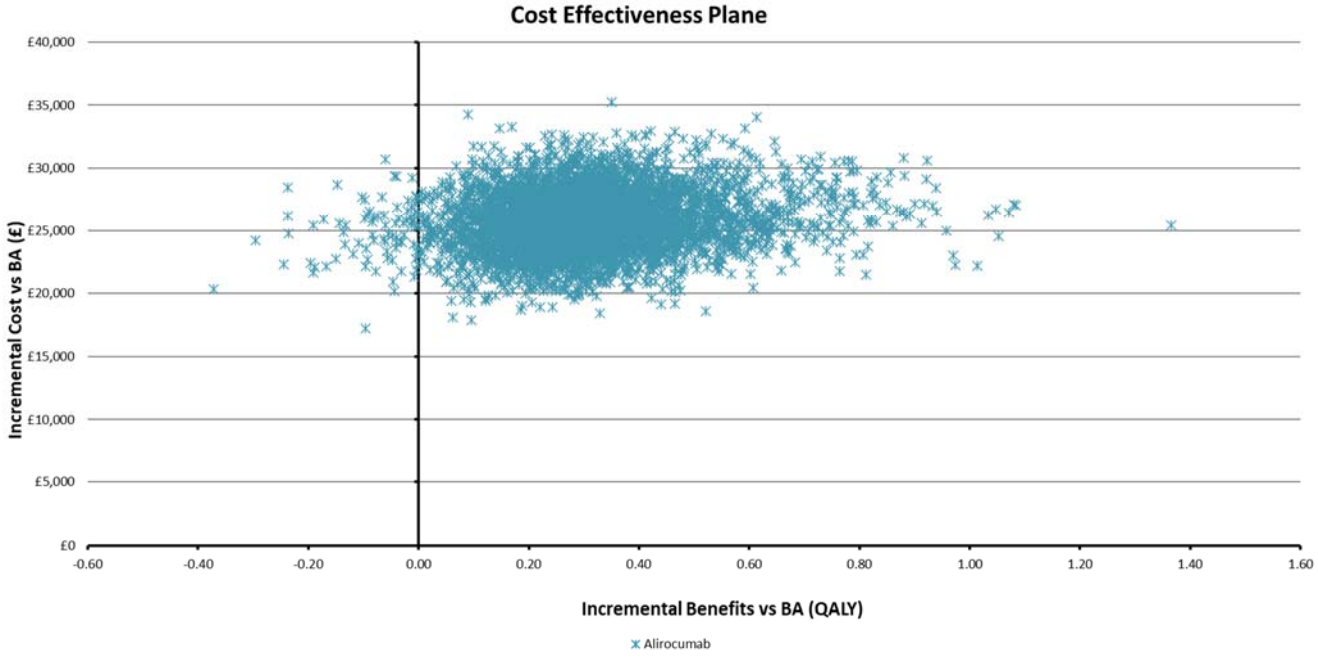


Figure 3. Probabilistic results: Expanded ERG analysis post ACM1: Position 4b: Alirocumab + EZE versus BA + EZE

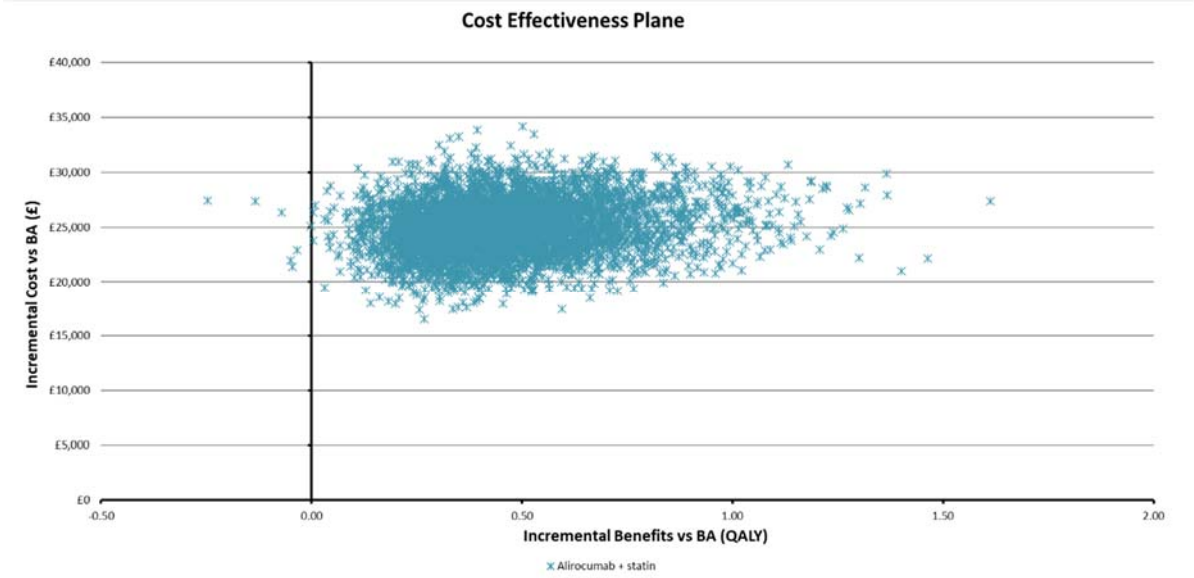


Figure 4. Probabilistic results: Company additional analysis post ACM1: Position 2a: EZE versus BA + EZE

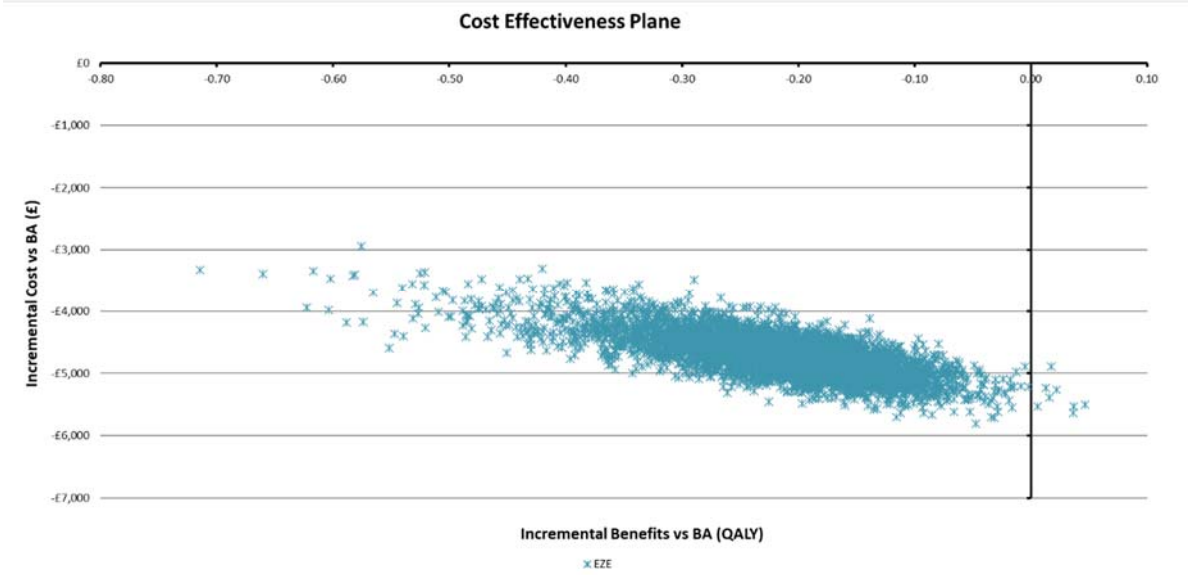
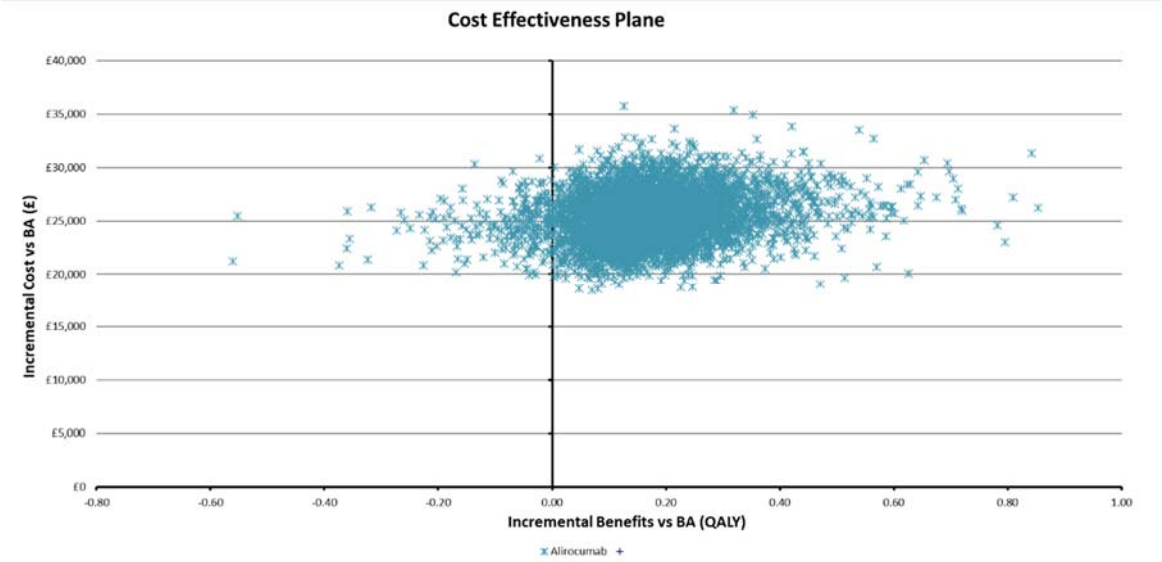


Figure 5. Probabilistic results: Company additional analysis post ACM1: Position 2b: Alirocumab versus BA + EZE



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NICE National Institute for Health and Care Excellence

Response to Request for Additional Information of 19 August 2020 Post ACM1

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Document date: 15 September, 2020

About you

Your name	Kyle Dunton
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Daiichi Sankyo
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Abbreviations: ALI = alirocumab; BA = Bempedoic acid; BA/EZE FDC = bempedoic acid / ezetimibe fixed dose combination pill; CrI = credible interval; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; CVD = cardiovascular disease; DIC = Deviance information criterion; DS = Daiichi Sankyo; EPAR = European public assessment report; ERG = evidence review group; EVO = evolocumab; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolaemia; HES = Hospital Episode Statistics; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life-year; NA = not applicable; NHS = National Health Service; NMA = network meta-analysis; NMB = Net monetary benefit; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; pD = effective number of parameters.; QALY = quality-adjusted life-year; THIN = The Health Improvement Network; UK = United Kingdom.

Re: Clarification Letter following the 1st Appraisal Committee meeting: Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

Company response

Thank you for providing us the background on the appraisal committee concerns around decision making regarding our submission, we welcome the opportunity to address those during this process. Daiichi Sankyo is committed to working collaboratively with NICE to support timely access for patients to bempedoic acid in England and Wales.

Positioning of bempedoic acid

The SmPCs for Nilemdo and Nustendi are now published (Available at: https://www.medicines.org.uk/emc/search?q=bempedoic+acid)

Daiichi Sankyo proposes that bempedoic acid (BA) and bempedoic acid plus ezetimibe fixed dose combination (BA+EZE FDC) should be considered as add-on treatment options on top of existing lipid lowering therapies (statin and ezetimibe), in line with clinical expert opinion. The availability of additional first-in-class and low cost therapeutic interventions with proven efficacy in reducing LDL-C, in addition to existing treatment regimens, can help improve patient outcomes and help to deliver upon the national policy priority in England to improve the prevention of CVD events over the course of the next decade supporting objectives outlined in the NHS Long Term Plan.

A recent EU wide observational study (DA VINCI, Ray et al., 2020) has demonstrated low ezetimibe use in combination with moderate- or high-intensity statins (only 9% of patients) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors use in combination with statins and/or ezetimibe in 1% of patients. This verifies previously reported studies such as the EUROASPIRE and CPRD studies. Recently the ESC 2020 congress experts called upon the need for intensifying treatment combinations as there is a large proportion of patients (more than 70%) who are not at their recommended LDL-C goals.

Treatment with BA as demonstrated in a large pooled analysis of 3623 adults with hypercholesterolaemia/mixed dyslipidaemia enrolled in four phase 3 randomized clinical trials (Banach et al., 2020)was associated with significantly decreased LDL-C levels compared with placebo (maximally tolerated lipid lowering therapies including statins). The decreased LDL-C levels were maintained throughout the treatment period, and were observed on a background of stable LLT, including statins, ezetimibe, or other non-statin agents. In general, a decrease in the LDL-C level associated with BA vs placebo was consistent in all individual clinical trial subgroup analyses. The results of the present pooled analysis suggested the consistency of the effect associated with BA treatment across the majority of demographic and disease-related subgroups.

It is appropriate to assume based on available data, and verified through clinical expert opinion, that the treatment effect of BA (in terms of relative % LDL-C reduction) is consistent in patients regardless of whether they have received prior ezetimibe. BA inhibits cholesterol synthesis through HMG-CoA reductase inhibition in the liver, unlike ezetimibe which blocks reabsorption of cholesterol in the small intestine. The European Medicines Agency states that pharmacokinetics of BA was not affected by ezetimibe. The company presented a pooled analysis of the patients previously treated with ezetimibe in CLEAR Harmony and CLEAR

Wisdom (population 4) and CLEAR Tranquility and CLEAR Serenity (population 2). The mean percentage LDL-C reduction for the groups with and without previous treatment with ezetimibe therapy were presented, and the ERG acknowledged results were similar between the two subgroups. Further, no evidence was identified by the ERG or the company systematic reviews which suggests a difference in treatment effect for the comparator interventions in patients with or without prior ezetimibe therapy.

With regards to background statin therapy, as presented in the company evidence submission (section B.2.4.1.1), LDL-C lowering with BA was slightly greater in the absence of background statin therapy such as in statin intolerance (CLEAR Tranquility and CLEAR Serenity) than in the presence of background statin therapy (CLEAR Harmony, CLEAR Wisdom, and study 1002FDC-053). However, within patients receiving background statin therapy in CLEAR Harmony, CLEAR Wisdom, and study 1002FDC-053, the treatment effect for BA was highly significant both for patient subgroups on high-dose statin and subgroups on low-to-moderate dose statin (presented in Figure 7, Figure 8, Figure 11, and Table 30 of the company evidence submission). Published pooled subgroup results from the CLEAR studies (Banach et al., 2020) and the comparator studies indicated that no statistical differences could be observed outside this differentiation. As discussed in the pooled analysis (Banach et al., 2020), a greater treatment effect was observed among patients in the pool of patients with statin intolerance who were receiving no dose, low-dose, or very low-dose background statin therapy (82% were receiving no background statin), as evidenced by the greater magnitude of the LDL-C level decrease compared with the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, 91% of whom were receiving a moderate- or high-intensity statin regimen. Attenuation of the magnitude of LDL-C level decrease for patients receiving a statin regimen was not unexpected based on the shared mechanism of inhibition of hepatic cholesterol synthesis by both statins and BA. Nonetheless, the additional LDL-C level decrease achieved when BA was added to background statin therapy was greater than the anticipated LDL-C level decrease of 5% to 6% that would be achieved by doubling the statin dose.

The treatment effect for BA and BA/EZE FDC was consistent for patients with and without prior atherosclerotic cardiovascular disease (Banach et al., 2020; see also Figure 7, Figure 8, Figure 9, and Figure 11 of the company evidence submission). UK clinical expert opinion has verified that there is no reason to assume differential treatment effect dependent on ASCVD risk.

These conclusions support the assumptions which fed into the originally submitted Company network meta-analyses. However, in order to inform decision making, Daiichi Sankyo has aimed to address the analyses requested by the NICE Appraisal Committee following the ACM1 on 4th August 2020.

In consideration of the cost effectiveness results using the current analyses in position 4a (when maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: alirocumab and evolocumab are not appropriate), Daiichi Sankyo is not seeking a recommendation for use of BA in this position. As such, cost-effectiveness results for position 4a will not be presented in this response.

Revised NMA approach

Based on the NICE appraisal committee requested clarifications detailed under *"Analyses to*

consider following ACM1" in the Clarification Letter received on 19th August 2020, we have reviewed the data inputting into the two main network meta-analyses (NMAs). The below outlines the Company approach to the additional information request which aims to build upon and reduce the limitations of the ERG NMAs and limit heterogeneity in the networks to support decision-making for this appraisal. These are referred to as the "**Company additional analyses post ACM1**."

Following further clarification from NICE on the requested primary analyses following ACM1, we have also performed NMAs in which the ERGs networks were expanded only to include all available data for BA in patients receiving ezetimibe at baseline from the CLEAR studies. These are referred to as the "**expanded ERG analyses post ACM1"**. As all patients in these networks were on background ezetimibe, the interventions are referred to accordingly (BA+EZE, alirocumab+EZE, and EZE). As evolocumab is not represented in these networks, the efficacy of evolocumab+EZE was assumed to be the same as alirocumab+EZE in the cost-effectiveness model – i.e. a 'class-effect' is assumed as recommended in the letter received on 19th August 2020 from NICE.

It should be noted that the expanded ERG NMAs provide estimates for alirocumab+EZE (as all alirocumab patients were also receiving EZE), while the company analyses provide estimates for alirocumab (as full trial data were used rather than EZE subgroup data). Whilst we understand the request for one primary analysis for decision-making, it is important to be able to provide estimates for alirocumab without co-administered EZE as this is an important intervention in routine clinical practice. As outlined in the company response to Technical Engagement, based on UK clinical expert opinion not all patients receiving alirocumab or evolocumab would be expected to also receive ezetimibe. In a study of 105 patients who were prescribed a PCSK9i in two UK clinical centres (70 in a university hospital and 35 in a district general hospital), 54% were also receiving ezetimibe (Kohli et al., 2010). Therefore, the company proposes that both analyses should be considered for decision-making purposes.

Daiichi Sankyo maintains that the Company NMA submitted as part of the Technical Engagement (also presented in this response document for completeness) is the most robust source for decision-making and makes most use of the available data.

Expanded ERG analysis post ACM1

The trial data included in the expanded ERG analyses post ACM1 are summarized in Table 1

Table 1. Trial data included in the expanded ERG analyses post ACM1

Maximally tolerated statin NMA[a]	Statin intolerant NMA[b]
CLEAR Harmony EZE subgroup	CLEAR Tranquility
CLEAR Wisdom EZE subgroup	CLEAR Serenity EZE subgroup
ODYSSEY Longterm EZE subgroup	ODYSSEY Choice II EZE subgroup

[a] Study 1002FDC-053 is not included as only 4 patients were receiving ezetimibe at baseline, spread across the 4 study arms. Phase 2 trial 1002-009 is not included as ezetimibe treatment was not permitted.

[b] Phase 2 trial 1002-008 was not included because few patients received ezetimibe at baseline (3 patients in the BA180+EZE arm and 13 patients in the BA180 arm).

Company additional analysis post ACM1

The Company additional analysis post ACM1 aimed to address the considerations laid out in

the NICE Request for Additional Information, 19th August 2020. Each of the points raised are considered in turn below. The trials included in the Company additional analysis post ACM1 are presented in Appendix A, along with the rationale for inclusion and exclusion of studies from the analysis.

Trials with use of ezetimibe to randomisation or at baseline

An analysis in which the network is dedicated to trials with high background ezetimibe use (80% or more) is not feasible in the maximally tolerated statin dose (MTD) network, as all trials reported less than 20% of patients on ezetimibe at baseline (or data were not reported).

In the statin intolerant (SI) network, although ODYSSEY CHOICE II could be added to the ERG's NMA if the ezetimibe threshold were relaxed to 60%, this results in a disconnected network. All other trials had less than 20% of patients on ezetimibe at baseline (or data were not reported).

*Limiting studies on the basis of b*aseline LDL-C

Baseline LDL-C is often a parameter reflecting baseline characteristics and background therapy which in turn reflect trial entry criteria. Therefore, we have revisited studies to ensure they are in similar patient populations with similar background therapy and/or comparable LDL at baseline. The following studies were removed from the MTD NMA as patients were not receiving maximally tolerated statin at baseline: Dujovne, Knopp, Krysiak, Melani. The GAUSS-2 and ODYSSEY ALTERNATIVE studies were removed from the SI NMA because the entry criteria (for example high cardiovascular risk) are skewed in comparison with current guidelines and resulted in very high baseline LDL-C; clinical expert opinion was sought on these two studies, verifying rationale for their exclusion, and confirming baseline LDL-C in SI patients is expected to be ~140mg/dL (as in line with BA and comparator studies, and analysis of patients within the EUROASPIRE registry [data on file]).

Primary/secondary prevention

Limiting to primary prevention and secondary prevention trials in order to inform relevant positions is challenging. Most of the trials in dyslipidaemia have been conducted in mixed populations, as there are primary prevention patients with CV risk factors who are at high CV risk and were therefore deemed eligible for further lipid-lowering treatment; many studies excluded patients with a recent cardiovascular event but do not report information about prior events, it is therefore unclear if these patients can be considered secondary or primary prevention and in some trials reporting is unclear. Because of these limitations (and because the percentage reduction in LDL-C has been observed to be consistent among primary and secondary prevention patients as long as other characteristics remain the same such as background therapy, baseline LDL-C), we planned to limit trials by primary/secondary prevention in scenario analyses rather than the main analysis. However, recognising the request from NICE to restrict the number of analyses to aid in decision-making, we have not presented these scenario analyses.

Other baseline characteristics

It is difficult to include studies in which all of the suggested baseline characteristics are similar. However, we are able to remove studies that were conducted in a particular ethnicity such as trials strictly in Asian populations. This removed ODYSSEY NIPPON, ODYSSEY Japan,

ODYSSEY KT, Yakawa and Yakawa-2 (which were conducted in Asia) from the MTD NMA.

We also made the following changes to explore whether heterogeneity is further reduced.

- Remove all of the Alirocumab 75mg data, as this dose is not required (the model uses data for the 150mg dose)
- Remove the ODYSSEY OPTIONS I and II statin control arms from the MTD network as patients randomised to these arms did not just continue the baseline statin, but the baseline statin dose was doubled.

The trials selected for inclusion in the Company additional analyses post ACM1 are presented in Table 2. Details of the trials and the rationale for inclusion/exclusion are provided in Appendix A.

Table 2. Trial data included in the Company additional analyses post ACM1

Maximally tolerated statin NMA	Statin intolerant NMA
CLEAR Harmony EZE subgroup CLEAR Wisdom EZE subgroup ODYSSEY Longterm ODYSSEY Choice I ODYSSEY Options I ODYSSEY Options II ODYSSEY Combo I ODYSSEY Combo II FOURIER LAPLACE-2 LAPLACE-TIMI McKenney 2012 Masana 2005	CLEAR Tranquility CLEAR Serenity EZE subgroup ODYSSEY Choice I ODYSSEY Choice II 1002-008

Note: trial arm labelling in the Company additional analysis post ACM1 was consistent with that in the previous analyses presented by the Company (see Appendix A).

Requested *scenario analyses*

The NICE Request for Additional Information, 19th August 2020, requested scenario analyses according to eligibility for PCSK9i therapy. The NICE recommendations for PSCK9is use a combination of baseline LDL-C thresholds, cardiovascular history categories, and presence of HeFH. The baseline characteristics and efficacy data for these particular patient subpopulations are not available from the PCSK9i NICE appraisals or any other published sources for use in the company NMAs.

The most informative analysis we are able to provide for decision-making uses a similar approach, i.e., cost-effectiveness analyses for populations with baseline LDL-C and cardiovascular history which reflect the PCSK9i eligible populations. Results from these analyses were provided in the Technical Engagement response.

The percentage reduction in LDL-C for patients in the BA studies meeting the criteria for PCSK9i treatment are presented in Table 3. Across the trials, the percentage reduction was similar in patients meeting the criteria for PCSK9i therapy and those who do not.

Table 3. **Percentage reduction in LDL-C for BA in patients meeting PCSK9i criteria**

Study	PSCK9i non-eligible		PSCK9i 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	596	[redacted]	183	[redacted]
Clear Harmony	2030	[redacted]	200	[redacted]
1002-FDC	192	[redacted]	190	[redacted]
Clear Tranquility	251	[redacted]	18	[redacted]
Clear Serenity	278	[redacted]	67	[redacted]

Patients with the following characteristics are eligible for PCSK9i therapy: patients at high risk for CVD and LDL-C persistently above 4.0 mmol/l; patients at very high risk for CVD and LDL-C persistently above 3.5 mmol/l; patients with HeFH and LDL-C persistently above 5.0 mmol/l; and patients with HeFH at high or very high risk for CVD and LDL-C persistently above 3.5 mmol/l. 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. 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). Note that the identification of patients in the BA trials meeting these criteria was somewhat limited by the cardiovascular history available in the trial datasets.

Sensitivity analyses

The NICE Request for Additional Information, 19th August 2020, requested sensitivity analyses in which the criteria for trial selection suggested in the document are relaxed. We have relaxed the criteria for the Company additional analyses post ACM1 in order to build additional studies into the ERGs NMAs. Therefore, the sensitivity analyses requested have been incorporated in the Company additional analysis post ACM1.

Results

MTD Network

The results of the MTD NMA are presented in Table 4, alongside the most recent results provided at Technical Engagement. The following notation is used in the tables:

- **Expanded ERG analysis post ACM1:** relates to the ERG NMA expanded only to include all BA data in patients with ezetimibe at baseline.
- **Company additional analysis post ACM1:** relates to the analysis to address the request from NICE (19th August 2020).

Table 4. Post ACM 1 Analysis Results: MTD Network

Treatment	Estimated difference in % change in LDL−C from baseline compared with EZE		
	Mean	**95% CrIs**	**P value**
Technical Engagement analysis 10a. ODYSSEY LONGTERM included, ODYSSEY Mono excluded, no covariates, and 12 week data removed from the network where 24-week data for the same study was included			
BA+statin	[redacted]	[redacted]	0.9183
FDC+statin[a]	[redacted]	[redacted]	0.1370
EVO+statin	[redacted]	[redacted]	< 0.0001
ALI (75 mg)+statin	[redacted]	[redacted]	< 0.0001
ALI (150 mg)+statin	[redacted]	[redacted]	< 0.0001
Expanded ERG analysis post ACM1			
BA+EZE+statin	[redacted]	[redacted]	0.1417
ALI (150 mg)+EZE+statin	[redacted]	[redacted]	<0.0001
Company additional analysis post ACM1			
EVO+statin	[redacted]	[redacted]	<0.0001
ALI (150 mg)+statin	[redacted]	[redacted]	<0.0001

[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 (see Appendix A)

Table 5. Heterogeneity and model fit parameters – maximum tolerated NMA

Analysis	Total residual deviance	pD	DIC	I2	Between-study standard deviation (s) (95% CrI)
Technical Engagement analysis 10a	286.4	82.5	368.8	80.8%	8.20 (5.4505, 11.892)
Expanded ERG analysis post ACM1	31.4	5.7	37.1	4.8%	8.83 (0.40, 19.31)
Company additional analysis post ACM1	162.6	34	196.6	56.5%	4.58 (1.76, 8.61)

SI Network

Table 6. Post ACM 1 Analysis Results: SI Network

Treatment	Estimated difference in % change in LDL−C from baseline compared with EZE		
	Mean	**95% CrIs**	***P* value**
Technical Engagement Analysis 1. Baseline LDL-C covariate removed (i.e. no covariates)			
BA	[redacted]	[redacted]	0.0647
BA+EZE	[redacted]	[redacted]	0.0012

EVO	[redacted]	[redacted]	< 0.0001
EVO+EZE[a]	[redacted]	[redacted]	—
ALI (75 mg)	[redacted]	[redacted]	< 0.0001
ALI (150 mg)	[redacted]	[redacted]	< 0.0001
Expanded ERG NMA post ACM1			
BA+EZE	[redacted]	[redacted]	0.0157
ALI (150mg)+EZE	[redacted]	[redacted]	<0.0001
Company additional analysis post ACM1			
BA	[redacted]	[redacted]	0.0640
BA+EZE	[redacted]	[redacted]	0.0037
ALI (150 mg)	[redacted]	[redacted]	0.0030

Abbreviations: AC = appraisal committee; ALI = alirocumab; BA = bempedoic acid; CrI = credible interval; EVO = evolocumab; EZE = ezetimibe; ITT = intention-to-treat; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; SI = statin intolerant.

Table 7. Heterogeneity and model fit parameters – statin intolerant NMA

Analysis	Total residual deviance	pD	DIC	I^2 (95% CrI)	Between-study standard deviation (s) (95% CrI)
Technical Engagement Analysis 1	89.9	21.4	111.3	66.1%	5.38 (1.16-13.34)
Expanded ERG analysis post AMC1	29.0	6.4	35.4	65.9%	9.22 (0.62, 19.25)
Company additional analysis post ACM1	49.5	10.4	60.0	20.3%	5.57 (0.20-17.64)

Abbreviations: CrI = credible interval; DIC = deviance information criterion; NMA = network meta-analysis; pD = effective number of parameters.

Additional considerations for the cost-effectiveness analyses

Cost-effectiveness results in positions 2a, 2b and 4b using the updated NMAs will be provided in a subsequent version of this response document by 18 September, 2020.

Regarding the QRISK3 estimation using the patient characteristics from the CLEAR trials for the primary prevention analysis, we have analyzed the CLEAR trial data in order to identify the characteristics needed for the QRISK3 calculation. However, the algorithm requires parameters (such as family history, deprivation score or extensive medical history) which have not been captured in the trial datasets and cannot be obtained from published data. Therefore, we have been unable to provide these QRISK3 estimates. Limited if any data exist for QRISK3 in the UK population and NICE CG181 does not recommend use of QRISK3 as a tool for use in UK clinical practice.

Additionally, we are unable to use prior CV events from the CLEAR trials to estimate what prior events have occurred in the model. Data would be needed for prior unstable angina, stable angina, myocardial infarction, transient ischemic attack, and stroke. These data are not

available from the CLEAR studies.

The mean baseline LDL-C for patients in the CLEAR trials with and without ezetimibe at baseline are presented in Table 8. Statistical tests for differences between the baseline LDL-C levels derived from patients with prior ezetimibe use and baseline LDL-C levels derived from all patients (the values used in the company's base case analysis) have not been performed.

Table 8. Mean (SD) baseline LDL-C levels (mmol/L) in patients by ezetimibe use at baseline in the CLEAR trials

	STUDY	**Wisdom 1002-047**		**Harmony 1002-040**		**Tranquility 1002-048**		**Serenity 1002-046**	
	Ezetimibe Use	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
All patients	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=2 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=3 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=4 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=5 mmol/L	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCSK9i eligible	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not PCSK9i eligible**	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* There was one patient in the placebo group of Tranquility who didn't take any IMP, so there is one patient without baseline Ezetimibe

** Includes all patient not assigned to "PCSK9i eligible" and may also include patients with insufficient information

As a sensitivity analysis in subpopulations 2a and 4a (situations when alirocumab or evolocumab are not appropriate), please use baseline LDL-C levels from patients ineligible for PCSK9 inhibitors. Please consider the appropriateness of using baseline LDL-C levels derived from patients with prior ezetimibe as per the previous point.

The requested analysis in position 2a is presented in Table 9. Analyses for position 4a are not presented in this response as stated previously.

Table 9. Position 2a: only patients with prior ezetimibe and PSCK9 ineligible (Mean LDL-C: 3.29 mmol/L)

	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)	NMB (£20,000)	NMB (£30,000)
BA	14,398	9.26					
No further treatment/placebo with background ezetimibe	9,552	9.09	4,846	0.17	29,120	-1,518	146

Please explain why the FDC-1002-053 trial has been used to inform the baseline LDL-C level in all patients in population 4 (i.e. 2.91 mmol/L) and not the baseline LDL-C levels according to PCSK9i eligibility (subpopulations 4a and 4b).

The PCSK9i eligibility criteria use a combination of cardiovascular history, presence of HeFH and LDL-C thresholds. The reporting/coding of previous cardiovascular events is not consistent and differs slightly in the study databases among the three BA studies in patients on maximum tolerated dose of statins. In particular, the definition/coding of the complex parameter “polyvascular/recurrent events” varies.

The selection of patients that are PCSK9 eligible is of relevance for the calculation of baseline LDL-C in position 4b. To ensure consistency in how patients eligible for PCSK9i were identified across the studies, the FDC-053 study was not included in the base case calculation of LDL-C for position 4b as the reporting in this trial differed from CLEAR Harmony and CLEAR Wisdom.

However, when analyzing the baseline LDL-C without any PCSK9i restrictions (position 4), DS used the data set with the largest sample size (i.e. including FDC-053). Removing the FDC-053 trial from the calculation, the baseline LDL-C would be 2.79 mmol/L.

Using the full trial population from FDC-053 was considered appropriate in position 4a given that the majority of patients eligible for PCSK9i therapy in UK clinical practice do not receive these. Further analyses in position 4a are not presented as discussed previously.

Appendix A. Study Listings with Rationale for Inclusion/Exclusion in the Company NMAs

Table A-1 presents details of the studies included in the NMAs most recently provided to NICE during Technical Engagement, the studies that were included in the Company additional analyses post ACM1, and the rationale for removal of trials. The studies included in the Expanded ERG analyses post ACM1 also are indicated. The indicator labels within the tables are as follows.

Indicator label	Meaning
1	Included in the statin intolerant NMA
2	Included in the maximum tolerated statin NMA
0	Not included in the proposed NMA
Rationale for removal of study arms from the proposed NMA	
A	ITT data replaced with prior ezetimibe subgroup (see end of table)
B	alirocumab 75mg data removed
C	Ethnicity
D	Entry criteria misaligned with guidelines, high baseline LDL-C
E	Statin control arm was double baseline statin dose
F	Not maximally tolerated dose at baseline
G	Insufficient patients with prior/baseline ezetimibe

The columns in the tables below relate to the following analyses:

- **Tech Eng**: relates to the NMA that was provided most recently during Technical Engagement This is Analysis 10 of the MTD NMA which included ODYSSEY Longterm, excluded ODYSSEY Mono, included adalimumab data at week 24, but excluded adalimumab data at week 12 for those studies reporting both adalimumab 75mg data at week 12 and data at week 24 from those uptitrated from 75mg to 150mg. For the SI network, this represents analysis 1 presented at Technical Engagement. Details of these analyses and the results are provided in Appendix B for reference.
- **Company additional analysis post ACM1:** relates to the Company additional analysis post ACM1 designed to address the request from NICE (19th August 2020). Trials have been removed due to reasons A-G.
- **Expanded ERG analysis post ACM1:** relates to the ERG analysis with ezetimibe subgroup data also included for the bempedoic acid trials.

Table A-1. Trial arms included in the Technical Engagement NMA, Expanded ERG analysis post ACM1, and the Company Additional (CA) Analysis Post ACM1

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
5	CLEAR.Harmony	BA	12	-16.5	20.1	1488	103.6	7.8	99.8	>75% prior CVE	2	0	A	0
5	CLEAR.Harmony	Placebo	12	1.6	23.4	742	102.3	7.5	100.0	>75% prior CVE	2	0	A	0
82	ODYSSEY OUTCOMES	AliMab_75mg	12	-55.8	29.2	9462	92.0			Removed	2	0	B	0
82	ODYSSEY OUTCOMES	Placebo	12	4.4	29.2	9462	92.0			Removed	2	0	B	0
36	ODYSSEY.NIPPON	AliMab_150mg	12	-70.1	16.7	53	149.2	19.6	34.6	Removed	2	0	C	0
36	ODYSSEY.NIPPON	Placebo	12	-4.3	16.5	56	149.4	19.6	33.9	Removed	2	0	C	0
6	CLEAR.Serenity	BA	12	-22.6	19.7	234	158.5		7.7	Mixed	1	0	A	0
6	CLEAR.Serenity	Placebo	12	-1.2	15.0	111	155.6		9.9	Mixed	1	0	A	0
4	CLEAR.Tranquility	BA_EZE	12	[redacted]	[redacted]	175	[redacted]	100.0	32.6	No recent CVE	1	1		1
4	CLEAR.Tranquility	EZE	12	5.0	21.6	82	123.0	100.0	28.4	No recent CVE	1	1		1
3	ODYSSEY KT.24w	AliMab_150mg	24	-57.1	29.5	97	97.0	14.4	100.0	Removed	2	0	C	0
3	ODYSSEY KT.24w	Placebo	24	6.3	29.3	102	99.3	11.8	100.0	Removed	2	0	C	0
11	FOURIER	EvoMab	12	-69.6	14.1	13784	92.0	5.0	100.0	>75% prior CVE	2	2		0
11	FOURIER	Placebo	12	-4.5	14.1	13780	92.0	5.2	100.0	>75% prior CVE	2	2		0
45	ODYSSEY.CHOICE.	AliMab_150m	24	-51.6	28.8	76	114.9	13.8	99.4	No recent CVE	2	2		0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
	l.24w	g												
45	ODYSSEY.CHOICE. I.24w	Placebo	24	-0.1	28.7	156	112.1	14.0	100.0	No recent CVE	2	2		0
43	ODYSSEY.CHOICE. I.24wSI	AliMab_150m g	24	-50.2	22.5	37	154.7	6.8	1.4	No recent CVE	1	1		0
43	ODYSSEY.CHOICE. I.24wSI	Placebo	24	-0.3	22.8	71	134.1	15.1	0.0	No recent CVE	1	1		0
47	ODYSSEY.CHOICE. II.24w	AliMab_150m g	24	-53.5	12.2	58	167.5	59.3	0.0	Unclear	1	1		0
47	ODYSSEY.CHOICE. II.24w	Placebo	24	4.7	17.4	57	156.6	60.3	0.0	Unclear	1	1		0
10	1002-009	BA	12	-24.3	27.8	45	141.7		100.0	No recent CVE	2	0	G	0
10	1002-009	Placebo	12	-4.2	28.1	45	130.9		100.0	No recent CVE	2	0	G	0
1	1002-008	BA	12	-31.4	12.9	50	170.5	0.0	100.0	No recent CVE	1	1		0
1	1002-008	BA_EZE	12	-49.6	6.0	10	164.2	100.0	100.0	No recent CVE	1	1		0
1	1002-008	EZE	12	-19.8	10.0	51	169.5	100.0	100.0	No recent CVE	1	1		0
67	YUKAWA-2 (Kiyosue 2016 hs)	EvoMab	12	-75.2	27.9	51	97.0		100.0		2	0	C	0
67	YUKAWA-2 (Kiyosue 2016 hs)	Placebo	12	0.7	9.0	51	91.0		100.0		2	0	C	0
62	ODYSSEY Japan (Teramoto 2016) 24w	AliMab_150m g	24	-62.5	15.6	144	143.1		100.0		2	0	C	0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
62	ODYSSEY Japan (Teramoto 2016) 24w	Placebo	24	1.6	15.3	72	143.1		100.0		2	0	C	0
23	ODYSSEY.alternative.24	AliMab_150mg	24	-45.0	24.7	126	191.1		0.0		1	0	D	0
23	ODYSSEY.alternative.24	EZE	24	-14.6	24.6	125	193.5		0.0		1	0	D	0
25	ODYSSEY.COMBO.I.24	AliMab_150mg	24	-47.9	29.1	205	100.3	7.2	99.5	>75% prior CVE	2	2		0
25	ODYSSEY.COMBO.I.24	Placebo	24	-2.5	24.9	106	104.6	10.3	100.0	>75% prior CVE	2	2		0
49	ODYSSEY OPTIONS I (Bays 2015.hs) 24wk	AliMab_150mg	24	-54.0	29.5	47	116.4	0.0	100.0	Mixed	2	2		0
49	ODYSSEY OPTIONS I (Bays 2015.hs) 24wk	EZE	24	-22.6	29.5	47	98.9	0.0	100.0	Mixed	2	2		0
49	ODYSSEY OPTIONS I (Bays 2015.hs) 24wk	Placebo	24	-4.8	28.8	47	108.6	0.0	100.0	Mixed	2	0	E	0
48	ODYSSEY OPTIONS I (Bays 2015.ls) 24wk	AliMab_150mg	24	-44.1	34.0	57	103.9	0.0	100.0	Mixed	2	2		0
48	ODYSSEY OPTIONS I (Bays	EZE	24	-20.5	34.9	55	100.4	0.0	100.0	Mixed	2	2		0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
	2015.ls) 24wk													
48	ODYSSEY OPTIONS I (Bays 2015.ls) 24wk	Placebo	24	-5.0	34.7	57	100.3	0.0	100.0	Mixed	2	0	E	0
27	ODYSSEY.COMBO. II.24	AliMab_150mg	24	-50.6	30.6	479	108.3		99.8	Mixed	2	2		0
27	ODYSSEY.COMBO. II.24	EZE	24	-20.7	29.5	241	104.4		100.0	Mixed	2	2		0
13	GAUSS-2Q2W	EvoMab	12	-56.1	19.4	103	192.0		18.4		1	0	D	0
13	GAUSS-2Q2W	EZE	12	-18.1	18.2	51	195.0		17.6		1	0	D	0
87	YUKAWA.Q2W	EvoMab	12	-71.3	15.9	52	139.2		100.0		2	0	C	0
87	YUKAWA.Q2W	Placebo	12	-2.7	15.9	52	143.1		100.0		2	0	C	0
68	LAPLACE-2 (Robinson 2014 hs1) Q2W	EvoMab	11	-61.8	29.3	109	94.2	0.0	100.0	Mixed	2	2		0
68	LAPLACE-2 (Robinson 2014 hs1) Q2W	EZE	11	-16.9	28.9	55	98.7	0.0	100.0	Mixed	2	2		0
68	LAPLACE-2 (Robinson 2014 hs1) Q2W	Placebo	11	13.1	30.0	56	100.3	0.0	100.0	Mixed	2	2		0
70	LAPLACE-2 (Robinson 2014 hs2) Q2W	EvoMab	11	-59.1	23.7	111	88.5	0.0	100.0	Mixed	2	2		0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
70	LAPLACE-2 (Robinson 2014 hs2) Q2W	Placebo	11	6.6	23.5	56	77.4	0.0	100.0	Mixed	2	2		0
74	LAPLACE-2 (Robinson 2014 ms2) Q2W	EvoMab	11	-66.2	31.5	113	114.9	0.0	100.0	Mixed	2	2		0
74	LAPLACE-2 (Robinson 2014 ms2) Q2W	Placebo	11	3.3	26.0	58	110.3	0.0	100.0	Mixed	2	2		0
78	LAPLACE-TIMI-57aQ2W	EvoMab	12	-68.0	31.4	78	119.9	8.9	99.2	<25% prior CVE	2	2		0
78	LAPLACE-TIMI-57aQ2W	Placebo	12	1.2	30.4	78	123.7	9.0	100.0	<25% prior CVE	2	2		0
83	McKenney 2012	AliMab_150mg	12	-72.4	17.8	31	123.9		100.0	<25% prior CVE	2	2		0
83	McKenney 2012	Placebo	12	-5.1	17.3	31	130.2		100.0	<25% prior CVE	2	2		0
81	Krysiak 2011.s	EZE	12	-46.0	8.9	35	183.0			Removed	2	0	F	0
81	Krysiak 2011.s	Placebo	12	-34.0	9.5	33	182.0			Removed	2	0	F	0
65	Masana 2005	EZE	12	-23.7	33.9	355	136.6	0.0	100.0	Unclear	2	2		0
65	Masana 2005	Placebo	12	3.3	23.0	78	131.4	0.0	100.0	Unclear	2	2		0
18	Melani 2003.ns	EZE	12	-18.7	12.8	64	177.9		21.9	Removed	2	0	F	0
18	Melani 2003.ns	Placebo	12	1.3	12.9	65	177.9		23.1	Removed	2	0	F	0
19	Melani 2003.s	EZE	12	-37.7	12.9	204	177.9		30.9	Removed	2	0	F	0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
19	Melani 2003.s	Placebo	12	-24.3	22.9	205	177.9		23.1	Removed	2	0	F	0
17	Knopp 2003	EZE	12	-17.7	14.7	621	165.1		21.7	Removed	2	0	F	0
17	Knopp 2003	Placebo	12	0.8	12.4	204	164.3		18.5	Removed	2	0	F	0
8	Dujovne 2002	EZE	12	-16.9	14.2	666	167.8		22.4	Removed	2	0	F	0
8	Dujovne 2002	Placebo	12	0.4	12.5	226	168.0		23.0	Removed	2	0	F	0
53	ODYSSEY OPTIONS II (Farnier 2016.hs) 24wk	AliMab_150mg	24	-36.3	31.6	54	118.3	0.0	100.0		2	2		0
53	ODYSSEY OPTIONS II (Farnier 2016.hs) 24wk	EZE	24	-11.0	32.0	53	119.0	0.0	100.0		2	2		0
53	ODYSSEY OPTIONS II (Farnier 2016.hs) 24wk	Placebo	24	-15.9	31.3	53	112.9	0.0	100.0		2	0	E	0
52	ODYSSEY OPTIONS II (Farnier 2016.ls) 24wk	AliMab_150mg	24	-50.6	30.1	49	107.3	0.0	100.0		2	2		0
52	ODYSSEY OPTIONS II (Farnier 2016.ls) 24wk	EZE	24	-14.4	30.5	48	102.4	0.0	100.0		2	2		0
52	ODYSSEY OPTIONS II (Farnier 2016.ls) 24wk	Placebo	24	-16.3	29.8	48	105.9	0.0	100.0		2	0	E	0

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
33	ODYSSEY.LONGTERM	AliMab_150mg	12	-60.2	26.5	1436	122.8	13.9	100.0	<25% prior CVE	2	2		0
33	ODYSSEY.LONGTERM	Placebo	12	-1.6	27.3	746	122.0	15.0	100.0	<25% prior CVE	2	2		0
9	1002FDC-053	BA	12	-17.7	23.9	110	146.4			Mixed	2	0	G	0
9	1002FDC-053	BA_EZE_FDC	12	-31.5	26.0	108	152.0			Mixed	2	0	G	0
9	1002FDC-053	EZE	12	-21.0	21.3	109	147.5			Mixed	2	0	G	0
9	1002FDC-053	Placebo	12	-2.5	22.8	55	152.6			Mixed	2	0	G	0
7	CLEAR.Wisdom	BA	12	-15.1	24.5	522	119.4			>75% prior CVE	2	0	A	0
7	CLEAR.Wisdom	Placebo	12	2.4	23.2	257	122.4			>75% prior CVE	2	0	A	0
5	CLEAR.Harmony.e	BA	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
5	CLEAR.Harmony.e	Placebo	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
7	CLEAR.Wisdom.e	BA	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
7	CLEAR.Wisdom.e	Placebo	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	2		2
6	CLEAR.Serenity.e	BA	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	1		1
6	CLEAR.Serenity.e	Placebo	12	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		0	1		1
330	ODYSSEY.LONGTERM.e	AliMab_150mg_EZE	24	-59.2	30.8	215		100			0	0		2
330	ODYSSEY.LONGTERM.e	EZE	24	5.6	30.4	118		100			0	0		2
470	ODYSSEY.CHOICE.	AliMab_150m	24	-54.3	17.3	68		100			0	0		1

Study	Study.name	Treatment	Week	perchangeLDL_C	perchange_LDL_Csd	n	Baseline_LDL_C	Baseline_ezetimibe	Baseline_statin	Primay/secondary prevention	Tech Eng	Company additional analysis post ACM1	Rationale	Expanded ERG analysis post ACM1*
	II.24w.e	g_EZE												
470	ODYSSEY.CHOICE. II.24w.e	EZE	24	4.4	17.5	34		100			0	0		1

CVE = cardiovascular events; * labelling of treatment arms in the ERG expanded analysis was as we understand was performed in the ERG analysis.

Appendix B. Updated Cost-effectiveness Results

Updated cost-effectiveness results will be presented in a subsequent version of this document by 18 September 2020.

References

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Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]

ERG review of company's response to the request for additional information of 19 August 2020 post ACM1

September 2020

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1 Summary

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the National Institute for Health and Care Excellence (NICE) technology appraisal committee's request for additional information of 19 August 2020, post ACM1 for the appraisal of bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515]. The committee request reported that the committee was particularly keen to see analyses that eliminated heterogeneity as far as possible and recommended that the company:

1. Conduct a primary analysis where they build upon the NMAs conducted by the ERG and identify any additional studies in the wider group of trials included in the company's NMAs that:
    a. Have use of ezetimibe prior to randomisation;
    b. Have similar unadjusted baseline low-density lipoprotein cholesterol (LDL-C) levels;
    c. Use appropriate trials to inform treatment efficacy for primary prevention (population 2a) and secondary prevention (populations 2b, 4a, and 4b);
    d. Also have other similar baseline characteristics such as cardiovascular disease (CVD) risk, Heterozygous Familial Hypercholesterolemia (HeFH), type of statin, sex, and ethnicity.
2. Conduct scenario analyses in:
    a. subpopulations 2b and 4b (situations when alirocumab or evolocumab are appropriate) using a network of studies that reflects the eligibility criteria for PCSK9 inhibitors; and
    b. subpopulations 2a and 4a (situations when alirocumab or evolocumab are not appropriate) using a network of studies that reflects the ineligibility criteria for PCSK9 inhibitors.
3. Conduct a sensitivity analysis by relaxing the assumptions used in the primary analysis to enable a larger network of studies but still applying restrictions to provide a more homogenous network compared to those previously presented by the company; e.g. relax the prior ezetimibe use criterion.
4. Implement the results from the NMAs requested for the primary analysis, scenario analyses and sensitivity analyses in the economic model.
5. Explore further patient's characteristics from the CLEAR trials in the cost-effectiveness analyses.

Please note that the subpopulations are referred to as positions 2 (subpopulation 2a and 2b) and 4 (subpopulation 4b) in this report.

The company is no longer seeking a recommendation for use of bempedoic acid in subpopulation 4a (when maximally tolerated statin dose with EZE does not appropriately control LDL-C, and ALI and EVO are not appropriate). Therefore, subpopulation 4a is not discussed further in this report and the cost-effectiveness results for subpopulation 4a are not presented.

2 Clinical effectiveness

In response to the request for additional information of 19 August 2020 (post appraisal committee meeting 1 [ACM1]), the company presented four further network meta-analyses, two for each of the pre-exiting statin intolerant and maximally tolerated statin populations:

- Expanded ERG (evidence review group) analysis post ACM1;
- Company additional analysis post ACM1.

The original ERG NMAs comprised of restricted networks of trials for the statin intolerant (SI) and maximum tolerated dose statin (MTD) populations in which all patients were on EZE at baseline and thus were aligned with the company's proposed positioning of BA in the treatment pathway. However, the ERG did not have access to all of the appropriate data from the CLEAR studies and additionally the ERG did not have sufficient time to fully appraise all the potentially relevant comparator studies. The company's expanded ERG analyses post ACM1 include the data from the CLEAR studies that the ERG did not have access to at the time of conducting the original ERG analyses and the company reported that there were no additional comparator data from other non-BA studies that could be included in the NMAs. The ERG considers the expanded ERG analyses meet the primary analysis request in the NICE request for additional information although the ERG notes that like the ERG, the company did not identify any data on evolocumab (EVO) suitable for inclusion in the NMAs. The company has agreed with the ERG that it would be reasonable to assume a class-effect for the PCKSI-9 inhibitors alirocumab (ALI + EZE) and EVO (+ EZE).

The ERG also notes that the expanded ERG NMAs provide estimates for ALI+EZE as all ALI patients were receiving EZE at baseline. In contrast, in the company analyses the estimates for ALI do not include EZE as full trial data were used rather than EZE subgroup data and EZE use at baseline was generally either not reported or utilised in a very small proportion of patients (<50%). The company argues that both the expanded ERG NMAs and company analyses are relevant for decision-making as not all patients would be expected to receive ALI with co-administered EZE in routine clinical practice. The company also considers the company NMA submitted in the company response to technical engagement to be the most robust source for decision-making and to make the most use of available data. However, the ERG notes that the proposed positioning of BA is in patients who have received prior EZE and therefore the ERG considers the ERG analyses to be more in keeping with the proposed positioning of BA. The ERG also considers it important to highlight that the company NMAs from technical engagement were associated with high levels of clinical and statistical heterogeneity and thus the results were unreliable.

The ERG's view as to the most appropriate data to inform decision making remains unchanged from the original ERG report, with the ERG recommending that only BA data from the prior EZE population are used. The ERG considers the ERG updated NMAs (ERG SI NMA V2 and ERG MTD NMA V2) that incorporate all available BA prior ezetimibe subgroup data to now be the best available data for decision making.

2.1 Expanded ERG analysis post ACM1

The trial data included in the original ERG NMA and the company expanded ERG analyses post ACM1 are summarised in Table 1. The ERG agrees with the studies included by the company in the expanded ERG analyses post ACM1.

Table 1. Trial data included in the original ERG NMA and the company expanded ERG analyses post ACM1

Study name	*ERG NMA*	*Expanded ERG analysis post ACM 1*
Maximally tolerated statin NMA (position 4)[a]		
CLEAR Harmony EZE subgroup	Yes	Yes
CLEAR Wisdom EZE subgroup	Data unavailable to ERG	Yes
ODYSSEY Long Term EZE subgroup	Yes	Yes
Statin intolerant NMA (position 2)[b]		
CLEAR Tranquility	Yes	Yes
CLEAR Serenity EZE subgroup	No	Yes
ODYSSEY Choice II EZE subgroup	Yes	Yes

Notes: [a] Study 1002FDC-053 is not included as only 4 patients were receiving ezetimibe at baseline, spread across the 4 study arms. Phase 2 trial 1002-009 is not included as ezetimibe treatment was not permitted.

[b] Phase 2 trial 1002-008 was not included because few patients received ezetimibe at baseline (3 patients in the BA180+EZE arm and 13 patients in the BA180 arm).

Abbreviations: ACM, appraisal committee meeting; ERG, evidence review group; EZE, ezetimibe; NMA, network meta-analysis.

2.2 Company additional analysis post ACM1

The company additional analysis post ACM1 was reported to be aiming to address the considerations laid out in the NICE Request for Additional Information, 19 August 2020. The ERG considers the company additional analysis post ACM1 to be a sensitivity analysis whereas the ERG considers the expanded ERG analysis post ACM1 to meet the specification of the primary analysis in the NICE request for additional information.

The company provided details of the trials included in the Company additional analysis post ACM1 in Appendix A of the company response document. In relation to the suggestions laid out in the NICE Request for Additional Information the company reported that:

- **Ezetimibe (EZE) use:** All trials reported less than 20% of patients on EZE at baseline (or data were not reported) and so an analysis in which the network is dedicated to trials with high background EZE use (80% or more) is not feasible in the maximally tolerated statin dose (MTD) network. In the statin intolerant (SI) network, the full trial population of ODYSSEY CHOICE II could be added to the ERG's NMA rather than just the prior EZE subgroup if the EZE threshold were relaxed to 60% but all other trials had less than 20% of patients on EZE at baseline (or data were not reported).
- **Baseline LDL-C:** The company has excluded four studies from the MTD NMA where patients were not receiving maximally tolerated statin at baseline. In addition, two studies were removed from the SI NMA because the company considered the entry criteria (for example high cardiovascular risk) to be skewed in comparison with current guidelines and that they had resulted in very high baseline LDL-C.
- **Primary/secondary prevention:** No changes to either the MTD or SI NMA were made in relation to this characteristic. The company reported that limiting to the NMAs to primary prevention and secondary prevention trials in order to inform relevant positions is challenging and gave reasons such as many trials having mixed populations or not reporting information about prior events.
- **Other baseline characteristics:** Five studies were removed from the MTD NMA because they were conducted in Asian populations.
- **Other changes implemented by the company to attempt to reduce heterogeneity:** All of the ALI 75mg data were removed from the NMAs as this dose is not required in the cost-effectiveness model. In addition, the statin control arms in ODYSSEY OPTIONS I and II were removed from the MTD NMA as patients randomised to these arms did not just continue the baseline statin, but the baseline statin dose was doubled.

The resulting trials that were included in the Company additional analyses post ACM1 for the MTD and SI NMAs are detailed in Table 2. The ERG remains concerned that there is clinical heterogeneity between the trials included in the company's NMAs. Further details of the ERG's key concerns in relation to the studies included in the company's NMAs are provided in the text below for each of the MTD and SI NMA's.

Table 2. Trial data included in the Company additional analyses post ACM1 (Adapted from Company response, Table 2)

Maximally tolerated statin NMA (position 4)	*Statin intolerant NMA (position 2)*
CLEAR Harmony EZE subgroup CLEAR Wisdom EZE subgroup ODYSSEY Long Term	CLEAR Tranquility CLEAR Serenity EZE subgroup ODYSSEY Choice I

ODYSSEY Choice I ODYSSEY Options I ODYSSEY Options II ODYSSEY Combo I ODYSSEY Combo II FOURIER LAPLACE-2 LAPLACE-TIMI McKenney 2012 Masana 2005	ODYSSEY Choice II 1002-008

Note: trial arm labelling in the Company additional analysis post ACM1 was consistent with that in the previous analyses presented by the Company.

Abbreviations: EZE, ezetimibe; NMA, network meta-analysis.

In terms of the MTD NMA, firstly the ERG notes that only the prior EZE subgroups of CLEAR Harmony and CLEAR Wisdom are included, whereas the full trial population of the other studies are used despite a similar prior EZE subgroup being available from ODYSSEY LONG TERM. The company has used the prior EZE subgroup data from CLEAR Harmony and CLEAR Wisdom for placebo as well as for BA rather than the full trial placebo data.

The ERG also notes that there is clinical heterogeneity in the data for ALI 150mg as only two studies (ODYSSEY LONG TERM and McKenney 2012) comprise of patients randomised to ALI 150mg and assessed for change from baseline LDL-C at 12 weeks. The remaining five studies informing ALI 150mg in the MTD NMA comprise of studies where patients were randomised to ALI 75 mg and then up titrated at week 12 if they met specific criteria and the results at 24 weeks irrespective of ALI dose are used in the NMA. The ERG notes that fewer than 30% of the patients in these studies received the 150mg ALI dose.

The company is using the MTD NMA to inform the efficacy of treatments in a population when maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C. The ERG notes that patients in ODYSSEY OPTIONS I and ODYSSEY OPTIONS II were not on maximally tolerated statin dose at baseline as one of the randomised treatments was a doubling of the baseline statin dose. In addition, the ERG notes that despite separate trial arm data, both the low dose statin (atorvastatin 20mg or rosuvastatin 10mg) and high dose statin (atorvastatin 40mg or rosuvastatin 20mg) data from ODYSSEY OPTIONS I and ODYSSEY OPTIONS II respectively, were included and treated as maximally tolerated doses of statin in the company NMA.

Masana 2005 was a study comparing EZE and placebo and the ERG additionally notes that patients in Masana 2005 were not on maximally tolerated statins at baseline as the study protocol allowed the statin dose to be doubled at study visits beyond week 12. The 48 week results for Masana 2005 show that 50% of patients underwent statin dose up titration during the study.

The results from the MTD NMA are also potentially inaccurate as data on change from baseline in LDL-C level at the mean of weeks 10 and 12 are used from LAPLACE-2 rather than 12 week data, which the ERG notes are publicly available in the supplementary material for the study publication. The ERG notes that the differences in the data are small but it impacts on seven datapoints in the NMA: three for EVO, three for placebo and one for EZE. These different datapoints were a result of different background statin therapy drugs and doses (e.g. Rosuvastatin 40mg and Atorvastatin 80mg) which are a further potential source of clinical heterogeneity.

In the company's additional analysis SI NMA post ACM1, there were only five studies, and three of these were BA studies (CLEAR Tranquility, CLEAR Serenity and study 1002-008). The remaining two studies compared ALI to placebo (ODYSSEY CHOICE I and ODYSSEY CHOICE II).

In terms of the BA data in the company's additional analysis for the SI population, the ERG considers there to be clinical heterogeneity in the BA data as the patients from 1002-008 were not on EZE at baseline, whereas all patients in the EZE subgroup of CLEAR Serenity were on EZE at baseline. In CLEAR Tranquillity the study used to inform BA + EZE, the 12-week randomised study assessment period was BA compared to placebo after a 4-week run-in period of ezetimibe. The ERG considers the EZE subgroup from CLEAR Serenity is similar to the CLEAR Tranquillity population and should be used to inform the estimate of BA + EZE in the NMA rather than BA alone (assuming that patients on EZE at baseline in CLEAR Serenity continued on their EZE therapy).

The ERG also notes that in both ODYSSEY CHOICE I and ODYSSEY CHOICE II, 24 week data were used for ALI 150mg rather than 12 week data because patients were randomised to 75mg ALI and only up titrated to 150mg ALI at 12 weeks if they failed to meet the required LDL-C targets. The 24-week data that were used in the company additional NMA comprises of patients who continued on the 75mg dose of ALI as well as those who received the 150mg dose and less than 50% of the ALI patients in either study received ALI 150mg. The ERG notes that this issue also applies to the original ERG NMA and the expanded ERG NMA post ACM1.

In summary, the ERG considers there to be substantial unresolved clinical heterogeneity in both the SI and MTD company additional analyses and the ERG therefore considers the updated ERG NMAs (ERG SI NMA V2 and ERG MTD NMA V2) to be the most robust NMAs for assessing the clinical efficacy of BA.

2.3 Results

2.3.1 SI Network (position 2)

The ERG has updated the ERG NMA (hereafter referred to as ERG SI NMA V2) to include the data from CLEAR Serenity provided by the company. As such, the ERG SI NMA V2 and the company expanded ERG analysis post ACM1 both contain the same clinical data. However, the results from the ERG SI NMA V2 differ slightly from those reported by the company and the ERG is unable to explain the reason for the difference in the results. The ERG notes that the mean change in LDL-C is similar in both the ERG and company versions of the analysis but the credible intervals are considerably wider in the company's results (Table 3).

The ERG also sought to validate the company additional analysis post ACM1 for the SI population by running an NMA using the trial data supplied by the company for this analysis (although as described in Section 2.2, the ERG does not consider this analysis to be suitable for decision making due to heterogeneity in the included trials and concerns around trials included in the analysis). The ERG's validation NMA demonstrates that a random effects model has a similar model fit to the fixed effects model (DIC with fixed effects 35.68 and with random effects 35.42) and so the ERG considers the random effects model to be most appropriate given the likely clinical heterogeneity in the NMA.

The results of the ERG SI NMA V2 and the ERG validation NMA are presented in Table 3, alongside the results of the company's NMAs. As for the MTD population, the ERG considers the results of the ERG SI NMA V2 to be the most robust and to address the primary analysis requested in the NICE request for additional information. The results of the ERG validation NMA suggest treatment with [redacted]

Table 3. Post ACM1 SI NMA results (position 2) (Adapted from Company response, Table 6)

Treatment	*Estimated difference in % change in LDL−C from baseline compared with EZE*		
	Mean	*95% CrIs*	*P value*
ERG SI NMA V2			
BA+EZE	[redacted]	[redacted]	-
ALI (150mg)+EZE	[redacted]	[redacted]	-
Company's Expanded ERG NMA post ACM1			
BA+EZE	[redacted]	[redacted]	0.0157
ALI (150mg)+EZE	[redacted]	[redacted]	<0.0001
Company additional analysis post ACM1			
BA	[redacted]	[redacted]	0.0640
BA+EZE	[redacted]	[redacted]	0.0037
ALI (150 mg)	[redacted]	[redacted]	0.0030

ERG validation NMA			
BA	[redacted]	[redacted]	-
BA+EZE	[redacted]	[redacted]	-
ALI (150mg)	[redacted]	[redacted]	-

Abbreviations: ACM, appraisal committee meeting; ALI, alirocumab; BA, bempedoic acid; CrI, credible interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; SI, statin intolerant.

The company provided model fit statistics, I^2 values and the between study standard deviation for each of their SI NMAs (Table 4). While the ERG acknowledges that the company's new analyses tend to have less statistical heterogeneity than the analysis presented at technical engagement, the ERG does not consider the Company additional analysis post ACM1 to be suitable for decision making due to the clinical heterogeneity in the trials included (as described in Section 2.2.

Table 4. Heterogeneity and model fit parameters for the company's SI NMAs (position 2) (Reproduced from Company response, Table 7)

Analysis	*Total residual deviance*	*pD*	*DIC*	*I^2 (95% CrI)*	*Between-study standard deviation (s) (95% CrI)*
Technical Engagement Analysis 1	89.9	21.4	111.3	66.1%	5.38 (1.16 to 13.34)
Expanded ERG analysis post AMC1	29.0	6.4	35.4	65.9%	9.22 (0.62 to 19.25)
Company additional analysis post ACM1	49.5	10.4	60.0	20.3%	5.57 (0.20 to 17.64)

Abbreviations: ACM, appraisal committee meeting; CrI, credible interval; DIC, deviance information criterion; ERG, evidence review group; NMA, network meta-analysis; pD, effective number of parameters.

2.3.2 MTD Network (position 4)

The ERG has updated the ERG NMA (hereafter referred to as ERG MTD NMA V2) to include the data from CLEAR Wisdom provided by the company. As such, the ERG MTD NMA V2 and the company expanded ERG analysis post ACM1 both contain the same clinical data. However, similar to for the SI NMA, the results from the ERG MTD NMA V2 differ slightly from those reported by the company and the ERG is unable to explain the reason for the differences in the results. The ERG notes that the mean change in LDL-C is similar in both the ERG and company versions of the analysis but the credible intervals are considerably wider in the company's results (Table 5).

The ERG also sought to validate the company additional analysis post ACM1 by running an NMA using the trial data supplied by the company for this analysis (although as described in Section 2.2, the ERG does not consider this analysis to be suitable for decision making due to the clinical heterogeneity in the included trials and concerns around trials included in the analysis). The ERG's validation NMA demonstrates that the fixed effects model has a better model fit than the random

effects model (DIC with fixed effects 153.9 and with random effects 195.9) . The results from the company additional analysis post ACM1 do not include results for BA+EZE as the FDC trial was excluded from the revised network. The company also did not present results for BA without EZE whereas the ERG reports these results.

The results of the ERG NMA V2 and the ERG validation NMA are presented in Table 5, alongside the results of the company's two new NMAs:

- **Company's expanded ERG analysis post ACM1:** relates to the company's version of the ERG NMA expanded to include all BA data in patients with EZE at baseline.
- **Company additional analysis post ACM1:** relates to the analysis provided by the company to address the request from NICE (19 August 2020).

The ERG considers the results from the ERG MTD NMA V2 to be the most robust and to address the primary analysis requested in the NICE request for additional information. The results of the ERG MTD NMA V2 suggest treatment [redacted]

The ERG also notes that while it does not consider the Company additional analysis post ACM to be robust, the results of the ERG validation NMA demonstrate that BA would be considered significantly less effective than ezetimibe alone. The ERG also notes that the BA data in this analysis comprises only data in patients on ezetimibe at baseline (subgroup data from CLEAR Harmony and CLEAR Wisdom) and the comparator data do not necessarily match this population.

Table 5. Post ACM 1 NMA results for the MTD Network (position 4) (Adapted from Company response, Table 4)

Treatment	*Estimated difference in % change in LDL−C from baseline compared with EZE*		
	Mean	*95% CrIs*	*P value*
ERG NMA MTD V2			
BA+EZE	[redacted]	[redacted]	-
ALI (150mg)+EZE	[redacted]	[redacted]	-
Company's expanded ERG analysis post ACM1			
BA+EZE+statin	[redacted]	[redacted]	0.1417
ALI (150 mg)+EZE+statin	[redacted]	[redacted]	<0.0001
Company additional analysis post ACM1[a]			
EVO+statin	[redacted]	[redacted]	<0.0001
ALI (150 mg)+statin	[redacted]	[redacted]	<0.0001
ERG validation NMA			
BA	[redacted]	[redacted]	-
EVO	[redacted]	[redacted]	-
ALI (150mg)	[redacted]	[redacted]	-

Notes: [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.

Abbreviations: ACM, appraisal committee meeting; ALI, alirocumab; BA, bempedoic acid; CRIs, credible intervals; ERG, evidence review group; EVO, evolocumab; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis.

Similar to for the SI NMAs, the company provided model fit statistics, I^2 values and the between study standard deviation for each of their analyses (Table 6). While the ERG acknowledges that the company's new analyses tend to have less statistical heterogeneity than the analysis presented at technical engagement, the ERG does not consider the Company additional analysis post ACM1 to be suitable for decision making due to the clinical heterogeneity in the trials included (as described in Section 2.2).

Table 6. Heterogeneity and model fit parameters for the company's MTD NMAs (position 4) (Reproduced from Company response, Table 5)

Analysis	*Total residual deviance*	*pD*	*DIC*	*I^2*	*Between-study standard deviation (s) (95% CrI)*
Technical Engagement analysis 10a	286.4	82.5	368.8	80.8%	8.20 (5.4505 to 11.892)
Expanded ERG analysis post ACM1	31.4	5.7	37.1	4.8%	8.83 (0.40 to 19.31)
Company additional analysis post ACM1	162.6	34	196.6	56.5%	4.58 (1.76 to 8.61)

Abbreviations: ACM, appraisal committee meeting; CrI, credible interval; DIC, deviance information criterion; ERG, evidence review group; NMA, network meta-analysis; pD, effective number of parameters.

2.4 Scenario analyses

The Committee had concerns that populations ending "b" (situations when ALI or EVO are appropriate) were not informed by networks of studies that reflect only patients eligible for PCSK9 inhibitors and populations ending "a" (situations when ALI or EVO are not appropriate) were not informed by networks of studies that reflect only patients ineligible for PCSK9 inhibitors. The company reported that there is no suitable efficacy data to inform these analyses in the equivalent patient subpopulations that are detailed in the NICE recommendations for the PCSK9is and that were requested as scenario analyses in the NICE Request for Additional Information, 19 August 2020. However, the company has provided a breakdown of the percentage reduction in LDL-C for patients in the BA studies meeting the criteria for PCSK9i treatment (Table 7). The ERG notes that for the [redacted]), the percentage reduction in LDL-C at 12 weeks was similar in patients meeting the criteria for PCSK9i therapy compared to in those who do not. However, the ERG notes that in 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.

Table 7. Percentage reduction in LDL-C for BA in patients meeting PCSK9i eligibility criteria (Reproduced from Company response, Table 3)

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	[redacted]	[redacted]	[redacted]	[redacted]
Clear Harmony	[redacted]	[redacted]	[redacted]	[redacted]
1002-FDC	[redacted]	[redacted]	[redacted]	[redacted]
Clear Tranquility	[redacted]	[redacted]	[redacted]	[redacted]
Clear Serenity	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Patients with the following characteristics are eligible for PCSK9i therapy: patients at high risk for CVD and LDL-C persistently above 4.0 mmol/l; patients at very high risk for CVD and LDL-C persistently above 3.5 mmol/l; patients with HeFH and LDL-C persistently above 5.0 mmol/l; and patients with HeFH at high or very high risk for CVD and LDL-C persistently above 3.5 mmol/l. 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. 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). Note that the company reported that the identification of patients in the BA trials meeting these criteria was somewhat limited by the cardiovascular history available in the trial datasets.

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

3 Cost-effectiveness

3.1 Company's cost-effectiveness estimates

In response to the Committee's request for additional information, the company provided cost-effectiveness results using the revised NMAs described in Section 2. The company also provided results using the head-to-head trial data from CLEAR Tranquility for position 2a.

As noted in Section 2, the company considered it reasonable to assume a class effect for the PCSK9i treatments ALI and EVO in the absence of treatment effectiveness data for EVO. Despite this, the company did not provide cost-effectiveness results for EVO, these are considered further by the ERG in Section 3.3.

According to the NICE guide to the methods of technology appraisal, the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS. As such, the ERG only presents results for comparisons with the FDC (the cheapest preparation of bempedoic acid). The ERG also notes that there is only a small difference in the cost-effectiveness results for bempedoic acid as a single agent product and as a combination product (the FDC) because the efficacy between the two preparations is assumed to be equivalent.

The company's deterministic cost-effectiveness results for positions 2a, 2b and 4b are given in Table 8, Table 9 and Table 10, respectively.

The expanded ERG analysis post ACM1 does not provide estimates for the treatment effect of EZE versus placebo at baseline. As such, the company set the treatment effect of EZE versus placebo to zero in the cost-effectiveness model. The ERG considers this to be a reasonable approach given that all patients are on background EZE treatment. As for the company additional analysis post ACM1, the treatment effect of EZE versus placebo was set to [redacted] to reflect the data obtained from the NMA.

Table 8. Company's cost effectiveness results for position 2a, FDC vs comparators

Technologies	*Total costs (£)*	*Total LYs*	*Total QALYs*	*Incremental estimates*			*ICER (£/QALYs)*
				Costs (£)	*LYs*	*QALYs*	
Expanded ERG analysis post ACM1							
EZE	9,989	11.94	8.92	-	-	-	-
BA/EZE FDC	14,558	12.15	9.10	4,568	0.21	0.19	24,641
Company additional analysis post ACM1							
EZE	9,800	12.01	8.98	-	-	-	-

BA/EZE FDC	14,322	12.25	9.19	4,522	0.24	0.21	21,507
CLEAR Tranquility							
EZE	9,889	12.02	8.98	-	-	-	-
BA/EZE FDC	14,470	12.23	9.16	4,581	0.21	0.19	24,756

Abbreviations: ACM1, first appraisal committee meeting; Ali, alirocumab; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Table 9. Company's cost effectiveness results for position 2b, FDC vs comparators

Technologies	*Total costs (£)*	*Total LYs*	*Total QALYs*	*Incremental estimates*			*ICER (£/QALYs)*	*NMB*	
				Costs (£)	*LYs*	*QALYs*		*£20,000/ QALY*	*£30,000/ QALY*
Expanded ERG analysis post ACM1									
BA/EZE FDC	22,155	10.14	6.84	-	-	-		-	-
ALI + EZE	47,875	10.55	7.14	-25,721	-0.41	-0.30	85,053*	19,672	16,648
Company additional analysis post ACM1									
BA/EZE FDC	22,175	10.30	6.96	-	-	-		-	-
ALI	47,665	10.53	7.12	-25,490	-0.23	-0.17	153,380*	22,167	20,505

Abbreviations: ACM1, first appraisal committee meeting; Ali, alirocumab; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years.

*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs and less costs than ALI).

Table 10. Company's cost effectiveness results for position 4b, FDC vs comparators

Technologies	*Total costs (£)*	*Total LYs*	*Total QALYs*	*Incremental estimates*			*ICER (£/QALYs)*	*NMB*	
				Costs (£)	*LYs*	*QALYs*		*£20,000/ QALY*	*£30,000/ QALY*
Expanded ERG analysis post ACM1									
BA/EZE FDC	21,312	9.56	6.43	-	-	-	-	-	-
ALI +EZE	46,490	10.18	6.88	-25,177	-0.62	-0.45	55,530*	16,109	11,575

Abbreviations: ACM1, first appraisal committee meeting; Ali, alirocumab; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years.

*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs and less costs than ALI).

The company also provided probabilistic estimates in their response based on 5,000 iterations. As part of the ERG's quality assessment, the ERG ran the company's PSA (Table 11). Following this, the ERG identified large discrepancies between the company's mean PSA estimate and the ERG's mean PSA estimate in positions 2a and 2b using the expanded ERG analysis post ACM1. As explained in Section 3.3, the ERG's higher ICERs appear to be driven by smaller incremental QALYs. Nonetheless, the ERG would like the company to clarify if their probabilistic ICERs have been reported erroneously for positions 2a and 2b (£24,887 and £83,997, respectively).

Table 11. Probabilistic results obtained from the company's analyses, FDC vs comparators

Analysis	*PSA estimate*	*When statins are contraindicated or not tolerated*		*Patients receiving maximally tolerated statin (Position 4b)**
		Position 2a	*Position 2b**	
Expanded ERG analysis post ACM1	Company	£24,887	£83,997	£53,676
	ERG	£27,650 £27,533 £27,319	£91,070 £91,324 £91,752	£53,922 £54,314 £54,076
Company additional analysis post ACM1	Company	£21,453	£154,376	-
	ERG	£21,209 £21,441	£151,815 £149,810	-

Abbreviations: ACM1, first appraisal committee meeting; PSA, probabilistic sensitivity analysis.
*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs and less costs than ALI).

3.2 ERG's cost effectiveness estimates

3.2.1 CLEAR Tranquility

The ERG has an issue with how the company has applied LDL-C reductions in the model for the CLEAR Tranquility scenario. Instead of applying the EZE treatment effect versus placebo recorded in CLEAR Tranquility [redacted] the company set the treatment effect for EZE to zero. Then, to obtain the FDC treatment effect versus placebo, the company added the EZE treatment effect versus placebo [redacted] to the FDC treatment effect versus EZE [redacted] to estimate a treatment effect of [redacted] for the FDC versus placebo. The ERG disagrees with the company's calculation because a [redacted] for EZE should not be treated as [redacted] for the FDC. To aid interpretation, these calculations are illustrated in the Appendix (Figure A).

In consequence, the ERG amended the company's scenario analysis to better reflect CLEAR Tranquility. This included employing an estimate of [redacted] for the EZE treatment effect versus placebo and an estimate of [redacted] for the FDC treatment effect versus EZE (leading to an estimate of [redacted] for the FDC treatment effect versus placebo). The ERG's approach led to an increase in the ICER of approximately £5,000 (Table 12).

Table 12. ERG's scenario analysis using CLEAR Tranquility for position 2a

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			ICER (£/QALYs)
				Costs (£)	LYs	QALYs	
EZE	9,993	11.98	8.94	-	-	-	-
BA/EZE FDC	14,639	12.16	9.10	4,645	0.18	0.16	29,545

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

3.2.2 Expanded ERG analysis post ACM1

As described in Section 2, the ERG considers the results of the updated ERG NMAs (referred to as ERG NMA V2 in Section 2.3) to be the most robust and to address the primary analysis requested in the NICE request for additional information. Cost-effectiveness results using the updated ERG NMAs are given in Table 13 and these differ slightly from the company's cost-effectiveness results. The ERG has also provided cost-effectiveness results for comparisons with EVO in positions 2b and 4b assuming a class effect for ALI and EVO. Consequently, the only difference between the results for ALI and EVO is the acquisition cost of treatment (£4,437.79 per annum for EVO and £4,383.00 per annum for ALI).

Table 13. Deterministic results using ERG NMA V2

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental estimates			ICER (£/QALYs)	NMB	
				Costs (£)	LYs	QALYs		£20,000/ QALY	£30,000/ QALY
Position 2a									
EZE	9,989	11.94	8.92	-	-	-	-	-	-
BA/EZE FDC	14,543	12.15	9.11	4,554	0.22	0.19	23,869	-738	1,170
Position 2b									
BA/EZE FDC	22,156	10.15	6.85	-	-	-	-	-	-
ALI + EZE	47,879	10.55	7.14	-25,724	-0.41	-0.30	86,698*	19,790	16,823
EVO + EZE	48,244	10.55	7.14	-26,089	-0.41	-0.30	87,929*	20,155	17,188
Position 4b									
BA/EZE FDC	21,312	9.57	6.44	-	-	-	-	-	-
ALI +EZE	46,495	10.18	6.88	-25,183	-0.61	-0.45	56,221*	16,224	11,745
EVO + EZE	46,852	10.18	6.88	-25,540	-0.61	-0.45	57,019*	16,581	12,102

Abbreviations: ACM1, first appraisal committee meeting; Ali, alirocumab; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years.
* ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs and less costs than ALI and EVO).

The ERG's probabilistic results are given in Table 14. In position 4b, the ERG's probabilistic results are comparable to the deterministic results. However, the ERG consistently produced probabilistic ICERs for position 2a that are around £3,000 higher than the deterministic ICER. Similarly, the ERG consistently produced probabilistic ICERs for position 2b that are around £5,000 higher than the deterministic ICER. The ERG came across similar issues when replicating the company's PSA (see Section 3.1).

In positions 2a and 2b, the ERG notes that the total costs are similar in the deterministic analysis and probabilistic analysis, but more QALYs are generated in both treatment arms in the probabilistic analysis. More importantly, the incremental QALYs are reduced in the probabilistic analysis. Unfortunately, only total QALYs are shown in the calculations for PSA and therefore the ERG cannot

ascertain which health states additional QALYs are being generated in. Furthermore, there are no obvious modelling assumptions in position 2 that are not seen in position 4.

The ERG also examined descriptive statistics of the CODA, but this was also inconclusive (for example, indistinguishable means and medians). Given that the ERG ran into similar issues using the company's Expanded ERG analysis post ACM1, the ERG would like to give the company an opportunity to explain these discrepancies.

Finally, cost-effectiveness planes for one PSA run can be found in the Appendix (similar eclipses were produced in each run). There is nothing from these planes to suggest any abnormal variation in costs or QALYs.

Table 14. PSA results using ERG NMA V2

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Position 2a					
EZE	9,661	9.17	-	-	-
BA/EZE FDC	14,324	9.35	4,663	0.18	26,356
Position 2b					
BA/EZE FDC	22,511	7.10	-	-	-
ALI + EZE	48,750	7.38	-26,239	-0.28	91,417*
Position 2b					
BA/EZE FDC	22,509	7.10	-	-	-
EVO + EZE	49,110	7.39	-26,601	-0.28	93,676*
Position 4b					
BA/EZE FDC	21,450	6.45	-	-	-
ALI + EZE	46,657	6.91	-25,160	-0.46	55,388*
Position 4b					
BA/EZE FDC	21,395	6.43	-	-	-
EVO + EZE	46,850	6.88	-25,455	-0.45	56,387*

Abbreviations: ACM1, first appraisal committee meeting; Ali, alirocumab; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; LYs, life years; NMB, net monetary benefit; QALYs, quality-adjusted life years.
* ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs and less costs than ALI and EVO).

3.2.3 Patient characteristics from the CLEAR trials

In response to the request for additional data on patient characteristics from the CLEAR trials, the company explained that some of the patient's characteristics needed for the QRISK3 algorithm (to calculate baseline CV risks in a primary prevention population) were not captured. As such, the ERG considers it important to highlight the scenario provided at technical engagement where a baseline CV risk based on CG181 and TA385 was employed (a 10-year risk of 20% for MI, IS or CV death). Using this risk on top of the updated ERG NMA SI V2 increased the ICER by around £7,000 (Table 15).

A similar increase in the ICER was seen at technical engagement. However, as stated at technical engagement, this scenario 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 and TA385 because the proposed position of bempedoic acid is after EZE where patients are likely to be at a higher CV risk.

Table 15. ERG scenario using the baseline CV risk for primary prevention accepted in CG181 and TA385

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
EZE	7,904	9.57	-	-	-
BA/EZE FDC	12,724	9.72	4,821	0.15	31,469

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed dose combination; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

The Committee also had concerns that data on prior CV event types (to inform the starting health state in a secondary prevention population) were not taken from the CLEAR trials. In their response, the company affirmed that data on prior CV events were not available from the CLEAR trials. In consequence, the ERG considers the use of Ward *et al.* 2007 to inform the distribution of prior CV events to be a reasonable alternative given that this source is based on UK prevalence data and consistent with CG181 and TA385. The ERG also notes that details of prior CV event types are not reported in TA394 and TA393 as these submissions included models with composite health states (combining different CV event types into one health state).

3.2.4 Baseline LDL-C levels

The company was also asked to provide baseline LDL-C levels from the CLEAR trials in patients with prior EZE use and without prior EZE use as these data were aggregated in the company's base case analysis. The data provided by the company are given in Table 16. Except for CLEAR Serenity, baseline LDL-C levels are generally higher in patients with prior EZE use. However, the data must be interpreted with caution due to the small patient numbers receiving prior EZE and the limited data used to determine PCSK9i eligibility.

When the ERG modelled the baseline LDL-C levels to reflect the intended positioning for bempedoic acid (baseline LDL-C levels from patients who received prior EZE and are ineligible for PCSK9i treatments in position 2a and baseline LDL-C levels from patients who received prior EZE and are eligible for PCSK9i treatments in positions 2b and 4b) the ICER increased by around £4,000 in position 2a and around £1,000 in position 2b. The ICER decreased by around £4,000 in position 4b. Further cost-effectiveness results can be found in Tables A and B of the Appendix. As noted above,

the ERG does not consider these scenarios to be reliable for decision making. The ERG also notes that these scenarios were performed on top of the ERG version of the Expanded ERG analysis post ACM1 (referred to as ERG NMA V2 in Section 2.3).

Table 16. Baseline LDL-C levels (mmol/L) in patients by EZE use at baseline in the CLEAR trials

LDL-C level	*Population 4 (max dose statin)*					*Population 2 (statin intolerant)*				
	CLEAR Wisdom		*CLEAR Harmony*		*Weighted average*	*CLEAR Tranquility*		*CLEAR Serenity*		*Weighted average*
EZE use	*No*	*Yes*	*No*	*Yes*	*Yes*	*No**	*Yes*	*No*	*Yes*	*Yes*
All patients										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCSK9i eligible										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCSK9i ineligible**										
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EZE, ezetimibe; ICER incremental cost-effectiveness ratio; IMP, investigational medicinal product; LDL-C, low density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SD, standard deviation.

* There was one patient in the placebo group of Tranquility who didn't take any IMP, so there is one patient without baseline ezetimibe.

**Includes all patient not assigned to "PCSK9i eligible" and may also include patients with insufficient information.

4 Appendices

Figure A. CLEAR Tranquility, estimated differences in % change in LDL–C from baseline

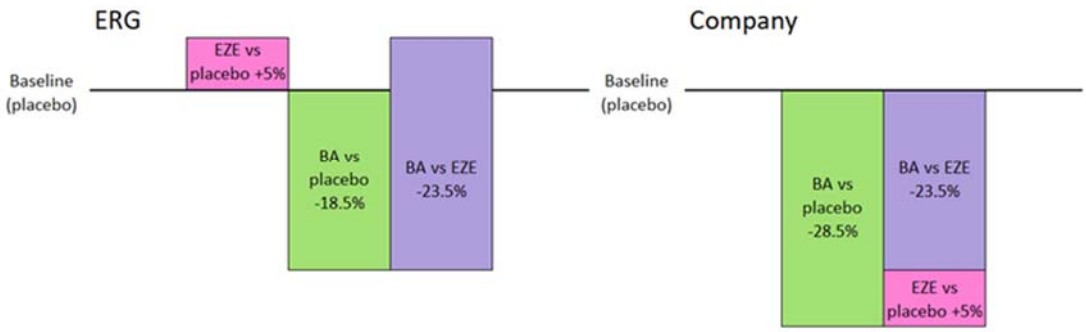

Figure B. Cost effectiveness plane, position 2a, FDC vs EZE

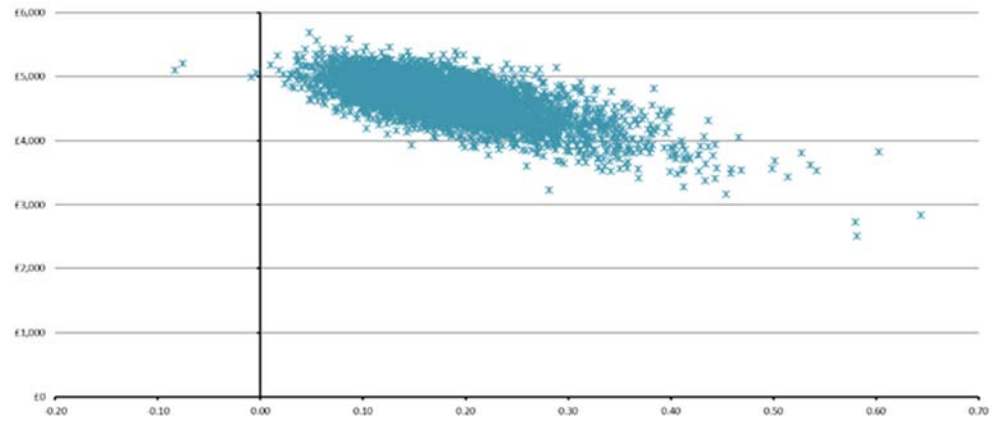

Figure C. Cost effectiveness plane, position 2b, FDC vs ALI+EZE

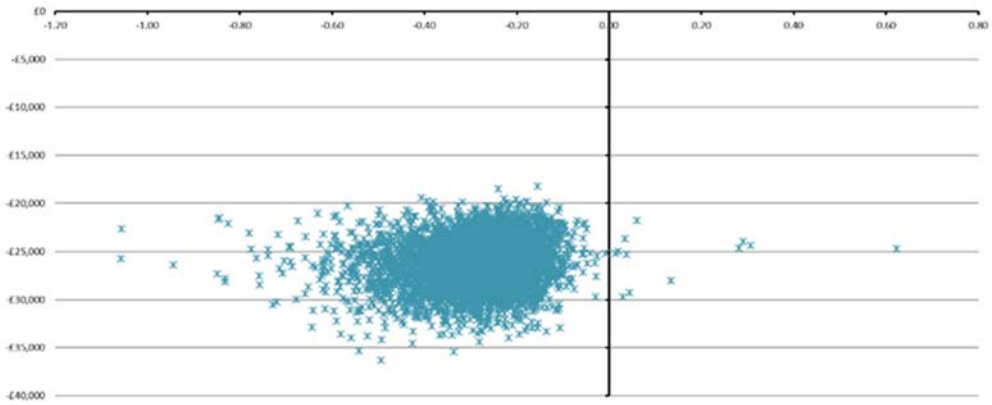

Figure D. Cost effectiveness plane, position 2b, FDC vs EVO+EZE

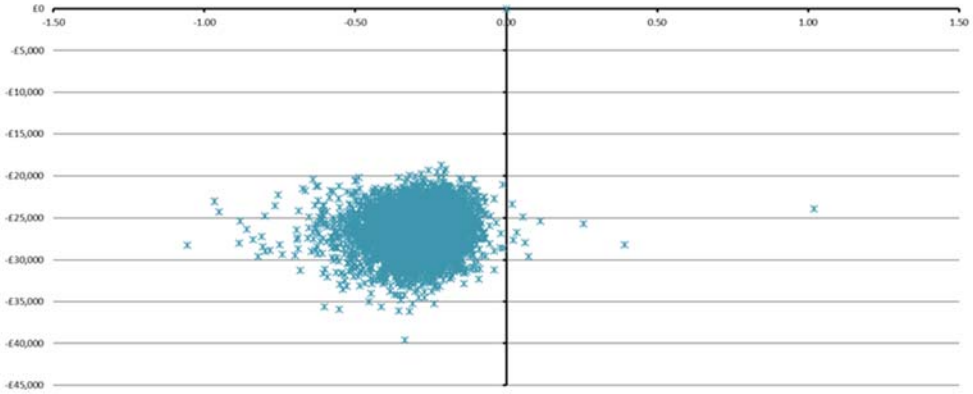

Figure E. Cost effectiveness plane, position 4b, FDC vs ALI+EZE

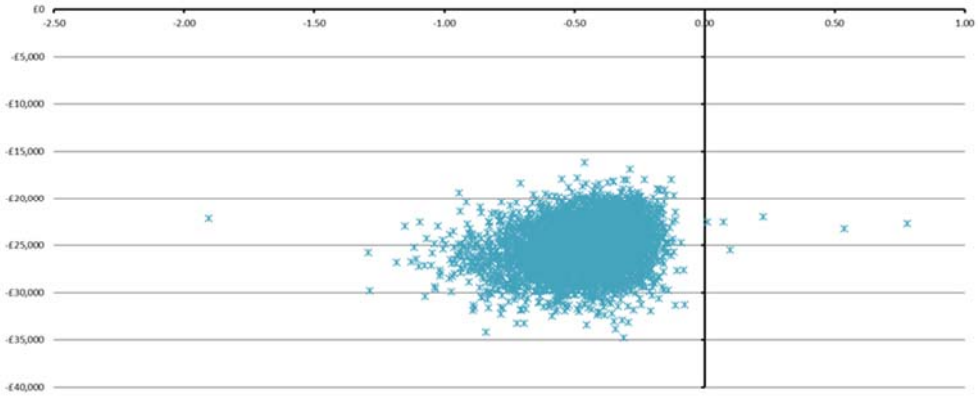

Figure F. Cost effectiveness plane, position 4b, FDC vs EVO+EZE

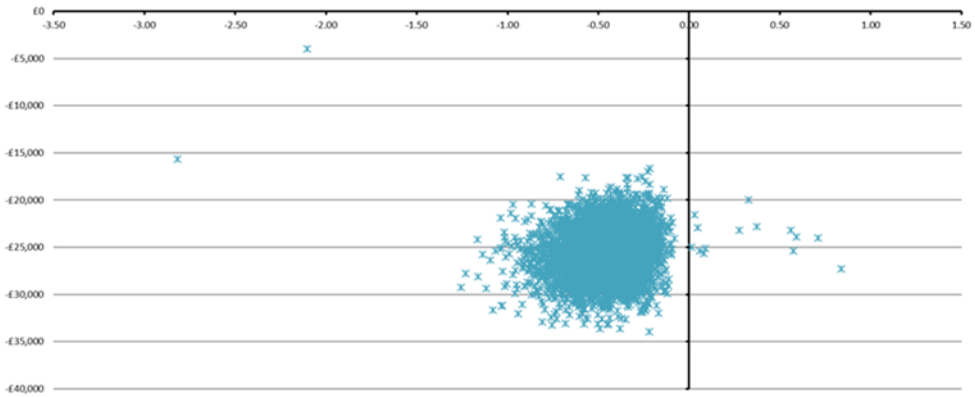

Table A. ERG scenarios on LDL-C levels. Position 2a (PCSK9i ineligible)

	Base case (baseline LDL-C levels from all patients)	*Baseline LDL-C levels from patients ineligible for PCSK9i treatment (with or without prior EZE use)*	*Baseline LDL-C levels from all patients who received prior EZE (PCSK9i eligible and ineligible)*	*Baseline LDL-C levels from patients who received prior EZE and are ineligible for PCSK9i treatments*
LDL-C level (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]
ICER (FDC vs. EZE)	£23,869	£24,764	£27,123	£28,319

Abbreviations: EZE, ezetimibe; FDC, fixed dose combination; ICER incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Table B. ERG scenarios on LDL-C levels. Positions 2b and 4b (PCSK9i eligible)

	Base case (baseline LDL-C levels from patients eligible for PCSK9i treatment)	*Baseline LDL-C levels from patients who received prior EZE and are eligible for PCSK9i treatments*
Position 2b		
LDL-C level (mmol/L)	[redacted]	[redacted]
ICER (FDC vs. ALI+EZE)	£86,698*	£88,090*
ICER (FDC vs. EVO+EZE)	£87,929*	£89,341*
Position 4b		
LDL-C level (mmol/L)	[redacted]	[redacted]
ICER (FDC vs. ALI+EZE)	£56,221*	£51,633*
ICER (FDC vs. EVO+EZE)	£57,019*	£52,366*

Abbreviations: ALI, alirocumab; EZE, ezetimibe; FDC, fixed dose combination; ICER incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. FDC generates less QALYs and less costs than ALI and EVO).